CURRENT

SURGICAL THERAPY

THIRTEENTH EDITION

JOHN L. CAMERON
ANDREW M. CAMERON

ELSEVIER

CURRENT SURGICAL THERAPY

13th EDITION

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TRAUMATIC NECROTIZING FASCIITIS

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USE OF SURVEILLANCE SCANS

LOCALLY ADVANCED CHOLANGIOCARCINOMA: ASSESSMENT AND ACCESS

MANAGEMENT OF PRIMARY CYSTIC TUMORS

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MANAGEMENT OF ACUTE LIVER FAILURE

MANAGEMENT OF ACUTE MESENTERIC ISCHEMIA

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MANAGEMENT OF DUODENAL DIVERTICULOSIS OF THE COLON

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PENETRATING ABDOMINAL TRAUMA

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INTRODUCTION: PREVALENCE AND DIAGNOSIS OF THE PANCREAS

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PNEUMATOSIS INTESTINALIS AND THE PERFORATED VISCUS

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CARCINOMA, METASTATIC: SURGICAL MANAGEMENT OF LESIONS IN LUNG

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MANAGEMENT OF CARCINOID TUMORS

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MANAGEMENT OF COLONIC GASTROINTESTINAL STROMAL TUMORS

ILEOCECAL AND COLORECTAL TUMORS

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IMAGE-GUIDED BIOPSY OF LESIONS OF THE ABDOMEN AND PELVIS

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BURN WOUND MANAGEMENT

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MANAGEMENT OF FATIGUE-RELATED DISORDERS

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MANAGEMENT OF BILIARY TRACT DISEASE

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SPECIFIC COMPLICATIONS OF LAPAROSCOPIC DISSECTION

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MANAGEMENT OF SPIGELIAN, UMBILICAL, AND OTHER UNCOMMON HERNIAS

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MANAGEMENT OF BENIGN ANORECTAL DISEASES

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RESECTION OF COLORECTAL LIVER METASTASES

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MANAGEMENT OF ACUTE MECHANICAL OBSTRUCTION

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MANAGEMENT OF UNRUPTURED ABDOMINAL AORTIC ANEURYSMS

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MANAGEMENT OF PERIANAL CROHN DISEASE

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ABDOMINAL WALL RECONSTRUCTION

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ENDOVASCULAR THERAPY

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METAL INJURY AND ITS TREATMENT

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ARTERIAL ACCESS, ENDOVASCULAR DEVICE SELECTION, AND CLOSURE

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THE UNDERSERVED AND VULNERABLE POPULATIONS

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CHOLANGIOCARCINOMA

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USE OF ESOPHAGEAL STENTS
MANAGEMENT OF NONMELANOMA SKIN TUMORS

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INITIAL ASSESSMENT AND RESUSCITATION OF THE TRAUMA PATIENT

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ACUTE ISCHEMIA
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DUCTAL CARCINOMA IN SITU

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THE PHYSICAL MANIFESTATIONS OF CHRONIC VENOUS INSUFFICIENCY

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ROLE OF NEOADJUVANT BREAST BIOPSY IN THE MANAGEMENT OF BREAST CANCER

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NONMELANOMA SKIN CANCERS: EVALUATION AND MANAGEMENT OF LOCOREGIONAL DISEASE

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ANATOMIC PERSPECTIVE: "SPACES OF HEAD AND NECK"

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MANAGEMENT OF SOFT TISSUE SARCOMA

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SOFT TISSUE DISEASE OF THE RETROPERITONEUM, OMENTUM

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MANAGEMENT OF EMERGENCIES OF THE SMALL BOWEL

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MANAGEMENT OF SMALL BREAST CANCER

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ENTERAL STENTING FOR MALIGNANT COLONIC OBSTRUCTION

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ABDOMINAL COMPARTMENT SYNDROME AND MANAGEMENT OF THE OPEN ABDOMEN

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MANAGEMENT OF INFECTIOUS FAILURE

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MANAGEMENT OF PANCREATIC CANCER

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HAND BOOK PANIC IN CONSULTATION

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CARCINOMA OF UNKNOWN ORIGIN

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BIOPSY OF THE COLORECTAL WALL AND BIOPSY BY THE MANAGEMENT OF BENIGN DISEASE

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BREAST RECONSTRUCTION FOLLOWING MASTECTOMY, BREAST CANCER, AND BENIGN DISEASE

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ENDOCRINE CHANGES IN CRITICAL ILLNESS

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MOLECULAR MARGINS IN BREAST CANCER

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CURATIVE THERAPY IN LOCALLY ADVANCED COLON CANCER

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ABLATION OF COLORECTAL LIVER METASTASES

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MULTIDISCIPLINARY APPROACH TO BREAST CANCER

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BENIGN BREAST DISEASE
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BLUNT CARDIAC INJURY

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BREAST RECONSTRUCTION FOLLOWING MASTECTOMY: INDICATIONS, TECHNIQUES, AND OUTCOMES

NERVE INJURY AND REPAIR

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Preface

The first edition of Current Surgical Therapy was published in 1984. [illegible]

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ESOPHAGEAL FUNCTION TESTS

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The swallowing mechanism is a dynamic process that involves the coordinated interplay between the central and peripheral nervous systems, the esophagus, and the esophageal sphincters. Esophageal motility disorders can be broadly classified as primary esophageal motility disorders, secondary esophageal motility disorders, and mechanical obstruction. Primary esophageal motility disorders are those in which the esophagus is the only organ involved in the pathologic process. Secondary esophageal motility disorders are those in which the esophagus is involved as part of a systemic disease process. Mechanical obstruction is a process that results in esophageal dysfunction because of an intraluminal, intramural, or extramural process that physically impairs the passage of food from the mouth to the stomach. Esophageal manometry and ambulatory pH monitoring are the most commonly performed tests in the evaluation of esophageal motility disorders. Esophageal manometry is the only test that can accurately measure the pressure and coordination of esophageal contractions. Ambulatory pH monitoring is the most sensitive test for detecting pathologic gastroesophageal reflux. Esophageal manometry and ambulatory pH monitoring are complementary tests that provide different but important information about esophageal function. Each of these tests possesses its own diagnostic and interpretive pitfalls that must be understood to avoid misdiagnosis and inappropriate therapy.

ESOPHAGEAL MANOMETRY

Esophageal manometry has been considered the gold standard for the diagnosis of esophageal motility disorders. Esophageal manometry is performed by placing a pressure catheter through the nose into the esophagus and measuring the pressure changes that occur during swallowing. Esophageal manometry is the only test that can accurately measure the pressure and coordination of esophageal contractions. Esophageal manometry is performed by placing a pressure catheter through the nose into the esophagus and measuring the pressure changes that occur during swallowing. Esophageal manometry is the only test that can accurately measure the pressure and coordination of esophageal contractions.

Technique

Access to the body is usually gained through the nose. Patients are usually sedated with a topical anesthetic and an intravenous sedative. Although many centers have used water-perfused catheters, most centers now use solid-state catheters. The catheter is passed through the nose into the esophagus and positioned so that the pressure sensors are in the body of the esophagus. The patient is then asked to swallow a series of 5-mL water swallows. The pressure changes that occur during swallowing are recorded and analyzed.

ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

EGJ outflow obstruction was formerly called hypertensive lower esophageal sphincter. Using a definition of EGJ outflow obstruction based solely on the IRP with the exclusion of achalasia allows this diagnosis to be combined with another diagnosis dependent on the esophageal body motility. EGJ outflow obstruction may be

BOX 1 Indications for Esophageal Manometry

Definite

- Evaluation of unexplained esophageal symptoms
- Accurate placement of pH, pH impedance probes
- Evaluation of peristaltic function before antireflux surgery or esophageal myotomy
- Evaluation of postoperative dysphagia
- Evaluation of transplantation with impedance
- Evaluation of scleroderma

Likely

- Evaluation of peristaltic function before bariatric surgery and lung transplantation
- Diagnosis of achalasia prior therapy

From Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol 2013;108:1238–49; quiz 1250. http://doi.org/10.1038/ajg.2013.196.

FIG. 1 Classic barium esophagram appearance of achalasia on a lateral esophagram.

caused by an anatomic abnormality in the cardia (hiatal hernia, diseases of the esophageal wall, etc.) or be idiopathic with normal anatomy. In the setting of an anatomic abnormality, such as a paraesophageal hernia, surgical correction is associated with excellent durable results. In patients without an anatomic abnormality, the clinical significance of this diagnosis is still uncertain because some investigators believe that EGJ outflow obstruction may be an early or incomplete expression of a variant of achalasia. Because a significant number of patients with EGJ outflow obstruction report a spontaneous resolution of their symptoms over time without intervention, the recommendation for invasive interventions such as POEM or laparoscopic distal esophageal myotomy should be made only in those patients with persistent symptoms and associated weight loss.

DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm (DES) is an uncommon condition that accounts for less than 10% of esophageal motility abnormalities. DES is characterized by uncoordinated contractions of the esophagus that typically result in symptoms of chest pain, dysphagia, or both. The esophagogram may be abnormal, but manometry is usually necessary for the diagnosis. As with achalasia, the introduction of high-resolution manometry changed the diagnostic criteria for DES. Initially, the Chicago Classification based both high-resolution manometry (HRM) and conventional manometry on the same criteria of rapid or simultaneous contractions but modified this to a parameter known as distal latency, or which is only apparent with HRM and is a more reliable indicator of DES. Distal latency is more likely associated with the onset of inhibitory peristaltic sensory activity after contractions and seems shorter in patients with DES. This results in an increased state of contractions in the distal esophagus. Current guidelines define DES by HRM as patients who have a normal integrated relaxation pressure at the LES but who have a distal latency less than 4.5 seconds in 20% of wet swallows. Medical treatment options include nitrates, sildenafil, and tricyclic antidepressants, which may help to alleviate the noncardiac chest pain. Diazepam and lorazepam have been used if nitrates, sildenafil, or tricyclic antidepressants have failed to control symptoms. Use of proton pump inhibitors (PPIs) for treatment of concomitant GERD also may be helpful. Surgical interventions such as laparoscopic or thoracoscopic extended myotomy can be effective in well-selected patients with refractory DES.

HYPERCONTRACTILE "NUTCRACKER" ESOPHAGUS

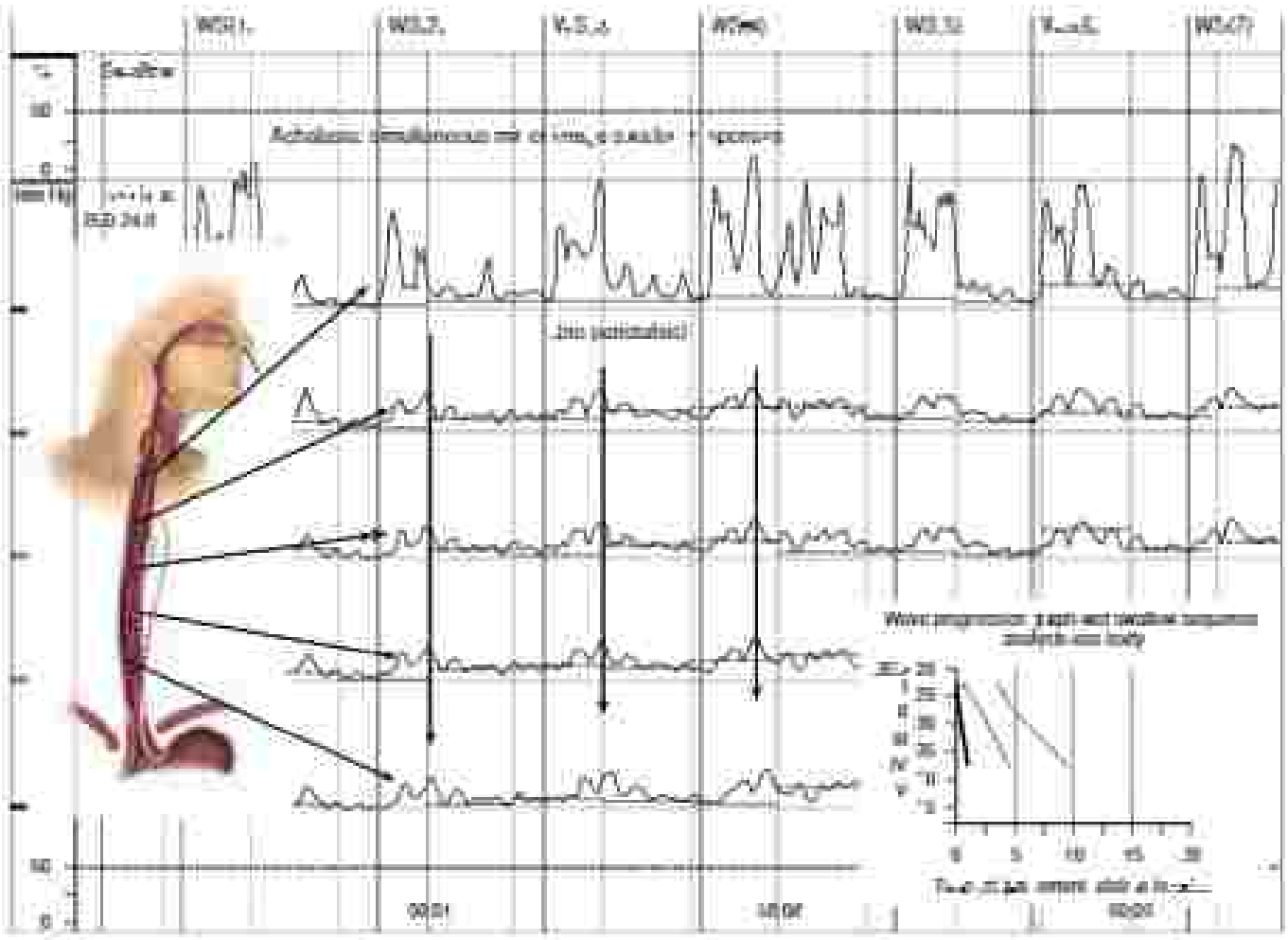
The definition of hypercontractile or "nutcracker" esophagus was updated in the latest version of the Chicago Classification to include [illegible] with a DCI greater than 8000 mm Hg cm in more than 20% of swallows, excluding patients with a single abnormal swallow (Figs. 5 and 6). In comparison to diffuse esophageal spasm, the peristaltic contractions propagate normally, and the LES relaxes appropriately. Diltiazem has been shown to lower distal peristaltic pressures and may reduce chest pain; however, these results are not reliably reproducible. As in DES, nitrates, sildenafil, and tricyclic antidepressants may be useful in the treatment of the noncardiac chest pain.

INEFFECTIVE ESOPHAGEAL MOTILITY

Ineffective esophageal motility is defined in the Chicago Classification system as a DCI of less than 450 mm Hg cm in 50% of the swallows. A variant of ineffective esophageal motility called fragmented peristalsis occurs when the patient's high-resolution manometry demonstrates normal DCI but greater than 5 cm breaks in more than 50% of the swallows. Finally, absent contractility is defined as a DCI less than 100 mm Hg cm in 100% of the swallows and is primarily observed in patients with connective tissue disorders such as scleroderma. Because there are no pharmacologic agents that restore or improve peristalsis in these patients, the patient's associated GERD is usually the focus of therapy.

GASTROESOPHAGEAL REFLUX DISEASE

GERD is a common disorder that often brings patients to medical attention for acid suppression therapy. It is reported to affect approximately 9% of the US population and is associated with a significant cost to the US healthcare system. There is a degree of physiologic reflux that is considered normal and usually is limited and not substantial. The association of patient-reported symptoms and pathologic confirmed GERD is approximately 70% in many studies. Before recommending esophageal testing for diagnosis, most patients are empirically treated with a trial of PPI therapy. For those patients who



develop recurrent symptoms after a trial of PPI therapy, upper endoscopy with esophageal biopsy is the next step in the diagnostic algorithm. The identification of high-grade esophagitis (grades C or D), Barrett's metaplasia (Fig. 7), or a peptic stricture are considered confirmatory evidence for GERD. Grade B esophagitis provides adequate evidence for initiation of medical management of GERD. However, additional testing is warranted to confirm the diagnosis before committing a patient to long-term PPI therapy or antireflux surgery.

AMBULATORY ACID REFLUX MONITORING

Acid exposure in the esophagus is monitored with an intraluminal pH probe with one of two methods, either an intraluminal tube with a nasopharyngeal catheter or a wireless Bravo pH probe (Medtronic). Both methods provide the physician with similar data, particularly relating to the amount of time the esophagus is exposed to acid reflux. When the information is correlated with a symptom log, determination is possible of whether the patient's symptoms are related to acid exposure within the esophagus. This information is commonly expressed using the standard parameters (Box 2) to calculate a DeMeester score or a composite pH score. A score of less than 14.72 (fiftieth percentile of normal) is considered physiologic reflux, whereas a score greater than 14.72 is considered abnormal. Acid exposure in the esophagus is recorded according to the position of the patient (supine or upright) and the relation of acid exposure with meals. Accurate placement of either the indwelling esophageal catheter or the wireless probe is facilitated by placement during high-resolution esophageal manometry, and so these tests are often scheduled together.

ESOPHAGEAL IMPEDANCE

Impedance monitoring measures bolus transport by measuring the resistance to electrical conductivity of the esophagus and its contents. Impedance testing is an important adjunct to traditional pH testing because it can be useful for the evaluation of acid and bile (nonacid) reflux. Impedance measurement works by using low AC voltage to apply an electrical potential between two electrodes on a catheter separated by an isolator. Because air, liquid, and esophageal mucosa have unique impedance characteristics, identification of the material that is bridging the electrodes can be accurately assessed. Air is resistant to current flow and has a high impedance. Liquid has a low impedance value. Esophageal tissue has an indeterminate range and is used as a baseline during monitoring. With multiple electrodes along a catheter system, identification of changes in impedance makes possible determination of the direction of bolus transport within the esophagus and identification of reflux of a bolus that has cleared the esophagus but comes back up from the stomach (Fig. 8).

GERD Classification

The recently introduced classification of motor disorders in GERD characterizes morphologic and motor abnormalities in GERD, and this GERD classification is intended to be used in conjunction with the

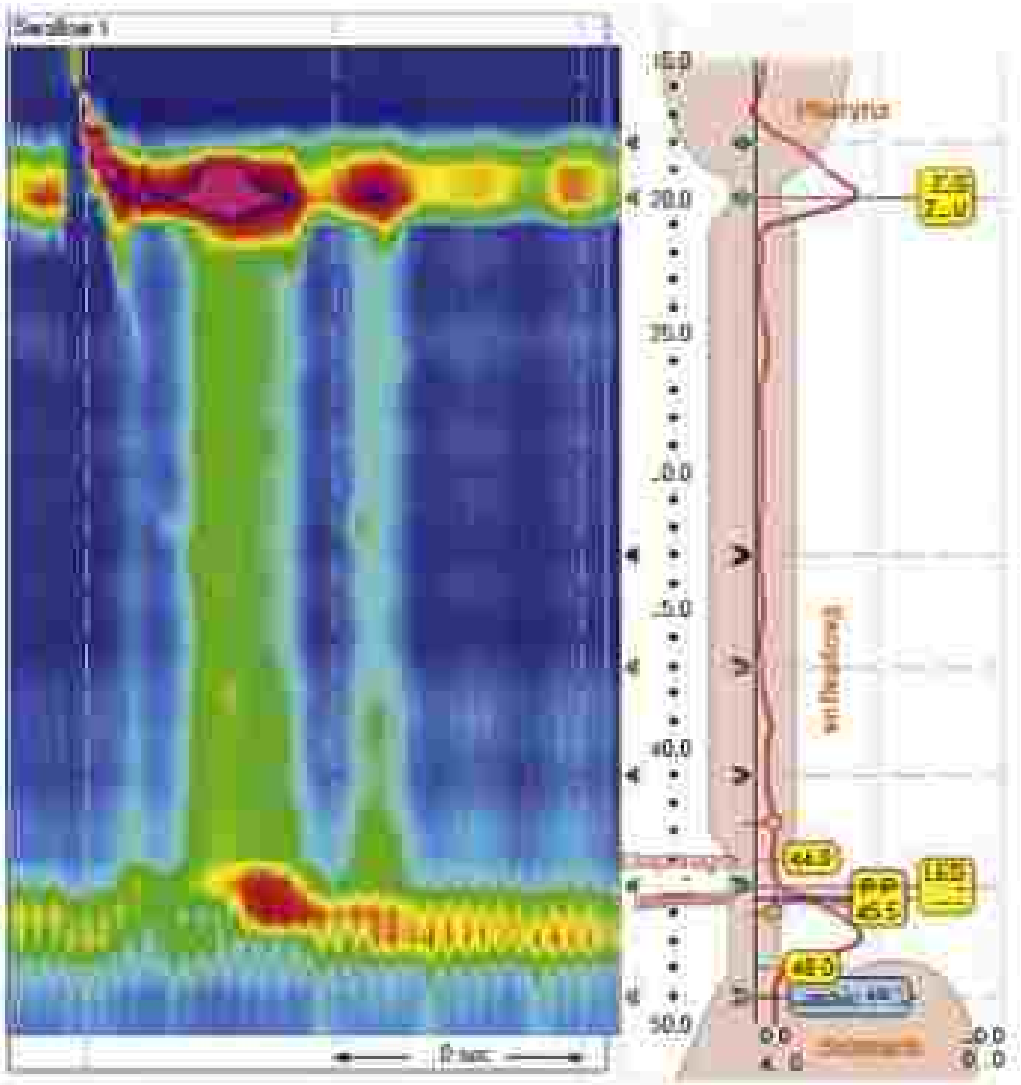


FIG. 3 High-resolution manometry in a patient with achalasia. Note the simultaneous contractions as a result of retrograde propagation. The lower esophageal sphincter is not hypertensive (i.e., no complete relaxation is not seen). LES, lower esophageal sphincter; P_{LES}, pressure in sphincter zone; —, upper esophageal sphincter.

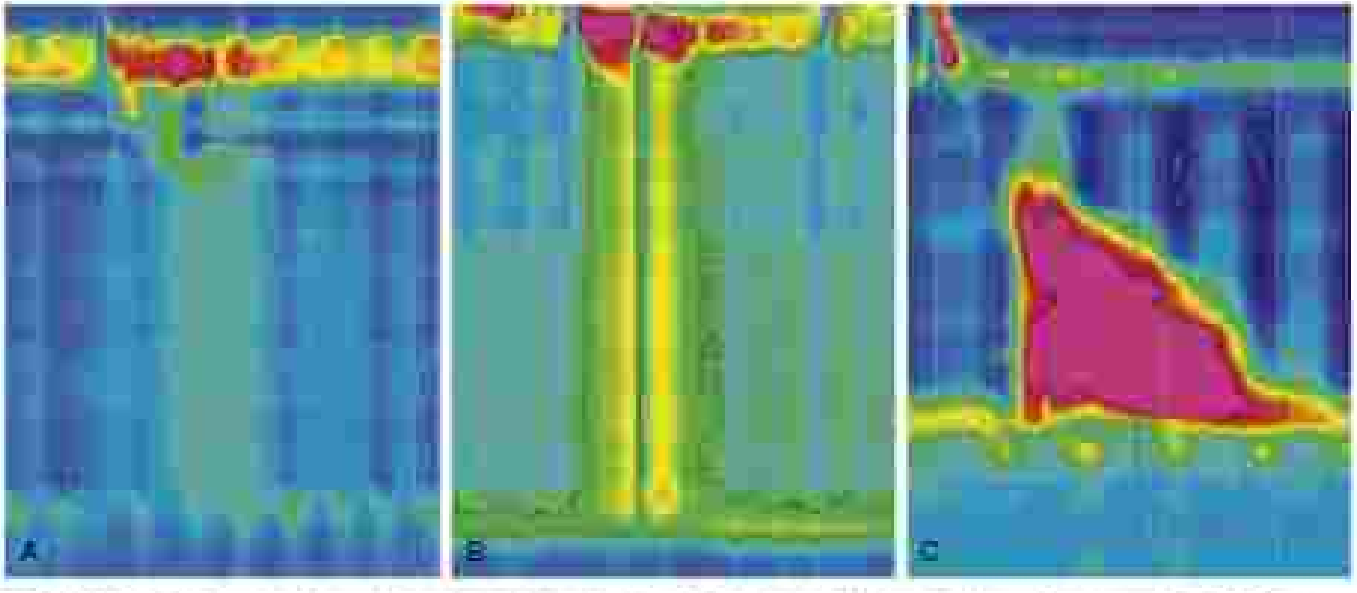


FIG. 4 High-resolution manometry demonstrating achalasia subtypes. (A) Type I is characterized by minimal esophageal pressurization. (B) Type II, with pan-esophageal pressurization was noted. (Bar denotes 20 mm Hg contour.) (C) Type III, with premature spastic contractions.

TABLE 1 Interpretation of High-Resolution Esophageal Manometry Chicago Classification V3.0

Subject	Metric	Motility disorder	Diagnostic criteria
EVALUATION OF ESOPHAGEAL FUNCTION			
Evaluation of EGJ function	Integrated relaxation pressure (IRP) abnormal if median value greater than upper limit of normal	Esophagogastric obstruction	EGJ obstruction present if IRP abnormal in ≥2 swallows Borderline EGJ obstruction present if IRP abnormal in 1 swallow
Evaluation for major motility disorders	Distal contractile integral (DCI): mean of distal contractile vigor (4–9 cm proximal to LES) in supine position Absent if DCI < 100 mm Hg·cm·s Weak if DCI 100–450 mm Hg·cm·s Normal if DCI > 450–8000 mm Hg·cm·s	Major motility disorder	Hypercontractile peristalsis: DCI > 8000 mm Hg·cm·s in ≥20% of wet swallows Distal esophageal spasm: DCI < 450 mm Hg·cm·s in ≥20% of wet swallows Absent contractility: DCI < 100 mm Hg·cm·s in ≥50% of wet swallows
Evaluation for minor motility disorder	Distal contractile integral (DCI): mean of distal contractile vigor (4–9 cm proximal to LES) in supine position Weak if DCI 100–450 mm Hg·cm·s Normal if DCI > 450–8000 mm Hg·cm·s	Minor motility disorder	Ineffective esophageal motility: DCI < 450 mm Hg·cm·s in ≥50% of wet swallows Distal esophageal spasm: DCI < 450 mm Hg·cm·s in ≥20% of wet swallows Fragmented peristalsis: ≥50% of wet swallows with DCI > 450 mm Hg·cm·s and a break ≥5 cm
CLASSIFICATION OF GERD			
Evaluation of EGJ			
Morphology	Separation between LES and CD	Hiatal hernia Hypotensive LES	Type I: superimposed LES and CD Type II: axially separated LES and CD pressure signals separated by <3 cm Type IIIa: >3 cm separation between the LES and CD pressure signatures with respiratory inversion point at the level of the CD Type IIIb: >3 cm separation between the LES and CD pressure signatures with respiratory inversion point at the level of the LES
Vigor	EGJ CI (mm Hg·cm)		DCI box set to encompass the LES and CD for a period of three complete respiratory cycles above a threshold pressure of the gastric baseline
Evaluation of Esophageal Motor Function			
	Distal contractile integral: DCI (mm Hg·cm·s) Defect (measure at 20 mm Hg isobaric contour)	Esophageal body motility	Intact: ≥50% of contractions with DCI >450 mm Hg·cm/s and no defect Fragmented: ≥50% of contractions with DCI >450 mm Hg·cm/s and defect >5 cm Ineffective esophageal motility: ≥50% of contractions with DCI <450 mm Hg·cm/s Absent peristalsis: 100% of contractions with DCI <100 mm Hg·cm/s
Provocative Tests			
MBS (five liquid swallows (2 mL each) taken 1 s apart)	Contractile response Failure of contractile response		Post-MBS DCI augmentation Absent post-MBS contraction
RRC (rapid water drinking of 200 mL of water within 30 s)	Retrograde premature LES relaxation Effective post-RRC contraction		

Abbreviations: DCI, distal esophageal contractile integral; EGJ, esophagogastric junction; LES, lower esophageal sphincter; MBS, multiple rapid swallows; RRC, rapid drink challenge.

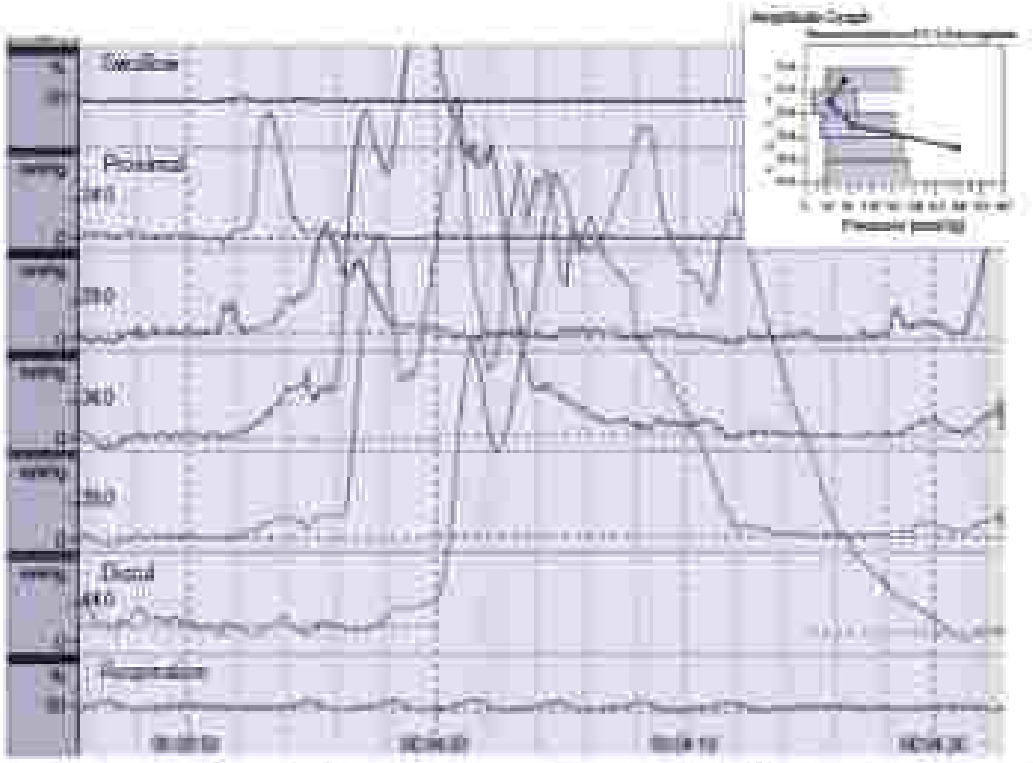


FIG. 5 Manometry showing hypercontractile esophageal body with pressure more than 180 mm Hg which is designated as a "nutcracker" esophagus.

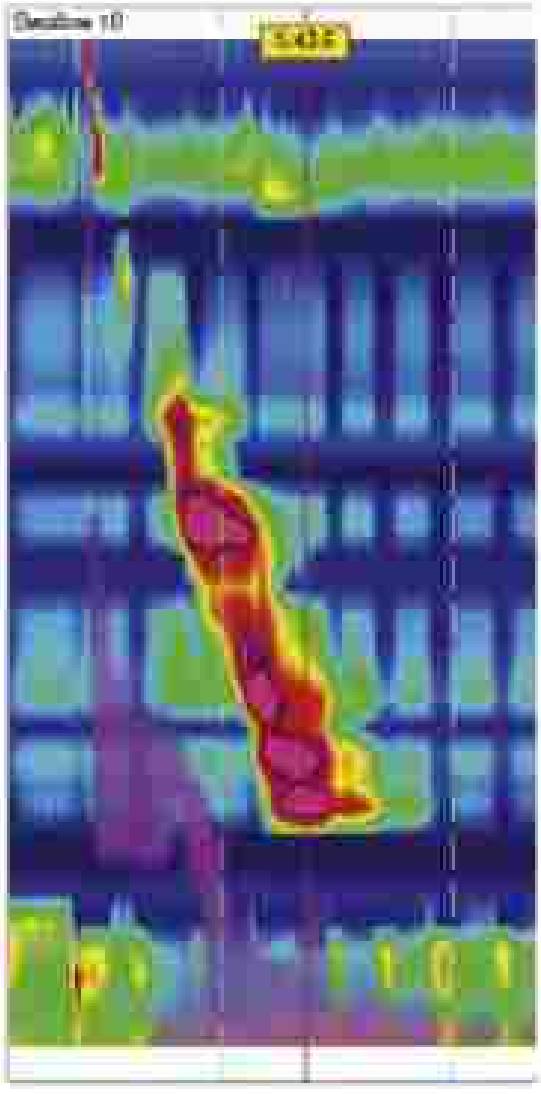


FIG. 6 High-resolution manometry showing "nutcracker" esophagus and relaxation after the swallow.

Chicago Classification. Two EGJ barrier characteristics are assessed: morphology and type. The intrinsic LES and the CD are normally superimposed to form an effective EGJ barrier against reflux of gastric contents into the esophagus (type 1 EGJ). A hiatus hernia exists when there is separation between the LES and CD. A type 2 EGJ is defined as being less than a 1 cm separation. A type 3 EGJ is defined as being greater than 3 cm. A mechanically dilated LES is diagnosed

FIG. 7 Saline-assisted maximal dilation seen in Barrett's esophagus.

BOX 2 Measured Parameters During 24-Hour Esophageal pH Monitoring

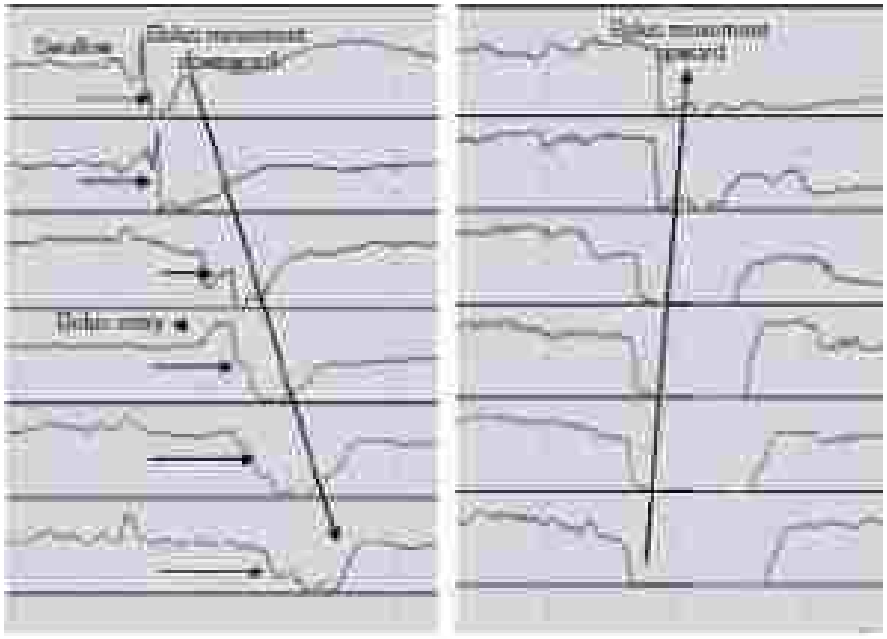
- Percent total time pH <4
- Percent upright time pH <
- Percent supine time pH <
- Number of reflux episodes
- Number of reflux episodes >5 minutes
- Duration of longest episode (in minutes)

when any one of three anatomic components is abnormal (pressure <6 mm Hg, total length <2 cm, abdominal length <1 cm). Invariably, the risk of GERD increases as the number of defective components rises and reaches more than 90% when all three LES components are abnormal.

The vigor of the EGJ barrier is assessed using a DCI like tool that measures length and pressure over three respiratory cycles (EGJ contractile integral). This metric is corrected for respiration by dividing the value with the duration of three respiratory cycles. Esophageal body motor function is characterized with Chicago Classification metrics into normal, fragmented peristalsis, ineffective, and absent contractility discussed above. Finally, the presence or absence of contraction reserve is assessed using the multiple rapid swallow (MRS) provocative test.

CLASSIFICATION OF MOTILITY FINDINGS IN GASTROESOPHAGEAL REFLUX DISEASE

The most common motility pattern in GERD is a normal study. However, either the EGJ or the esophageal body, or both can be abnormal. The EGJ can be hypotensive, with or without a hiatus hernia. Peristalsis can be fragmented, ineffective, or absent, with or without contraction reserve. The Lyon Consensus endorses the hierarchical classification of motility findings in GERD by first evaluating EGJ morphology and function with the LES and CD separation and the EGJ contractile integral (CI), which uses a nonwater test that encompasses length and vigor of the EGJ above the gastric baseline (Table 1). The measurement is made over three respiratory cycles during quiet rest, and corrected for duration of inspiration. The second level of evaluation is characterizing the integrity of peristalsis as normal, weak, fragmented, or absent. The third level, evaluating for contraction reserve. With MRS, five 2 mL swallows are taken less than 4 seconds apart, and with a rapid drink challenge 200 mL of water is swallowed within 30 seconds. The Lyon Consensus proposes that every HRM study should be accompanied by at least one of these provocative tests. Post-MRS contractions are an indication of contraction reserve in the esophagus, the phenomenon wherein the post-MRS contraction has greater DCI than the preceding test swallows. Recent data suggest three MRS sequences for reliable assessment of contraction reserve. The absence of contraction reserve in HRM is predictive



A B

FIG. Impedance study showing antegrade (A) and retrograde (B) movement of a swallowed bolus.

of the poor efficacy of proton pump drugs, higher acid exposure time in nonerosive reflux disease, and EGJ outlet obstruction. The absence of contraction reserve in IEM is also predictive of the subsequent benefit from dilation after antireflux surgery and the persistence or development of IEM after antireflux surgery. Absent contraction reserve is also the most common manometric finding in scleroderma. In contrast to the MRS provocative test, the most important clinical application of the rapid drinking challenge is in distinguishing EGJ obstruction from achalasia (by identifying LES relaxation in the former, and an exaggerated pressure gradient across a normalized EGJ in the latter). Therefore the rapid drinking challenge is most helpful in detecting paraesophageal herniation in achalasia, identifying increased resistance to EGJ outflow, and uncovering latent hypercontractility.

SUMMARY

The diagnosis of esophageal function disorders can be made from a careful history and the use of appropriate diagnostic testing. Several tests frequently are needed for the thorough evaluation of these disorders. Surgeons must understand the utility of these tests to evaluate whether a patient is a good surgical candidate for intervention and to determine the best treatment for a particular patient. A surgeon who is not familiar with these tests is not able to achieve optimal outcomes in the management of complex esophageal disorders. We also stress the importance of close collaboration between the radiologist, gastroenterologist, and surgeon in evaluating and treating this complicated group of patients.

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SURGICAL MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE

[illegible] and [illegible]

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal diagnosis in the Western world, impacting 10% to 20% of the population and resulting in approximately $11 billion annually in healthcare spending. GERD refers to the symptoms that result from reflux of stomach contents through the lower esophageal sphincter, primarily into the esophagus but also into the pharynx, larynx, and airway. This refluxed fluid results in inflammation and irritation, leading to the clinical manifestations of GERD. If untreated, the inflammation can progress to esophagitis, stricture, columnar metaplasia of the normal squamous epithelium (Barrett esophagus), and adenocarcinoma of the esophagus.

PRESENTATION OF GERD

The classic presentation of GERD is burning chest pain, often nocturnal, and often in a chronic and relapsing fashion. Patients will sometimes report sleeping upright to minimize the nocturnal symptoms. Risk factors include obesity, hiatal hernia, pregnancy, delayed gastric emptying, and connective tissue disorders. Although the symptoms alone are usually enough to diagnose GERD and begin medical therapy, it is necessary to consider and rule out more alarming conditions. These include acute coronary syndrome, achalasia, and esophageal cancer.

The symptoms of GERD can be divided into typical (esophageal) symptoms, atypical (extraesophageal) symptoms, and alarm symptoms that should warn of the development of complications. These are summarized in Table 1. Classic symptoms include burning "heartburn" chest pain (pyrosis), regurgitation of a sour fluid (water brash), a sensation of a lump or tightness in the throat (globus sensation), and pain on swallowing (odynophagia). Atypical symptoms, caused by reflux into the pharynx, larynx, or airway, can include cough, wheezing, hoarse voice, sore throat, postnasal drip, dental erosion, recurrent pneumonia, and ear pain. The presence of atypical symptoms in the absence of typical symptoms is "silent reflux."

Alarm symptoms include dysphagia, early satiety, hematemesis, melena, vomiting, and weight loss. The presence of alarm symptoms should raise concern for the development of complications of long-term reflux, including esophagitis, strictures, or esophageal cancer. These symptoms warrant immediate referral for upper endoscopy.

DIAGNOSIS AND PREOPERATIVE EVALUATION

The preoperative evaluation of patients referred for antireflux surgery (ARS) has three distinct goals: (1) confirm the diagnosis of GERD; (2) rule out other etiologies for the symptoms; and (3) define the anatomy. The standard preoperative tests are summarized in Table 2.

Confirm the Diagnosis

1. Ambulatory pH monitoring. This is the gold standard in diagnosing acid reflux. A pH sensor is connected either to a transnasally placed catheter or a wireless capsule that is attached to the distal esophagus with endoscopy. Patients eat a normal diet and record symptoms. A reflux episode is defined when the esophageal pH drops below 4. After 24 hours, the sensor is removed and the tracing is computer analyzed. The best predictor of endoscopic damage is the total amount of time with pH less than 4, although the computer program will also calculate the number of reflux episodes, the duration of episodes, and the relationship between pH and patient-reported symptoms. The result is a composite or DeMeester score. A DeMeester score greater than 14.7 is considered diagnostic of GERD.
2. Upper gastrointestinal endoscopy. Endoscopy can identify a hiatal hernia or short esophagus, diagnose an esophageal mass, and show complications of GERD, such as esophagitis, strictures, Barrett's esophagus, or cancer. Endoscopy can also classify the severity of esophagitis (see Table 3).

of the poor efficacy of proton pump drugs, higher acid exposure time in nonerosive reflux disease, and EGJ outlet obstruction. The absence of contraction reserve in IEM is also predictive of the subsequent benefit from dilation after antireflux surgery and the persistence or development of IEM after antireflux surgery. Absent contraction reserve is also the most common manometric finding in scleroderma. In contrast to the MRS provocative test, the most important clinical application of the rapid drinking challenge is in distinguishing EGJ obstruction from achalasia (by identifying LES relaxation in the former, and an exaggerated pressure gradient across a normalized EGJ in the latter). Therefore the rapid drinking challenge is most helpful in detecting paraesophageal herniation in achalasia, identifying increased resistance to EGJ outflow, and uncovering latent hypercontractility.

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Surgical Management of Gastroesophageal Reflux Disease

Laura M. Mazzei, MD, MS, and Dan E. Azagury, MD

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2. Upper gastrointestinal endoscopy. Endoscopy can identify a hiatal hernia or short esophagus, diagnose an esophageal mass, and show complications of GERD, such as esophagitis, strictures, Barrett's esophagus, or cancer. Endoscopy can also classify the severity of esophagitis (Table 3).

TABLE 1 Presentation of Gastroesophageal Reflux Disease

Typical (Esophageal) Symptoms	Atypical (Extraesophageal) Symptoms	Alarm Symptoms
Pyrosis	Coughing	Dysphagia
Water brash	Wheezing	Bloody saliva
Globus sensation	Hoarse voice	Hematemesis
Odynophagia	Sore throat	Melena
	Postnasal drip	Vomiting
	Dental erosion	Weight loss

TABLE 2 Preoperative Evaluation

Study	Findings
CONFIRM THE DIAGNOSIS OF GERD	
Ambulatory pH monitoring	Gold standard: DeMeester score >14.7 (calculated as a composite based on duration of time pH <4, number and duration of reflux episodes)
Upper gastrointestinal endoscopy	Complications of GERD (esophagitis, strictures, Barrett's)
RULE OUT OTHER ETIOLOGIES OF SYMPTOMS	
Esophageal manometry	Rule out achalasia, evaluate esophageal motility
Gastric scintigraphy	Diagnose gastroparesis
DEFINE THE ANATOMY	
Upper gastrointestinal series	Presence/size of hiatal hernia, presence of short esophagus
Computed tomography scan	General anatomy

GERD, gastroesophageal reflux disease.

TABLE 3 Los Angeles Classification of Esophagitis

Grade A	One or more mucosal break >5 mm that does not extend between the tops of two mucosal folds
Grade B	One or more mucosal break >5 mm that does not extend between the tops of two mucosal folds
Grade C	One or more mucosal break that is continuous between the tops of two or more mucosal folds but <75% of the circumference
Grade D	One or more mucosal break which involves at least 75% of the esophageal circumference

Rule Out Other Etiologies: Achalasia, Delayed Gastric Emptying

1. Esophageal manometry: It is essential to rule out achalasia and evaluate esophageal motility prior to surgical treatment of GERD in patients with esophageal dysmotility who also have confirmed reflux, there is a higher risk of postoperative dysphagia. On the other hand, effective GERD control will improve esophageal motility for some patients. Some surgeons elect to perform a partial rather than total fundoplication in this population to minimize postoperative dysphagia; others will perform a Nissen fundoplication in the setting of dysmotility to maximize GERD relief.
2. Gastric scintigraphy: Delayed gastric emptying (gastroparesis) can cause or exacerbate symptoms of GERD, and it is hard to differentiate postoperatively an iatrogenic vagal nerve injury from preexisting gastroparesis. ...how diagnosed preoperatively, the fundoplication can be combined with a pyloroplasty to facilitate drainage. Gastric scintigraphy is not routinely performed before surgery, however, and should be reserved for patients with suspected gastroparesis. A thorough history and physical, including long standing diabetes or symptoms of delayed gastric emptying, can help identify patients who need this test.

Define the Anatomy

1. Upper gastrointestinal series (UGI): UGI is a double contrast barium esophagogastrogram followed by video fluoroscopy. This test can document the presence and size of a hiatal hernia, the presence of a short esophagus, and esophagogastric dysmotility. Although UGI can show reflux of contrast, this test cannot conclusively diagnose GERD and does not eliminate the need for pH monitoring.
2. Computed tomography scan: A computed tomography scan can help understand the anatomy, especially in cases of a very large hiatal hernia to assist with preoperative planning. CT is preferred in most instances for preoperative planning.

INDICATIONS FOR SURGICAL MANAGEMENT

There are three goals for treatment of GERD: (1) control of symptoms, (2) healing of reflux esophagitis, and (3) prevention of complications. Initial management is medical, and proton pump inhibitors (PPIs) have dramatically changed management of GERD. Most patients obtain significant symptom relief with a combination of lifestyle modification, including weight loss and abstaining from trigger foods, and once-daily PPI. When this treatment is not effective, it should prompt a diagnostic workup to rule out complications or other diagnoses including motility disorders. If the workup confirms a diagnosis of GERD, PPI dosage can be increased to twice daily or an H2 receptor blocker can be added. Most patients with GERD have excellent response to medical therapy. A poor response may indicate a misdiagnosis, development of a complication of GERD, or poor compliance. In the latter two situations, ARS should be considered. ARS can also be considered for patients who experience side effects from PPIs, most commonly headache, nausea and vomiting, or diarrhea. In general, studies have shown that ARS and PPIs are equally effective at symptom management, with both strategies showing 80% to 90% resolution of symptoms at 5 years. Neither strategy is without risk, including long-term PPI use, which carries an increased risk of osteoporosis and opportunistic infections. Patients with a good response to PPI may elect to proceed with surgery if they do not wish to continue on lifelong medical therapy. Specific indications for surgery are listed in Table 4.

Contraindications to ARS, in addition to patient inability to tolerate the operation, include esophageal cancer or high-grade dysplasia, which should be managed with appropriate resection rather than ARS. Additionally, morbid obesity is a relative contraindication, increasing the likelihood of recurrent symptoms after ARS. Patients should be referred for bariatric surgery evaluation, specifically Roux-en-Y gastric bypass, which should be the procedure of choice for patients with a body mass index of 35 kg/m^2 or greater and should be considered in patients with a body mass index greater than 30 kg/m^2.

TABLE 1 Indications and Contraindications for Surgical Treatment

Indications	Contraindications
Failed medical management	Inability to tolerate surgery
Patient preference	Esophageal cancer or high-grade dysplasia
Gastroesophageal reflux disease complications (stricture, esophagitis)	Morbid obesity (consider gastric bypass)
Contraindications to proton pump inhibitor	
Lung transplant patients	
Atypical symptoms with documented reflux	

SURGICAL TECHNIQUE

Type of Fundoplication

The relationship between hiatal hernia and GERD was not appreciated until the 1950s, when Allison and Barrett in London published what can be considered the first modern antireflux surgery. They described a transthoracic reduction of the herniated stomach with fixation to the diaphragm and reapproximation of the crura, but with a recurrence rate that approached 50%. In the following decade, identification of the lower esophageal sphincter and the first use of manometry provided the physiologic basis to advance ARS. In the late 1950s, Rudolf Nissen described wrapping the stomach around the esophagus, initially to prevent leakage after a repair of an esophageal perforation. He also first described repair of hiatal hernia through an abdominal incision. Dor later described an anterior fundoplication in 1963, and Toupet proposed a posterior fundoplication in 1963.[3] More recently, the procedures have transitioned to laparoscopic and robotic techniques, and endoscopic options are currently being explored.

The most common types of fundoplication are the total, 360 degree wrap (Nissen), the 180 to 270 degree posterior wrap (Toupet), and the 180 degree anterior wrap (Dor) (Fig. 1). Other, less common, options include the DOR procedure, which involves a posterior gastropexy, or the Belsey procedure, a transthoracic posterior plication. Several randomized clinical trials have compared the three most common methods of fundoplication and mostly show equivalent outcomes in terms of safety and symptom resolution. Overall, the Nissen fundoplication provides better GERD control with a slightly increased rate of dysphagia and gas bloat. In general, we favor the total fundoplication with an emphasis on performing a "floppy" Nissen. Some surgeons will perform a partial wrap in patients who have some degree of esophageal dysmotility.

Steps of the Procedure

The steps below describe the most common type of antireflux surgery, a laparoscopic 360 degree Nissen fundoplication. There are a few considerations that can alter this approach in specific patients specifically, the need for mesh placement or an esophageal lengthening procedure. We briefly mention these options, but our focus is on the standard laparoscopic Nissen fundoplication for a patient with a small- to moderate-sized hiatal hernia.

1. Setup and port placement
   a. The patient is placed supine in split-leg positioning. The surgeon usually stands between the patient's legs, with the assistant on the patient's left side. Laparoscopic towers, suction, and camera should be at the head (Fig. 2). The patient will be in a steep reverse Trendelenburg position during the procedure, so some combination of a beanbag "saddle," an axillary pad, foot boards, and/or leg and chest straps are necessary.
   b. Access to the abdomen can be gained either with a Veress needle at Palmer's point or an open Hasson cut down at the 10 mm supraumbilical camera port. The remaining ports are placed roughly in a straight line, with a 5 mm right lateral liver retractor, one 10 mm operating port, one 5 mm right working port, and a 5 mm left lateral assistant port (Fig. 3).
   c. A 10 mm 30 degree scope is typically used. A 0 degree scope can be very useful during the mediastinal dissection.
2. Dissection of the crura and reduction of hiatal hernia
   a. Divide the gastrohepatic (gastrohepatic ligament). There may be an accessory or replaced left hepatic artery here arising from the left gastric; this is preserved if possible and sacrificed if necessary. If the decision is made to take the replaced left hepatic, its actual diameter should be assessed. Some surgeons advocate for temporary reversible clamping if there is a doubt as to its level of contribution. The hepatic branch of the vagus nerve can typically be preserved (Fig. 4).
   b. Identify the right crus and open the pleuroesophageal ligament. Mobilize the right crus away from the esophagus, starting at the 12 o'clock position and working posteriorly to identify the left crus. The dissection is completed bluntly, with care to identify and preserve the anterior vagus nerve. The dissection plane should leave the peritoneal covering on the muscle of the crura. Stripping the peritoneum off the muscle will weaken the crural repair (Fig. 5).
3. Mobilize the esophagus
   a. When the crural dissection is complete, a ¼ inch Penrose drain is placed around the esophagus. It can be secured with large clips or a loop suture tie. This can then be used to provide safe but adequate traction on the esophagus.
   b. The dissection should be carried up into the chest circumferentially around the esophagus, taking care to avoid injuring the anterior and posterior vagus nerves. This dissection can usually be done bluntly, using a bipolar-type cautery device as necessary when small vascular structures are visualized (Fig. 6).
   c. Continue mobilizing cephalad until at least 3 cm and ideally 5 cm of esophagus comes into the abdomen without tension.
4. Ligate and divide the short gastrics
   a. The gastrosplenic ligament is identified and the lesser sac entered at around the level of the bottom of the spleen. Using an energy device, divide the short gastric vessels along the greater curve up to the angle of His, stay slightly away from the stomach to avoid causing thermal injury. Care must be taken to avoid tearing the capsule of the spleen superiorly (Fig. 7).
   b. Confirm that the stomach is mobile enough and that all posterior attachments are fully cleared before crural closure. We will typically place a marking stitch on the lateral edge of the stomach wall, approximately 5 cm distal to the gastroesophageal junction. Pass the fundus posterior to the gastroesophageal junction. The marking stitch should become visible as the fundus is passed from left to right. The fundus should remain in place to the right of the esophagus; if it retracts back after it is released, it is a sign there are more attachments to the spleen or diaphragm that need to be released. Perform a "shoeshine" maneuver by grasping both sides of the fundus and pulling back and forth around the esophagus to demonstrate that the stomach is adequately mobilized (Fig. 8).
5. Crural closure
   a. Release the stomach back to its anatomic position and begin crural closure. At this point, the right crus tends to run mostly straight up and down, whereas the left crus is at an angle. The crural stitches should be placed at a right angle to a line bisecting the triangle made by the two crura, meaning that the stitches will look like they slant downward to the patient's left. This prevents unnecessary tension on the left crus (Fig. 9A).
   b. The crura are reapproximated with three to four nonabsorbable 0 sutures. We prefer to use small polytetrafluoroethylene pledgets for these stitches, taking care to make sure they lie flush against the muscle (Fig. 9B).

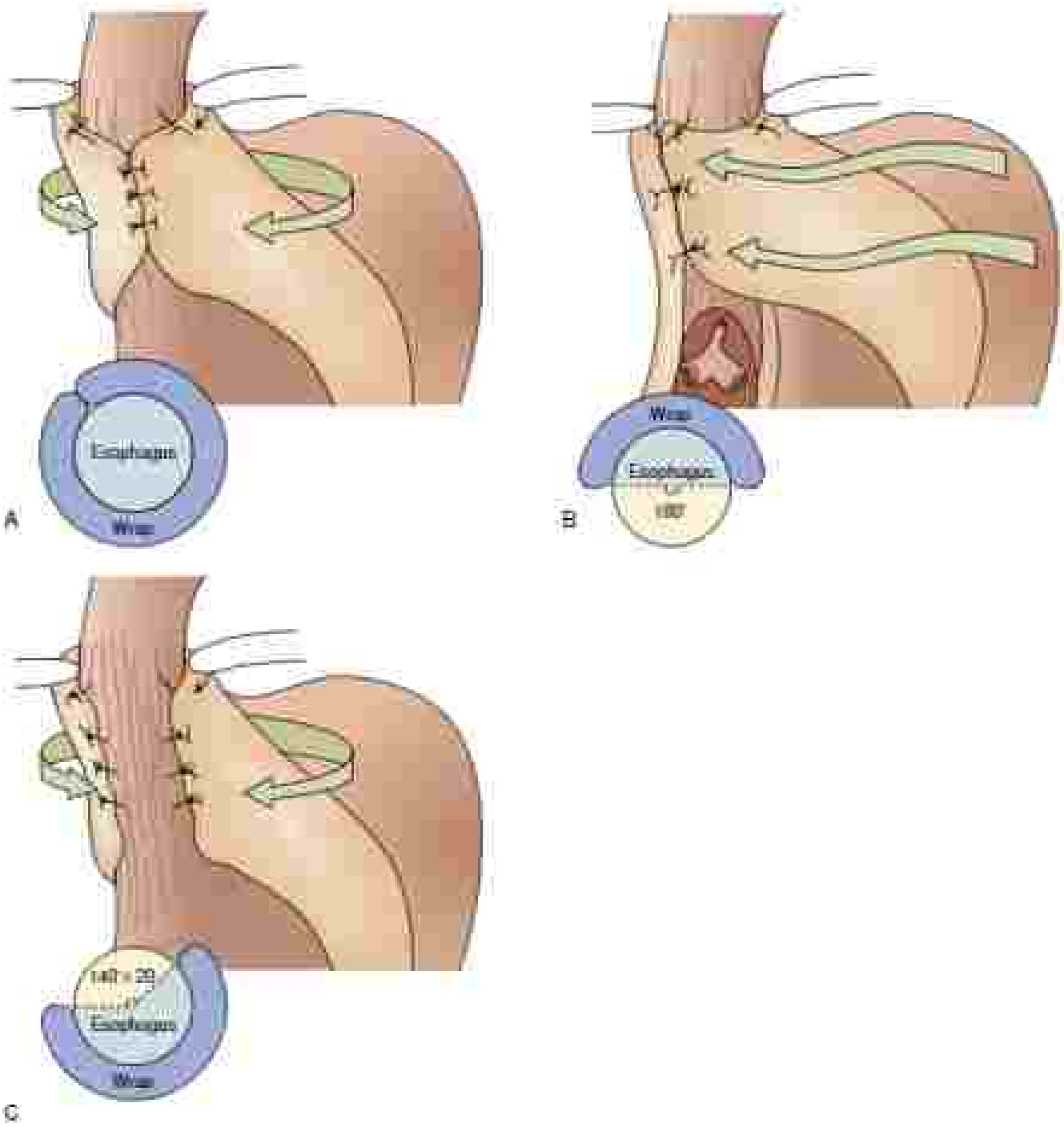

FIG. 1 Types of fundoplication. The most common types of fundoplication are pictured. (**A**) A 360-degree Nissen fundoplication. (**B**) A 180-degree anterior Toupet fundoplication. (**C**) A 300-degree posterior Thal fundoplication.

c. Fundoplication
   a. It is critical not to twist the stomach; the marking stitch helps confirm that the stomach has not twisted as it is passed behind the esophagus.
   b. It is easier to begin the fundoplication before placing a bougie down the esophagus because there will be more laxity. The first two stitches, starting at the marking stitch, should grab stomach on each side. We use nonabsorbable 2-0 braided sutures. The wrap needs to incorporate the fundus, not the body of the stomach.
   c. After the first two stitches are in place, a 52 bougie is placed down the esophagus. There should be no resistance.
   d. Before the third stitch is placed, the thickness of the wrap is verified by easily passing two instruments under the wrap and lifting it away from the esophagus. The third stitch is now placed, taking a small bite of esophageal musculature as well as stomach.
   e. The goal is to create a short, floppy wrap, no more than 3 cm in length (Fig. 1B).
   f. The Penrose is cut and pulled out of the abdomen.

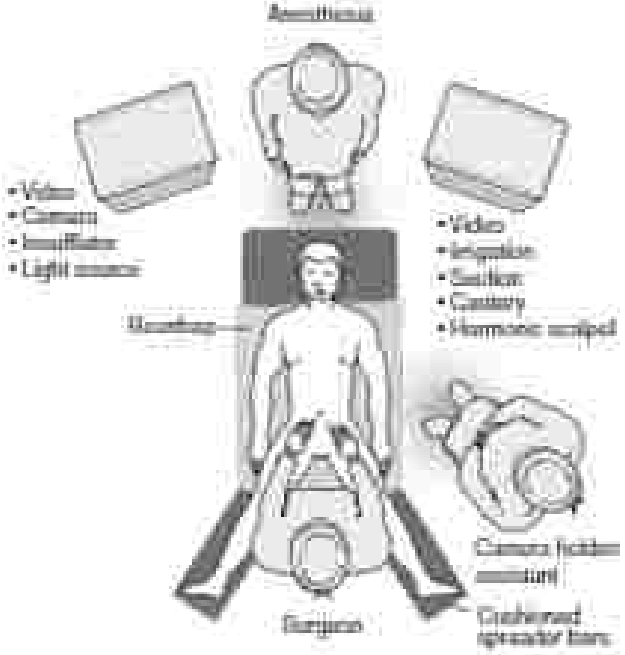

FIG. 2 Patient and room setup for laparoscopic hiatal hernia repair and fundoplication.

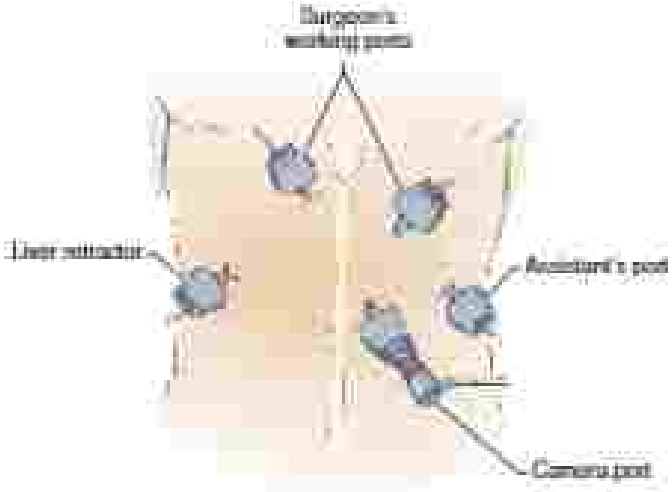

FIG. 3 Typical port positioning for laparoscopic fundoplication. (From Peterson CA, Pearson's Diseases and Disorders. Surgery, ed 2. Philadelphia: Churchill Livingstone; 2008.)

SPECIAL CONSIDERATIONS

When to Use Mesh

Use of prosthetic or biologic mesh has been proposed to further support the crural repair and prevent recurrences and recurrence. The risks of mesh include erosion or infection. Unfortunately, the indications for mesh use are not well defined, and most data come from single surgeon or single center case series. At this time, there are insufficient data to support routine mesh use. In selected patients with very attenuated diaphragm muscles, where crural stitches are very tenuous, surgeons may elect to use a mesh to reinforce the repair. We typically never use mesh in our practice.

When to Do a Lengthening Procedure

Rarely, it is impossible to get adequate intra-abdominal esophageal length because of a short esophagus. In this situation, a Collis

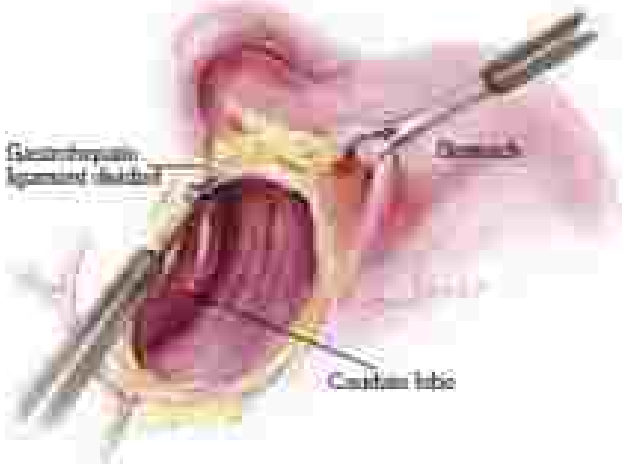

FIG. 4 Entering the lesser sac. (Courtesy Connor Sanders. From Gamblin TC, Sanders C. Atlas of GI [illegible] ed [illegible]; and [illegible] Online. [illegible] Medical Publishing; 2007.)

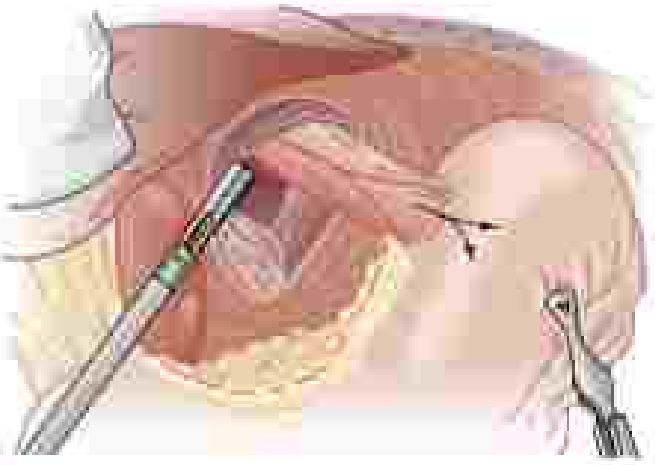

FIG. 5 Dissection of the crura. (From Ferri FF, Ostchega JH, Hollyer CA. Gastroesophageal reflux disease and hiatal hernia. In: Ferri FF, ed. Ferri's Textbook of Surgery 2008 ed. Elsevier; 2011.)

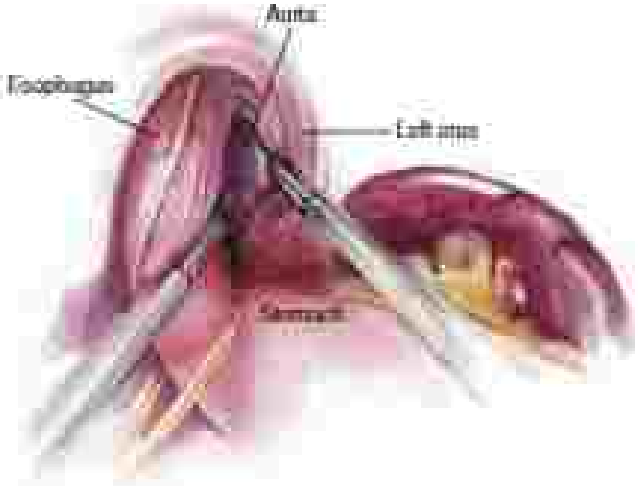

FIG. 6 Dissection around the esophagus. Using a Penrose (nondistensible) for retraction, dissection is completed mostly bluntly with an energy device to minimize axial flaws or muscle that may bleed. (Courtesy Connor Sanders. From Gamblin TC, Sanders C. Atlas of Gastrointestinal Surgery, ed 1. Philadelphia: Lippincott Williams & Wilkins; 2007.)

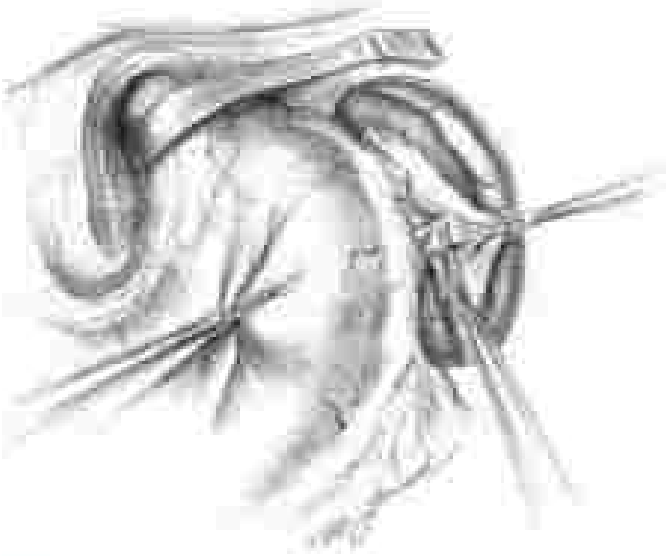

FIG. 7 Dividing the short gastrics. (From Taylor MJ, Swanstrom LL, Colavita PD, et al. Mastery of Endoscopic and Laparoscopic Surgery. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005:139.)

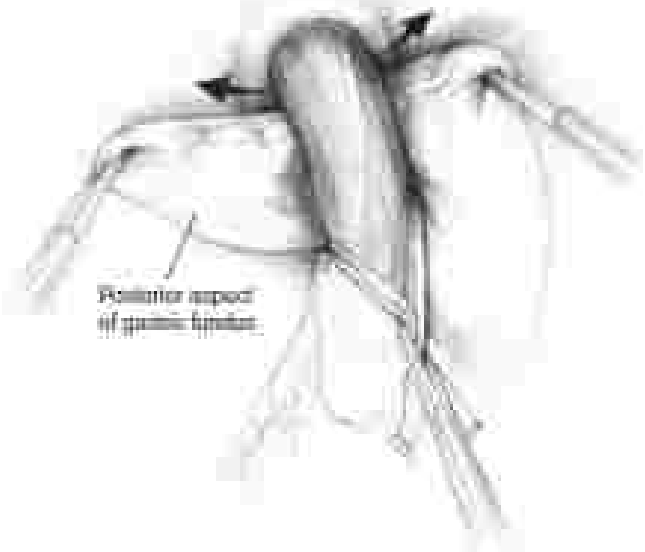

FIG. 8 Posterior mobilization. (From Atlas of Minimally Invasive Surgical Operations. New York: McGraw-Hill; 2000. Fig. 6.2 courtesy Caroline Sanders; copyright John Hopkins University.)

gastroplasty is necessary. A linear stapler is used to create a 4- to 5-cm tube of proximal stomach, using a bougie to prevent narrowing the neoesophagus. The gastric tube still contains acid-secreting mucosa, so ongoing acid reflux is more likely when a gastroplasty is performed. In our experience, in the absence of risk factors such as radiation or prior antireflux surgery, this procedure is rarely necessary if adequate time and care is taken for the esophageal dissection.

When to Consider an Open Approach

An open approach is usually needed only if the laparoscopic approach is not possible because of adhesions, technical difficulties, or uncontrolled bleeding. An upper midline laparotomy from the xiphoid process to the umbilicus is made. The left triangular ligament is divided to retract the left lobe of the liver laterally. From there, the steps of the operation are the same as described for the laparoscopic approach.

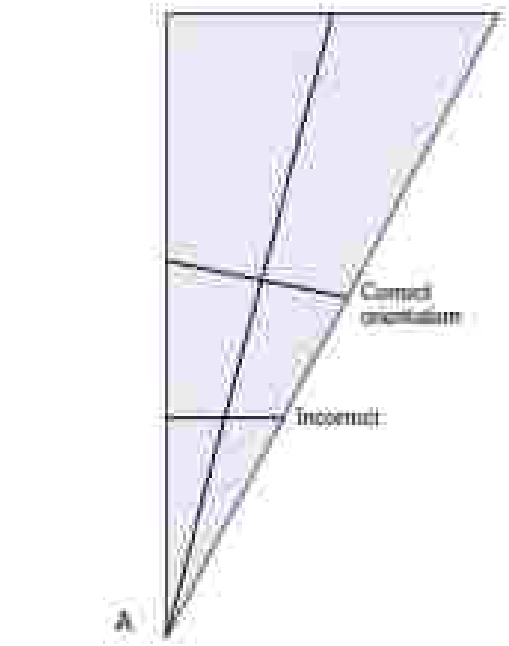

FIG. 9 Closure of the crura. (A) Anatomy of the crura; the right crus is oriented mostly vertical and the left crus is angled. Sutures should be placed at a right angle to a line bisecting the change, rather than at a right angle to the crus itself. (B) Three crural stitch.

When to Consider a Thoracic Approach

It is possible to perform a fundoplication through a thoracotomy. This approach can be helpful in the setting of a hostile abdomen, extremely large hiatal hernia, or short esophagus. The 270 degree Belsey Mark IV fundoplication is performed through a thoracic approach.

POSTOPERATIVE CARE

Patients are generally admitted overnight, with medications for pain and nausea. Many surgeons choose to obtain a barium esophagogram on the first postoperative day. After the swallow study, patients are started on a full liquid diet and discharged. They stay on a soft diet for 4 to 6 weeks. Acid reducing medications should be discontinued after 6 weeks at the latest, and all pills should be crushed

for the first 3 to 4 weeks. Although most patients will complain of dull upper abdominal and chest pain from the midsternal dissection, acute onset of severe chest pain or respiratory distress in the immediate postoperative period should trigger a UGIS to rule out acute wrap herniation.

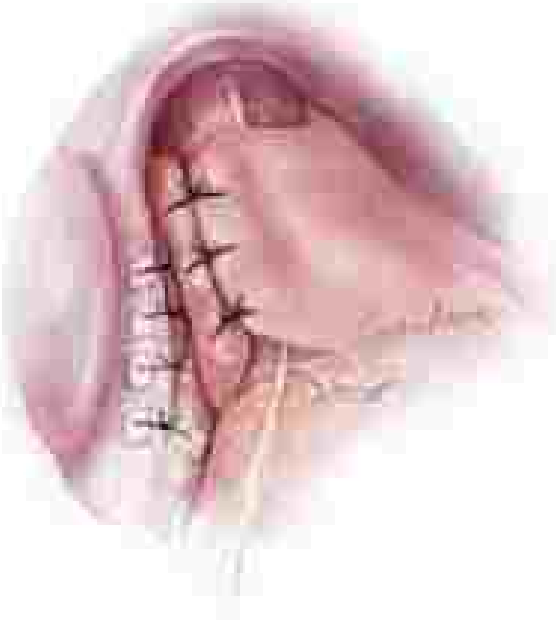

FIG. 10 Completed fundoplication. (Courtesy Cotton Sanders from Cameron JL, Sanders C. Atlas of Gastrointestinal Surgery, ed 1. Hamilton, Ontario: B.C. Decker's Medical Publishing; 2004.)

POSTOPERATIVE COMPLICATIONS AND REDO FUNDOPLICATION

1. Dysphagia. Mild dysphagia is extremely common and patients can usually be instructed to eat a soft diet until symptoms resolve. In less than 5% of patients, dysphagia persists beyond 6 weeks and requires further workup. Causes include a tight wrap, slippage, or herniation. For a tight wrap, endoscopic dilation is safe beginning at six weeks postoperatively.
2. Gas bloat syndrome. The wrap can prevent patients from belching, and the accumulation of gas in the stomach can present as epigastric pain, abdominal distention, and inability to belch or vomit, with increased flatus. Most patients will experience some level of gas bloating and should be appropriately counseled preoperatively. With adequate dietary and lifestyle modifications, symptom improvement or resolution usually occurs within 6 weeks, but if severe symptoms persist, an endoscopy for possible dilation might be useful.
3. Recurrent GERD. The majority of patients with recurrent symptoms do not actually have documented reflux on pH testing. This emphasizes the importance of pH testing preoperatively to have a comparison study. True recurrence of reflux can be treated with PPI or considered for revision of the fundoplication, especially if it is accompanied by an anatomic failure.
4. Esophageal or gastric dysmotility. Dysmotility that is present preoperatively can result in a failure of ARS postoperatively, and again highlights the importance of a preoperative workup. If the esophagus had normal motility preoperatively, postoperative dysmotility can result from an overtight wrap. If there was no gastroparesis preoperatively, symptoms of gastric dysmotility can be caused by an iatrogenic vagal injury. Treatment options include pyloric flutes, gastric pacing, or pyloromyotomy.
5. Anatomic failures (Fig. 11). Anatomic failure of the wrap can result in any of the symptoms mentioned. Most failures occur within 2 years of the primary operation. By far the most common

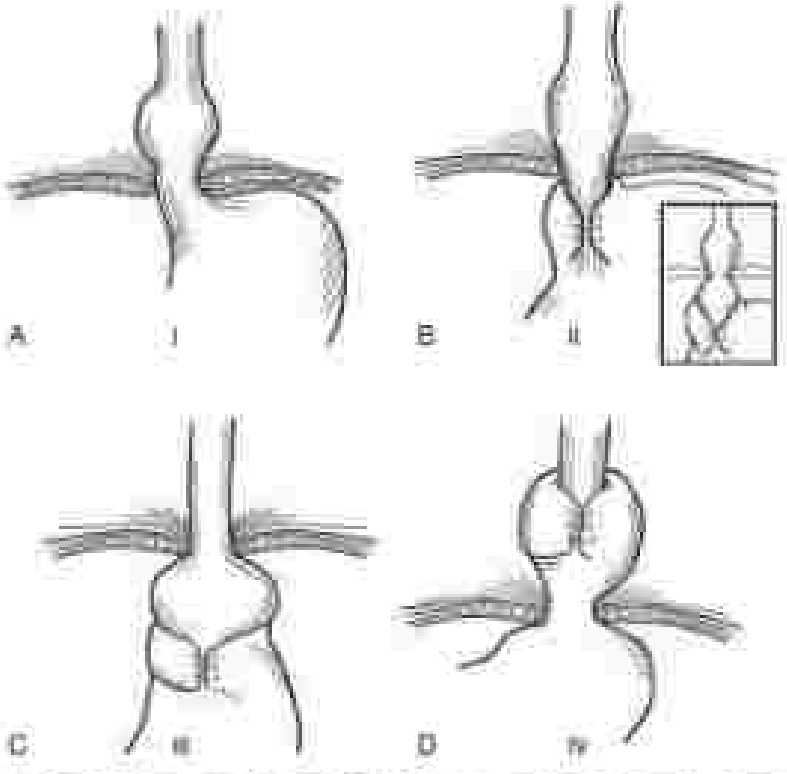

FIG. 11 Patterns of wrap failure. (A) Complete disruption. (B) "Upper" wrap. (C) Migrated wrap. (D) Paraesophageal herniation. (From Mellow MH, Carson esophageal reflux disease. In: Bell RJ, Gibbons RJ, Mulholland MW, eds. Digestive Tract Surgery. Scientific and Action Philadelphia: Lippincott-Raven; 1995:1.)

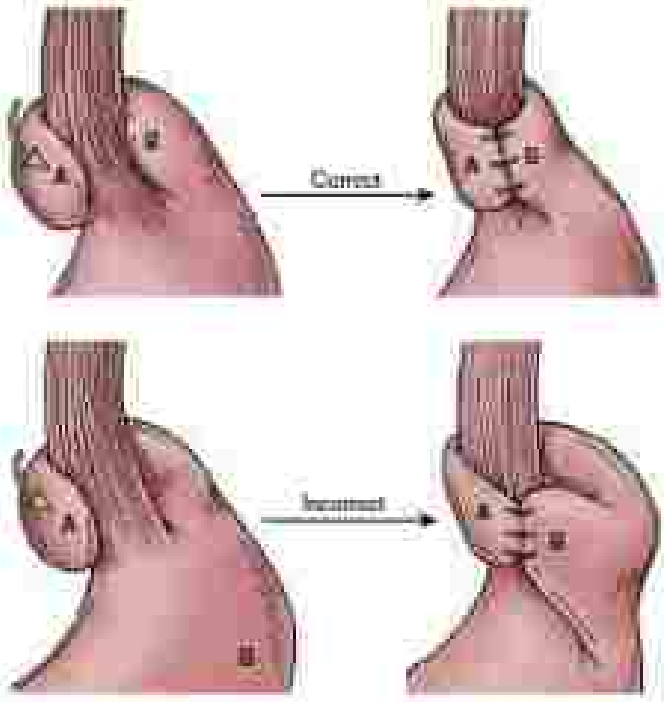

FIG. 12 Plain radiograph of misplaced wrap. The wrap is rotated with the gastric body instead of the fundus. (From Small CJ, McCluskey DA, Brand MA, Todorovic M, Hazey JL. Does fundoplication fail well? Ann Surg 2005;241[5]:861–869.)

reason for failure is herniation of the wrap into the chest (Fig. 11D). Other causes include wrap disruption (Fig. 11A), slipped wrap (Fig. 11B), or crural stenosis/tight wrap. Technical errors from the index operation can result in a need for reoperation, but in experienced hands this is rare. The most common technical failure is a misplaced fundoplication, using the gastric body instead of the fundus for the wrap (Fig. 12).

Suggested Readings

Asaggay O, Murray J. Surgical anti-reflux options: beyond fundoplication. Curr Gastroenterol Rep. 2013;15(7):331.

Collings AT, Kohlnhofer B, Perretta S, Worth J, Arkenau S, Irfan F, et al. Laparoscopic repair of paraesophageal hernia: long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. Ann Surg 2014;259(2):291–296.

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Tippens D, Duranceau JM, Azagury D, Velanovic J, Horn K, Mansfield S, Haller G, Morel P. Reflux, dysphagia, and gas bloat after laparoscopic fundoplication in patients with incidentally discovered hiatal hernia and in a control group. Surgery. 2008;143(2):235–242.

Magnetic Augmentation of the Lower Esophageal Sphincter

Andrew M. Bauer, MD, et al

HISTORY

Gastroesophageal reflux disease (GERD) is a condition of high prevalence and increasing incidence in the western world linked to the development of Barrett's metaplasia and its progression through dysplasia to esophageal cancer. The magnetic sphincter augmentation device (MSA) (LINX, Torax Medical) provides an equally efficacious alternative to circumferential gastric fundoplication of the esophagus to treat GERD. The MSA can be used regardless of the presence of a hiatal hernia or the surgical absence of the gastric fundus, with lower rates of a postoperative inability to belch or vomit than with traditional procedures. The MSA device is associated with early dysphagia and odynophagia, which improves over time and resolves completely in more than 95% patients.

MECHANICS AND PHYSIOLOGY

The MSA device is operatively placed proximally to the anatomic gastroesophageal junction (GEJ) at the high pressure efferent zone of the lower esophageal sphincter (LES). The device's function is optimized by alignment with the compressive force exerted by the diaphragmatic crura and, as such, requires the reduction of any hiatal hernia and the restoration of normal physiologic approximation of the crural rails at the time of implantation. (See sphincter legend text). In this position, the MSA dynamically augments the pathologically weak LES, restoring a competent physiologic acid barrier with minimal impact on normal peristaltic or regurgitative functions of the stomach and esophagus. The device is not compressive and does not squeeze the LES closed. The device rests loosely around the esophagus and prevents opening of the LES, thereby increasing the yield pressure. The MSA expands by bead separation to allow passage of a liquid or solid bolus propelled distally by peristalsis, or as a bolus or retrieval bolus moves proximally from the stomach into the esophagus. After bolus transit, the magnetic beads are reapproximated by the force of magnetic attraction (Fig. 1). Normal or near normal peristaltic force is required to reliably open the MSA device during swallowing and to avoid troublesome postoperative dysphagia and stasis.

INDICATIONS

The MSA device is indicated in the treatment of any patient with adequate esophageal motility and an appropriate work up confirming a diagnosis of GERD, with several exceptions. The MSA device cannot be implanted in the setting of intraabdominal infection, at the time of resection of an enteric lumen, in patients with a nickel or titanium allergy or in those who have a future need for magnetic resonance imaging greater than 1.5 Tesla. In addition to these contraindications, precautions currently listed by the Food and Drug Administration can be seen in Box 1. The MSA device is useful not only as an alternative to complete (Nissen) fundoplication, but also potentially in patients who have previously undergone sleeve gastrectomy—a population in whom fundoplication is generally not an option due to inadequate gastric fundus. Clinical trials on its efficacy in this population are currently ongoing. Like the Nissen fundoplication, the MSA

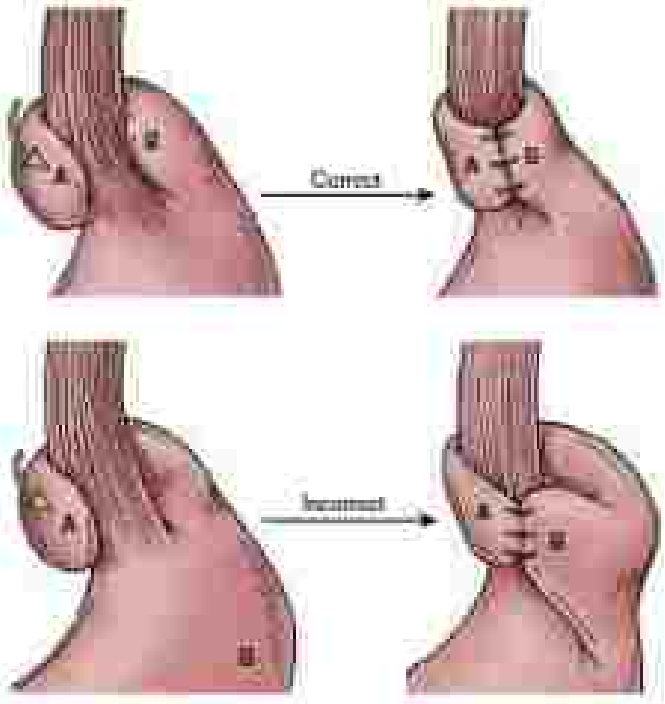

FIG. 12 Plain anterior view of implanted wrap. The wrap is secured with the gastric body instead of the fundus. (From Small CJ, McCarthy DA, Brand MA, Lederman AB, Hazey JC. When fundoplication fails redo? Ann Surg 2005;241[5]:861–869.)

reason for failure is herniation of the wrap into the chest (Fig. 11D). Other causes include wrap disruption (Fig. 11A), slipped wrap (Fig. 11B), or cranial stenosis/tight wrap. Technical errors from the index operation can result in a need for reoperation, but in experienced hands this is rare. The most common technical failure is a misplaced fundoplication, using the gastric body instead of the fundus for the wrap (Fig. 12).

Suggested Readings

Asagary D, Mittal J. Surgical anti-reflux options: beyond fundoplication. Curr Gastroenterol Rep. 2013;15(7):331.

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Magnetic Augmentation of the Lower Esophageal Sphincter

James M. Tatum, MD, and John C. Lipham, MD

HISTORY

Gastroesophageal reflux disease (GERD) is a condition of high prevalence and increasing incidence in the western world linked to the development of Barrett's metaplasia and its progression through dysplasia to esophageal cancer. The magnetic sphincter augmentation device (MSA) (LINX, Torax Medical) provides an equally efficacious alternative to circumferential gastric fundoplication of the esophagus to treat GERD. The MSA can be used regardless of the presence of a hiatal hernia or the surgical absence of the gastric fundus, with lower rates of a postoperative inability to belch or vomit than with traditional procedures. The MSA device is associated with early dysphagia and odynophagia, which improves over time and resolves completely in more than 95% patients.

MECHANICS AND PHYSIOLOGY

The MSA device is operatively placed proximally to the anatomic gastroesophageal junction (GEJ) at the high pressure efferent zone of the lower esophageal sphincter (LES). The device's function is optimized by alignment with the compressive force exerted by the diaphragmatic crura and, as such, requires the reduction of any hiatal hernia and the restoration of normal physiologic approximation of the crural rails at the time of implantation. (See sphincter legend ends). In this position, the MSA dynamically augments the pathologically weak LES, restoring a competent physiologic acid barrier with minimal impact on normal peristaltic or regurgitative functions of the stomach and esophagus. The device is not compressive and does not squeeze the LES closed. The device rests loosely around the esophagus and prevents opening of the LES, thereby increasing the yield pressure. The MSA expands by bead separation to allow passage of a liquid or solid bolus propelled distally by peristalsis, or as a bolus or retrieval bolus moves proximally from the stomach into the esophagus. After bolus transit, the magnetic beads are reapproximated by the force of magnetic attraction (Fig. 1). Normal or near normal peristaltic force is required to reliably open the MSA device during swallowing and to avoid troublesome postoperative dysphagia and stasis.

INDICATIONS

The MSA device is indicated in the treatment of any patient with adequate esophageal motility and an appropriate work up confirming a diagnosis of GERD, with several exceptions. The MSA device cannot be implanted in the setting of intraabdominal infection, at the time of resection of an enteric lumen, in patients with a nickel or titanium allergy or in those who have a future need for magnetic resonance imaging greater than 1.5 Tesla. In addition to these contraindications, precautions currently listed by the Food and Drug Administration can be seen in Box 1. The MSA device is useful not only as an alternative to complete (Nissen) fundoplication, but also potentially in patients who have previously undergone sleeve gastrectomy – a population in whom fundoplication is generally not an option due to inadequate gastric fundus. Clinical trials on its efficacy in this population are currently ongoing. Like the Nissen fundoplication, the MSA

FIG. 1 Magnetic sphincter augmentation device (LINX). The MSA device consists of an expandable bracelet-like ring of magnetic beads as its placed around the distal esophagus. The beads are connected by interposed titanium wires, limiting meaningful separation and maintaining basal spacing. (A) At rest the magnetic forces keep the MSA device in the closed configuration without creating pressure on the wall of the esophagus, maintaining its configuration to human anti-design. (B) It passes. (Courtesy Torax Medical, Inc.)

BOX 1 Contraindication and Precautions to the Use of the MSA

Contraindications

- Known or suspected allergy to titanium, nickel, steel, or any implant metal

Precautions

- Scleroderma
- Suspected or confirmed esophageal or gastric cancer
- Prior esophageal or gastric surgery or endoscopic intervention
- Distal esophageal motility < 45 mm Hg peristaltic amplitude on wet swallows or <70% (productive) peristaltic sequences on high-resolution manometry equivalent, or known motility disorder
- Symptoms of dysphagia more than once wk within the last 3 months
- Esophageal or gastric varices
- Lactating, pregnant, or planning to become pregnant
- Age <21 yr
- Los Angeles Classification grade C or D esophagitis or known Barrett's metaplasia
- Patients with electrical implants such as pacemaker, defibrillator, or other metallic abdominal implants

Warning

- Conditional compatibility with MR imaging up to 0.7 0.7T MRI or 1.5 1.5T, depending on early or late generation MSA device

MRI, Magnetic resonance imaging; MSA, magnetic sphincter augmentation device.

device to be advised in patients with abnormal esophageal motility. These patients may be better served by partial fundoplication, bypass, or medical therapy alone.

The MSA device, although not initially indicated for use in patients at the time of the repair of a large hiatal hernia, has in preliminary studies been shown to be equally effective while also potentially preventing early recurrence of hiatal hernias. The low hiatal hernia recurrence rate is likely the result of the adhesive inflammatory response generated at the diaphragmatic hiatus after implantation, as well as the improved ability to vent the stomach when compared with a Nissen fundoplication, preventing early mechanical stress on the healing crural plication.

PATIENT EVALUATION, SELECTION, AND EXCLUSION

The evaluation of patients with suspected reflux is the same as it would be in preparation for a fundoplication procedure. Upper endoscopy must be performed to assess for hiatal hernia, esophagitis, metaplasia, dysplasia, or tumor. We routinely perform endoscopic biopsy of squamocolumnar junction, as well as any abnormal appearing tissue at the time of endoscopy and deploy an ambulatory pH probe. The diagnosis of GERD requires the objective documentation of pathologic levels of acid reflux into the esophagus, because such pH testing is performed in all patients. Adequate motility must be confirmed before offering any surgical procedure. All patients in our practice undergo diagnostic evaluation with a video swallow esophagram to assess for both hiatal hernia and adequacy of bolus transport. Any suggestion of motility disorder or pseudoesophagus is followed by formal high-resolution manometric (HRM) studies. Patients with evidence of inadequate peristalsis are not candidates for MSA. HRM demonstrating ineffective esophageal motility by the Chicago Classification Criteria (v3.0) (>50% ineffective swallows with a distal contractive index <450 mm Hg • s • cm) are offered at most partial fundoplication.

SURGICAL TECHNIQUE

Preparation and Positioning

The patient is placed in low lithotomy with arms tucked and legs secured to facilitate deep reverse Trendelenburg positioning. Legs are kept neutral at the hips and spread at an angle to accommodate the surgeon positioned between the patient's legs. This is the same patient positioning used when performing laparoscopic Nissen fundoplication.

An initial 5-mm optically guided trocar is placed without insufflation into the supra-abdomen, approximately 2 cm superior and 2 cm to the left of midline with a 0 degree scope. The abdomen is insufflated, and the 5-mm 0 degree laparoscope is switched to a 5-mm 30-degree laparoscope. An 8 mm trocar is introduced through the left upper quadrant to midclavicular line 2 cm caudal to the costal margin. This 8-mm trocar facilitates the later introduction of the MSA device, as well as suture to repair the hiatal hernia. A 5-mm trocar is then placed in the right upper quadrant at the mid-clavicular line 2 cm inferior to the costal margin. A Nathanson liver retractor is introduced through a trocar stab wound directly below the xiphoid along the midline. An additional 5-mm assistant's port is placed approximately 5 cm caudal and 5 cm lateral to the 8 mm port.

Dissection of the Crura and Hiatus

Complete dissection of the GEJ at the hiatus is standard in our practice, given the poor sensitivity and reliability of videoesophagography or endoscopy for the diagnosis of small hiatal hernia and the added benefit of a right hiatus in maintaining the competence of the physiologic acid barrier. The gore flaccida is opened toward the hiatus with the hepatic branch of the posterior vagus

nerve. Taken with impunity. If encountered, an accessory left hepatic artery can be compressed to occlusion with an atraumatic grasper while the left lobe of the liver is observed. A change in perfusion mandates preservation of the artery; otherwise when encountered is ligated and divided. Sharp then blunt dissection of peritoneum and phrenoesophageal membrane is carried out in a clockwise fashion around the crura. The stomach is then again retracted laterally toward the patient's left, and careful dissection inferior to the esophagus is completed with the creation of a retroesophageal window, through which a Penrose drain is passed and secured around the esophagus and grasped by the assistant. Retraction on the Penrose facilitates exposure and traction of the esophagus allowing completion of the hiatal dissection and reduction of hiatal hernia if present. At least 3 cm of esophagus should be easily reducible into the abdomen.

Crural Closure

The right and left crura are approximated with two to three figure-of-eight 0 braided absorbable sutures to create a snug hiatal opening. The esophageal hiatus should only allow the easy passage of a single 5 mm laparoscopic grasper (Fig. 2).

Identification and Dissection of the Posterior Vagus Nerve

After the hiatal portion of the procedure, the posterior vagus nerve must be identified. The nerve passes from the posterior to the right side of the intraabdominal esophagus. The nerve is taut and has a character reminiscent of the vas deferens. Once identified, a site approximately just proximal to the anatomic GEJ (located approximately where the phrenoesophageal ligament/hiatal hernia sac inserts on the esophageal wall) is identified, and the nerve is gently hooked and pulled away from the body of the esophagus with a Maryland grasper. A passage is dissected between the nerve and the esophageal body by gentle and precise dissection with the closed scissors and closed Maryland grasper. The passage between the vagus and esophageal body must only be large enough for the grasper to easily fit through. A grasper is then passed between the posterior vagus nerve and the esophagus from medial to lateral and through the retroesophageal window (Fig. 3). A Penrose drain is placed into the left-hand grasper with the surgeon's right hand and then retracted medially through the tunnel, anterior to the posterior vagus nerve and around the esophagus. The ends of the drain are dropped.

Device Sizing

Any temperature probe or gastric tubes placed by anesthesia are to be removed before sizing. Torax medical has a proprietary measurement that is necessary for device sizing. The instrument consists of a magnet tipped probe extendable from a hard plastic housing. The device is placed following the course of the previously placed Penrose drain, between the posterior vagus nerve and the esophageal wall. The magnet tipped probe is the extended and wrapped around the esophagus, loosely attaching by means of magnetism to a metal band on the rigid plastic housing and making a loop around the esophagus (Fig. 4). To obtain the appropriate measurement, we use two visual cues. A ratcheting device on the tool's handle is gently retracted, tightening the sizing loop as a lasso. The first visual cue is when the sizing loop rests comfortably around the esophagus, without compression of the tissue. The device should not compress the esophagus; instead, it should rest loosely around the esophagus. The second visual cue is obtained by continuing to ratchet down the sizing loop until the magnet separates and the sizing loop opens. There sizes above the loop separation measurement is the appropriate size and should correlate with the first visual cue—where the sizing loop rests comfortably around the esophagus without compression. The two sizing methods are then compared. If they do not correlate, the larger one is used for device selection. A window on the device's handle indicates the size of the esophagus throughout this process. The measuring procedure is repeated twice to ensure correct measurement.

FIG. 2 Closure of the esophageal crura (Illustrated by Tiki Ly, copyright UIC Department of Surgery).

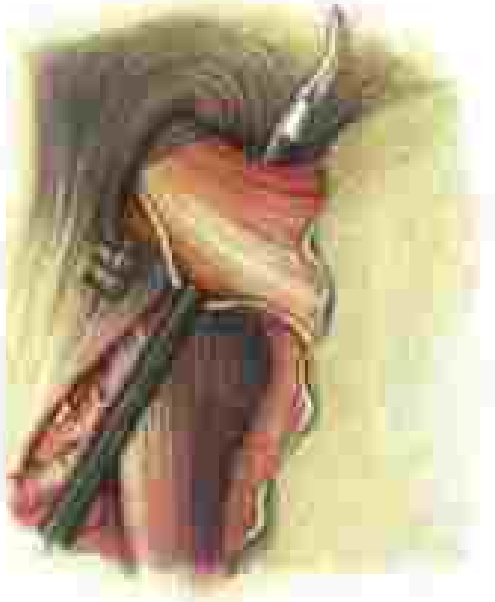

FIG. 3 Dissection of the posterior vagus nerve from the esophageal wall. (Illustrated by Tiki Ly, copyright UIC Department of Surgery)

Device Placement

The sizing device is removed, and the Penrose drain is left in place. The MSA device is then brought into the abdomen through the 8 mm trocar. There is a looped suture at each end of the

FIG. 4 Insertion of ring dilator between the posterior vagus nerve and esophageal wall. (Illustrated by Yale Jay, copyright UNC Department of Surgery)

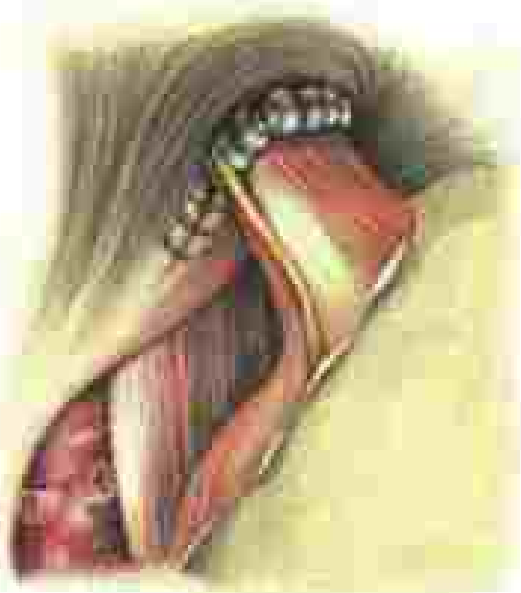

FIG. 5 MSA device placed with clasp secured in its final position, approximately 3 cm caudad to the insertion of the gastroesophageal ligament on the esophageal wall, in the plane and flush with the diaphragmatic crura. (Illustrated by Yale Jay, copyright UNC Department of Surgery)

device, allowing it to be grasped with the laparoscopic graspers. The device is brought from lateral to medial around the esophagus in the same fashion as the Penrose drain was initially placed. The Penrose drain should be left in place, with the ends free, during insertion to aid in its passage through the retroesophageal tunnel. The free ends of the MSA device are then brought together, with care being taken not to capture loose tissue between the two joining magnets. Gentle agitation of the two magnets with a grasper prompts coupling. The Penrose drain is then removed, and the looped sutures are snipped free from the device, completing the procedure (Fig. 5).

Postoperative Care

Patients who undergo repair of a large hiatal hernia are admitted overnight. Other patients are routinely discharged home the day of surgery. All patients are sent home on a soft diet immediately after surgery, with a regular diet as tolerated. The diet of patients after MSA implantation is different and more important to long-term patient outcome and satisfaction than the diet after fundoplication. In the first 4 weeks after implantation, it is critical that MSA patients take frequent small meals of a soft or regular diet every 2 to 3 hours while awake to get the device to open and close, preventing it from becoming encapsulated in the closed position. Patients are told that this is physical therapy for the device in much the same way that a prosthetic knee needs to be exercised in the early postoperative period. These early and frequent small meals have seemingly decreased the incidence of long-term dysphagia.

RESULTS OF TREATMENT

Postoperative Complications

Immediate postoperative dysphagia is the most common side effect of MSA placement. Incidence and speed of resolution is reduced in patients who can take multiple (6) small meals per day for the first 4 weeks after surgery. If patients are unable to tolerate solid foods and are struggling with oral intake, a short course of steroids usually will help them get back to eating solid food and continuing the physical therapy of the device. We refrain from balloon dilation via endoscopy within the first 3 months, because this usually causes more inflammation and makes the dysphagia worse. If patients have persistent dysphagia after 3 months, dilating the area with a 15- to 18-mm balloon does seem to help.

Erosion, Persistent Dysphagia and Device Removal

Erosion occurs in 0.3% to 0.4% of patients. Erosions present with new-onset dysphagia 1 to 3 years after surgery, usually with 1 or 2 beads having eroded into the esophageal lumen, creating a contained perforation of the esophagus into the capsule surrounding the MSA device. Eroded devices can be removed endoscopically or with a combination of endoscopy and laparoscopy. No patient has needed an esophagectomy or gastrectomy due to device erosion.

Persistent dysphagia accounts for most of reported incidences of device removal. In the current series, between 2% to 6% of MSA devices require removal at follow up, out to 10 years in the longest series. Removal of the device is accomplished laparoscopically via exposure identical to that used for placement. An intense inflammatory capsule is present around the MSA device in the early postoperative period, but, by 8 weeks after surgery, this has begun to mature. The MSA device is located within the adhesive capsule around the esophagus, electrocautery is then used to expose the body of several beads anteriorly. The beads are made of titanium and do not transmit electrical current to underlying esophageal wall. Each bead to be torn grasped, retracted, and dissected free from the capsule. A single inter-bead wire is then cut with heavy shears, and the entire device is pulled free from its capsule in one piece and removed from the body. Fundoplication may then be accomplished in an immediate or staged fashion when the device is removed for persistent reflux. In our experience, fundoplication has not been needed to prevent reflux symptoms when the device is removed exclusively for dysphagia, likely owing to the inflammatory capsule alone often preventing recurrent acid reflux (Tatum).

Immediate Outcomes

The antireflux effects of the MSA procedure are immediate. Patients can be weaned from antireflux medications starting the day of surgery, with most patients being off of all pharmacologic therapy by 2 weeks after surgery. The importance of frequent oral intake in the 3 month period after surgery must be emphasized to patients to ensure good outcomes. Failure to induce frequent expansion of the MSA device with swallowing results in the MSA device becoming encapsulated in the contracted position, resulting in persistent dysphagia.

Long-Term Outcomes

Long term control of GERD symptoms is similar to the results after Nissen fundoplication in series extending nearly a decade since the adoption of the MSA into surgical practice (Ganz, 2016). Early results suggest that the MSA device may affect some regression of Barrett's esophagus at a rate similar to what has been experienced with Nissen fundoplication (Abraham, 2018). A randomized controlled trial by Bell and Lipham (2016) randomized patients with regurgitation symptoms on once daily proton pump inhibitor (PPI) to either twice daily PPI or MSA device implantation and found that 100% of patients had relief of regurgitation at 6 months compared with MSA vs only 10% of patients on PPI therapy alone, demonstrating that MSA is effective for not only the pain of reflux, but also the regurgitation that remains troubling to many patients on PPI therapy. Reflux control at 5-years' follow up has remained excellent—more than 84% of patients remain off of PPI, and moderate to severe regurgitation in 97% of patients before surgery remains low at 1.3% (Ganz, 2016). The repair of large hiatal hernia and placement of the MSA instead of performing a Nissen fundoplication has become widely accepted. Rates of hiatal hernia recurrence after repair accompanied by MSA device placement are at least equivalent to those after repair with fundoplication, with only a 4% recurrence at a median of 19 months in a recent series (Reiter, 2018).

CONCLUSION

The MSA device has not replaced fundoplication for patients with GERD, but it has provided a less invasive, durable alternative to Nissen fundoplication. It has also been shown to control reflux in patients with large hiatal hernias with an acceptably low recurrence rate. The advantages of MSA over the Nissen in the correct patient are a faster operative and recovery time, retention of the ability to belch or vomit, and the reversibility of an easily removable device that does not permanently alter gastric anatomy. The MSA is an acceptable alternative to Nissen fundoplication with what appears to be many advantages.

Suggested Readings

Abraham I, Bell R, John S, et al. Worldwide experience with revision of the magnetic sphincter device. J Gastrointest Surg. 2018. [epub ahead of print].

Abraham I, Tatum J, Bilchkiewicz, et al. Regression of intestinal metaplasia following magnetic sphincter augmentation device placement. Surg Endosc. 2018;32(3):1570–1576.

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Management of Barrett's Esophagus

Anna Sophia Jackson, MD, and Brian C. [illegible], M.D., MHA, M.H.S., F.A.C.S., A.C.S.

DEFINITION OF BARRETT'S ESOPHAGUS AND TREATMENT OBJECTIVES

Barrett's esophagus (BE) is defined as the replacement of the normal squamous epithelium lining the distal esophagus with metaplastic columnar epithelium containing goblet cells. The contemporary definition of BE requires endoscopy, with biopsy demonstrating a visible segment of columnar epithelium and intestinal metaplasia with goblet cells (Fig. 1). BE is an acquired condition secondary to chronic esophageal injury and inflammation caused by both acidic and alkaline gastroesophageal reflux disease (GERD). It is conservatively estimated that 6% to 10% of GERD patients with GERD will develop BE, with a large majority of cases going unrecognized. BE is the major risk factor for esophageal adenocarcinoma (EAC), and management goals for patients with BE are directed at treating the underlying cause of BE (GERD), preventing progression of BE, and treatment of dysplastic BE before it transforms into EAC.

CLINICAL EFFECT AND FEATURES OF BARRETT'S ESOPHAGUS

The greatest clinical concern with BE is the risk of progression to EAC, a malignancy that has been rising in incidence over the past several decades. Many studies have shown that the presence of BE can

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Anna Sophia Jackson, MD, and Brian E. Louie, MD, MHA, MPH, FRCSC, FACS

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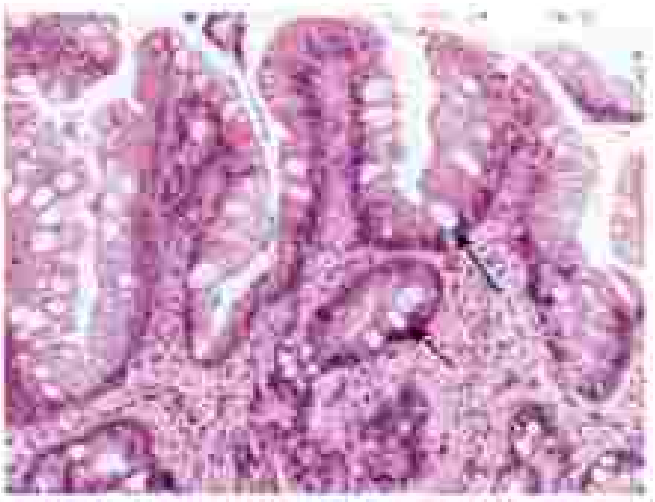

FIG. 1 Intestinal metaplasia with goblet cells present.

center at least a 40-fold increase in the risk for development of EAC compared with the general population, with some studies showing up to a 125-fold increase in risk. Despite the increased cancer risk, most patients do not progress to EAC, with an overall annual rate of neoplastic transformation estimated at 0.13% to 0.5%. In a study by Cameron and colleagues, the estimated median age of the development of BE is approximately 40 years; however, the mean age for the first endoscopic diagnosis of BE without carcinoma was 63 years. This demonstrates that BE may develop approximately 20 years before it is clinically recognized.

The natural progression of BE to carcinoma develops over time from nondysplastic columnar epithelium to dysplasia to carcinoma. Within the dysplastic phase, there is a progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD). LGD is differentiated from HGD by degree of architectural and cytologic distortions. There is much reported interobserver variability in diagnosing LGD versus HGD. The sequence of progression is driven by genetic and epigenetic events that eventually lead to a loss of genetic stability. The progression of BE to cancer is unpredictable, with a recent meta-analysis reporting that the overall risk of progression from HGD to EAC is 6% per patient per year.

Chronic exposure of the squamous-lined esophagus to both acid and duodenal secretions during reflux causes damage to the epithelium, inducing mucosal injury. With exposure to both acidic and alkaline gastroesophageal reflux activity alterations, the inflammatory cascade is initiated, promoting cellular proliferation and inducing genetic alterations and causing genetic destabilization through transcription factors, inflammatory cytokines, and other stimulators such as free radicals. The genetic alterations have been shown to correlate with the severity of GERD. In addition to chronic reflux, additional risk factors for the development of BE include family history, tobacco use, obesity, presence of hiatal hernia, white race, male gender, and age greater than 50 years.

SCREENING AND EVALUATION OF BARRETT'S ESOPHAGUS

Screening

Routine screening for BE of the general population is not recommended; however, based on duration and frequency of reflux combined with other risk factors, screening may be considered in high-risk patients based on current guidelines. A thorough history from patients helps elucidate the duration and frequency of their symptoms as well as additional risk factors they may have for the development of BE or EAC. The American College of Gastroenterology Clinical Guidelines recommend screening for BE with white light endoscopy in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of GERD and two or more risk factors for BE or EAC including age greater than 50 years, white, elevated body mass index, history of smoking, and family history of BE or EAC. Given the substantially lower risk of EAC in females with chronic GERD, screening is not recommended; however, in individual cases of female patients, it can be considered based on risk factors.

Evaluation

On endoscopy, BE should be suspected when the columnar epithelium that appears salmon pink in color is noted proximal to the gastroesophageal junction (GEJ), which is defined endoscopically as the most proximal extent of the gastric folds (Fig. 2). The goal is to identify any areas of columnar replacement of the esophagus as well as any areas of irregularity within the columnar segments. For reporting purposes, BE is often divided into short or long segment with short segment BE defined as <3 cm; however, currently it is recommended to use the more objective Prague classification that defines the circumferential and maximal extent of BE. Measurements are taken from the proximal margin of the rugal folds during moderate insufflation to the proximal limit of the circumferential Barrett's segment (circumferential extent) and the longest tongue of Barrett's (maximal extent).

Biopsies of the distal esophagus are required during endoscopy regardless of whether BE is suspected or not. In my practice, biopsies are taken from the stomach, gastric cardia just below the GEJ, and above the GEJ, including all the columnar mucosa to the squamocolumnar junction. The purpose of gastric biopsies is to differentiate gastric intestinal metaplasia from Barrett's metaplasia. The Seattle Protocol is widely accepted as the standard of care in BE screening and surveillance and is used to detect dysplasia and EAC by obtaining four-quadrant biopsy samples at 1- to 2-cm intervals throughout the area of suspected BE. In addition, targeted biopsies of any other irregularities, including ulceration and raised areas, should be biopsied. The pathology should be reviewed by two pathologists, preferably with one having a gastrointestinal specialization, especially in the diagnosis of dysplasia.

Standard white light endoscopy can be enhanced for greater detection of BE by using chromoendoscopy. Traditionally, chromoendoscopy consisted of applying a chemical solution (Lugol's, methylene blue, and acetic acid have been described) onto the esophageal lining to enhance the visualization of both the mucosal surface and vascular patterns, highlighting mucosal irregularities. Although safe and inexpensive, its disadvantages include the use of a staining agent and high interobserver variability in the ability to identify abnormal areas. Most current-version endoscopes have an electronic version of chromoendoscopy that provides contrast enhancement of the mucosal surface without the need for dye by relying on optical filters applied to the spectrum of light. The most well-known of these is narrow band imaging (Olympus Medical Systems), but each endoscope manufacturer has its own postprocessing software system. A recent meta-analysis suggested that electronic chromoendoscopy may increase detection of dysplasia.

More recently, novel advanced imaging and sampling techniques have emerged that we have begun to incorporate into our practice to improve the accuracy of endoscopic surveillance and detection for BE. These include probe-based confocal laser endomicroscopy and wide area transepithelial sampling with three-dimensional analysis (WATS®; CDx Diagnostics). Probe-based confocal laser endomicroscopy (Mauna Kea Technologies) uses confocal concepts to capture microscopic images of tissue in vivo with the aid of a contrast agent—intravenous fluorescein. Probe-based confocal laser endomicroscopy allows for identification of intestinal metaplasia, dysplasia, and adenocarcinoma. WATS® uses a special abrasive brushing instrument to obtain tissue samples from a broad area of BE, so the very sampling more tissue than the Seattle Protocol alone. The tissue samples are then computer analyzed to identify the most suspicious

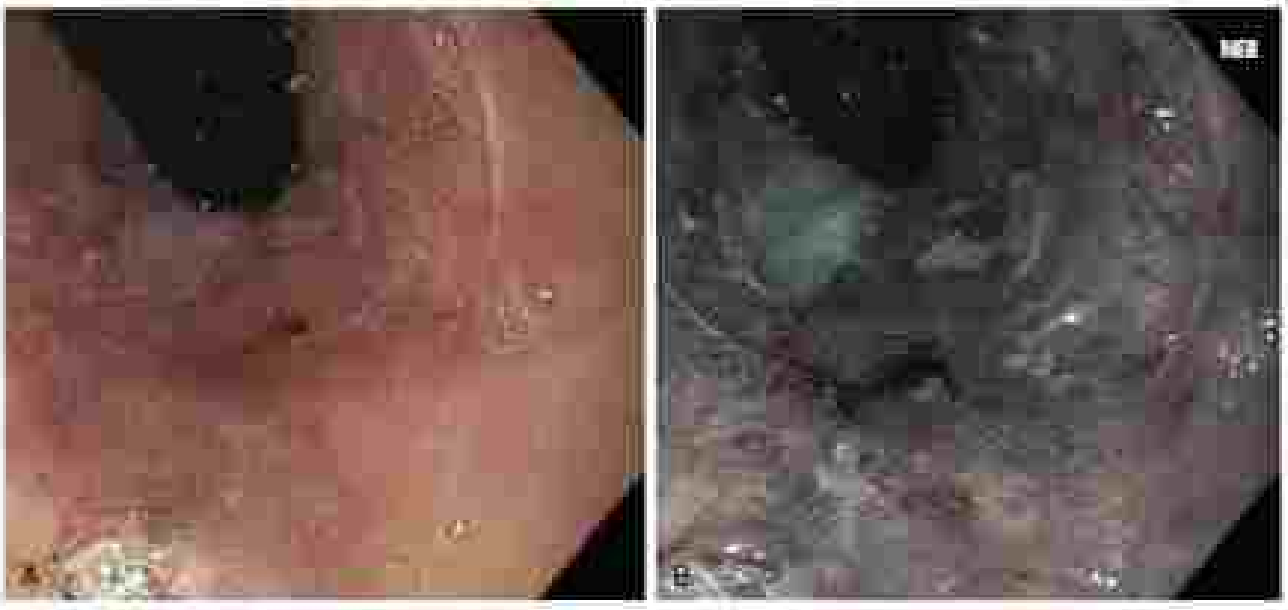

FIG. 1 Barrett's esophagus seen on endoscopy under both (A) white light endoscopy and (B) narrow band imaging.

TABLE 1 Risk Calculator for the Progression of Barrett's Esophagus

Risk Factor	Points Assigned	Score
Each 1-cm increase in the length of Barrett's esophagus	1 (to a maximum of 10)	0–10 points: low risk Annual risk of progression, 0.13%
Smoker or smoking history	5	11–20 points: intermediate risk Annual risk of progression, 0.73%
Male	9	>20 points: high risk
Diagnosis of low-grade dysplasia	11	Annual risk of progression, 2.1%

Modified from Parasa S, Vennalaganti S, Gaddam S, et al. Development and validation of a model to determine risk of progression of Barrett's esophagus to neoplasia. Gastroenterology. 2018;154(5):1282–1289.e2.

cells that are then reviewed by a pathologist. WATS[39] in combination with the Seattle Protocol has been shown in a multicenter prospective study to detect more cases of IMCD and neoplasia than the Seattle Protocol alone.

SURVEILLANCE OF BARRETT'S ESOPHAGUS

Once BE has been identified, a crucial step in management of patients with BE is surveillance of disease. Current guidelines recommend endoscopic surveillance intervals using the Seattle Protocol that vary with the presence and grade of dysplasia. After the diagnosis of BE is made on index endoscopy, we often will repeat the endoscopy 1 year after initial diagnosis to confirm the presence of BE and rule out dysplasia. For patients with BE without dysplasia, surveillance endoscopy should be performed every 3 to 5 years based on current guidelines. In our practice, however, surveillance for these patients ranges from 3 to 5 years, influenced by the length of BE (longer surveyed more frequently because the risk of developing EAC increases with length) and the initial grade of esophagitis (patients with grades C and D have a higher risk of developing BE) along with the other risk factors.

For patients indefinite for dysplasia on endoscopy, a repeat endoscopy should be performed 3 to 6 months after optimization of acid suppressive medications. If the indefinite for dysplasia diagnosis is confirmed, a surveillance endoscopy is recommended annually while indefinite for dysplasia. In the presence of LGD, surveillance is performed every 6 to 12 months. For those patients with HGD who do not undergo intervention, surveillance is recommended every 3 months. After intervention, continued surveillance is necessary. The nuances of surveillance after intervention are discussed in the sections that follow.

For counseling patients, a risk calculator has been developed that assigns points to risk factors to identify a patient at low, intermediate, or high risk of progression (Table 1). Although this risk model has not been externally validated, our Barrett's working group has been looking at how it can be used clinically to inform patients of their risk of progression and prognosis.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITHOUT DYSPLASIA

In patients with nondysplastic BE, the principle treatment goal is to provide relief of the patient's GERD symptoms while protecting the esophageal mucosa and BE from progression to dysplasia from ongoing acid reflux injury. Medical therapy with proton pump inhibitors (PPIs) has been considered the first-line therapy for any patient with BE to control GERD. The American College of Gastroenterology Clinical Guidelines recommend patients with BE should receive once-daily PPI therapy for chemoprevention. Twice-daily dosing is not routinely needed unless necessitated by poor control of reflux symptoms or esophagitis. Medical therapy with PPIs treats esophagitis and therefore allows for more accurate surveillance of the esophagus. In a 2004 US

study by El-Serag and colleagues, 236 veterans with IM and no dysplasia at baseline were followed for 1470 patient-years. The study demonstrated a 75% reduction in the development of dysplasia in PPI users versus nonusers. Overall, PPIs are generally well tolerated by patients; however, the long-term safety of PPIs has been called into question.

Antireflux surgery is an alternative therapy when GERD symptoms are inadequately controlled with acid suppression medications and/or are an impairment to quality of life; however, many advocate for surgical intervention with an antireflux surgery earlier in the course of treatment given its proven effectiveness. Unlike medical therapy, antireflux surgery aims to address the underlying defects: the incompetent lower esophageal sphincter (LES) and hiatal hernia if present. If successful, this prevents reflux of all substances into the distal esophagus (see Surgical Considerations and Surgical Management of Barrett's Esophagus).

Patients will often ask if antireflux surgery will prevent the development of cancer; however, the concern for progression and the risk of cancer development is insufficient to recommend surgery to patients solely for these reasons. Similarly, the role or benefit of mucosal ablation with radiofrequency or other devices in unproven in patients with nondysplastic IM. It may have a role in patients with ultralong segment IM (>8 cm) to reduce the inferior complexity of appropriate four-quadrant surveillance biopsies every 1 to 2 cm. The simple approach with these patients is to counsel them about the need to provide excellent control of GERD regardless of whether the treatment is PPIs or surgery.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITH LOW-GRADE DYSPLASIA

LGD is associated with an increased risk for progression to adenocarcinoma compared with nondysplastic IM. Given the high interobserver variability in diagnosing LGD in IM from inflammatory atypia, however, there is controversy on the best treatment when LGD is found on biopsy. Preferred societies, both gastroenterology and surgical, agree on the need for confirmation of LGD by two skilled pathologists. If patients are not already on a PPI, one should be started or the dose escalated if already prescribed one. After interventions to control the underlying reflux, a repeat endoscopy within 6 months to evaluate response to treatment is recommended. If there is resolution of LGD on surveillance biopsies, then patients can be maintained on PPI therapy. Alternatively, antireflux surgery with Nissen fundoplication can also be performed to control reflux. In a study by Rossi and colleagues, medical therapy with high-dose PPIs was compared with Nissen fundoplication to evaluate regression of LGD. Of the 19 patients treated with PPIs, 13 (63.2%) had regression of their LGD to IM without dysplasia, whereas 15 of 16 patients (93.8%) who received a Nissen had regression of LGD ($P = .03$).

If the diagnosis of LGD is persistent, endoscopic ablation therapy is recommended in the absence of mucosal abnormality. Although some argue for continued surveillance of patients with confirmed LGD, in a randomized clinical trial published in 2014, Phoa and colleagues demonstrated that radiofrequency ablation (RFA) resulted in a reduced risk of neoplastic progression over 3 years of follow-up compared with surveillance alone. After RFA is performed, patients require ongoing surveillance to detect any further progression or new lesions of dysplasia and a discussion about long-term management of their GERD with PPIs or antireflux surgery.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

The first step in management of patients with HGD is careful repeat endoscopy to map out the locations of any nodules or lesions such as ulcers within the columnar mucosa using both white light endoscopy and narrow band imaging. The additional use of chromoendoscopy can aid in the identification of any lesions within the mucosa. HGD is an indication for intervention in the vast majority of patients because of the high risk for progression to EAC.

Endoscopic mucosal resection should be used to excise small discrete mucosal nodules. Endoscopic mucosal resection is performed with a cap attached to the end of the endoscope. The lesion is suctioned into the cap and a rubber band applied to the base to create a "pseudopolyp" that can be snared and removed for pathologic assessment. A good specimen will include mucosa and submucosa with a clean base of muscle seen at the resection site. In lesions larger than 1 to 2 cm, endoscopic ultrasound should be used to evaluate the depth of invasion and presence of enlarged lymph nodes. If the lesion identified is small or there is no lesion, endoscopic ultrasound is not useful because the accuracy of T staging is poor.

Patients found to have HGD alone or adenocarcinoma confirmed at the mucosa level only (T1a) without lymphovascular invasion are candidates for endoscopic therapy to preserve the esophagus. Invasion into the submucosa (T1b), however, should lead to esophagectomy and lymph node dissection in most patients because of the increased likelihood of nodal metastases once the cancer reaches the submucosa. Patients undergoing esophageal preservation should have complete endoscopic resection of all raised lesions in one or more sessions 4 to 8 weeks apart until all dysplastic tissue has been eradicated. Even after complete endoscopic resection, a concomitant mucosal ablative procedure with RFA is frequently required to ensure complete eradication of disease because of the frequent multifocality of IM. RFA is performed at 8-week intervals until all the intestinal metaplasia has been eradicated.

After complete eradication of both dysplasia and intestinal metaplasia, ongoing surveillance is recommended every 3 months for the first year, every 6 months for the second year, and annually thereafter because there is a risk for recurrence or inadequately treated lesions. Furthermore, patients undergoing endoscopic therapy should be on maximum medical therapy (e.g., esomeprazole 40 mg twice daily) and long-term GERD control after endoscopic therapy either in the form of PPIs or antireflux surgery.

Esophagectomy in High-Grade Dysplasia

Although endoscopic treatments have become the standard of care, there is still a role for esophagectomy in the treatment of HGD. Advantages of esophagectomy include immediate disease eradication and no need for further surveillance; however, it carries the potential morbidity associated with the surgery. Operative mortality for esophagectomy in HGD and early tumors is low, at less than 1% at high-volume centers. Esophagectomy should be strongly considered in patients with the following characteristics:

- Poor prognostic risk factors of the lesion: large (>2 to 3 cm), lymphovascular invasion, multifocality
- Patient prefers surgery
- Unable to comply with the repeat endoscopic treatments and surveillance
- Inability to eradicate HGD and/or adenocarcinoma or progression of disease
- Failed ablation techniques
- End-stage esophageal function (from motility disorder, stricture, obstructed hiatal hernia)

For these patients, the best surgical approach is often a minimally invasive vagal-sparing esophagectomy that can eradicate disease while minimizing potential morbidity by sparing both vagal nerves (Figs. 3 and 4).

SURGICAL CONSIDERATIONS AND THE ROLE OF ANTIREFLUX SURGERY IN MANAGEMENT OF BARRETT'S

Patients with GERD and BE have been shown to have an increased amount of reflux compared with patients with GERD alone as well

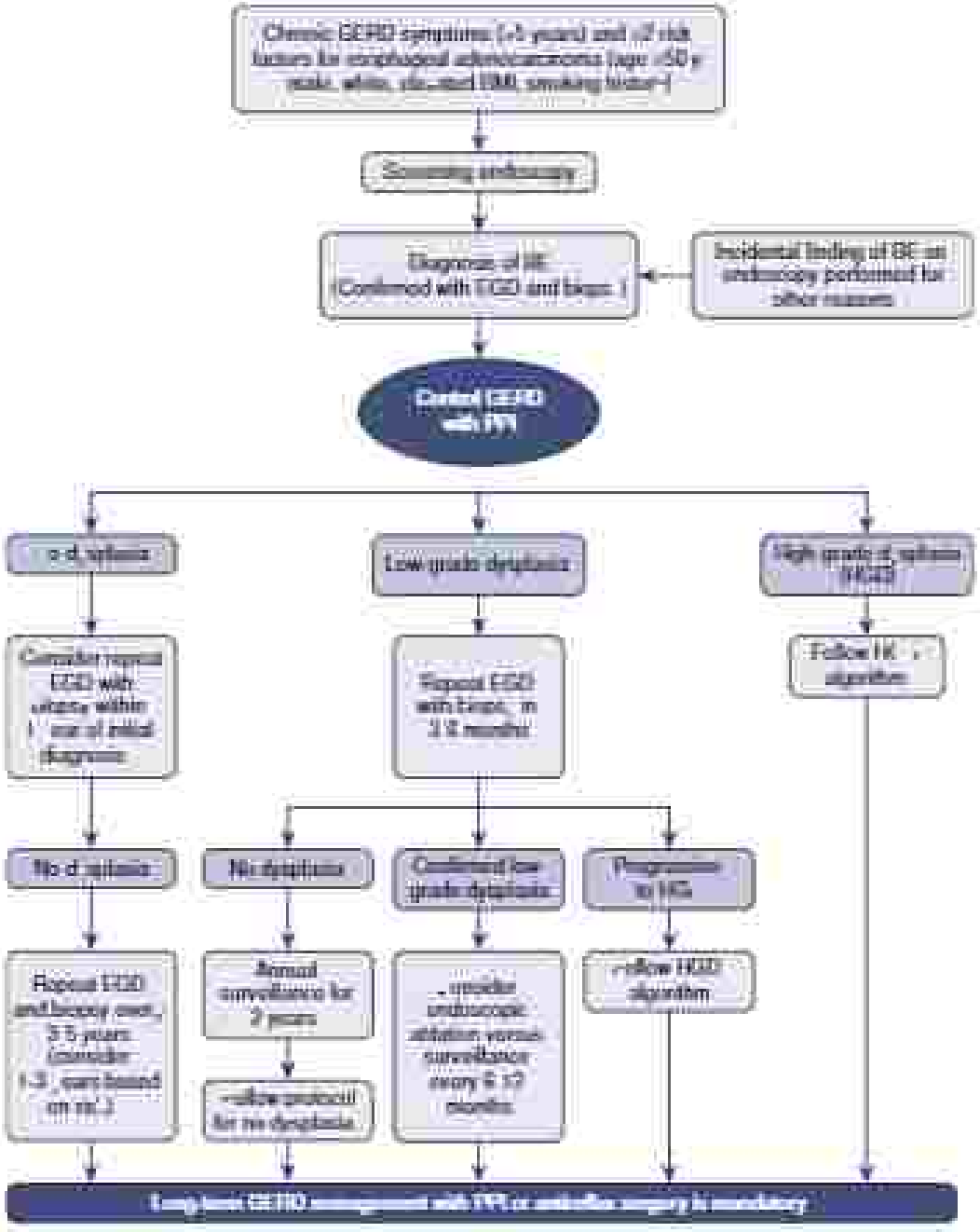

FIG. 3 Management of Barrett's esophagus. BE, Barrett's esophagus; BMI, body mass index; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux; PPI, proton pump inhibitor.

as a higher prevalence of incompetent LES, impaired esophageal motility, and hiatal hernias, making it difficult to control reflux with medical management alone. Antireflux surgery has several theoretical benefits in the management of GERD, including the control of both acid and bile pancreatic substrates that are contributing to the mucosal injury and therefore reducing inflammatory markers that are key in the development of BE including interleukin 8 and Cox-2. Furthermore, antireflux surgery aims to fix the incompetent LES and hiatal hernia if present. The complete reflux control can prevent progression of BE and even lead to regression and healing of the neoplastic mucosa, as shown in several studies. Oelschlager and colleagues assessed 189 patients treated with antireflux surgery for BE, of which 66 returned for endoscopic surveillance. At a median follow up of 30 months, 35% had complete regression of BE and only 3.3% had progression. Further, in a recent meta-analysis, Manner and colleagues found that antireflux surgery may prevent EAC better than medical therapy in patients with BE.

The esophageal injury sufficient to cause mucosal injury leading to BE can also cause edema, spasm, fibrosis, strictures, and shortening of the esophagus, leading to a more complex fundoplication. In addition, patients with BE more often have a hiatal hernia. These factors lead to a higher failure rate for fundoplication in the setting of BE at 10% to 20% at 3 to 5 years postoperatively (compared with 5% to 10% for those patients without BE). A failed fundoplication is a risk factor for disease progression because there is continued postoperative acid exposure to the distal esophagus. Careful selection of patients for fundoplication is critical and postoperative surveillance with serial endoscopies is mandatory.

For those patients considering antireflux surgery, further workup should include high resolution manometry and video esophagram

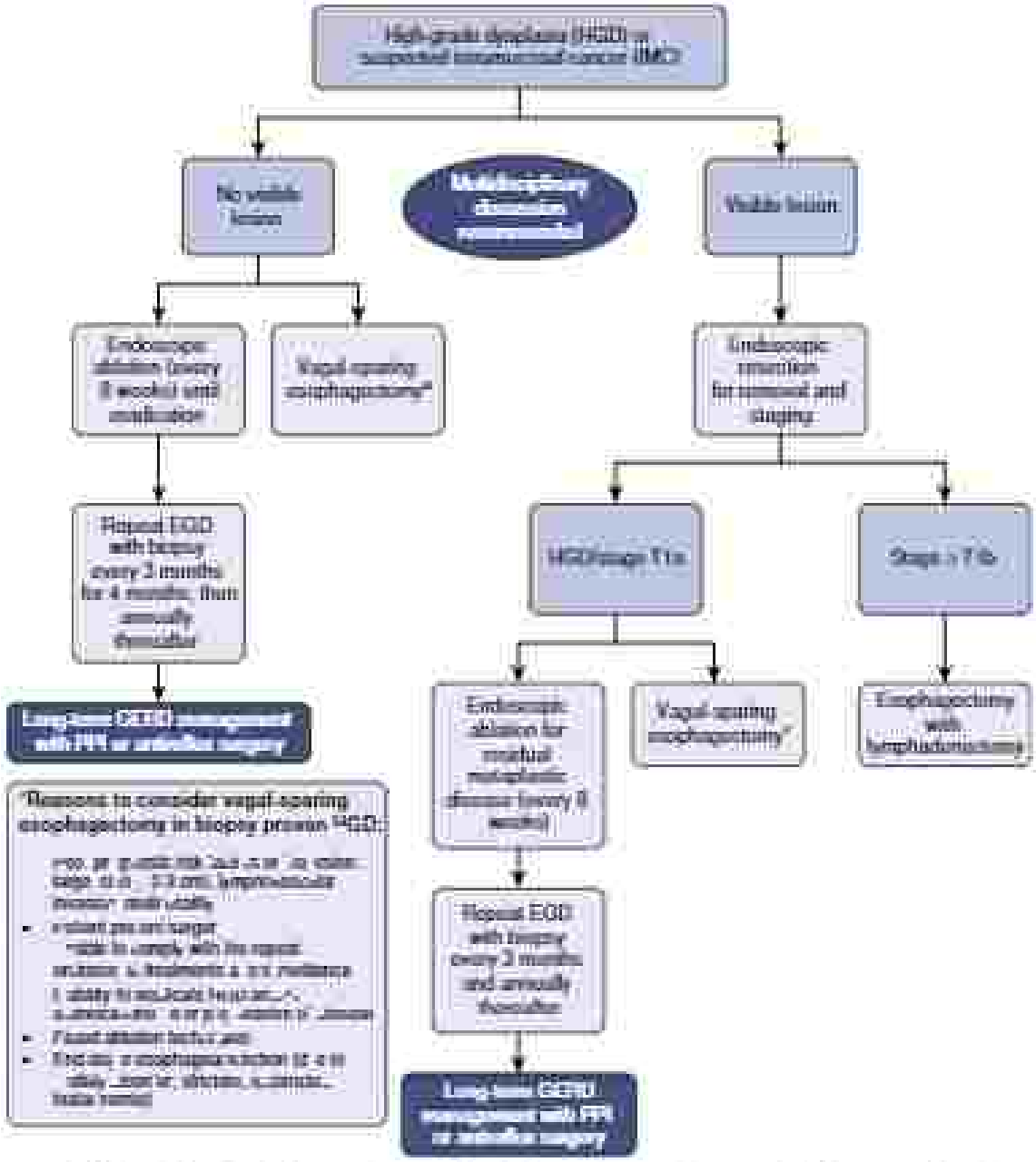

FIG. 4 Management of high-grade dysplasia and intramucosal cancer (IMC). EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux; PPI, proton pump inhibitor.

We favor obtaining a pH test, not to diagnose GERD, but to prioritize baseline assessment of the patient's reflux. This allows comparison to any postfundoplication confirmatory testing that is performed. If esophageal dysmotility is a significant problem, a partial fundoplication can be performed to prevent postoperative problems with dysphagia; however, the efficacy of a partial fundoplication in patients with HG is questionable, with some studies suggesting decreased long-term control of reflux. Patients in this situation should be selected carefully and informed that they likely will need to remain on PPIs to ensure control of their GERD.

After intervention with RFA or endoscopic resection and surveillance of at least 1 year, our practice has been to have a discussion with the patients about long-term GERD control. Patients who remain incompletely controlled on PPI therapy with reasonable motility are considered for fundoplication. In a multicenter series, we demonstrated that fundoplication after endoscopic therapy results in similar durability and recurrence of HG when compared with patients managed with PPIs; however, fundoplication seemed to prevent further progression and the development of cancer.

CONCLUSION

Management of the patient with HG is intricately tethered to the treatment of the patient's underlying chronic GERD. When presenting this complex problem to the patient, it can often be broken down into two separate but related pathways: (1) treatment and subsequent surveillance of the Barrett's metaplasia and (2) treatment of the underlying GERD. Antireflux surgery can be beneficial to eradicate GERD symptoms and even induce regression of existing dysplasia and prevent progression. Patients must be carefully selected for surgery because those with HG are more likely to have a fundoplication failure and recurrence of hiatal hernia compared with those patients without HG; a failed antireflux surgery is a risk factor for the progression

of IM. Endoscopic treatments have transformed management of dysplastic Barrett's and now allow preservation of the esophagus in most patients, but esophagectomy continues to have a role in selected patients not amenable to or cured by endoscopic therapy.

Suggested Readings

Johnson CS, Lunde OC, Wills A, et al. The durability of endoscopic therapy for treatment of Barrett's neoplasia, dysplasia, and mucosal cancer after histologic complete remission. J Gastrointest Surg 2013;17(5):1795–801.

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Endoscopic Treatment of Barrett's Esophagus

Anne F. Ehlers, MD, MPH, and Brant K. Oelschlager, MD

Barrett's esophagus (BE) is a disease characterized by the gradual replacement of the normal stratified squamous epithelium of the esophagus with columnar, intestinal metaplasia (Fig. 1A, B) [1]. This transformation is due to chronic exposure to gastric contents, often within the context of gastroesophageal reflux disease (GERD). Patients at risk for BE are screened with endoscopy and biopsy. The major concern with BE is that it is a precursor lesion for esophageal adenocarcinoma (EAC), a disease with poor prognosis and poor long-term survival. In addition, EAC is a disease that continues to increase in incidence. Given this, identifying and eradicating BE before progression to adenocarcinoma is a top priority. In the past, patients with BE often were recommended for esophagectomy. More recently, evolving endoscopic techniques have replaced esophagectomy for many of these patients, allowing for eradication of BE with less morbidity and fewer complications.

SURVEILLANCE AND MANAGEMENT ALGORITHM

Screening

The primary risk factor for BE is longstanding GERD, along with male sex, age older than 50 years, and central obesity. Patients with GERD have a 10% to 15% risk of BE, increasing age and long segment BE (>3 cm) are risk factors for progression to dysplasia. Overall, the rate of progression from BE to esophageal adenocarcinoma is low, perhaps as low as 0.12% per year. Other evidence suggests that for patients with nondysplastic BE, the annual risk of progression to EAC is 0.33% per year among all patients with BE, and 0.19% per year among patients with short segment BE (<3 cm). For patients with low grade dysplasia (LGD), this risk increases to 0.5% per year. The risk increases substantially among those with high grade dysplasia (HGD), up to 19% in some studies. Early detection of invasive cancer is important because patients detected at an early stage have a much higher 5 year survival rate (80%–90%) compared with patients who present symptomatically with more advanced disease (10%–30%).

Identifying the most appropriate pool of patients for screening is an area of active debate, especially with the large number of adults who have GERD. Because only a minority of patients with GERD will ever develop BE, screening every patient with GERD is not cost-effective nor efficient. However, evidence suggests that surveillance of BE is associated with diagnosis of EAC at an earlier stage, which may be associated with improved outcomes. For these reasons, accurately identifying the population of patients with BE is critical. Current guidelines from the American College of Gastroenterology (ACG) recommend screening male patients with *five or more years* of GERD symptoms AND two or more risk factors for BE or EAC (age >50 years, white race, central obesity, history of smoking, family history of BE or EAC). Screening for female patients is generally not recommended, except for patients with multiple risk factors, as outlined previously.

Screening is generally undertaken using high resolution endoscopy with liberal use of narrow band imaging and biopsy, but as previously stated this can be very labor and time intensive. Several novel screening modalities have been proposed to reduce this burden. One alternative is transnasal esophagoscopy, which is an office based procedure that uses topical anesthetic to pass an endoscope through the nares and into the esophagus. Compared with traditional high resolution endoscopy, the image quality is reduced and the biopsies are smaller, but often are sufficient for histologic analysis to allow a diagnosis of BE to be made without a formal endoscopy. A second option for screening is the Cytosponge, which is a gelatin coated capsule attached to a string that is then swallowed by the patient. Once in the stomach, the gelatin coating dissolves leaving behind a sponge that is then retrieved by pulling on the string. As the sponge comes back through the esophagus, it picks up cells that can then be examined for abnormalities. It currently holds promise as a screening tool for BE but is not adequate to screen for EAC because transnasal esophagoscopy and Cytosponge are still relatively new, high resolution endoscopy is still the *gold standard for diagnosis of BE*.

Surveillance

Patients with confirmed BE in the absence of dysplasia or EAC should be regularly surveilled to detect disease progression. A challenge in the past has been lack of universal criteria for describing the extent of disease. To address this challenge, the Prague Criteria are a set of endoscopic data developed and validated by a working group specifically focused on esophagitis using standardized videos of endoscopies. The purpose was to improve on the previously used vague descriptions of "long" versus "short" segment disease, and to facilitate communication between providers. The Prague Criteria measure the extent of disease based on circumference and maximum extent (C&M) criteria, with C being the maximum circumferential extent of disease and M the maximum length, including any isolated tongues of disease.

Once a patient has been diagnosed with BE, the next step is to evaluate for any dysplasia or invasive cancer. The current recommendation is to evaluate the patient with high resolution or high definition white light endoscopy followed by meticulous inspection of the esophageal lumen, after both insufflation and desufflation, including inspection of the gastroesophageal junction in the retroflexed view. Some data suggest that longer inspection time is associated with better detection of dysplasia or EAC. Suspicious lesions such as erosions, ulcerations, nodules, plaques, and other mucosal or luminal abnormalities should be selectively sampled. Random biopsies are not recommended. Suspicious lesions in patients with known dysplasia are best removed via endoscopic mucosal resection (EMR), which will be described later in the chapter. Additionally, the ACG recommends against taking biopsies in areas of active, erosive esophagitis and instead to wait until the patient has been treated with antisecretory agents to allow the inflammation to subside.

Ongoing surveillance is dependent on the pathology determined at the time of biopsy. For patients who have BE without evidence of dysplasia, the recommendation is that they undergo repeat

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Ongoing surveillance is dependent on the pathology determined at the time of biopsy. For patients who have BE without evidence of dysplasia, the recommendation is that they undergo repeat

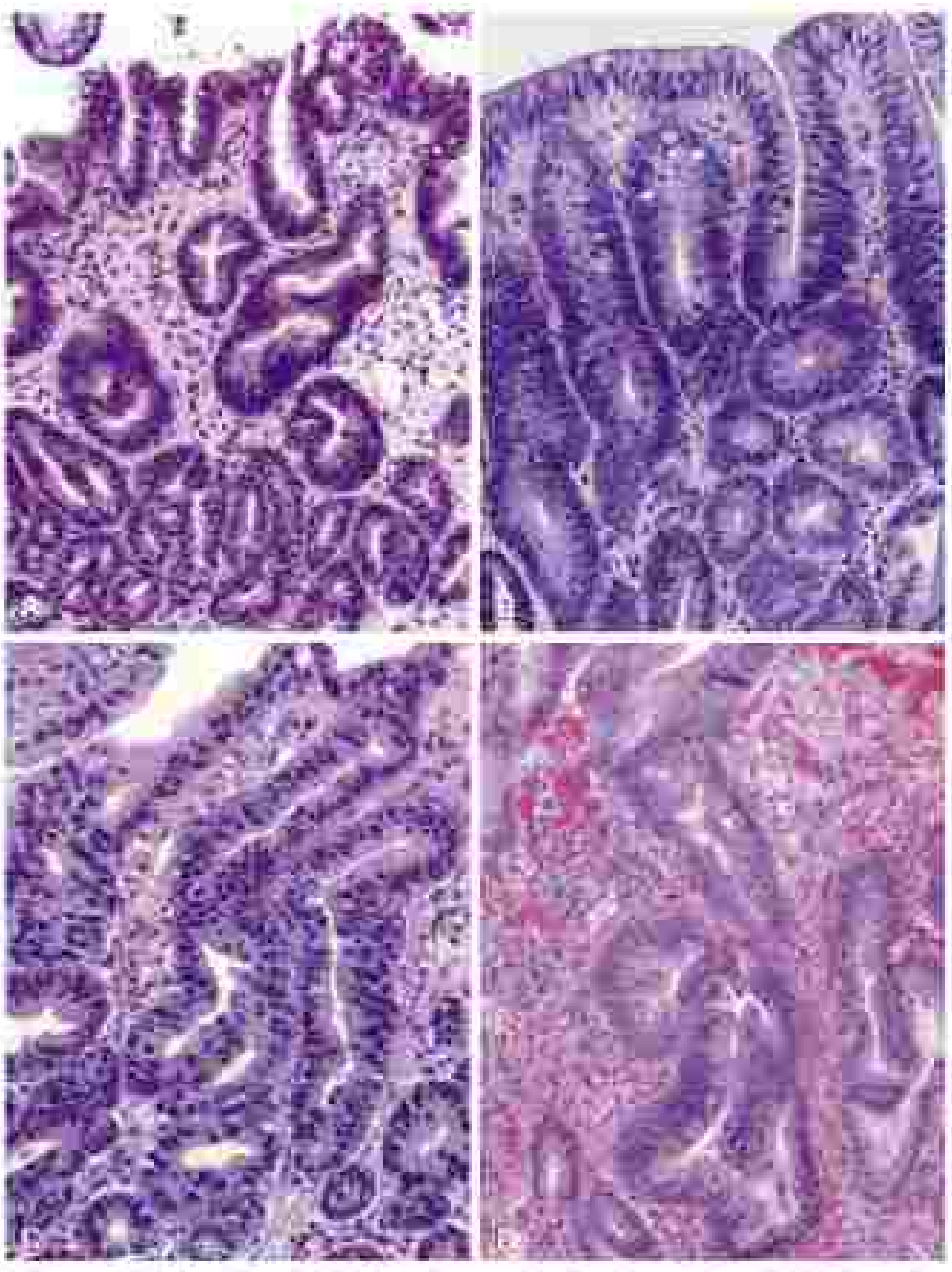

FIG. 1. Spectrum of dysplasia grading. (A) Negative for dysplasia. Although some nuclear hyperchromasia is present, it is limited to the normal proliferative zone with evidence of surface maturation. (B) Low-grade dysplasia shows basally oriented, hyperchromatic nuclei with pseudostratification. Crypt architecture is preserved. (C) High-grade dysplasia demonstrates prominent mitotic activity, enlarged nuclei, and loss of nuclear polarity with evidence of glandular crowding. (D) This lesion shows epithelial-lined papilla, reminiscent of that of low-grade dysplasia, in the deep glands. However, given the presence of surface maturation and the stromal changes suggestive of a reparative process, it is best classified as indefinite for dysplasia. *(From Hayes CJ, Travers CF, Mathews KS, Kaushik M, Aronis AG, Hagen JA, et al. Esophageal dysplasia: challenges. Semin Diagn Pathol. 2019;36(2):105–111.)*

endoscopic surveillance every 3 to 5 years, as described previously. In cases in which biopsies are inconclusive for dysplasia, patients should be placed on an acid suppression regimen for 3 to 6 months, after which repeat endoscopy should be performed. If the biopsies are still inconclusive at that time, repeat endoscopy should be performed 12 months later. If dysplasia is diagnosed (LGD or HGD), the biopsies should be reviewed by two separate pathologists, one of whom is an expert in gastrointestinal pathology because there is a high level of interobserver variability when it comes to dysplasia.

Once dysplasia is confirmed, the next steps depend on the degree of dysplasia. For LGD, endoscopic therapy is preferred for patients without significant comorbidity; however, repeat endoscopy at 12 months is acceptable in these cases. For HGD, endoscopic therapy is recommended except in the case of life limiting comorbid conditions. Patients with a diagnosed cancer should undergo further staging workup to determine if the cancer is resectable, and some early adenocarcinomas can be managed endoscopically. For certain young patients with long segment multifocal HGD, recurrent HGD, or

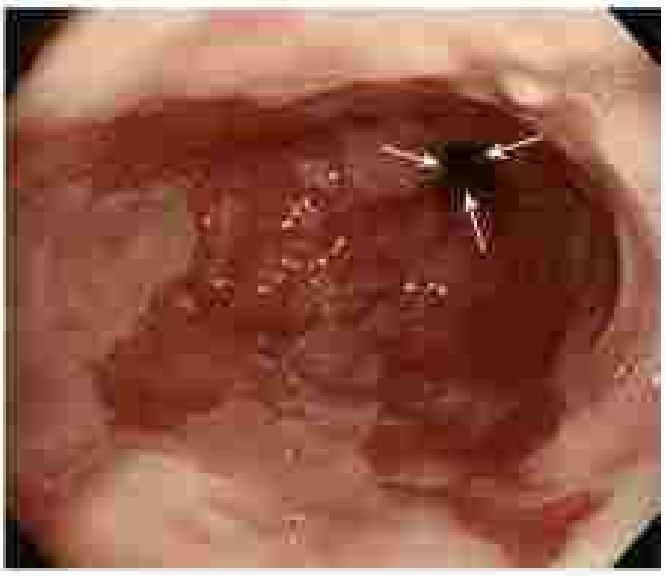

FIG. 3 Endoscopic image of Barrett's esophagus. The arrows mark the esophagogastric junction, which is identified endoscopically as the most proximal extent of the gastric folds. The mottled color and velvet-like texture of the Barrett's epithelium contrast sharply with the pale and glossy appearance of the esophageal squamous epithelium. Note that the Barrett's columnar epithelium extends well above the esophagogastric junction to the distal esophagus. (From Spechler SJ, Souza RF. Barrett's esophagus. In: Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Elsevier; 2016.)

intramucosal cancer, surgery should be considered. A summary of the surveillance and treatment algorithm is provided in Figs. 2 and 4.

PRINCIPLES OF ENDOSCOPIC THERAPIES

The current evidence supports that endoscopic therapy should be used for patients with BE who have LGD, HGD, and for some patients with early intramucosal (T1a) EAC because the risk of lymph node metastasis is unacceptable for LGD and HGD and is low for intramucosal EAC. Endoscopic techniques work by either removing or halting development of invasive disease or destroying abnormal tissue (ablative techniques). The intestinal metaplasia is then replaced with normal appearing squamous epithelium (Fig. 3).

ENDOSCOPIC RESECTION TECHNIQUES

Endoscopic Mucosal Resection

EMR is a technique that allows removal of lesion within segments of BE for complete histologic analysis, including dysplasia and superficial T1a adenocarcinoma. It offers an advantage over ablative techniques because it allows for examination of tissue specimens, rather than just destroying them. The AGC recommends EMR as the initial treatment modality for patients with nodular BE. For patients without high-risk features (submucosal invasion, poor differentiation, or lymphatic/vascular invasion), EMR has 98.8% eradication rate of BE; in patients with high-risk features, the rate is 85.6%. For T1a tumors, EMR has a 91% to 98% eradication rate.

There are several methods used for EMR. In the cap assisted method, the endoscope is fitted with a transparent cap. Once located, the target lesion is sucked into the cap and a specialized electrocautery snare is used to resect the lesion. A submucosal injection can be

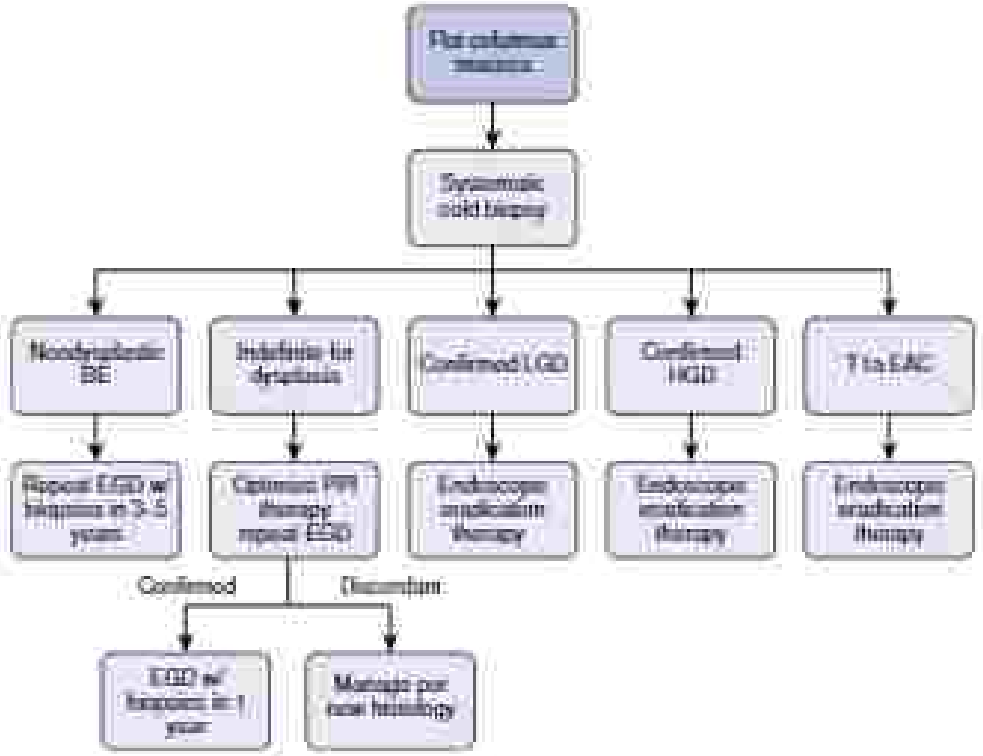

FIG. 2 Management of nonnodular Barrett's esophagus (BE). Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative. The algorithm assumes that the T1a esophageal adenocarcinoma (EAC) displays favorable characteristics for endoscopic therapy, including well-differentiated histology and lack of lymphovascular invasion. HGD, high-grade dysplasia; LGD, low-grade dysplasia; PPI, proton pump inhibitor. (From Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111(1):30-50.)

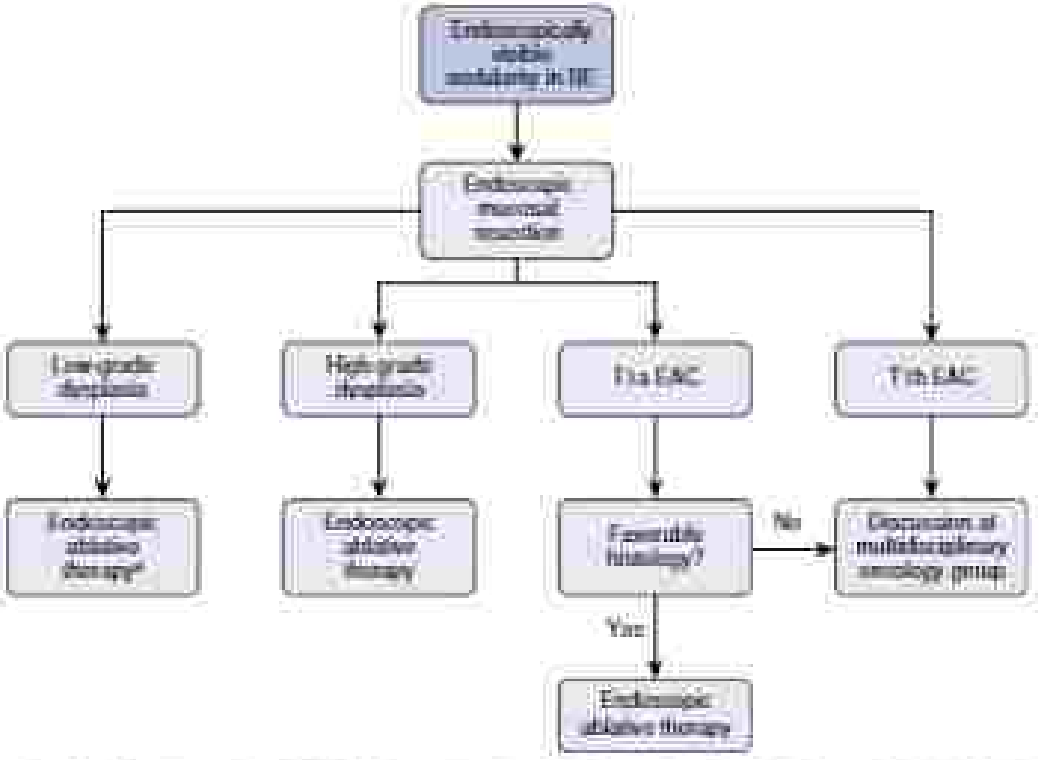

FIG. 4 Management of nodular Barrett's esophagus (BE). Note that aside from the clinical course of patients with low-grade dysplasia (LGD) managed by endoscopic surveillance following endoscopic mucosal resection (EMR), although this is an alternative treatment strategy. Endoscopic submucosal dissection is an alternative to EMR. Favorable histology consists of no lymphatic or vascular invasion and moderate to well-differentiated disease. EAC, esophageal adenocarcinoma. (From Wolfsen AJ, Gill GK, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111:30-51.)

performed to facilitate this. In the ligation-assisted method, lesions are resected using a band ligation device attached to the tip of the endoscope. Once identified, the target lesion is again sucked into the endoscope and the band is applied around the lesion to create a pseudopolyp. Electrocautery is then used to remove the pseudopolyp. In the injection-assisted technique, the submucosal space is injected to lift the lesion and allow it to be snared and cut.

One of the primary side effects of EMR is esophageal stricture, which occurs in up to 40% of patients. Typically, these lesions can be managed with endoscopic dilation or stents. EMR is often used in conjunction with radiofrequency ablation (RFA) with good effect. In a recent systematic review, EMR alone had a 33.3% risk of stricture, 7.5% risk of bleeding, and 1.3% risk of perforation compared with 10.2%, 1.1%, and 0.2%, respectively, in patients undergoing EMR in conjunction with RFA.

Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) is a technique that allows for complete, en bloc resection of suspicious lesions to allow for thorough histologic evaluation. When compared to EMR, it also allows for complete resection of lesions, rather than having to resect lesions in a piecemeal fashion, especially for larger lesions (>1.5–2 cm). The primary indication for ESD is resection of nodular lesions within a segment of BE to allow for complete histologic evaluation. Given the relative technical difficulty of this procedure, as well as the concern for significant adverse events, it is not as widely used. The ACG recommends that ESD only be performed in centers of clinical expertise.

The technique of ESD involves first marking the area of resection with coagulation. The submucosal space of the marked area is then injected with a saline solution to lift the area, and finally ESD resection knives are used to locate the muscularis and perform the submucosal dissection.

Most of the available data on ESD is from Europe or Asia, but a recent multicenter study performed in the United States showed that en bloc resection occurred in 95.2% of patients with a median resection size of 45 mm. Nearly half of patients required admission after the procedure, either for routine observation or for pain control. An R0 resection was achieved in 76.1%, and the overall cure rate was 69.6%. More than two-thirds of patients in this study were found to harbor EAC in the resected specimen, resulting in histologic upstaging in more than half of all patients. Adverse events occurred in 23.9% of patients, including bleeding (6.5%), perforation (2.2%), and esophageal stricture (15.2%). All adverse events were managed endoscopically.

These results were confirmed by a recent meta-analysis demonstrating that ESD has a 92.9% success rate of achieving en bloc resection, a 74.5% rate of achieving an R0 resection, and a 64.3% rate of achieving curative resection. Bleeding occurred in 1.8% of patients, and 1.5% of patients sustained esophageal perforation. Both the bleeding and perforation events were managed endoscopically. Overall esophageal stricture rate was 11.6%; these were managed with endoscopic dilation. The total rate of immediate and delayed adverse events was 4.9%.

ENDOSCOPIC ABLATION TECHNIQUE

Photodynamic Therapy

Photodynamic therapy (PDT) involves administration of a systemic photosensitizing agent that is taken up preferentially by neoplastic tissues. The photosensitizing agent then produces cytotoxicity after exposure to an appropriate wavelength and power of light, specific to the photosensitizing agent. The two most widely available photosensitizing agents are Photofrin and 5-aminolevulinic acid. Randomized trial data indicate that complete ablation of HGD can be achieved in 77% of patients with PDT, and 52% of patients had complete replacement of all BE tissue with normal squamous epithelium.

There is a relatively high complication rate associated with PDT. Because of its systemic administration, the photosensitizing agents can predispose to cutaneous photosensitivity similar to a sunburn to

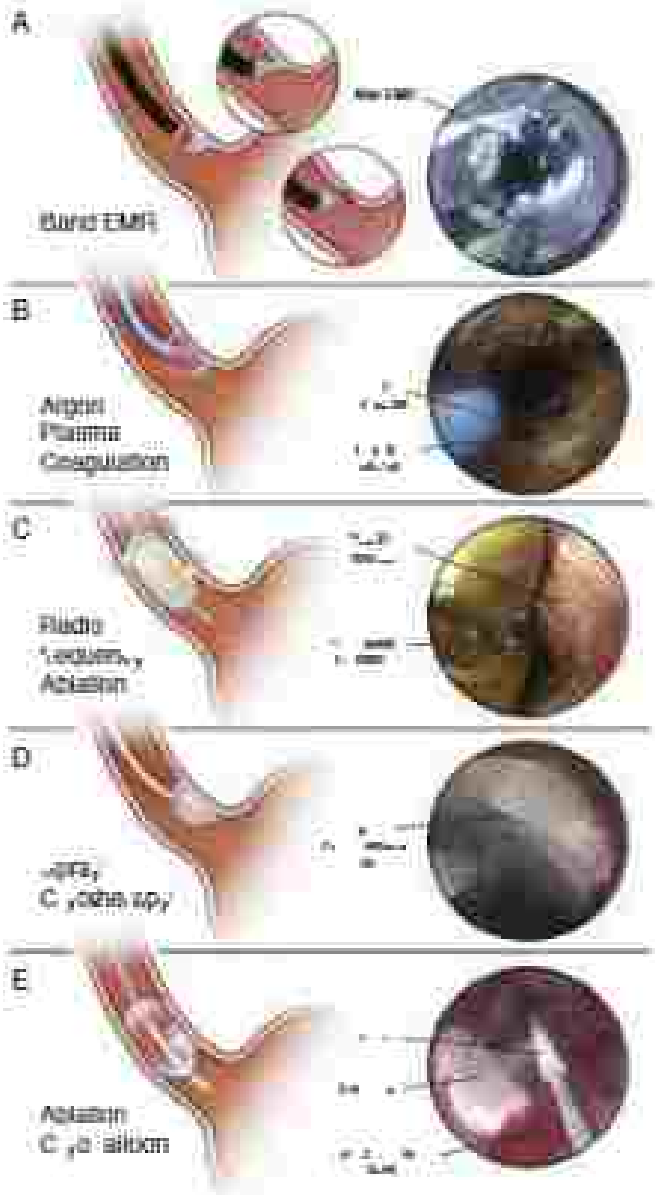

FIG. ... Endoscopic techniques for ablation of esophageal early neoplasia. (A) Band endoscopic mucosal resection involves suction and ligation (banding) of a target lesion, with or without prior submucosal injection, followed by resection using snare polypectomy technique. (B) Endoscopic photo shows the endoscopic view of the submucosa through the banding device after complete resection of well-differentiated adenocarcinoma. (B) Argon plasma coagulation (APC) involves conduction of heat energy with argon gas to the mucosa (arrow). Endoscopic image shows the APC catheter and white coagulation necrosis of treated BE mucosa (arrow). (C) Radiofrequency ablation (RFA) involves the application of a preset amount of heat energy (12 J) through electrodes on a circumferential (HALO 360) ablation catheter (arrow) inflated to make contact with the esophageal mucosa. Endoscopic image of post-RFA scarring. (D) Liquid nitrogen spray cryotherapy involves infusion of liquid nitrogen that expands to gas and freezes large areas of tissue to −196°C. The dosing of liquid nitrogen cryogen has varied from 15 to 30 seconds or less, followed by a thaw interval 4× seconds of thaw and repeated for three cycles. Endoscopic image of a nonconfluent island of ice on the esophageal mucosa. (E) The cryoballoon ablation system includes a portable handheld manual controller that delivers nitrous oxide gas into a low-pressure compliant, 30 mm, oval-shaped balloon at the end of a disposable balloon catheter passed through the endoscope channel. The balloon at the end of the catheter is inflated and simultaneously cooled by the gas expansion. The cryogen is directed toward a specific location by rotation of the diffuser. Endoscopic image shows the endoscopic view through the cryoballoon with a focal ice patch and thawed treated mucosa with post cryotherapy red color change (arrow). EMR, endoscopic mucosal resection. *(From di Pietro M, Canto MI, Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy. Gastroenterology. 2018;154(2):421–436.)*

more than two-thirds of patients. Other complications include odynophagia, constipation, vomiting, retrosternal chest pain, dehydration, dysphagia, and stricture formation (up to 36% in some studies). This was the first effective ablation technique, but because of the relatively high complication rate, PDT is no longer widely used.

Argon Plasma Coagulation

Argon plasma coagulation (APC) uses a beam of argon gas to conduct an electrical current, resulting in a noncontact form of thermal electrocoagulation. The depth of necrosis is relatively shallow (2–3 mm) and can be useful in conditions such as IM that involve the mucosa. In

the initial randomized controlled trial (RCT) conducted by Ackroyd et al., after a median of three treatments, patients treated with APC achieved complete macroscopic ablation 60% of the time, with the remaining patients achieving a significant decrease in the size of their BE. At the 1 year follow up, 50% of patients had no macroscopic evidence of disease compared with only 12% in the surveillance group. At 5 year follow up, 70% of patients in the APC group had sustained at least a 50% reduction in the surface area of BE, and 40% had no histologic or macroscopic disease compared with only 25% and 15%, respectively, in the surveillance group.

There were no early complications, and long term complications included strictures that were managed with endoscopic dilation. Other reported complications include chest pain, odynophagia, ulceration, bleeding, perforation, and death. One advantage of APC is that the equipment is widely available and is relatively inexpensive. However, as noted in the RCTs, it often requires multiple treatments over time to achieve regression of disease.

Cryotherapy

Cryotherapy directly destroys tissue by freezing it, resulting in both immediate and delayed tissue destruction. There are several cryotherapy systems available, but the most widely studied is liquid nitrogen. In a retrospective study of patients treated with liquid nitrogen, Shaheen et al. found that after an average of four treatments, 97% of patients had resolution of HGD, 87% had resolution of intestinal dysplasia, and 77% had resolution of intestinal metaplasia. There were no serious complications, but 9% of patients developed strictures that were managed with endoscopic dilation.

At the 5 year follow up, 93% of patients had complete resolution of high grade dysplasia, 88% had resolution of dysplasia, and 72% had resolution of intestinal metaplasia, although some of these patients underwent "touch up" therapy after the initial round of treatment. As with other endoscopic methods of treatment, ongoing endoscopic surveillance is required.

One advantage of cryotherapy is that it can be used both as a first-line treatment for BE with dysplasia, and as a second-line treatment in patients who have failed other treatments. As with other therapies, however, it often requires multiple treatments to completely eradicate disease. In a recent review of liquid nitrogen cryotherapy, the complication rate ranged from 0% to 3% with the most frequent complication being pain requiring narcotics (10% of patients), followed by stricture requiring dilation (up to 9%), then bleeding and perforation.

Radiofrequency Ablation

The most commonly used ablative technique is RFA. Using either a balloon catheter or a focal catheter, a generator and a bipolar electrode array deliver a fixed amount of thermal energy, resulting in a uniform burn to a depth of 0.5 mm. RFA can be performed in the outpatient setting and is targeted as either a circumferential ablation (using the balloon catheter) or a focal ablation (using the focal catheter). Circumferential ablation is for circumferential segments of BE that are longer than 2 cm, whereas focal ablation is for shorter segments, or islands, of BE. After treatment, follow up is recommended in approximately 2 months, and often multiple sessions of RFA are required to achieve complete eradication of dysplasia, with close follow up following eradication.

In an RCT comparing RFA with sham endoscopy, complete eradication of HGD occurred in 90.5% of patients and complete eradication of IMD occurred in 81% of patients following RFA, compared with only 22% and 19% in the sham group, respectively. Among all patients, RFA completely eradicated evidence of intestinal metaplasia in 77.4%, compared with only 2.3% in the control group. All three results were statistically significant. There is a known rate of progression to esophageal cancer, and in this study 19% of patients with HGD progressed to cancer over a 1 year timeframe. At 3 year follow up these results were found to be durable: complete eradication of dysplasia occurred in 90% of patients, and complete eradication of intestinal metaplasia occurred in 97% of patients; results were similar at 5 year follow up.

The primary side effects of RFA are chest pain and dysphagia lasting up to 8 days, and strictures occur in up to 8% of patients. Bleeding is rare. No deaths have been reported following RFA. RFA is the preferred therapy for nonnodular BE.

CONCLUSION

The management of BE continues to evolve as new technology and more effective treatments become available. Compared with esophagectomy, endoscopic techniques have the advantage of being less invasive with lower complications; however, in all cases, it is important to ensure that the correct technique is being used, which requires a baseline understanding of each technique. In general, patients with nodular disease should have this removed, and patients with early esophageal cancer should be referred for discussion at a multidisciplinary cancer group or tumor board to discuss alternative therapies to endoscopic ones.

Suggested Readings

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Peter S, Mwachumalla K. Ablative endoscopic therapies for Barrett's esophagus-related neoplasia. Gastroenterol Clin North Am. 2014;43:537–553.

Ming X, Abdelfatah MM, Othman MO. Endoscopic submucosal dissection and endoscopic mucosal resection for early stage esophageal cancer. Ann Cardiothorac Surg. 2017;6:20–30.

Wani Sumeet T, Pedersen J, Brown AM, et al. Incidence of advanced neoplasia among patients with Barrett's esophagus. N Engl J Med. 2018;378:2277–2287.

Management of Paraesophageal Hiatal Hernia

Francisco Schlottmann, MD, MPH, and Marco G. Patti, MD

Hiatal hernias result from a widening of the diaphragmatic esophageal hiatus and a weakening of the phrenoesophageal membrane. Consequently, the stomach and other intraabdominal organs may herniate through the diaphragmatic hiatus into the mediastinum. The incidence of these hernias in the general population is unclear because many patients are asymptomatic and how the hernia diagnosed incidentally in the context of chest or abdominal imaging for unrelated conditions. Other patients, however, present with a wide range of symptoms, and potentially lethal complications such as volvulus, strangulation, incarceration, and perforation.

Hiatal hernias are subclassified into four types:

- Type I: The esophagogastric junction (EGJ) herniates above the diaphragm into the mediastinum ("sliding hernia").
- Type II: A portion of the stomach is herniated into the mediastinum alongside a normally positioned (i.e., intraabdominal) EGJ.

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- Type II: A portion of the stomach is herniated into the mediastinum alongside a normally positioned (i.e., intraabdominal) EGJ.

- Type III. The GEJ is above the hiatus and a portion of the stomach is folded alongside the esophagus.
- Type IV. An intra-abdominal organ other than the stomach is additionally herniated through the hiatus.

Type I hernias are the most common form of hiatal hernia and account for up to 95% of the total prevalence. Type II, III, and IV hernias are together termed paraesophageal hernias (PEHs) and combined account for the remaining 5% of hiatal hernias.

SURGICAL INDICATION

Historically, surgical repair has been advocated in all patients with PEH, even when asymptomatic. In recent years, nonsurgical management has proven to be a better alternative to elective surgery in asymptomatic or minimally symptomatic patients; thus surgical treatment is now considered mainly for symptomatic PEH.

Associated symptoms can include heartburn, regurgitation, postprandial epigastric or chest pain, dysphagia, vomiting, weight loss, dyspnea, and anemia. Symptomatic patients without prohibitive operative risk should undergo laparoscopic repair.

PREOPERATIVE EVALUATION

In addition to a thorough history and physical evaluation, several tests are needed preoperatively to determine the anatomy and physiology of the esophagus and stomach.

Barium esophagram. This study is critical for the diagnosis of PEH and description of its anatomy. The ability to distinguish between different hernia types helps determine the complexity of the operation (Fig. 1).

Upper endoscopy. Endoscopy is important to rule out malignancy and determine the presence of esophagitis, Barrett's esophagus, gastritis, Cameron ulcers, and/or peptic ulcer disease.

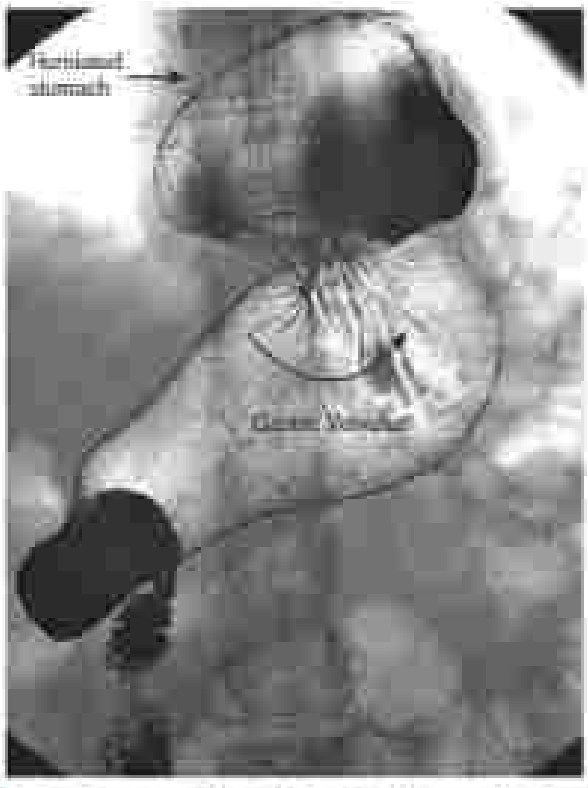

FIG. 1 Barium esophagram showing a large paraesophageal hernia with a gastric volvulus.

Abdominal and chest computed tomography scan. This test will add additional information if the presence of a type IV hernia is suspected (Fig. 2).

Esophageal manometry. Patients with PEH often have abnormal esophageal motility. In patients with complete upper third or severely impaired peristalsis, we tailor our operation and perform a partial fundoplication. If the manometry is technically unfeasible or the patient cannot tolerate the catheter, a partial fundoplication should also be performed.

Although patients with PEH may have pathologic reflux, obtaining a pH monitoring study does not add significant information preoperatively. The operation will alter the physiology of the GEJ and a fundoplication to prevent reflux will be performed regardless of the results of the study.

Cardiopulmonary risk assessment and related tests are performed on a case by case basis, particularly because these patients are often elderly.

SURGICAL TECHNIQUE

Traditionally, PEH repair required either a laparotomy or thoracotomy, which was accompanied by the morbidity associated with these approaches. Since its introduction, laparoscopic repair has been shown to be superior to other approaches in terms of improved postoperative outcomes; therefore, the vast majority of our patients are managed with a laparoscopic approach.

Positioning of the Patient

After induction of general endotracheal anesthesia, an orogastric tube is inserted to keep the stomach decompressed. The patient is positioned supine in low lithotomy position with the lower extremities extended on stirrups, with knees flexed 20 to 30 degrees. To avoid sliding because of the steep reverse Trendelenburg position used during the entire procedure, a bean bag is inflated to create a "saddle" under the perineum. Pneumatic compression stockings and subcutaneous heparin are always used as prophylaxis against deep vein thrombosis (particularly important as the increased abdominal pressure secondary to the pneumoperitoneum and the steep Trendelenburg position decrease venous return). The surgeon stands between the patient's legs, and the first and second assistants on the left and right side of the operating table, respectively.

Trocar Placement

Five 10-mm ports are used for the procedure: one for the camera, two for the operating surgeon, one for the assistant, and one for the liver retractor. The first port is usually placed in the midline about 14 cm below the xiphoid process; it can be also placed slightly to the left of the midline to be in line with the esophagus. This port is used for insertion of the scope. The second port is placed in the left midclavicular line at the same level of port 1 and is used for the insertion of a Babcock clamp for traction, a grasper to hold the Penrose drain while surrounding the esophagus, or for devices used to divide the short gastric vessels. The third port is placed in the right midclavicular line at the same level of the other two ports and is used for the liver retractor. The fourth and fifth ports are placed under the right and left costal margins so that their axes and the camera form an angle of about 120 degrees. These ports are used for the insertion of dissecting and suturing instruments (Fig. 3).

Troubleshooting

Extreme care must be taken when positioning the first port in the supraumbilical area because the site is just above the aorta and its bifurcation. We recommend using an optical trocar to obtain access after achieving a pneumoperitoneum of 15 mm Hg with a Veress needle. In addition, a common mistake is to place the trocars too low. This can make the operation more challenging (e.g., difficult to take down the proximal short gastric vessels and perform the mediastinal dissection).

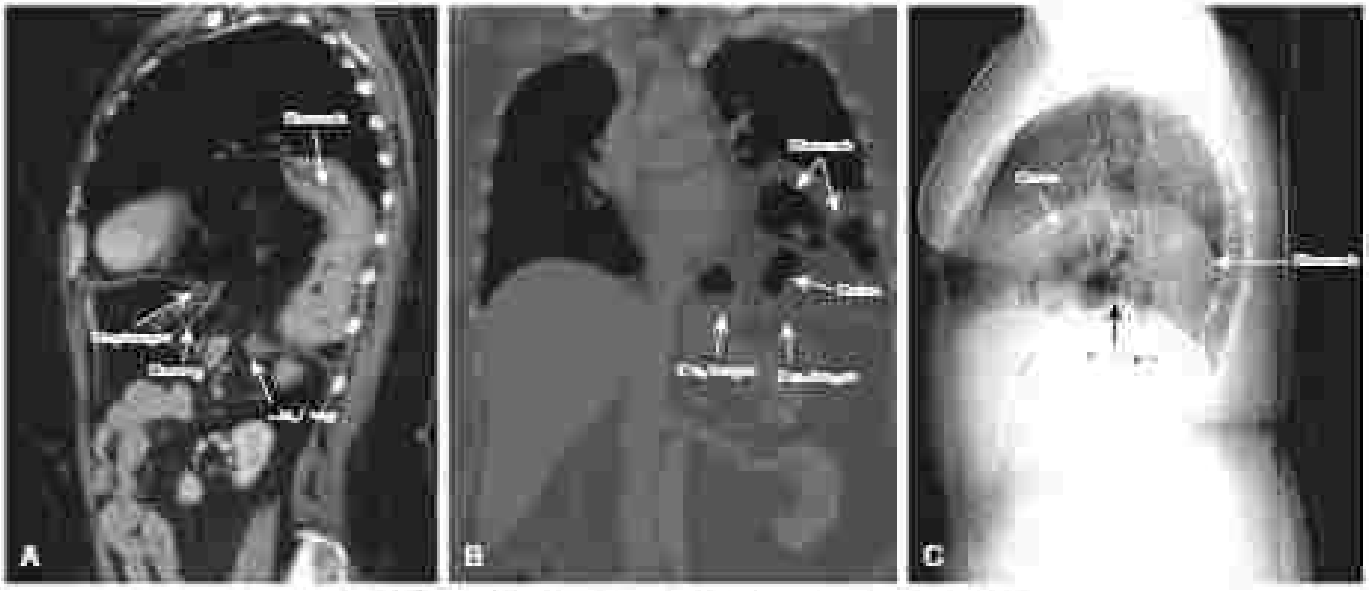

FIG. 2 Computed tomography scans showing a type IV paraesophageal hernia.

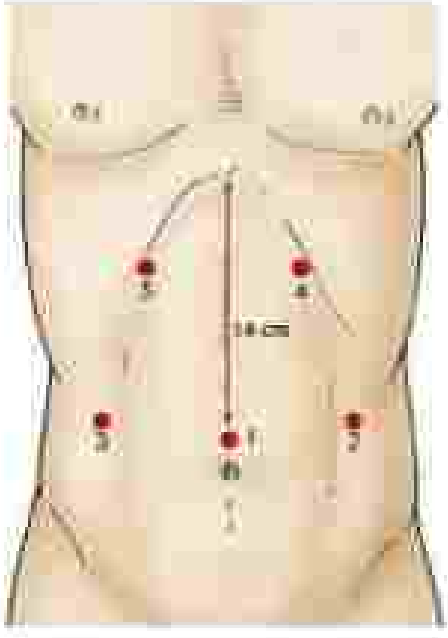

FIG. 3 Port placement for laparoscopic paraesophageal hernia repair. (From Patti MG, Feo CV, Arcerito M, Fisichella PM, Way LW. Laparoscopic paraesophageal hernia repair. J Am Coll Surg. 2000;191(3):331.)

Dissection and Reduction of Hernia Sac

After the initial abdominal exploration, an attempt is made to reduce the stomach. This is done by gently pulling the herniated stomach out of the posterior mediastinum down into the abdomen using a Babcock clamp. Excessive force should be avoided during this initial maneuver to prevent gastric injury or even perforation. The dissection is safely started along the greater curvature (left crus approach), the short gastric vessels are divided, and the left pillar of the crus is reached. Then, the hernia sac is incised at the junction with the left crus and an anterior and lateral mobilization of the esophagus is performed. Once the initial dissection from the left has been completed and more stomach is reduced, the gastrohepatic ligament is opened toward the right pillar of the crus and the esophagus is further dissected in the posterior mediastinum. A posterior window behind the esophagus is created and a Penrose drain is placed around the esophagus incorporating both the anterior and posterior vagus nerves. The hernia sac is then freed from mediastinal adhesions by blunt dissection. If the correct plane has been entered, the hernia sac should separate relatively easily, revealing the mediastinal pleura laterally, pericardium anteriorly, and aorta posteriorly. We do not routinely resect the entire sac, but rather transect it at the level of the esophageal hiatus to identify the esophagogastric junction.

Troubleshooting

Opposite to most of the surgical operations, in patients with PEH, we start along the greater curvature of the stomach by dividing the short gastric vessels. This approach reduces the risk of injury to a replaced or accessory left hepatic artery that can occur if the dissection is started over the gastrohepatic ligament. This resultant bleeding may be difficult to control if the proximal stump of the artery retracts above the diaphragm into the mediastinum. During blunt dissection of the hernia sac, tears in the pleura on either side can occur. The anesthesiologist should be informed, and in case of capnothorax that results in hypotension or increased airways pressure, the reduction in insufflation pressure usually corrects these abnormalities.

Esophageal mobilization and Lengthening

The mediastinal dissection is extended proximally to leave at least 3 cm of esophagus below the diaphragm. This limits the risk of recurrence and returns the EGJ to its most physiologic location. After extended mobilization of the esophagus in the posterior mediastinum, the presence of a short esophagus is rare. Therefore, esophageal lengthening procedures (e.g., stapled wedge gastroplasty) are seldom used.

Troubleshooting

While measuring the length of the esophagus below the diaphragm, it is critical to avoid caudal traction on the stomach because this can falsely lengthen the intraabdominal segment of the esophagus.

Closure of the Esophageal Hiatus

Retraction of the esophagus upward and toward the patient's left with the Penrose drain provides proper exposure. The closure of the

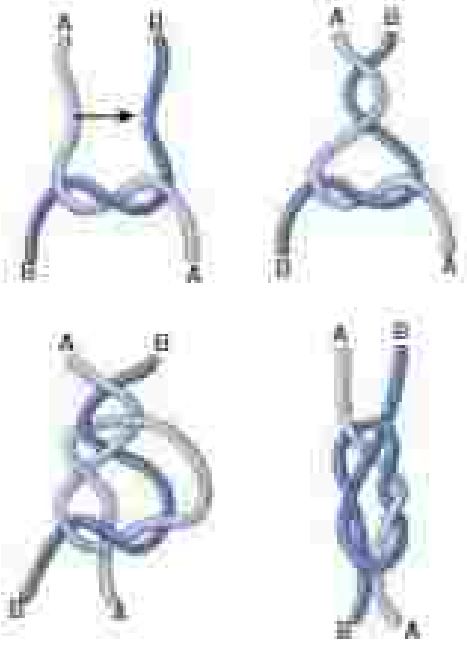

FIG. 4 Intracorporeal suture knot. (From Patti MG, Feo CV, Arcerito M, et al. Laparoscopic paraesophageal hernia repair. J Am Coll Surg. 2000;191(1):70–77.)

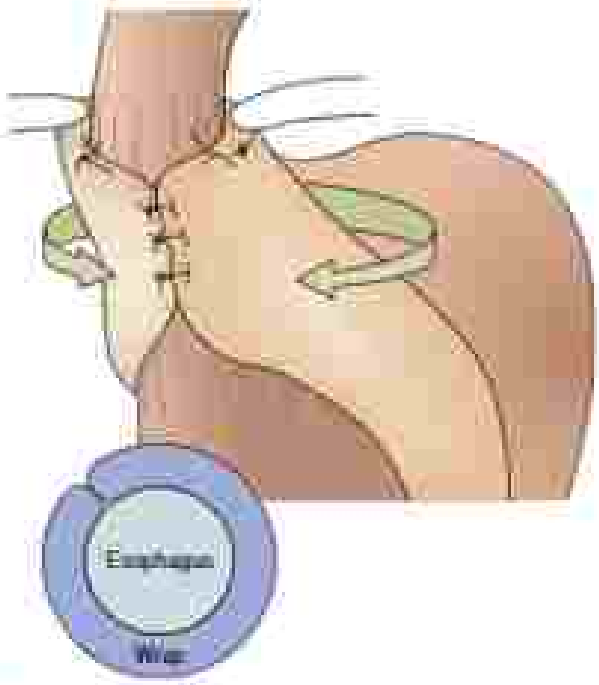

FIG. 5 Crural repair and total 360-degree fundoplication. (From Townsend CM, Beauchamp RD, Evers BM, et al. Sabiston Textbook of Surgery. 20th edition. Philadelphia: Elsevier; 2017.)

hiatus starts with the approximation of the right and left pillar of the crus behind the esophagus with interrupted nonabsorbable sutures. Because the hiatus is often very large, the closure of the crura can be under tension. The placement of the first stitch is critical because it decreases the tension and facilitates the placement of subsequent stitches. This first stitch is placed about 1 cm posterior to the esophagus and is secured with an extracorporeal jamming knot ("Capitan knot" in nautical terminology) to overcome tension (Fig. 4). Subsequent stitches are placed below the first one. Often only posterior sutures are necessary. Sometimes, however, one or two additional stitches anterior to the esophagus are needed to further narrow the hiatus. If there is considerable tension placed on the closure, a relaxing incision on the right hemidiaphragm (incision just lateral to the right crus) can help to approximate the right crus with the left one. If this is performed, a mesh patch over the resulting diaphragmatic defect is needed.

With the development and wide application of mesh placement for tension-free repair of inguinal and incisional hernias, many surgeons believed that the use of mesh for laparoscopic PHH repair would reduce recurrence rate. These beliefs were supported by two randomized trials that reported a significant reduction in recurrence rates by using synthetic mesh in hiatal hernia repairs. However, serious complications because of mesh erosion into the esophagus and even the aorta became a serious concern and brought the development of biological meshes with absorbable material. Interestingly, a randomized trial showed a significant reduction of the 6-month recurrence rate with the use of a biologic prosthesis as compared to cruroplasty alone (9% vs 24%). The same group, however, reported later a similar 5-year recurrence rate between the two groups (54% vs 50%). Based on the current evidence and our experience, the use of mesh is not routinely recommended and should be reserved for patients in whom a tension-free cruroplasty cannot be achieved.

Troubleshooting

Care must be taken with the inferior vena cava and aorta when placing the stitches. The crura should not be too tight, and a clear grasper should slide easily between the esophagus and the crura. The bougie should not be placed during this part of the procedure because it interferes with exposure and suturing.

Fundoplication

Once the hiatus is closed, the fundoplication is the last step of the procedure. The rationale for a fundoplication includes the following: (1) it increases the resting pressure of the lower esophageal sphincter, (2) it corrects gastroesophageal reflux, if present preoperatively, (3) it prevents the development of postoperative reflux secondary to the extensive dissection, and (4) it works as a gastropexy anchoring the stomach below the diaphragm.

The stomach is passed behind the esophagus and a three-dimensional maneuver is performed to verify sufficient fundic mobilization and to avoid having part of the gastric fundus above the wrap. For a total 360-degree fundoplication, a 56F bougie is inserted down the esophagus into the stomach to prevent postoperative dysphagia. The gastric fundus is then pulled under the esophagus with two graspers, and the left and right sides of the fundus are wrapped above the esophagogastric junction. A Babcock clamp is used to hold the two sides of the fundus during the placement of the first stitch. A 360-degree fundoplication is created by placing three stitches of nonabsorbable material at 1-cm intervals to approximate the right and left side of the fundoplication. The length of the anterior portion of the fundoplication should be approximately 2 cm (Fig. 5).

The partial posterior 240-degree fundoplication (Toupet fundoplication) is created by placing six stitches of nonabsorbable material. The right and left sides of the fundus are separately sutured to the right and left side of the esophagus, leaving 120 degrees of the anterior esophageal wall uncovered (Fig. 6).

Troubleshooting

The wrap should not be under tension. Essentially, if the wrap remains in the right side after pulling the fundus under the esophagus and does not retract back to the left, then it is floppy and suturing can be performed. If tension is still present after these maneuvers, a partial fundoplication is preferred.

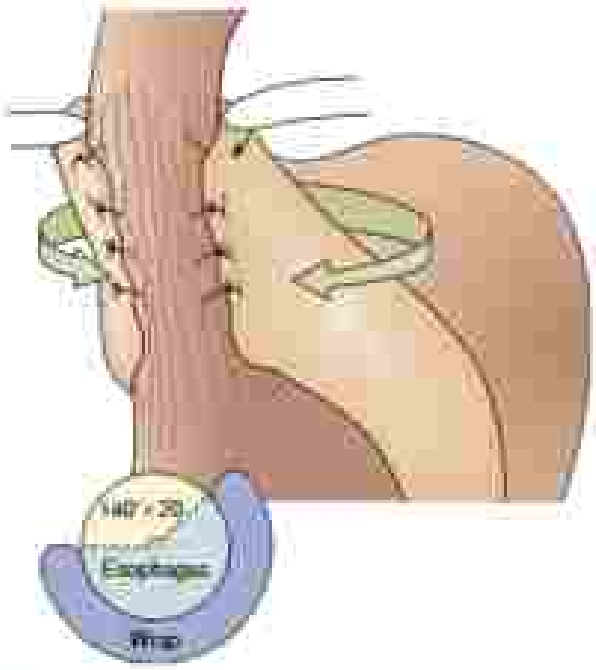

FIG. 6 Crural repair and partial posterior fundoplication. (From Townsend et al: Sabiston Textbook of Surgery, 20th edition. Philadelphia: Elsevier, 2017.)

POSTOPERATIVE CARE

Patients are typically extubated immediately after completion of the operation and the orogastric tube is pulled out. Patients are fed the morning after the procedure with clear liquids and then a soft diet. They are usually discharged after 24 to 48 hours and are instructed to avoid meat, bread, and carbonated beverages for the following 2 weeks. The time to full recovery ranges between 2 and 3 weeks.

OUTCOMES

The laparoscopic PEH repair has proven to be a durable repair with excellent long-term symptomatic relief. Although a high recurrence rate has been reported, in most cases it consists of small sliding hiatal hernias seen on follow-up radiographic imaging without any clinical significance.

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MANAGEMENT OF ZENKER'S DIVERTICULUM

Derek T. Moore, MD, John B. Romanelli, MD, FACS, and Katie S. Nason, MD, MPH

Zenker's diverticulum is a rare disorder that is the end result of chronically increased hypopharyngeal pressure, which creates a pulsion diverticulum by pushing the hypopharyngeal mucosa through Killian's triangle at the junction of the hypopharynx and the esophagus. Over time, the diverticulum enlarges and symptoms develop. Killian's triangle is an area of weakness between the thyropharyngeus muscles, which constrict the pharynx, and the cricopharyngeus, which acts as the upper esophageal sphincter. This impaired relaxation of the cricopharyngeus is opposed by the pulsion forces of the pharyngeal constrictors, thus creating Zenker's diverticulum. Occurring in approximately 2 of every 100,000 people, the pathology was first described by Abraham Ludlow in 1769, but is named after German pathologist Friedrich Albert von Zenker, who published a case series of 28 patients in 1877.

CLINICAL FEATURES

Zenker's diverticulum most commonly presents in patients in their seventh and eighth decades as dysphagia, but is also associated with regurgitation of undigested food, choking, cough, aspiration, halitosis, weight loss, and hoarseness. Etiology of these symptoms may stem either from incomplete relaxation of the upper esophageal sphincter or external esophageal compression by the diverticulum. Hematemesis, obstruction, or acute change in symptoms may signal malignancy in the diverticulum. Ulcers can also develop and may be a source of significant bleeding. In some patients, a neck mass may be palpable. In these patients, palpation of the mass may induce Boyce's sign, which is a rumbling or gurgling sense made by movement of gas and liquid (borborygmus) and may help to identify the swelling as a diverticulum rather than a cyst or other mass like structure.

The degree of dysphagia is typically quantified with a dysphagia scale such as the Dakkak and Bennett score (Table 1). This can be obtained in the preoperative setting and used to monitor symptoms for progression and postoperatively to determine degree of symptom relief. Initial symptom assessment should also include a comprehensive assessment of associated symptoms. As the diverticulum enlarges, dysphagia worsens. Weight loss and malnutrition are a common complaint, occurring in up to 20% of patients. Supplemental

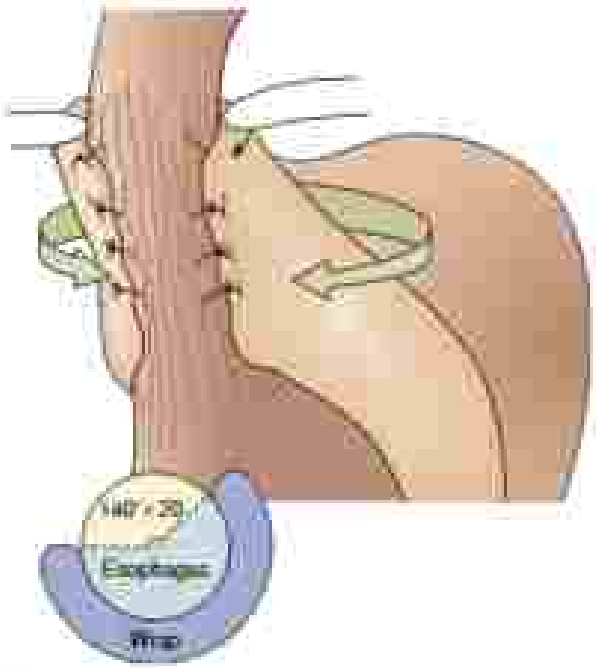

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TABLE 1 Dakkak and Bennett Score of Dysphagia

Grade 0	No dysphagia
Grade 1	Dysphagia to solids
Grade 2	Dysphagia to semisolids
Grade 3	Dysphagia to liquids
Grade 4	Aphagia

TABLE 2 Incidence of Symptoms in Patients with Zenker's Diverticulum

Symptom	Proportion Reporting Symptom
Dysphagia	80%-90%
Regurgitation	60%
Cough	30%-40%
Loud swallowing of liquids	30%
Hoarseness	20%
Loss of body weight	20%

Data from Peltier J, Koutsakis W. Zenker's (hypopharyngeal) diverticulum: surgical options. Curr Opin Otolaryngol Head Neck Surg 2013;21(5):484–90.

nutrition may be needed, including enteral feeding via a feeding tube in cases of severe malnutrition before operative intervention to prevent wound healing complications (Table 2).

DIAGNOSIS

Diagnosis of Zenker's diverticulum includes history and physical examination followed by radiographic assessment with either a contrast esophagram or computed tomography scan imaging of the neck. On contrast esophagram, Zenker's diverticulum is seen as an outpouching at the upper esophagus just proximal to the cricopharyngeus muscle (Fig. 1). In some cases, a cricopharyngeal bar or "stricture" may be noted. The esophagram allows the surgeon to note the presence of the diverticulum, measure size, and assess for mucosal lining abnormalities that may influence the choice of treatment. Computed tomography imaging will typically show a cystic mass adjacent to the hypopharynx with air and/or fluid. Subsequent evaluation with flexible endoscopy is often performed, but is not necessary if prior imaging shows a definitive diverticulum without mucosal abnormalities. There is some evidence that gastroesophageal reflux disease contributes to the development of hypertension of the upper esophageal sphincter in this population, so aggressive management of reflux with lifestyle modification and antireflux medications is warranted. Additional testing with manometry can provide useful information with regard to esophageal motility but must be approached cautiously because the catheter can perforate the diverticulum if the proceduralist is not aware of the patient's anatomy and attempts to force the catheter. Coiling of the catheter in the diverticulum is also a frequent problem.

SURGICAL TREATMENT

The options for surgical management currently include both transoral endoscopic and transcervical open approaches (Table 3). Regardless of the surgical approach, the primary tenet of repair is to relieve the area of high pressure created by impaired relaxation of the cricopharyngeus muscle by performing a complete cricopharyngeal myotomy.

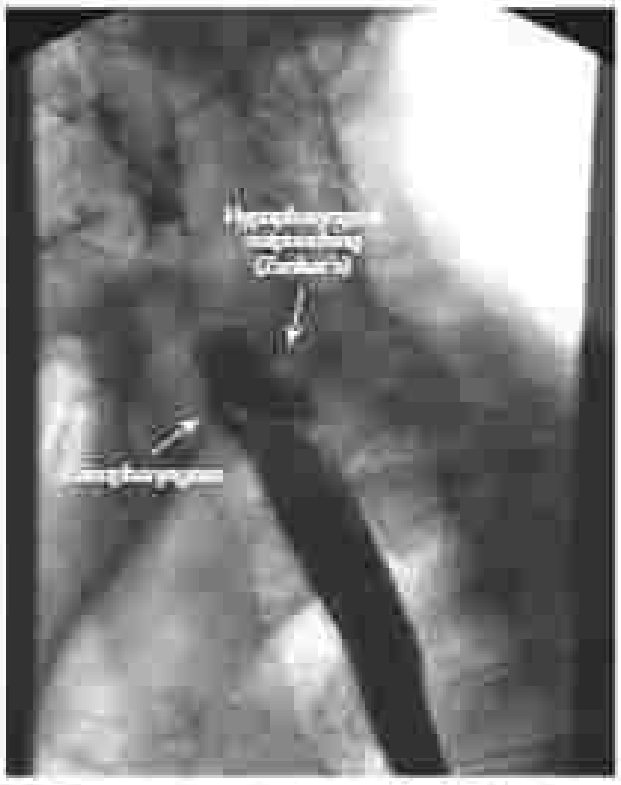

FIG. 1 Contrast esophagram showing outpouching of the hypopharynx just proximal to the cricopharyngeus muscle.

TABLE 3 Summary of Operative Techniques for Management of Zenker's Diverticulum

Technique	Description
Open diverticulectomy with myotomy	Excision of diverticulum with myotomy of the cricopharyngeus muscle
Open diverticulopexy with myotomy	Mobilization of the diverticulum with suture fixation above the neck of the diverticulum to the prevertebral fascia with myotomy of the cricopharyngeus muscle
Open myotomy alone	Myotomy of the cricopharyngeus muscle
Endoscopic diverticulotomy (rigid or flexible)	Transoral endoscopic division of cricopharyngeus muscle and the septum between the diverticulum and esophagus using electrocautery, laser, or stapler

failure to address this obstruction distal to the diverticulum will result in incomplete relief of symptoms and increase the likelihood of complications, such as a leak, at the site of the repair.

OPEN TRANSCERVICAL SURGICAL TREATMENT

Open surgical therapy was first performed by Wheeler in 1886, and was long considered the gold standard for treatment of Zenker's diverticulum. There are many approaches to open surgery that have

been developed over time, with the most common approach via a left cervical incision. Dissection is performed through the platysma down to the medial border of the sternocleidomastoid and carotid sheath. These are retracted laterally to expose the esophagus and diverticulum. A left-sided incision is always used, regardless of the location of the diverticulum because the cervical esophagus is positioned slightly off midline toward the left, behind the trachea at this level. Once the base of the diverticulum is exposed, the cricopharyngeus is divided completely, taking care to address all muscle fibers and to expose the underlying esophageal mucosa. Once all fibers have been divided for a complete myotomy, the diverticulum is either resected or undergoes diverticulopexy, depending on the anatomy and safety. Diverticulectomy is performed using a stapler across the base of the diverticulum, which is exposed by carefully separating the mucosa from the surrounding musculature. In some cases, the diverticulum can be sharply dissected and oversewn, but this is less commonly done. Other surgical options include performing a diverticulopexy by suturing the apex of the diverticulum to the prevertebral fascia to a nondependent location or invaginating the diverticulum and oversewing the neck to prevent recurrence. The advantage of performing a diverticulectomy is elimination of the small risk of diverticular carcinoma and complete elimination of the pouch, where food and liquid might otherwise be retained. The advantage of diverticulopexy and invagination is the decreased risk of a postoperative leak as neither approach violates the hypopharyngeal mucosa. Open surgical treatment of Zenker's diverticulum has become significantly less common but may still be indicated in extremely large or small diverticula because they present the most challenges to endoscopic treatment.

ENDOSCOPIC TREATMENT

Endoscopic treatment for Zenker's diverticulum has become the most common approach to surgical therapy over the past decade, with equivalent success rates and less invasive technique. Endoscopic approaches include rigid endoscopy and flexible endoscopy.

Rigid Endoscopic Treatment

First described in 1917 by Mosher, followed by the introduction of the rigid endoscope, stapler and Weerda diverticulascope (Fig. 2), rigid endoscopic stapled diverticulotomy became the minimally invasive standard of care in treatment of Zenker's diverticulum. The endoscopic approach offers comparable success rates while reducing postoperative pain and length of hospitalization. This approach capitalizes on the dependent positioning of most diverticula, which track along the esophagus and thus have a shared septum. The septum includes the esophageal mucosa and the underlying cricopharyngeus muscle and the dependent wall of the diverticulum externally. After induction of general anesthesia, the patient must be positioned with the neck fully extended. The Weerda diverticulascope is then inserted with one blade on each side the diverticular septum. Many surgeons use a laparoscopic or endoscopic suturing device to place a stay suture at the apex of the septum to provide traction (Fig. 3). An endoscopic stapler is modified by shaving off the nail of the anvil to allow the full length of the cutting portion of the stapler to be used in dividing the septum. The endoscopic stapler is then inserted with the jaws across the septum. The cartridge is placed in the esophagus, and the anvil is placed in the diverticulum. The stapler is then fired, which both divides the septum (including the cricopharyngeus muscle) and staples the cut edges.

Results with this procedure have been excellent. A recent systematic review by Yuan and colleagues included 1900 patients from 44 studies undergoing rigid endoscopy with stapling for management of Zenker's diverticulum. The overall complication rate was 7.1%, with a mortality rate of 0.3%. The most common complications included dental injuries (2%), esophageal mucosal damage (1.6%), and perforations (1.6%). Complications were increased in patients with larger diverticula requiring multiple staple loads. A limitation to the rigid endoscopic approach is a relatively high rate of abandonment, typically because of small diverticula. This was reported as 7.2% in one series (Leong et al.). Historically, diverticula smaller than 2 to 3 cm have not been amenable to stapling, but the use of the stay suture facilitates anchoring of the stapler to the diverticular pouch, although care must be taken not to perforate the diverticulum.

Alternatives to stapling of the septum include division with cautery using monopolar (as described by Dohlman et al.) or bipolar energy devices, as well as carbon dioxide laser. The risk of this method is potential failure of coagulation of the mucosal edges, but these may be approximated with clips. Systematic reviews of the publications reporting outcomes using the Dohlman technique show an overall complication rate of 7.8%, with a 0.2% mortality rate. Review of the carbon dioxide laser technique demonstrated an overall complication rate of 9.3%, with an identical mortality rate of 0.2% by comparison.

Flexible Endoscopic Treatment

Flexible endoscopic therapy for Zenker's diverticulum, first introduced in 1995, has become increasingly common over the past decade. Similar to the rigid endoscopic approach, the procedure is a diverticulotomy and not a diverticulectomy. It offers the significant advantage of not requiring neck extension, which is helpful for elderly patients in whom extension can be limited. Further, it can be performed under conscious sedation, so it is especially useful for patients who have significant surgical comorbidities limiting general

FIG. 2 Weerda diverticulascope.

FIG. 3 Endoscopic stay suture on the diverticular septum.

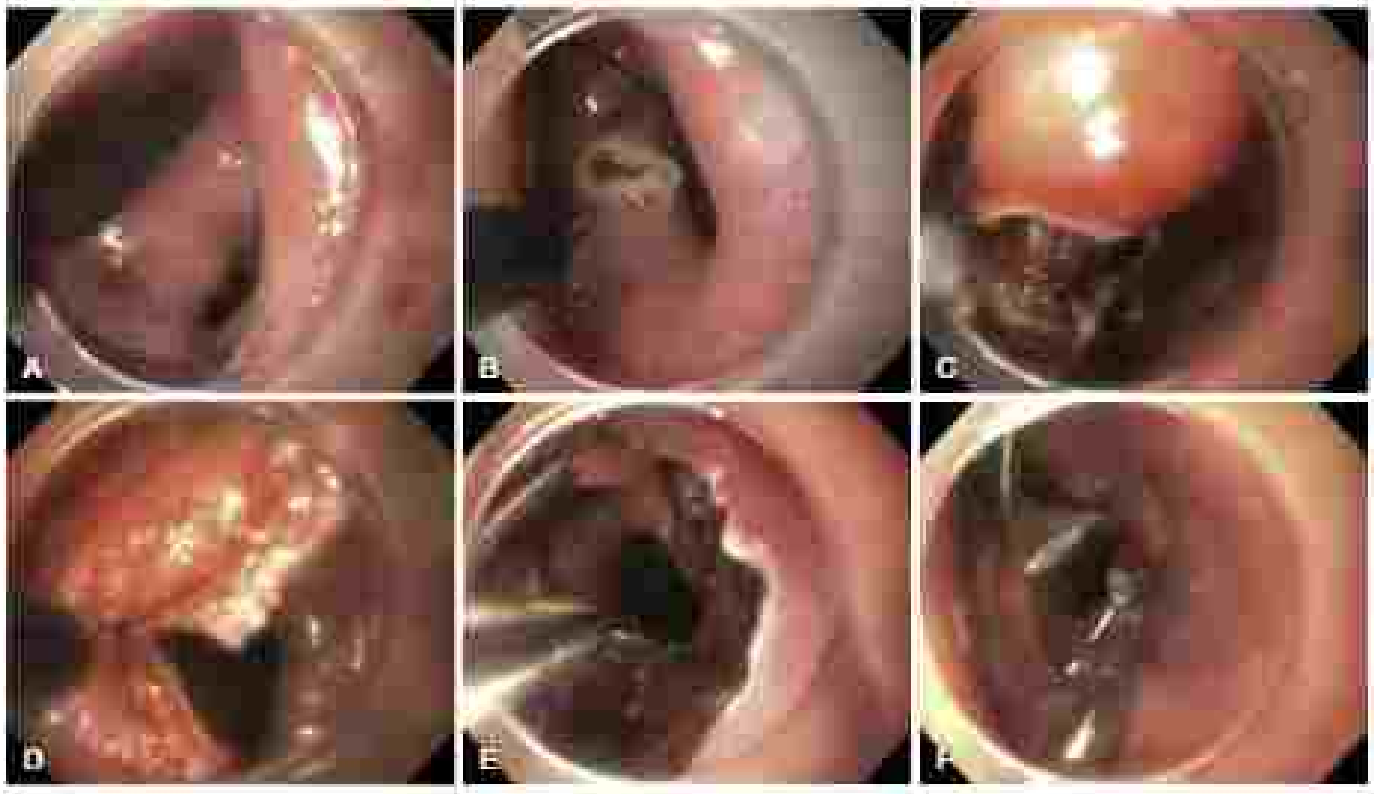

FIG. 4 Flexible endoscopic diverticulotomy with visualization of (A) the septum, (B) incision of the mucosa, (C) exposure of the cricopharyngeal muscle, (D) incision of the muscle, (E) closure of the mucosa and (F) final result after closure.

anesthesia. Although some authors describe the use of a rigid diverticuloscope, a simple endoscopic cap can also be used to open the esophageal and diverticular lumens to expose the diverticular septum. Often, a nasogastric tube or a guidewire is placed in the true esophageal lumen to help differentiate it from the false lumen (the diverticulum).

A major advantage to the flexible endoscopic technique is that it allows direct visualization of the cricopharyngeal muscle. One possible reason for recurrences or failure with a stapled or laser technique is that it can be difficult to ascertain if the muscle is completely divided. In the flexible endoscopic approach, the mucosa is opened first, exposing the muscle (Fig. 4A, C). The muscle is then completely divided until no further muscle fibers are visible without tunneling into the esophageal wall (Fig. 4D). With advancements in technology, multiple tools can then be used through or alongside of the flexible endoscope to incise the diverticular septum, such as hook knife cautery endoscopic shears, argon plasma coagulation, needle knife cautery, sling bridle knife, the dutch cutter knife, carbon dioxide laser, and the thulium laser. At the conclusion of the mucosal and muscular diversion, endoscopic clips are deployed to close the mucosa (Fig. 4E, F).

Across multiple studies, this approach has shown to be an effective and less invasive modality of treatment. Two recent review articles aggregated the results of multiple published series with both prospective and retrospective trials from around the globe. Composite clinical success rate (defined as complete resolution or significant improvement in symptoms) was 87.9% (Jain et al.) in one study and 91% (Ishaq et al.) in another. Of patients who failed initial treatment and elected for repeat flexible endoscopic therapy, 91.2% had subsequent clinical success. Outcomes were not stratified by diverticular size in all but one study. One prospective cohort study did find that diverticula larger than 50 mm led to increased clinical failure rates. Complication rates for the flexible endoscopic approach are low; in one series, there were reported rates of cervical emphysema (6.7%), perforation (1.8%), and bleeding (3.1%) (Yuan et al.).

CONCLUSION

The treatment of Zenker's diverticulum has undergone a true paradigm shift from dominance of open surgery to transoral endoscopic techniques as they have become more universally accepted as safe and effective. Meta-analysis by Albers and colleagues showed significant decrease in length of procedure and hospital stay and lower complication rates after endoscopic treatment, whereas open surgical therapy resulted in lower recurrence rates.

Endoscopic treatment itself has evolved significantly, with flexible endoscopy becoming significantly more prevalent in the past decade. Investigation is still under way comparing rigid with flexible techniques because there are no definitive randomized trials distinguishing superiority of one technique. Each modality is operator dependent, and outcomes are very likely to be related to the comfort of the surgeon using either the Weerda scope or flexible endoscope.

As technology continues to advance, the treatment of Zenker's will almost certainly continue to evolve. The variety of tools already available allows us to tailor our treatment to individual patients and diverticula, and as surgeons it is important for us to be facile with multiple modes of therapy to properly treat Zenker's in its different iterations.

SUGGESTED READINGS

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Achalasia of the Esophagus

Eric W. Etzkill, MD, MPH, and Stephen C. Yang, MD

Achalasia, defined as the failure or incomplete relaxation of the lower esophageal sphincter (LES) with accompanying esophageal body aperistalsis in the absence of mechanical obstruction, is the most common type of esophageal motility disorder. It has an incidence of 1 to 100,000 people, with a prevalence of 10 to 100,000. There is no difference in gender prevalence between the ages of 30 and 60 years. The primary cause of achalasia remains undetermined, but it is believed to arise from degeneration of inhibitory ganglion cells in the myenteric plexus of the LES and esophageal body. Factors associated with an increased risk of achalasia include viral neurodegenerative disorders, Chagas syndrome, type 1 diabetes mellitus, hypothyroidism, and autoimmune conditions such as Sjögren's syndrome, systemic lupus erythematosus, and uveitis. Familial cases are rare.

A diagnosis of achalasia should be suspected in patients with dysphagia to both solids and liquids that does not resolve despite the use of proton pump inhibitors. If left untreated, achalasia is a progressive disease that may advance to megaesophagus and is associated with an increased risk of esophageal squamous cell carcinoma.

Although no standardized criteria exist to determine severity of disease, the diameter and configuration of the esophagus within the thoracic cavity are generally considered the two primary factors. The Eckardt scale (Table 1) is one scale frequently used to assess disease severity and efficacy to therapy. Clinical stages of 0 to 4 are assigned based on the sum of the symptom scores, corresponding to 0 to 1, 2 to 3, 4 to 6, and more than 6, respectively. Stages 0 and 1 are associated with remission of the disease, whereas stages II and III represent treatment failure. Qualitatively, severe achalasia is defined as an esophageal diameter greater than 6 cm, and stage achalasia includes the distal angulation, a sigmoid or tortuous esophagus greater than 6 cm diameter, or megaesophagus greater than 10 cm in diameter. Roughly 2% to 15% of people with achalasia progress to end stage achalasia, are generally resistant to initial endoscopic and surgical treatments and ultimately require an esophagectomy.

DIAGNOSIS

More than 90% of patients with achalasia first present with dysphagia to both solids and liquids as the primary symptom. The majority also present with regurgitation of undigested food, which occurs most frequently while recumbent at night. They also may have additional symptoms of gastroesophageal reflux, chest pain, epigastric pain, weight loss, cough, hoarseness, wheezing, and a sore throat. This may result in a misdiagnosis of gastroesophageal reflux disease (GERD) and delay appropriate diagnosis and treatment. Additional disorders in the differential diagnosis include esophageal rings, webs, or strictures, peptic ulcer strictures, esophagitis, other esophageal motility disorders, prior fundoplication or bariatric surgery, malignancy causing intrinsic obstruction or extrinsic compression, paraesophageal achalasia, and systemic disorders, including sarcoidosis and amyloidosis. Aside from possible weight loss, there are generally no physical examination findings associated with achalasia.

TABLE 1 Eckardt Clinical Scoring System for Achalasia

	Symptom			
Score	Weight Loss (kg)	Dysphagia	Retrosternal Pain	Regurgitation
0	None	None	None	None
1	≤5	Occasional	Occasional	Occasional
2	5-10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

Final score is the sum of all four components, range 0–12.

Esophageal Function Tests

The diagnosis of esophageal achalasia is established with a combination of esophageal function tests. Initially barium esophagography (preferably with a video component), esophagogastroduodenoscopy (EGD), or both are required to exclude extrinsic or intrinsic mechanical obstruction due to malignancy. If the patient's clinical history or EGD findings raise suspicion for malignancy an endoscopic ultrasound (EUS) should be performed. Esophageal manometry followed by 24-hour pH monitoring are used to confirm the suspicion.

Barium Esophagogram

After initial screening test for dysphagia, patients should undergo radiographic evaluation with a barium esophagogram to evaluate esophageal emptying and assess gastroesophageal junction morphology. A video or cine technique may allow real-time assessment of motility disorders and assess esophageal emptying. Although this modality helps to confirm the diagnosis of achalasia, it is not sensitive enough to diagnose it alone. Classically the "bird beak" appearance with tapering at the GEJ is found. Additional findings include an epiphrenic diverticulum, sigmoidal esophageal dilation, retained food products, delayed emptying, and a decrease or absence of gastric air bubbles. These findings can assist in ruling out other esophageal disorders with similar presentations to achalasia, including pseudoachalasia due to malignant obstruction or infiltration. In addition to diagnosis, esophagrams are also used to assess esophageal emptying after any intervention.

Esophagogastroduodenoscopy

EGD allows for direct visualization, excluding mechanical obstruction, confirming other structural abnormalities such as diverticula, and ascertaining tissue biopsies. Although nearly one half of all patients with achalasia will have a normal EGD, findings consistent with achalasia include retained saliva or food products in the absence of mechanical obstruction, a hirsutism or dilated esophagus, inflamed mucosa, a thickened LES with a tapered configuration, a thickened GEJ, and exaggerated abnormal contractions. Although EGD findings alone are not sufficient for the diagnosis of achalasia, they are used to support its diagnosis.

Esophageal Manometry

Esophageal manometry remains the gold standard for diagnosing achalasia, irrespective of findings from other modalities. The classic findings diagnostic of achalasia include aperistalsis and a failure of LES relaxation with swallowing.

Once mechanical obstruction is excluded, patients should undergo esophageal manometry, preferably using a high-resolution system because it can simultaneously assess upper and lower esophageal sphincters and the entire length of the esophagus, compared to 5-cm intervals with traditional manometry. The functional assessment allows for the classification of achalasia into one of three types based on esophageal pressure topography (Fig. 1).

During manometry a pressure-sensing device placed through the nose down the esophagus and into the stomach is used to measure pressure throughout the esophagus and the LES, thereby studying

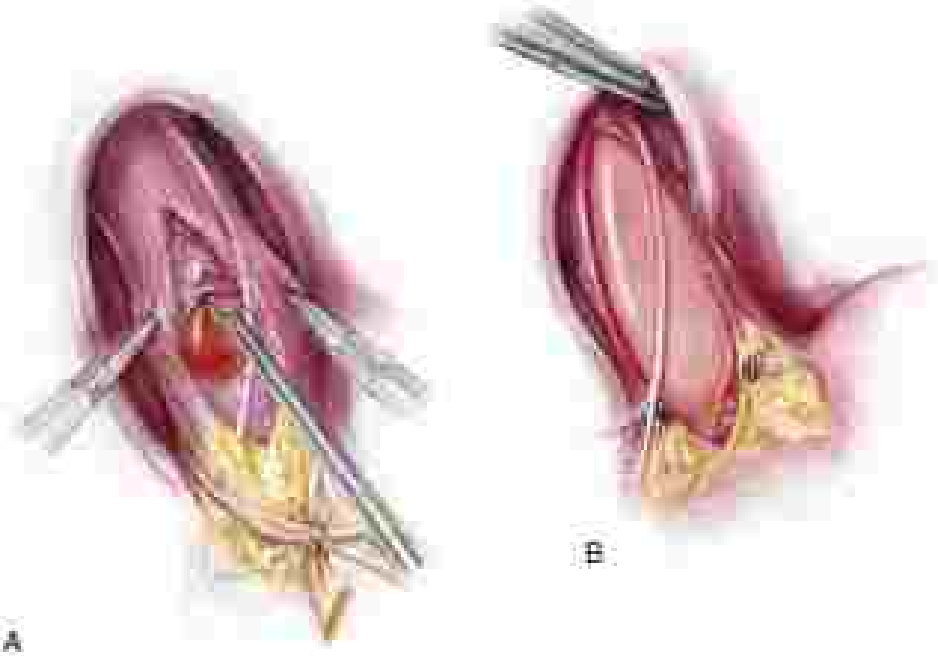


FIG. 1 Laparoscopic Heller myotomy. (A) Elevation and division of the submucosal esophagus plane. (B) Muscle fibers are separated from underlying mucosa until at least 50% of the mucosal circumference is exposed. (*Courtesy Cleveland Clinic Foundation Staff Members: From Cameron JL, Sandborn C. Atlas of Gastrointestinal Surgery, vol. 1. 2nd ed. Hamilton, ON: BC Decker Inc; 2007.*)

esophageal contractile strength and coordination. A diagnosis of achalasia is confirmed by the required combination of incomplete LES relaxation and aperistalsis in the absence of mechanical obstruction on high-resolution manometry. With conventional manometry, failure of LES relaxation is defined as a mean fall in resting pressure to a nadir greater than 8 mm Hg above gastric pressure. Aperistalsis is defined by an absence of contraction or the presence of simultaneous contractions with amplitudes less than 40 mm Hg in the distal two-thirds of the esophagus. With high-resolution manometry, impaired LES relaxation is defined by a mean 4-second integrated resting pressure (IRP) 15 mm Hg or more over ten swallows. Aperistalsis is characterized by lack of contractions or pressurization throughout the esophagus. Additional findings that support the diagnosis of achalasia but are not required include increased baseline LES pressure greater than 45 mm Hg, increased esophageal body baseline pressure, simultaneous nonperistaltic contractions, and a complete LES relaxation to gastric baseline of less than 4 seconds' duration.

Endoscopic Ultrasound

Endoscopic Ultrasound (EUS) is used to exclude pseudoachalasia, due to an extraluminal or infiltrating mass in patients with a strong suspicion for malignancy. Clinical factors that raise suspicion for malignancy include increased age, unexplained weight loss, and aggressive symptom onset. Endoscopic findings supporting malignancy include extrinsic compression, more severe outflow obstruction with increased GEJ resistance compared to that observed with achalasia, and mucosal ulceration. Fine needle aspiration can be performed with EUS to support the diagnosis of achalasia, which would include thickened inner circular muscular layer of the LES.

CLASSIFICATION

The use of high-resolution manometry has allowed for a greater understanding of and more focused treatments for achalasia. There are three primary types of achalasia based on high-resolution manometric findings, according to the Chicago Classification of Esophageal Motility Disorders v3.0. All three types have in common impaired LES relaxation, quantified by an IRP greater than 15 mm Hg, as well as aperistalsis. Definitions and criteria are listed in Table 2.

Vigorous Achalasia

Vigorous achalasia is a subtype of achalasia with clinical and manometric features of both achalasia and diffuse esophageal spasm. Its diagnosis is confirmed with manometry, which demonstrates simultaneous, repetitive, distalize high amplitude contractions or premature peristalsis with contractions greater than 40 mm Hg in the absence of coordinated LES relaxation, in contrast to low amplitude contractions seen with classic achalasia.

TREATMENT

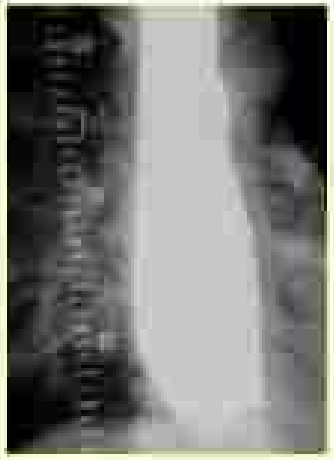
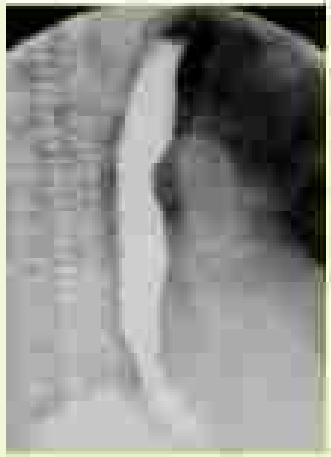
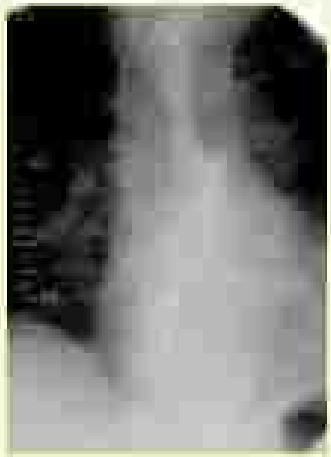
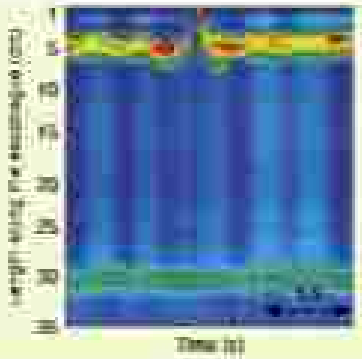
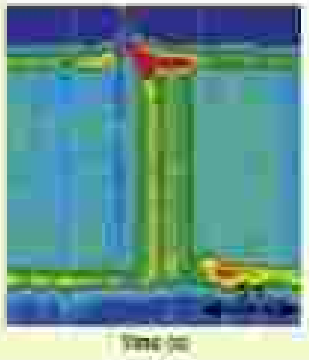
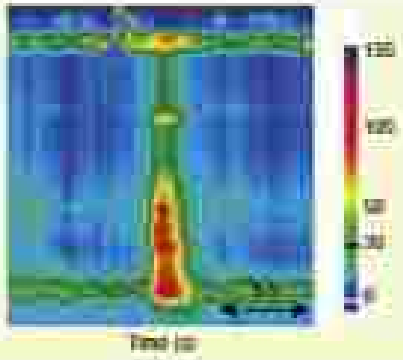
Achalasia is a chronic, incurable, progressive disease. As such, treatment is aimed at reducing the hypertonicity of the LES and improving or resolving symptoms by improving esophageal emptying and preventing further dilation. Treatment for esophageal achalasia can be categorized into pharmacologic, surgical, and endoscopic procedures, which are all intended to reduce the tone of the LES. Although most patients experience improvement in swallowing and other symptoms after treatment, peristalsis remains abnormal, and esophageal function never fully recovers. Risks associated with treatment include the progression to sigmoesophagus or end-stage achalasia, as well as esophageal squamous cell carcinoma.

Initial surgical and endoscopic treatments for achalasia in patients deemed good surgical candidates include pneumatic dilation, laparoscopic myotomy, and peroral endoscopic myotomy (POEM). Each of these methods has been shown to be equally effective, and choice of treatment often is based on type of achalasia, patient preference, and physician or institutional expertise.

Pneumatic Dilation

For patients who do not wish to undergo surgery or in whom initial surgical management has failed, pneumatic dilation (PD) is an effective first-line nonsurgical therapy. The risk of perforation is lower than

TABLE 2 Summary of Chicago Classification of Motility Disorders v3.0: Characteristics and Treatment Options for Achalasia

	Type 1: Classic Achalasia (10% of Patients)	Type 2: Achalasia With Pressurization (~15% of Patients)	Type 3: Spastic Achalasia (10% of Patients)
Barium swallow			
Manometry findings	High IRP Absent peristalsis Absent contractile activity	Normal IRP Simultaneous, normal-amplitude pressurization Absent peristalsis Absent contractile activity	High IRP Absent peristalsis ≥2 spastic contractions with or without periods of compartmentalized pressurization
High-resolution manometry			
Response to Therapy	Intermediate response	Most responsive Least likely to require further treatment within 12 months	Least responsive Botox ineffective Most likely to need multiple interventions Surgical myotomy more effective than POEM

IRP, integrated resting pressure; POEM, peroral endoscopic myotomy.
Modified from Kahrilas PJ, et al. Classification of achalasia [types 1 to 3]. [illegible] 2015;[illegible]:144.

with a myotomy, and 50% to 90% of patients experience symptomatic relief. Although the rate of perforation is lower, PD should only be recommended to patients who would also be surgical candidates and where surgical intervention is available because the possibility of perforation may necessitate surgical repair. Roughly one third of all patients will have recurrent symptoms requiring repeat PD within 5 years. Factors that increase the likelihood of successful outcomes with PD include age greater than 45 years, female sex, pendulation LES pressure less than 10 mm Hg, and type II achalasia.

During PD, the lumen of the LES is dilated using a nonlatex, opaque polyethylene pneumatic balloon on a flexible catheter under fluoroscopic or endoscopic guidance over a guidewire. A handheld manometer is used to inflate the balloon (30–40 mm) to a pressure of 7 to 15 psi and held for 15 to 60 seconds. This allows for dilation and disruption of the circular muscle layer of the LES. Dilation is usually started with a 30 mm balloon and serially increased using larger-diameter balloons according to treatment response and symptom severity. Greater improvement in symptoms is generally seen with the use of larger diameter balloons.

At the conclusion of the procedure, patients should undergo esophagography first with a water soluble contrast followed by barium contrast, if negative, to rule out perforation. If perforation is expected, computed tomography scanning should be performed to look for free air. If a perforation is confirmed, an endoscopically placed covered stent should be placed across the defect. Patients should also be instructed to seek immediate medical attention if they experience severe chest pain within several days of undergoing PD because this may be the first indication of a delayed perforation, a potentially catastrophic complication. Additional complications include esophagitis, hematoma, and gastroesophageal reflux disease, which occur in 15% to 30% of patients and frequently require acid-suppressing therapy.

Peroral Endoscopic Myotomy

POEM has emerged over the past several years as an effective endoscopic approach to treating achalasia as well as other esophageal motility disorders. This therapy uses ESD to perform a surgical myotomy. Indications for POEM as a minimally invasive treatment include patients who are surgical candidates but do not wish to undergo surgery or those for whom prior medical or surgical treatments, including PD and laparoscopic myotomy, have failed. POEM is safe and well tolerated and is associated with lower complications, shorter hospital stays, and quicker recovery compared with laparoscopic myotomy. Although long-term data have yet to emerge, POEM has been demonstrated to be equivalent to PD and surgical myotomy in the short term, with more than 90% of patients reporting improvement in symptoms. As such, this method has become the preferred modality in several institutions, especially in morbidly obese patients or those who have undergone previous surgeries in whom laparoscopic myotomy could be technically challenging.

Before undergoing POEM, patients should be prescribed proton pump and swallow for at least 5 days due to the high incidence of candida esophagitis associated with retained food in patients with achalasia. They should be placed on a clear liquid diet for 2 days before the procedure. POEM is performed in the operating room with the patient under general anesthesia. The patient should be positioned supine and receive perioperative first-generation cephalosporin and fluconazole before induction. Endoscopy with CO_2 insufflation is first used to identify the location of the anatomic GEJ. Methylene blue mixed with saline is then injected into the submucosal plane 15 cm proximal to the GEJ, creating a cushion to decrease the risk of esophageal perforation. Epinephrine is avoided due to potential ischemic damage caused by vasoconstriction. A 1.5- to 2-cm longitudinal incision is then made to the mucosa on the anterior wall of the esophagus, at the 1 o'clock position. This allows access into the submucosal space. A gastroscope with a transparent cap is then introduced into the submucosal space, and a submucosal tunnel of at least 3 cm is created, traversing significant bridging vessels with coagulation. The myotomy is begun 2 cm distal to the distal end of the mucosotomy, and the plane between the inner circular and outer longitudinal muscle is identified. From here, a myotomy of the circular layer is performed, extending distally to the gastric cardia for 2 to 3 cm or until large submucosal gastric vessels are identified. The endoscope is then passed back through the esophageal lumen to evaluate the myotomy and determine its adequacy by passing the scope through the GEJ. Once hemostasis is achieved, gentamicin in 20 mL normal saline is instilled into the submucosal tunnel, and the mucosal incision is closed with either endoscopic sutures or clips.

Patients should undergo esophagography the day after the procedure to evaluate for obstruction or leak. If negative, the patient should be started on a clear liquid diet and acid suppressive therapy. Six months after the procedure, the patient should undergo evaluation with esophageal pH testing to evaluate for reflux.

Complications associated with POEM include mucosal perforation, pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, and pleural effusions. Although POEM does not involve dividing the phrenoesophageal membrane or altering the angle of His, the intrinsic antireflux barrier should be preserved, and one would not expect increased rates of gastroesophageal reflux after POEM. However, studies indicate that the post-POEM reflux rate is similar to that seen with PD or surgical myotomy without partial fundoplication. Long-term outcomes, including durability of symptom improvement and reflux control, are currently unknown.

Laparoscopic Surgical Myotomy (Heller Myotomy)

Laparoscopic Heller myotomy (LHM) with partial fundoplication, first developed as a minimally invasive alternative to the traditional open anterior myotomy and later the Ombredanne myotomy, remains the gold standard for the treatment for achalasia over the past 3 decades. The goal of the myotomy is to completely open the LES and relieve dysphagia.

The LHM provides initial symptomatic relief from dysphagia in approximately 90% of patients for type I and II achalasia and 50% for type III achalasia while decreasing the rates of postoperative reflux. Compared with the open myotomy procedure, LHM is associated with decreased postoperative pain, shorter hospital stays, and earlier return to function.

LHM is indicated as a first-line treatment for all surgical candidates with achalasia willing to undergo surgery, or in those who have failed PD. The operation consists of dividing the muscles of the LES, followed by a fundoplication to decrease postsurgical reflux. Partial fundoplication is favored over total fundoplication because this reduces treatment failure. The two primary complications of the surgery are mucosal perforation and GERD.

The patient should be placed in the supine, split-legged position on the operating table with adequate footboard and padding to prevent sliding during the steep reverse Trendelenburg position that is commonly used. A rapid sequence induction may be performed due to potential risk of aspiration related to retained esophageal contents. Endoscopy is then performed to evaluate for any residual food particles in the esophagus, as well as to copiously irrigate and clean the esophagus to allow for a complete endoscopic evaluation. The endoscope is also used to locate the exact site of GEJ obstruction using illumination and insufflation. The endoscope is left in place to allow for endoscopic assessment throughout the operation.

With the primary surgeon between the patient's legs and the assistant to the patient's left, abdominal access is gained by either the Hasson cutdown technique or with a Veress needle system inserted into the left paramedian location two thirds down between the xiphoid and umbilicus. This will be the site of the 10 mm 30 degree laparoscope. Alternatively, a Veress needle could be used to insufflate the

abdomen initially, especially if the patient has had prior abdominal surgeries. The remaining trocars are placed under direct visualization and include a 10-mm port to the left midclavicular line approximately 2 cm below the costal margin, a 5-mm trocar to the right of the falciform ligament 2 cm below the costal margin, and a 5-mm trocar to the right of the xiphoid used to hold a Nathanson liver retractor for holding the left lateral segment away from the hiatus.

After the trocars are placed, the gastric fat pad is retracted inferiorly and laterally. The gastrohepatic ligament is opened, and the upper aspect of the right crural arch, as well as the phrenoesophageal ligament, are identified. The phrenoesophageal membrane is incised at the 10 o'clock position along the crural arc and extended clockwise over the anterior esophagus over to the left side of the crural arch. The most superior short gastric branches are divided to allow for sufficient mobilization of the upper fundus and identification of the GEJ and angle of His for eventual fundoplication. The hiatus is then evaluated for a hernia, and, if not present, the posterior attachments are left intact. If a hiatal hernia is identified, circumferential dissection around the hiatus is performed, and a posterior window is developed between the posterior vagus and esophagus. A Penrose drain is then passed through this window to facilitate traction for further circumferential dissection into the lower mediastinum. The gastrocolic fat pad is then dissected off the anterior surface of the stomach from left to right, exposing the surface for the myotomy.

To both minimize oozing and separate the muscular wall from the submucosa thereby facilitating identification of the proper plane for dissection and myotomy, normal saline instilled with 0.5% epinephrine is injected into the muscular wall of the distal esophagus, GEJ, and cardia of the stomach in the area of the anticipated myotomy.

The myotomy is then begun 2 cm proximal to the GEJ with sharp dissection or low-voltage diathermy (Fig. 1). The circular muscle is elevated and divided until the submucosal plane is identified. In this plane the myotomy is extended 5 cm proximal to the GEJ and distally 2.5 cm onto the gastric cardia, or until large veins of the transverse submucosal plexus are encountered. The muscle fibers are then separated from the underlying mucosa on either side of the myotomy until at least 50% of the mucosal circumference is exposed.

Extreme caution is required when extending the myotomy from the distal esophagus to the GEJ and cardia of the stomach because of the potentially extremely thin muscular wall and increased risk of perforation here. Once the myotomy is complete, the endoscope is used to confirm the integrity of the mucosa and adequacy of the myotomy. An underwater seal test with saline instilled around the myotomy and endoscopic insufflation is performed to verify the absence of leak. The adequacy of the myotomy is assessed by obliteration of the rugnae mucosa at the site of distraction, as well as easy entry of the endoscope into the stomach. Transillumination can be used to identify any bands of muscle that remain, which can then be divided.

Next, a partial fundoplication is performed to cover the myotomy and create a low-pressure valve, thereby decreasing the risk of postoperative reflux. Importantly, a complete fundoplication (Nissen) is not recommended because this results in significant obstruction to esophageal emptying and is thus counterproductive to the myotomy. Either an anterior (Dor) or partial posterior (Toupet) fundoplication can be performed, depending on surgeon preference and degree of posterior dissection performed during the operation. Some evidence suggests that the Dor fundoplication is associated with a significantly higher percentage of postoperative reflux at 6 months compared with the Toupet fundoplication, although there appear to be no differences in symptoms.

For the Dor fundoplication, the greater curvature of the stomach 2 cm distal to the anatomic GEJ is sutured to the left crus at the 2 o'clock position. The cut edge of the myotomy should be incorporated into this suture to accentuate the angle of His. From here, subsequent sutures should be taken along the greater curvature at 2 cm intervals and sutured to the hiatus from left to right, folding the anterior surface of the stomach over the myotomy. The fundus is then sutured to the right crus of the myotomy and the right crura at the 11 o'clock position. Finally, the mobilized fundus is sutured to the superior portion of the arcuate ligament, resulting in the fundus being in contact with the anterior esophagus. The esophagoscope is inserted into the stomach during this suturing to prevent esophageal obstruction.

With the partial posterior Toupet fundoplication, the gastric fundus is passed from left to right through the retroesophageal space. The fundoplication is aligned to the esophagus, and the bilateral triangulation sutures between the mobilized fundus, myotomy, and crural arc at the 11 and 12 o'clock positions. The fundus is then grasped and mobilized from left to right and sutured to the right crus to drape over the esophagomyotomy.

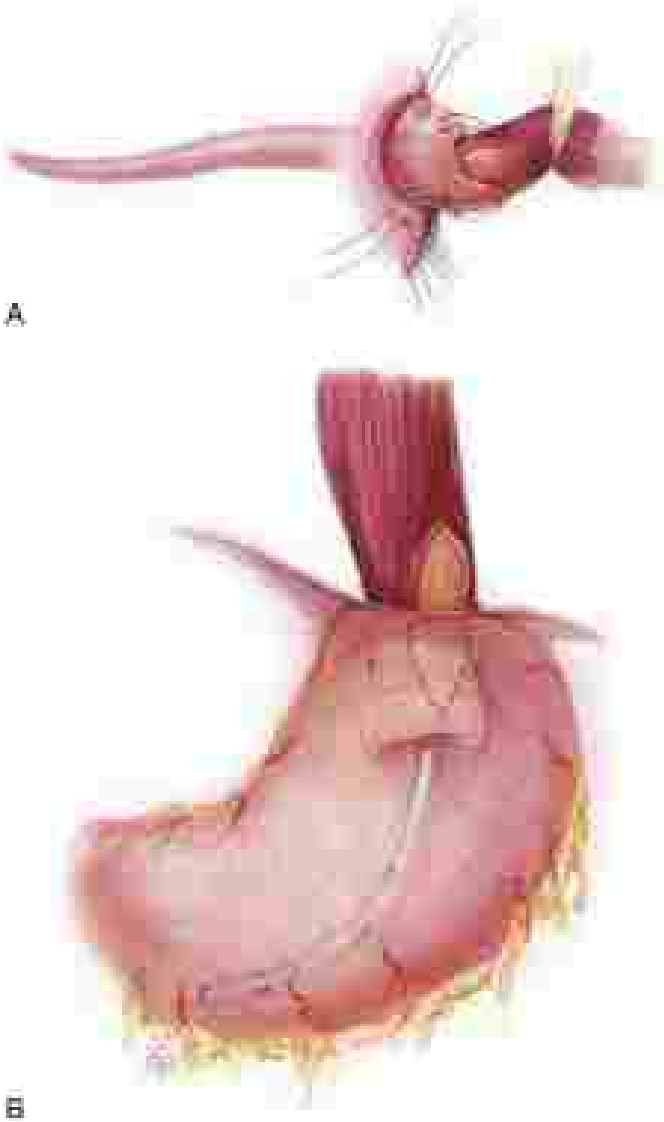
After either the Dor or Toupet fundoplication, esophagoscopy is performed after completion of the procedure to confirm adequacy of the myotomy, the integrity of the fundoplication, and to evaluate for any mucosal perforations. An esophagogram is obtained on postoperative day 1, and, if negative, the patient is started on a clear liquid diet and discharged on a soft diet for 2 weeks. Importantly, after myotomy, patients should be counseled to thoroughly chew food, swallow small bites, and avoid lying flat because this increases the risk of aspiration.

Transthoracic Myotomy

Transthoracic approaches to esophagomyotomy, including the left thoracoscopic myotomy, have largely been abandoned and are now almost exclusively reserved for patients in whom laparoscopic or abdominal approaches are not feasible. Difficulties with the thoracoscopic approach include the need for a Heller fundoplication to reduce reflux, difficulty extending the myotomy onto the gastric wall, patient intolerance to single lung ventilation, and longer postoperative stay and worse postoperative pain because of chest tube management and the thoracic incision. However, some centers prefer thoracic myotomy because, unlike with LHM, it allows control of the esophagus, cardia, and stomach but does not alter the normal anatomic interrelationship of these organs and surrounding structures.

After carotid intubation with a single-lumen endotracheal tube, an esophagoscopy is performed to visualize, clear, and clean the esophagus. A dual-lumen endotracheal tube, or bronchus blocker, is then placed to allow for single lung ventilation of the right lung and atelectasis of the left lung to facilitate esophageal dissection. The esophagoscope is left in place for transillumination and insufflation as necessary.

The patient is then placed in a right lateral decubitus position. A lateral muscle sparing minithoracotomy incision at the seventh intercostal space is the incision we frequently perform. The inferior pulmonary ligament is then divided to allow access to the distal esophagus. The esophagus is dissected from the level of the inferior pulmonary ligament to the anterior pericostal membrane. With the esophagoscope in place for alternatively a 50 Maloney dilator) within the esophagus, the esophagus is then encircled with a Penrose drain, with care taken to avoid injury to vagal nerve trunks. The pericostal reflection is then incised, the crural opening is expanded, and the most cephalad short gastric arcades are ligated. The GEJ and gastric cardia are then identified. Saline with 0.5% epinephrine is injected into the muscular wall of the distal esophagus and GEJ, reducing oozing and allowing for separation of the muscular wall from the submucosa. The esophagomyotomy is then performed in a similar fashion as with the LHM (Fig. 2A). A Belsey fundoplication is then performed to reduce reflux (Fig. 2B). A chest tube connected to an underwater seal drainage system is placed. The postoperative management, including barium esophagogram and clear liquid diet with advancement, is similar to that taken for the LHM.



A

B

FIG. 2 (A) Heller myotomy via left thoracotomy. (B) Completed Belsey fundoplication via left thoracotomy. (Fowler Carter Section. From Gamsu G, Goodman C, Atlas of Gastrointestinal Surgery vol 1, 2nd ed. Hagerstown: Medical Publishing; 2007.)

Esophagectomy

Despite symptomatic improvement with therapy, some patients may continue to experience ongoing incomplete esophageal emptying, resulting in progression to end stage disease and its associated complications. Diagnostic findings suggestive of end stage achalasia with barium esophagram include sigmoid esophagus with a tortuous, dilated course, megaesophagus, and pulsion diverticula.

Although severe or end stage achalasia was traditionally an indication for a partial esophagectomy because of the thought that the esophagus would never be able to adequately empty even with a myotomy, recent data suggest that surgical or endoscopic myotomies can improve symptoms in the overwhelming majority of patients. Partial esophagectomy with interposition is now generally indicated for the treatment of end stage achalasia and best reserved for patients who are refractory to all other treatments or who have another concomitant esophageal pathology for whom esophagectomy is indicated. In patients who are poor surgical candidates, refractory, and end stage achalasia can be managed with endoscopic botulinum toxin injection into the LES or with pharmacotherapy as described above.

PHARMACOTHERAPY

For patients who are deemed poor surgical candidates or who need temporary treatments while awaiting more definitive therapy, less effective but accepted treatment options include pharmacotherapy such as calcium channel blockers, long acting nitrates, isosorbide dinitrate, phosphodiesterase 5 inhibitors, or the injection of botulinum toxin into the LES endoscopically. Pharmacotherapy, the least effective option, is generally limited by its short duration of action, incomplete relief of symptoms, poor absorption, adverse effects, intolerance, and decreased efficacy with prolonged use. The most commonly used class of medical therapy is calcium channel blockers, most commonly nifedipine. They work by inhibiting LES muscle contraction and resting pressure. Nitrates are also commonly used and increase nitric oxide concentration in the smooth muscle of the LES, increasing cyclic adenosine monophosphate levels and resulting in muscle relaxation. Phosphodiesterase 5 inhibitors such as sildenafil inhibit cyclic guanosine monophosphate degradation, thus reducing muscle contraction.

Botulinum toxin therapy is generally indicated for patients who are not surgical candidates or have refractory symptoms after myotomy or PD. It is not indicated for type III achalasia. It is associated with an approximately 50% decrease in LES baseline pressure. At least four quadrants of the LES should be injected during EGD, just proximal to the squamocolumnar junction. Repeated injections every 6 to 24 months are frequently necessitated because relapse of symptoms is common with this therapy. Some evidence suggests that patients older than 65 years and those with lower LES (less than 50% of the upper reference limit) may experience a longer duration of symptom improvement with botulinum toxin. Complications associated with botulinum toxin include inflammatory or allergic reactions, chest pain, mediastinitis, and mucosal ulceration.

POSTTREATMENT MONITORING

Patients with achalasia should undergo ongoing monitoring after treatment to evaluate symptom improvement and esophageal emptying. Although patients may experience improvement in symptoms, esophageal emptying may continue to be impaired, thus increasing the risk of disease progression and associated complications. Barium esophagograms and manometry are the most common methods of monitoring. In addition to monitoring all patients with achalasia for the development of end stage achalasia or esophageal squamous cell carcinoma, these tools can help identify patients who require closer follow up because of increased risk of disease progression. Endoscopic surveillance is currently not routinely recommended, although some experts recommend monitoring with EGD every 3 years starting 10 years after the initial diagnosis of achalasia.

SUMMARY

Achalasia is a relatively rare disorder but represents the most common esophageal motility disorder. As the age of the United States population increases, surgeons will likely encounter more patients with achalasia due to its increasing prevalence and incidence with age. Many treatment options exist, and a proposed algorithm is shown in Fig. 3, based on the current quality of evidence and updated guidelines from numerous organizations. Choices of therapies should be guided by patients' demographics and preferences, and local institutional expertise.

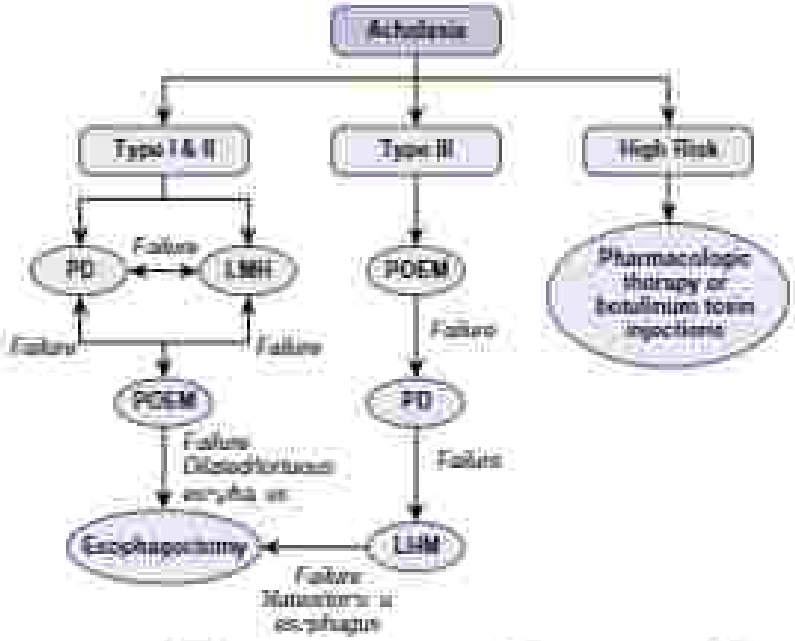


FIG. 3 Proposed treatment algorithm for achalasia. LHM, laparoscopic Heller's myotomy; PD, pneumatic dilation; POEM, peroral endoscopic myotomy.

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MANAGEMENT OF DISORDERS OF ESOPHAGEAL MOTILITY

T. Robert Qa'jah, MD, MSc, and Mark [illegible]atis, MD, FACS

Disorders of esophageal motility present a diagnostic and therapeutic challenge to gastroenterologists and surgeons. Achalasia, the most prevalent and best understood of these disorders, is addressed under "Management of Achalasia of the Esophagus" elsewhere in this textbook. Nonachalasia esophageal motility disorders are less prevalent, incompletely understood, and often difficult to treat. The optimal classification schema for this group of disorders is a work in progress. Management strategies are also controversial, and there is no universally accepted standard of care. In this chapter, we attempt to guide the surgeon in a review of nonachalasia esophageal motility disorders and the application of their most current classification, with recommendations for management based on recent data.

PRESENTATION

Patients with disorders of esophageal motility may present with chest pain, dysphagia, regurgitation, heartburn, globus sensation, upper respiratory complaints, or some combination of these. Because these symptoms are nonspecific and esophageal motility disorders are rare, workup for other life-threatening conditions is necessary. Cardiovascular and pulmonary causes usually have been ruled out already in the patient with chest pain before referral to the surgeon. A negative cardiac workup is reassurance enough for some patients who may be able to conservatively manage mild symptoms. Anxiety, depression, somatoform disorders, and other psychiatric diagnoses are more

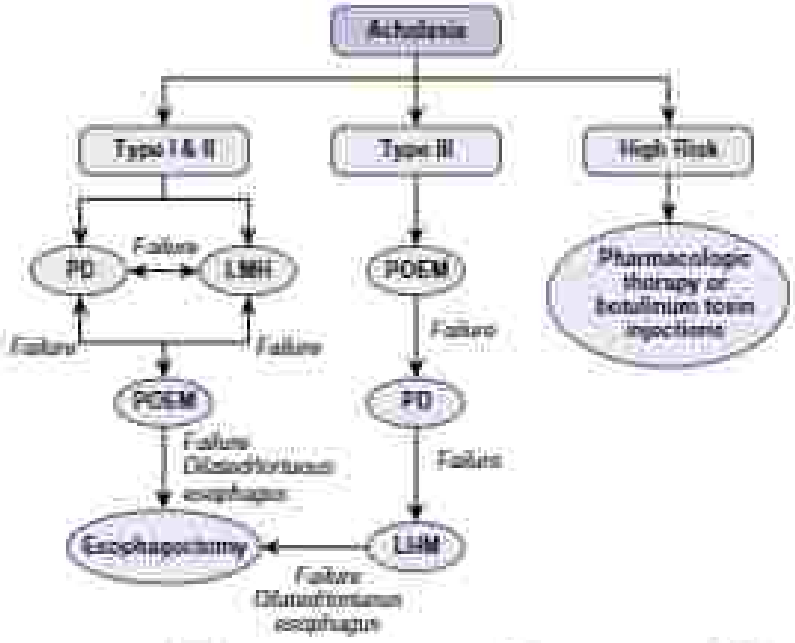

FIG. 3 Proposed treatment algorithm for achalasia. LHM, laparoscopic Heller's myotomy; PD, pneumatic dilation; POEM, peroral endoscopic myotomy.

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Management of Disorders of Esophageal Motility

T. Robert Qasim, MD, MSc, and Mark Kuhn, MD, FACS

Disorders of esophageal motility present a diagnostic and therapeutic challenge to gastroenterologists and surgeons. Achalasia, the most prevalent and best understood of these disorders, is addressed under "Management of Achalasia of the Esophagus" elsewhere in this textbook. Nonachalasia esophageal motility disorders are less prevalent, incompletely understood, and often difficult to treat. The optimal classification schema for this group of disorders is a work in progress. Management strategies are also controversial, and there is no universally accepted standard of care. In this chapter, we attempt to guide the surgeon in a review of nonachalasia esophageal motility disorders and the application of their most current classification, with recommendations for management based on recent data.

PRESENTATION

Patients with disorders of esophageal motility may present with chest pain, dysphagia, regurgitation, heartburn, globus sensation, upper respiratory complaints, or some combination of these. Because these symptoms are nonspecific and esophageal motility disorders are rare, workup for other life-threatening conditions is necessary. Cardiovascular and pulmonary causes usually have been ruled out already in the patient with chest pain before referral to the surgeon. A negative cardiac workup is reassurance enough for some patients who may be able to conservatively manage mild symptoms. Anxiety, depression, somatoform disorders, and other psychiatric diagnoses are more

common in the population of patients with esophageal motility disorders, thus a psychiatric history is an important part of the evaluation.

Gastroesophageal reflux disease (GERD) is another common cause of noncardiac chest pain. A trial of a proton pump inhibitor (PPI) is warranted, and, if troublesome symptoms persist, further diagnostic testing should be carried out. Concerning associated symptoms, such as dysphagia with weight loss, should heighten the suspicion for a mechanical or malignant process and prompt expedient and careful evaluation.

DIAGNOSTIC TESTING

All patients evaluated for esophageal motility disorders must undergo a comprehensive diagnostic workup. This includes a contrast esophagram to help visualize anatomy, esophageal length, and the presence of a diaphragmatic hernia or esophageal diverticulum. A pH study with or without impedance is important to identify GERD, which may be the primary or contributing cause of symptoms. Endoscopic evaluation with biopsy is also mandatory to identify Barrett's esophagus, malignancy, pepsin stricture or esophagitis related to acid exposure, eosinophilia, or infection. In the absence of mechanical obstruction or mucosal abnormalities, esophageal motility is evaluated next by manometry.

High-resolution manometry (HRM) with esophageal pressure topography (EPT) is the preferred method to evaluate for esophageal motility. HRM precisely defines esophageal contractile function, peristalsis, and bolus transit when impedance evaluation is included. Compared with conventional manometry, study acquisition is faster, more comfortable, and better tolerated by patients. For technicians and physicians, the topography contour plots increase diagnostic yield provide an intuitive visual presentation of anatomic and physiologic characteristics.

CLASSIFICATION OF DISEASE

Classifying esophageal motility disorders is an evolving process. Definitions of disease phenotype have changed over time, with improvements in diagnostic technology and better understanding of the clinical importance of various manometric patterns. In 2003, Richter systematically classified esophageal motility disorders using conventional manometric criteria. Using HRM, Khatibu and colleagues redefined this scheme in 2008 with the first edition of the Chicago Classification of esophageal motility disorders. The Chicago Classification is currently in its third edition (CC v3.0), which introduced to simplify and clarify recognition of EPT patterns and physiologic metrics to better define clinically relevant phenotypes of esophageal dysmotility. CC v3.0 classifies the various manometric entities as *Esophagogastric outflow obstruction, Major disorders of peristalsis*, or *Minor disorders of peristalsis* (Fig. 1). Manometric findings that do not meet criteria for these categories are considered normal. The most recent CC v3.0 has increased the number of normal findings when compared with CC v2.0 and augmented the relevance of abnormal findings. This chapter reviews nonachalasia disorders of esophageal motility according to the hierarchic analysis of the most current version of the Chicago Classification.

Esophagogastric Outflow Obstruction

Esophagogastric junction outflow obstruction (EGJOO) may be the result of intrinsic or extrinsic pathology, which highlights the

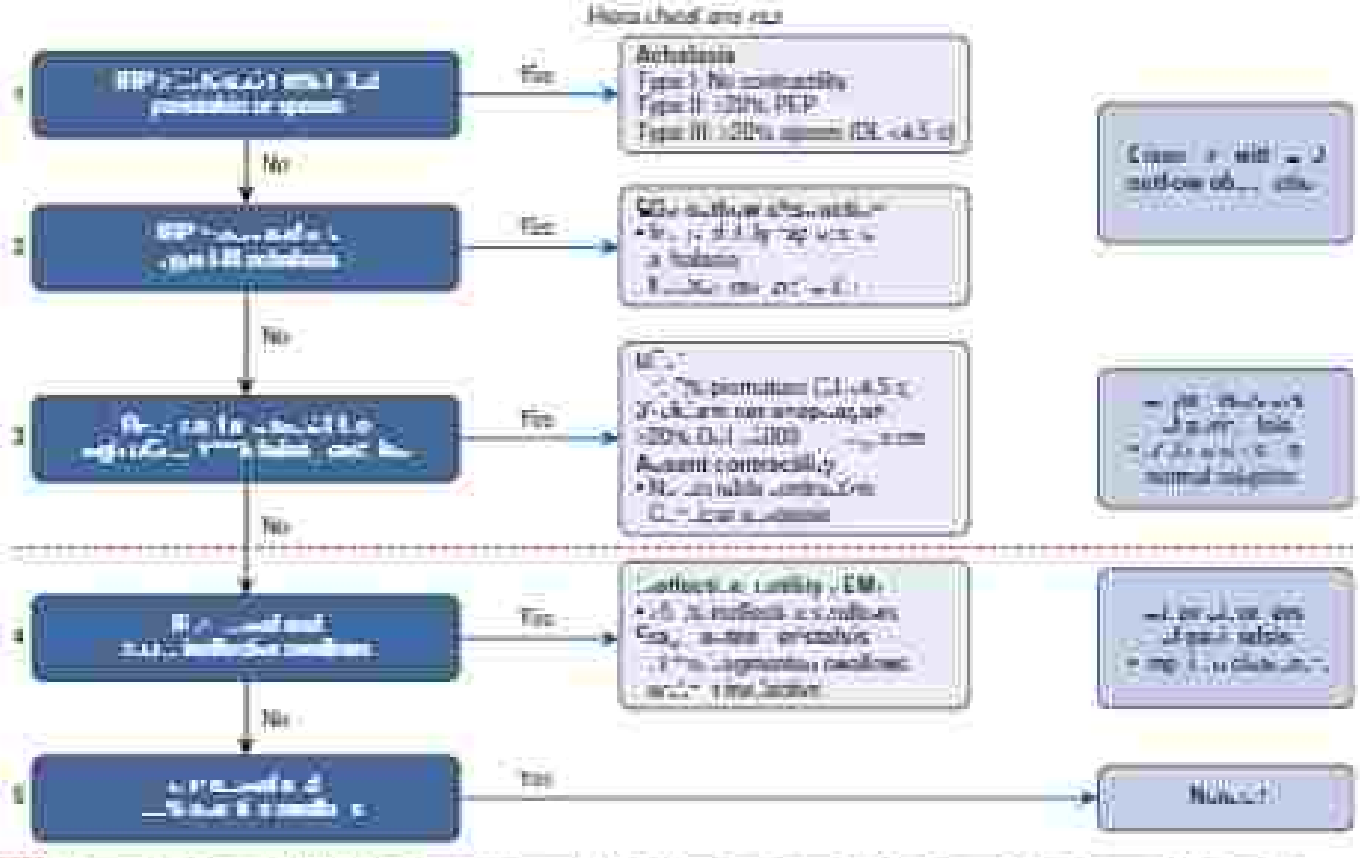

FIG. 1 Chicago Classification v3.0. DL, Distal contractile integral; DES, distal esophageal spasm; EGJ, esophagogastric junction; IRP, integrated relaxation pressure; PEP, pan-esophageal pressurization; ↑, upper limit normal. *From Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27:160–174.*

importance of the comprehensive esophageal workup. Distal ulcers, peptic stricture, stiff esophageal body resulting from scarring or radiation, prior surgical interventions, paraesophageal resulting from malignancy or vascular obstruction from a dilated aortic arch are potential sources of mechanical outflow obstruction (Fig. 2A). Prominent vascular artifact on manometry or a history suggestive of malignancy should prompt adjunct evaluation with endoscopic ultrasonography (EUS) or computed tomography. In a retrospective study, findings on selective EUS altered clinical management in as many as 15% of concerning cases. When other mechanical causes of esophagogastric outflow obstruction and achalasia have been ruled out, idiopathic cases remain. This is identified by incomplete relaxation of the EGJ, currently defined by HRM as elevated integrated relaxation pressure in the setting of preserved peristalsis (Fig. 2B), differentiating EGJOO from achalasia.

It is hypothesized that EGJOO may represent an incompletely expressed or precursor variant of achalasia, but this has not been verified in large numbers of patients. There are few data specific to this new entity since it has been redefined in CC v3.0. Cases previously classified as hypertensive lower esophageal sphincter (HTLES) by older versions of the Chicago Classification would most likely meet criteria for EGJOO. Interestingly, patients diagnosed with HTLES were found to have paradoxically elevated esophageal acid exposure about 25% of the time, despite relative EGJ obstruction. Therefore treatment of patients in this group should be tailored based on symptoms. PPIs should be considered if GERD is the major complaint. If dysphagia without abnormal esophageal acid exposure is identified, then medications directed to esophageal smooth muscle relaxation can be attempted. Endoscopic pneumatic dilation (PD) or botulinum toxin (Botox) injections are moderately effective options for relief of obstructive symptoms. Surgical therapy may be indicated in cases of severe or refractory symptoms. Esophageal myotomy, fundoplication, or a combination of the two can be tailored to the patient's symptoms and objective pathophysiology. Antireflux surgery without myotomy has been found to achieve good long term results for patients with reflux and mild EGJOO caused by acid induced spasm and inflammation, although preoperative dysphagia was found to predict a higher rate of failure. With dysphagia as the primary symptom, and other tested or normal esophageal acid exposure, laparoscopic Heller myotomy with partial fundoplication and peroral endoscopic myotomy (POEM) have been used successfully to describe such as EGJOO that do not affect the esophageal body. Abdominal approaches for surgery are favored over thoracic because adequate proximal dissection is possible without accessing the thoracic cavity. Abdominal fundoplication options also offer greater symptom relief and generally are considered less technically challenging.

Major Esophageal Motility Disorders

This group of disorders is defined by manometric parameters that are always associated with symptoms. Distal esophageal spasm (DES), also frequently referred to as *diffuse esophageal spasm*, is sometimes grouped with nutcracker esophagus or hypercontractile esophagus and achalasia type III as hypercontractile or "spastic" motility disorders. Patients with DES are symptomatic with chest pain, dysphagia, or regurgitation resulting from spastic contractions. The cause of DES is believed to be an impaired neurologic inhibitory pathway, allowing premature esophageal smooth muscle contractions. This disorder may overlap with or progress to achalasia. Rapid contractions previously categorized as DES by conventional manometry have been found to be nonspecific. With HRM these rapid contractions sometimes are identified in patients with EGJOO, GERD, and even in normal control subjects and therefore are no longer used to define DES. DES currently is defined by premature contractions in more than 20% of swallows. This is indicated on HRM as a low distal latency, a truncated interval between initiation and deceleration of pressure (Fig. 3A). Barium esophagram classically shows a corkscrew pattern of simultaneous contractions, although this pattern is actually

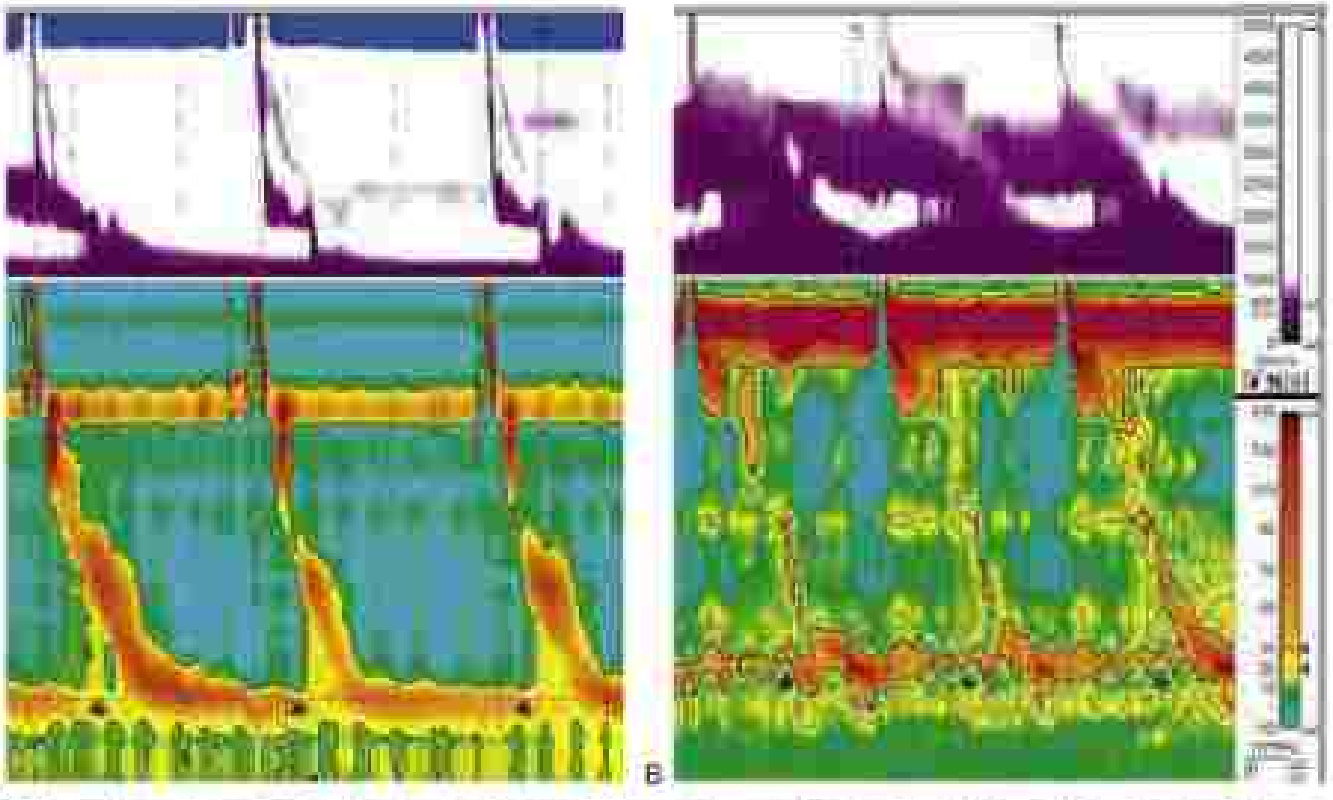

FIG. 2 Esophagogastric junction (EGJ) outflow obstruction. Note the high-pressure, increasing EGJ (see *dot*). (*A*) In this case caused by a hiatal hernia. (*B*) idiopathic, in the setting of ineffective motility and incomplete bolus clearance. *(Courtesy Ikr Gregori Clair.)*

uncommon and not required for diagnosis (Fig. 3B). Treatment options for IHS vary. Patients initially may benefit from reassurance with dietary and behavioral modifications or pharmacologic therapy. Persistent cases may require endoscopic intervention with PD or fistula, or surgical myotomy of variable length. Surgical approaches are discussed in more detail in the treatment section of this chapter.

Jackhammer esophagus was named to describe extreme hypercontractility and avoid confusion with IHS. This disorder's cause is believed to be excessive cholinergic drive, causing asynchronous contractions of circular and longitudinal muscle. Jackhammer is defined manometrically by at least two swallows with significant hypercontractile vigor as measured by a distal contractile integral (DCI) exceeding 8000 mm Hg • s • cm (Fig. 6A). The hypercontractile segment may involve the esophageal body or may be limited to the esophagogastric junction, with IRP relaxation pressure usually in the upper limit of normal.

Patients with jackhammer esophagus are consistently symptomatic with chest pain, dysphagia, or regurgitation. This differentiates jackhammer by CC v3.0 criteria from nutcracker esophagus, defined as hypercontractile peristalsis with DCI between 5000 to 8000 mm Hg • s • cm (Fig. 4B). Although some patients with DCI in this range are symptomatic, some symptom-free control patients also fall into this range. For this reason, the clinical relevance of nutcracker esophagus has been questioned. Some patients previously meeting criteria for nutcracker esophagus by manometry will now be classified as "normal" by CC v3.0, and the effect of that change has yet to be determined. Since CC v3.0 was published, few cases reports have been made specifically for management of jackhammer esophagus, so further study of outcomes for this hypercontractile group will be required with time. Treatment is aimed at controlling spasm and can include dietary and behavioral modification, pharmacologic therapy, or endoscopic or surgical treatments, which are subsequently discussed.

Absent contractility is another new clinical entity under CC v3.0. This disorder is defined by HRM with hypocontractility and failed peristalsis in 100% of swallows in the setting of an IRP with normal relaxation pressure. Premature hypocontractile swallows with failed peristalsis are grouped here. In cases with borderline DCI relaxation and evidence of esophageal pressurization, achalasia should be considered and the patient managed accordingly.

Systemic sclerosis (scleroderma) falls into the absent contractility category (Fig. 5). This figure demonstrates complete hypocontraction of esophageal smooth muscle, with preserved skeletal muscle contraction in the upper esophageal sphincter and diaphragm. Therapeutic options specific to diminished esophageal motility are limited, so treatment is directed primarily at the underlying systemic disorder, as well as relief of symptoms. Unfortunately, no specific pharmacologic therapy improves contractility and function of esophageal smooth muscle. Prokinetic agents are fraught with side effects and are primarily avoided. GERD has been identified frequently in these patients and should be treated aggressively with PPIs. Antireflux surgery can be considered carefully for refractory GERD cases in this setting but should be approached with caution at the risk of exacerbating dysphagia. Because connective tissue disorders such as scleroderma also can affect gastric motility, one should be aware that GERD symptoms may be a result of overflow reflux and should not be treated by fundoplication alone. A small retrospective review of scleroderma patients treated with fundoplication or Roux-en-Y gastric bypass (RYGBP) revealed improvement in control of reflux and dysphagia in the RYGBP group compared with fundoplication. In very carefully selected cases, RYGBP may be considered for primary management of refractory GERD in scleroderma. Less invasive endoscopic procedures such as suture plication or radiofrequency ablation may be more appealing for GERD in such fragile patients but are less effective at reducing reflux.

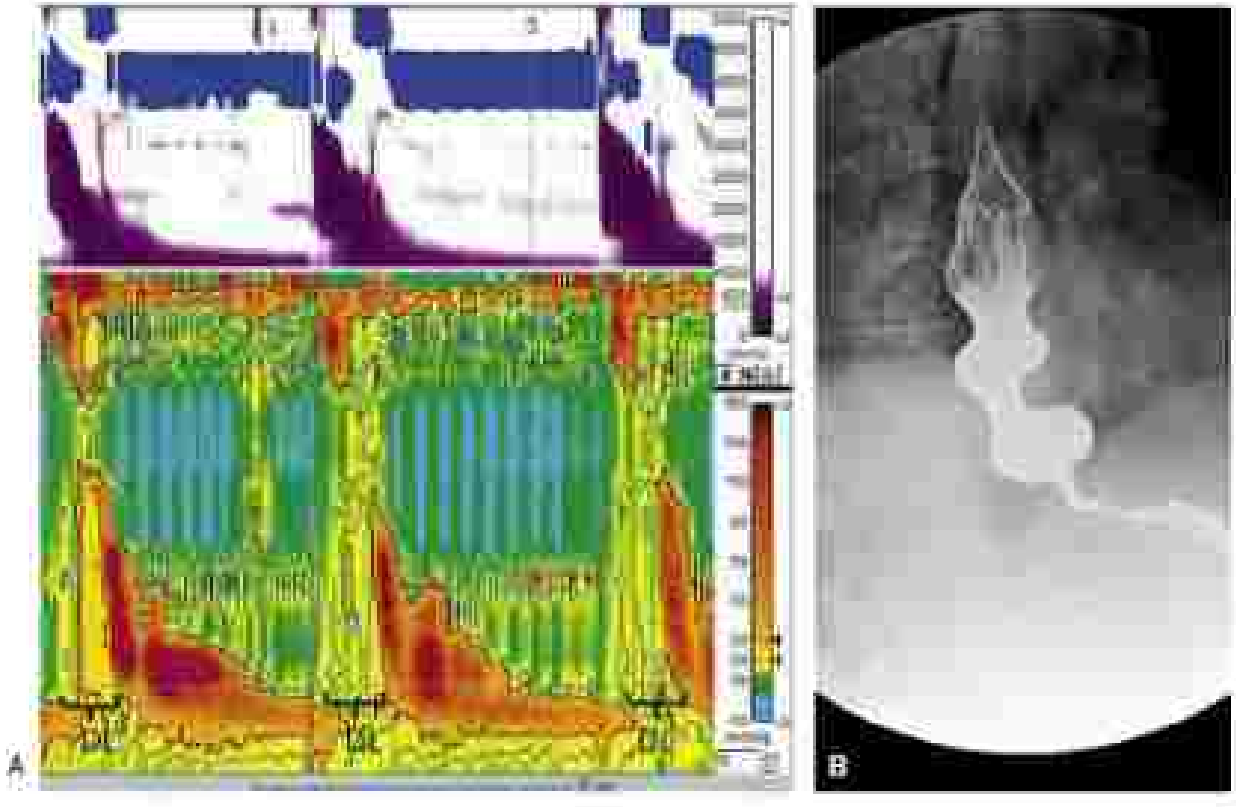

FIG. 3. Distal esophageal spasm. (A) Premature contractions with low distal integrity (normal between initiation and contraction of peristalsis). (B) Esophagogram with corkscrew pattern of simultaneous tertiary esophageal body contractions. (Courtesy The Oregon Clinic.)

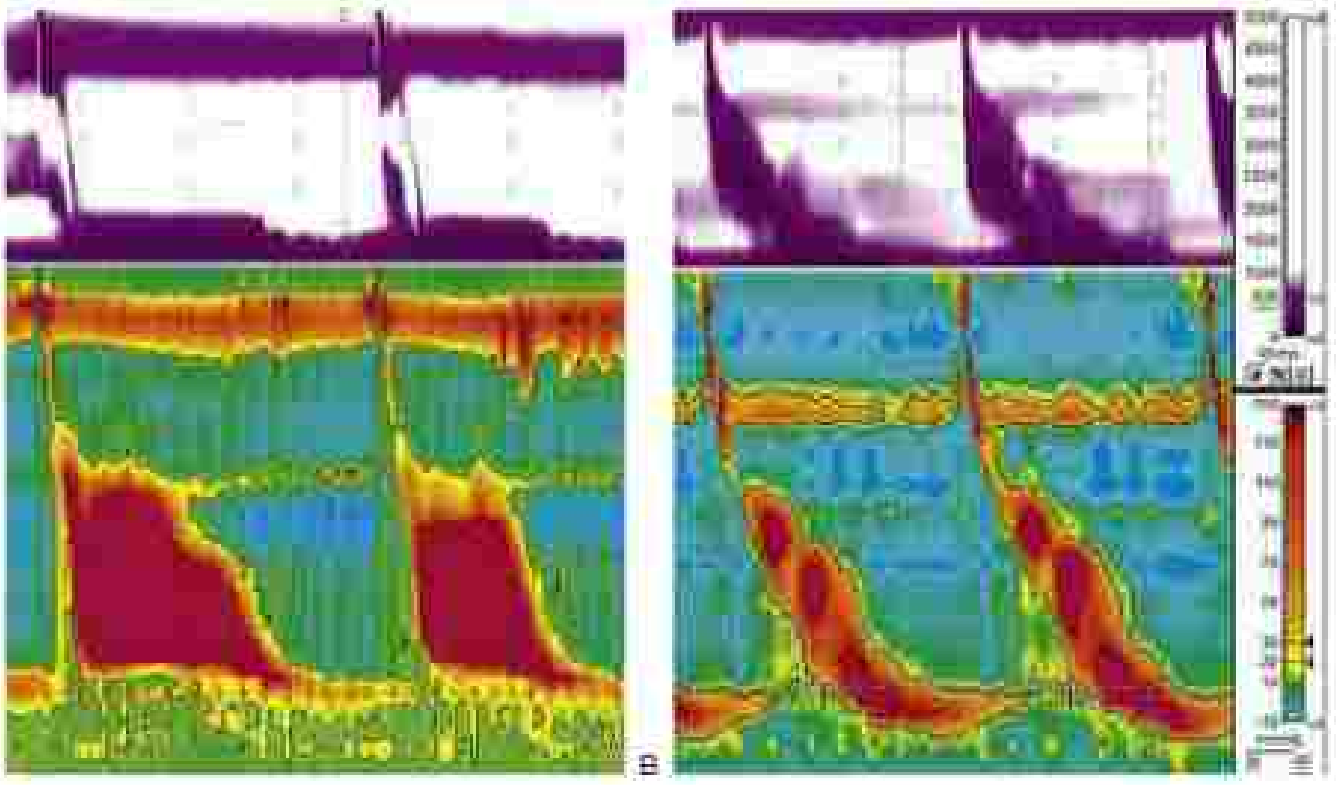

FIG. 4 (Hypercontractile disorder) (A) Jackhammer esophagus. Extremely elevated contractile vigor (DCI in this case ranged from 12,000 to 30,000) (B) Nutcracker esophagus. Periodic vigorous contractions with DCI 5000 to 8000. DCI, Distal contractile integral. (Courtesy Dr. Ginger Chen.)

Minor Esophageal Motility Disorders

Patients with minor motility disorders often have minimal symptoms and require fewer interventions over time, and, as such, the prognosis of these patients is overall better than for those with major esophageal motility disorders. Ineffective esophageal motility (IEM) is a minor esophageal motility disorder defined by a significant number of weak or failed swallows. Presentation may include heartburn and regurgitation with or without dysphagia, and symptoms tend to be mild. GERD often plays a significant role in the underlying cause of IEM because many of these patients are found to have underlying abnormal esophageal acid exposure. IEM is defined by HRM criteria as at least 50% of swallows with low or absent contractile vigor, indicated by DCI less than 450 mm Hg × s × cm (Fig. 4A). Interestingly, symptom-free healthy patients may also exhibit a manometric pattern consistent with IEM. In the patient with IEM, the manometry technician may elect to perform additional provocative testing with multiple repetitive swallow (MRS) assessment. Definitive inhibition of the esophageal body and EGJ occurs during MRS, usually followed by augmented esophageal contraction vigor and improved bolus transit. Augmented contraction with MRS may be reassuring to the physician who is considering an antireflux procedure to treat underlying GERD while avoiding iatrogenic postoperative dysphagia. When MRS does not augment subsequent contraction, it is predictive of late dysphagia after fundoplication. Although evidence would indicate that there is a relatively low risk of postoperative dysphagia with Nissen fundoplication for patients with IEM, many surgeons choose to carefully tailor a partial fundoplication to avoid the risk of postoperative dysphagia. Clinical implications of MRS findings in this setting have yet to be defined clearly and require further study because these provocative maneuvers are used more frequently with HRM.

Therapeutic options are limited for IEM patients. Because many, if not most, IEM cases are related to chronic reflux disease, correction of GERD may result in correction of the motility disorder. Reassurance along with dietary and behavioral modifications may be helpful. As in other motility disorders, prokinetic drugs generally are not recommended. Low dose antidepressants, especially tricyclic antidepressants or trazodone, may reduce functional chest discomfort, heartburn, and globus sensation but may not be effective for dysphagia.

Fragmented peristalsis is the final minor disorder of esophageal motility. It is defined manometrically by at least 50% of swallows with fragmented contractions, with a distal to peristaltic contraction of at least 5 cm, with preserved overall contraction vigor not meeting criteria for IEM (Fig. 4B). Outside of GC v3.0, no specific reports on this newly defined disorder have been made, and its clinical relevance is yet to be defined.

NONOPERATIVE MANAGEMENT

The main goals of any treatment for patients with esophageal motility disorders include reduction of chest pain and dysphagia. Treatment is focused on reducing spasm, GERD, and outflow obstruction to facilitate esophageal emptying. Reassurance alone can be beneficial. Reassurance not only helps to relieve anxiety but also has been shown to reduce severity of chest pain and frequency of healthcare use.

Dietary and Behavioral Modifications

Dietary and behavioral modifications can be very helpful for avoiding chest pain or dysphagia. These modifications include sitting upright and allowing plenty of time for meals, taking small bites, chewing thoroughly, and taking sips of liquid between bites. Foods such as bread, meat, and rice are notorious for worsening dysphagia and should be ingested with caution or minimized. Extremely hot or cold foods can exacerbate esophageal spasm. Chewing soft or liquefied foods can be helpful during symptom flares.

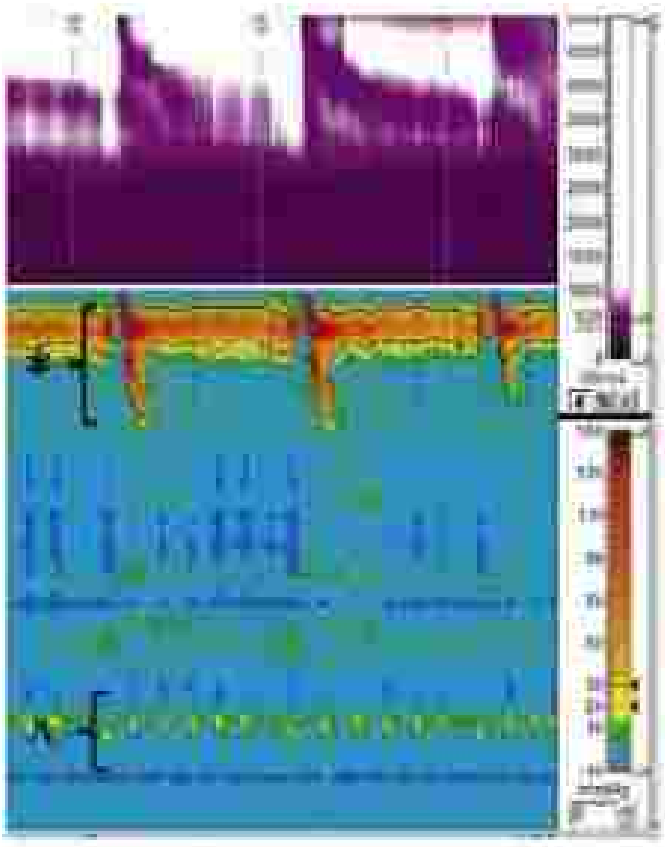

FIG. 5 Absent contractility. This is a case of scleroderma with complete hypomotility of esophageal smooth muscle, total preserved function of skeletal muscle of the upper esophageal sphincter (asterisk) and diaphragm (arrowheads). (Courtesy Per Gregersen, Chile.)

Pharmacologic Therapy

Before pharmacologic therapy is initiated, it is important to carefully review the patient's home medications and minimize those that affect esophageal motility. PPI in particular is associated with chronic opioid use and has been shown to improve with opioid cessation. A few classes of drugs have been used with some success in providing symptomatic relief of esophageal spasm. Smooth muscle relaxing agents (nitrates or calcium channel blockers) taken 15 minutes before meals may provide some symptomatic relief in spastic or hypercontractile disorders, including DES, some cases of EGJOO, and achalasia-esophagus. Phosphodiesterase 5 inhibitors such as sildenafil, which acts by blocking degradation of nitric oxide, also can be effective. These drugs may be tolerated poorly because of lightheadedness, headache, or other side effects, and tachyphylaxis has been noted. Cost of sildenafil may be prohibitive, and effects of daily long-term use of this agent in various populations of patients are unknown. Low dose antidepressants, including tricyclic agents and trazodone, may provide pain modulation and anxiety relief for noncardiac chest pain. As previously discussed, CSRD is frequently part of the clinical syndrome of esophageal dysmotility, although its role in pathogenesis is not understood completely. A trial of PPIs is warranted and may help reduce inflammation, pain, and spasm related to abnormal esophageal acid exposure.

Endoscopic Therapy

Pneumatic dilation (PD) has been used to treat spastic esophageal motility disorders affecting the EGJ, including EGJOO, DES, and nutcracker esophagus, with variable success. In small studies, 26% to 70% of DES and nutcracker patients had good response with PD, although there is concern that some of these cases may have been classified more accurately as achalasia. From the achalasia literature, there is a known risk of perforation with pneumatic dilation in the range of about 2% to 5% of cases performed by expert endoscopists. This rate of perforation is unacceptable to many endoscopists, who no longer use PD as first line therapy.

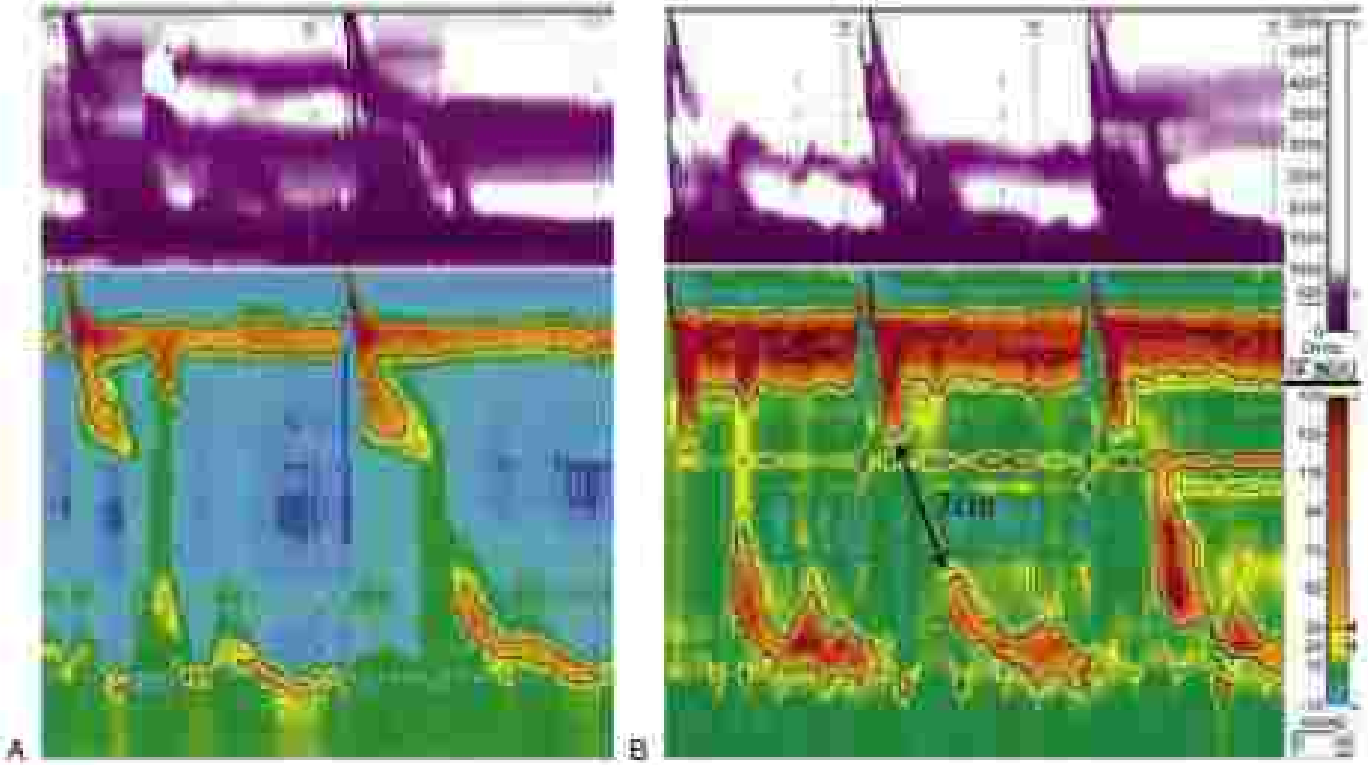

FIG. 6 Minor disorders of peristalsis. (A) Ineffective esophageal motility, weak peristalsis (DCI <450). (B) Fragmented peristalsis (Large breaks | 5 cm) with preserved contractile vigor (DCI ~450). DCI, distal contractile integral. (Courtesy Per Gregersen, Chile.)

Endoscopic injection of botulinum toxin (Botox) may be temporarily effective in relief of spasm in HOBO, DES, or jackhammer disorders. The technique for administration of botulinum toxin has not been standardized; some report injection of the EGJ alone and others include the esophageal body. Botox to the esophageal body may be helpful in cases such as DES or jackhammer, although it is uncertain exactly where and how much drug should be injected. Infection is an uncommon but serious risk of Botox injections. One death resulting from mediastinitis has been reported in a DES case treated with Botox, although other serious adverse events have been rare. Endoscopists may elect to use EUS to guide positioning and depth of injections into the thinner walled esophageal body. In small studies of patients with HOBO and DES, successful relief of symptoms with botulinum toxin injections was achieved in more than 50% of patients at 6 months, with further improvement from serial or alternate treatments thereafter. This was comparable to efficacy in achalasia. Fall off of symptom relief is present in each of these disorders with time, which may require repeat treatments or escalation to surgical intervention. Preexistent symptoms and spastic features may predict early recurrence of symptoms. Botulinum toxin before surgical myotomy has been noted to increase difficulty in identifying and maintaining the proper dissection plane. Prior Botox is not a contraindication to surgery and is sometimes useful as a trial to determine if a patient may respond well to surgical myotomy. Long term studies are not available evaluating the efficacy of repeated botulinum toxin injection for spasm.

SURGICAL MANAGEMENT

Surgical therapy is an option for nonachalasia esophageal motility disorders, but optimal timing and approach are controversial. Surgery generally has been reserved for medically refractory cases because outcomes are variable, sometimes unpredictable, and may be associated with surgical morbidity. As mentioned before, EGJ patients with GERD, whether they also have dysphagia, tolerate antireflux surgery well, and treatment of the reflux often corrects the motility disorder as well. Classically, these patients have a partial fundoplication, most commonly a 270-degree posterior wrap (Fig. 7). Nissen fundoplication also has been shown to be well tolerated in this setting; however, a full wrap should be reserved for EGJ patients with minimal symptoms of dysphagia before surgery. Endoluminal antireflux procedures such as Stretta radiofrequency or transoral incisionless fundoplication, which provide less aggressive valve reconstruction, also may be good options for these patients.

Data on surgical outcomes for EGJOO, DES, and hypercontractile disorders are limited to a few series, mostly small and nonrandomized over the last 50 years. As diagnostic modalities have improved and disease classifications have evolved, these data become even more difficult to interpret. In general, outcomes for surgery are better for relief of chest pain and dysphagia compared with medical or endoscopic therapies. In DES, which is the most frequently studied esophageal motility disorder aside from achalasia, good symptomatic outcomes are reported in about 70% of cases treated with surgical myotomy via an abdominal or thoracic approach at highly skilled centers. These outcomes are notably less successful than those for surgical myotomy for achalasia, so surgery often is reserved as a last resort for patients with nonachalasia motility disorders. Therefore many of these patients endure long courses of medical or endoscopic therapy because there is no clear definition of "medical failure."

Surgical techniques for esophageal myotomy are varied. Traditional open surgery largely has been replaced by minimally invasive techniques, and now endoscopic options are available. Length of the esophageal body myotomy, inclusion of the EGJ in the myotomy, and addition of a concomitant antireflux procedure are variable from surgeon to surgeon. Previous authors in this text have recommended a long thoracic myotomy for the treatment of DES or other esophageal body motility disorders and have described the technique in detail (Fig. 8). Thoracic access allows myotomy extension for the full length of the esophageal body, which is not possible with laparoscopic Heller myotomy. However, thoracic myotomy has the disadvantage of requiring single lung ventilation, chest tube placement, and typically a longer length of stay. The thoracic approach is complicated further if the surgeon desires a fundoplication or extended gastric myotomy.

FIG. 7 Completed laparoscopic 270-degree posterior fundoplication.

POEM offers several advantages for esophageal myotomy and is preferred as a less invasive technique for patients with hypercontractile/spastic esophageal motility disorders. This natural orifice transluminal endoscopic surgery procedure is completely endoscopic and intraluminal. It provides the ability to tailor the length and location of the myotomy with ease because the entire affected esophageal body and EGJ are accessible. POEM allows the surgeon to produce a selective circular myotomy and avoids the risk of vagus nerve injury or disruption of the diaphragmatic crural component of the EGJ. Single lung ventilation, lateral or prone positioning, and chest tubes are not required. Moreover, postoperative pain is usually minimal.

POEM was first applied clinically for achalasia by Inoue in 2008, and since then more than 4000 cases have been performed worldwide with an excellent safety profile and good clinical results, mostly for patients with achalasia. Until recently, studies of POEM for nonachalasia esophageal motility disorders included only a few adult cases and have not always been stratified by subtype. POEM is also used for spastic esophageal disorders such as DES, jackhammer esophagus, and EGJ outflow obstruction (including cases of sigmoider esophagus and EGJ 0.8 as classified before CC v3.0) with good results. POEM has reported success rates of more than 80% for these disorders with relatively low morbidity at expert centers. In a recent meta-analysis by Khan et al, examining the clinical success of POEM in spastic esophageal disorders including type III spastic achalasia, DES and sigmoid esophagus, 179 patients were pooled for analysis from 8 observational studies. Clinical success for all types of spastic esophageal disorders was 87%. Although these studies are small, they suggest comparable outcomes for extended POEM with low morbidity as compared with traditional open or laparoscopic/thoracoscopic approaches for extended esophageal myotomy.

There is controversy about whether myotomy for esophageal body motility disorders should be extended through the EGJ. Given the subsequent weakening of peristalsis after esophageal body myotomy, it is recommended to extend the myotomy through the EGJ onto the stomach to prevent refluxing outflow obstruction and postoperative

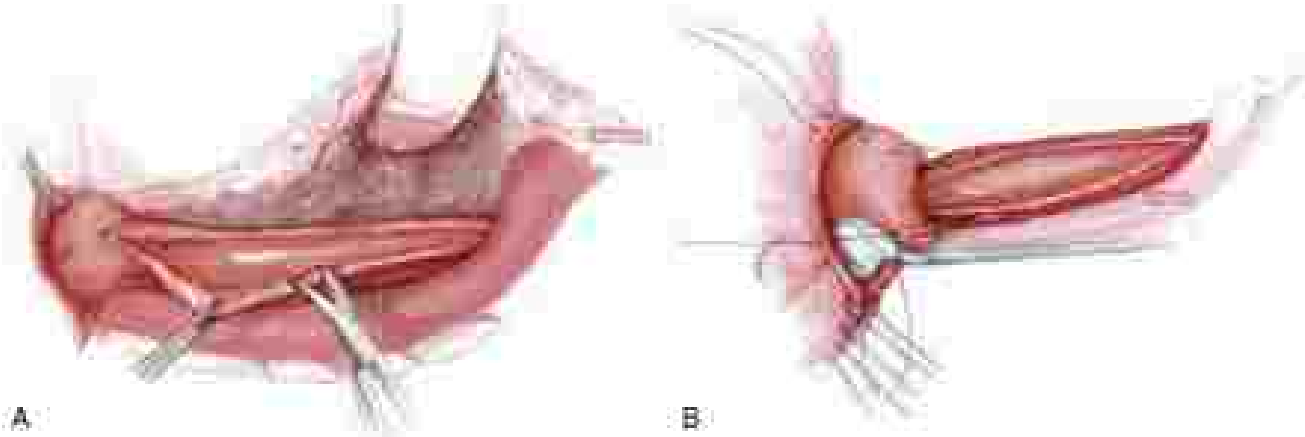

FIG. 8 (A) Thoracic myotomy and (B) distal myotomy. (*Courtesy Carmen Scalise, from Carmen JF, Scalise C, Atlas of Gastrointestinal Surgery, vol 1, 2nd ed. Hudson OH: People's Medical Publishing; 2007.*)

dysphagia, even in the setting of a normally relaxing EGJ. POEM myotomy length should be tailored based on HRM topography and endoscopic measurement of the high pressure zone and has been extended proximally anywhere between 6 and 25 cm above the gastric cardia in such cases. POEM with variable length of myotomy was comparable to other surgical techniques for relief of dysphagia and chest pain and had low morbidity.

A disadvantage of POEM is the requisite learning curve, which is about 20 cases for experienced endoscopists as demonstrated by Kurian and colleagues. GERD is also a long-term risk of POEM, currently with a 20% to 80% risk based on cumulative data. This is in fact comparable to Heller myotomy with partial fundoplication, which has a postoperative rate of GERD between 20% and 62%, depending on the fundoplication technique. Postoperative GERD is asymptomatic in half of patients, so routine follow-up pH testing or endoscopy is prudent. Patients identified with GERD have been treated successfully with PPIs with avoidance of long-term sequelae of reflux. Because the POEM results in a low rate of clinically significant leak or stricture and has been shown to be safe and effective in revision after Heller myotomy, Botox, and pneumatic dilation, POEM does not preclude subsequent endoscopic, laparoscopic, or thoracoscopic procedures should they be required. Due to these benefits, extended myotomy by POEM should be the preferred approach for primary spastic motility disorders requiring intervention.

OPERATIVE TECHNIQUE

Previous chapters in this and other texts have described esophageal myotomy with or without fundoplication via abdominal and thoracic approaches, so these are not repeated in detail here.

POEM is performed in the operating room under general anesthesia. The procedure requires a high definition endoscope for optimal visualization and CO_2 insufflation because it has a better safety profile than room air. The patient is placed in the supine position to allow access to the abdomen or chest. For a few days before the procedure, patients are given a Nystatin rinse prophylactically to clear any *Candida* esophagitis related to esophageal stasis and allowed only a liquid diet for 1 day to allow clearance of retained food. A preoperative antibiotic is administered, as well as a single preoperative dose of intravenous steroid to prevent development of mucosal edema.

Upper endoscopy is performed to evaluate the anatomy, rule out *Candida* spp., and clear any fluid or food debris within the esophagus before proceeding. EndoFLIP (endoscopic functional luminal imaging probe) is used to measure baseline esophageal diameter, pressure, cross sectional area, distensibility, and compliance. An overtube is used for distal myotomy to stabilize the scope from overlonging. No overtube is used for extended myotomy. The gastric wall is tattooed with indigo carmine 2 cm distal to the EGJ in the anterior position along the lesser curvature, marking the target for the distal extent of the myotomy. The location and extent of the myotomy and mucosotomy are calculated based on careful evaluation of the preoperative manometry and intraoperative evaluation of the high pressure zone. An angled dissecting cap is attached to the high definition endoscope to facilitate dissection and visualization. A mucosal lift is created with injectable saline with dilute indigo carmine in the anterior esophagus 2 to 4 cm proximal to the proximal extent of the planned myotomy (Fig. 9).

An endoscopic cautery knife is used to create a 1.5-cm longitudinal mucosal incision to expose the submucosa. Using the dissecting cap, the surgeon advances the endoscope through the mucosotomy and into the submucosal plane. Once inside, spray cautery and serial injections of lifting solution are used to create a submucosal tunnel, separating the mucosa from the circular muscle. Visible vessels are coagulated with the dissecting knife or grasped with hot biopsy forceps. The submucosal tunnel is extended distally across the GEJ and onto the gastric wall until the distal darker blue tattoo is reached.

Once satisfied with the extent of the tunnel, the endoscope is brought back, and the myotomy is created by selectively dividing the circular muscle layer. The thin longitudinal muscle layer is left intact whenever possible. Full-thickness breaches of the muscle are usually not critical as the submucosal adventitial tissue is left intact. The myotomy is extended across the EGJ and into the proximal gastric wall. During the procedure, exiting the tunnel to deflate insufflated gas from the stomach may be required to relieve gastric distension. Capnoperitoneum may develop in up to 30% of cases; it is often minor and self-limited but is evacuated easily with a Veress needle if abdominal overdistension or respiratory compromise develops.

After the myotomy is completed, the surgeon withdraws the endoscope, checking for hemostasis. Completion endoscopy identifies any inadvertent mucosal injuries, which are treated with endoscopic clips. The EndoFLIP catheter is replaced, and measurements are compared with those obtained before surgery to ensure adequacy of the myotomy before closure. Endoscopic clips then are used to close the proximal mucosotomy in a longitudinal fashion from distal to proximal.

Postoperative Care

The patient is kept NPO overnight, and a routine contrast esophagogram is obtained on the first postoperative day. If no leaks or obstruction are identified, the patient is allowed clear liquids and crushed medications. The patient may be discharged on postoperative day 1 if liquids are tolerated and should maintain a pure-consistency diet for 1 week to avoid disruption of the mucosal closure clips. In most cases, postoperative pain is minimal and usually does not require narcotics.

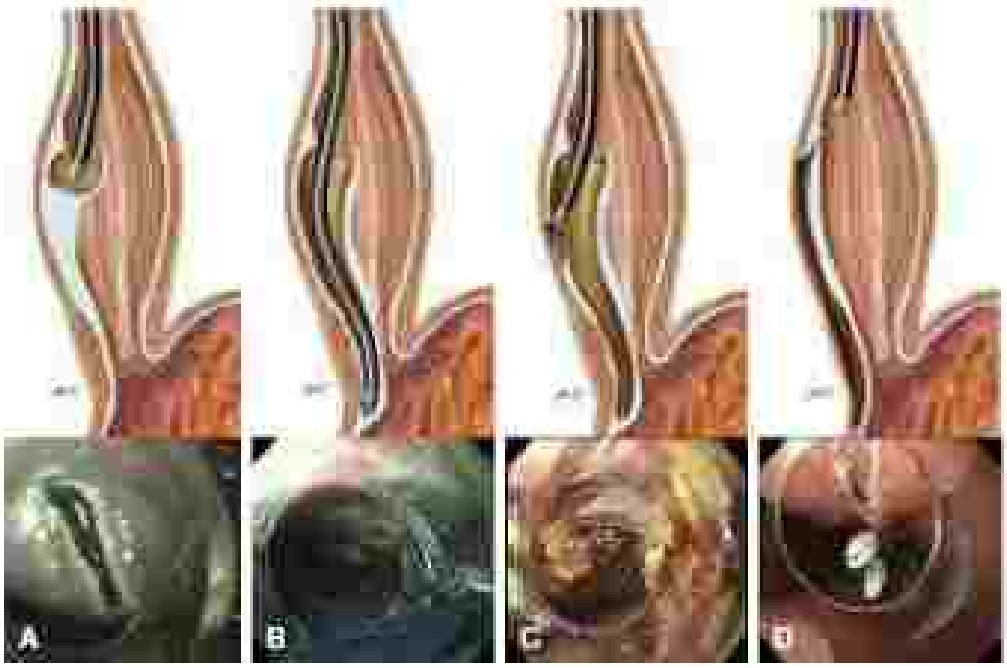

FIG. 9 Per oral endoscopic myotomy. (A) Entry into submucosal plane. (B) Creation of submucosal tunnel (mucosa is intact at circular muscle at superior). (C) Myotomy of circular muscle. (D) Closure of mucosal entry site with clips. (From Inoue H, Sato H, Ikeda H, et al. Per-oral endoscopic myotomy: a series of 500 patients. J Am Coll Surg 2015;221:256–264.)

Complications

Acute postoperative complications can include barotrauma bleeding, mucosal leak or dehiscence, or mediastinitis. No deaths have been reported. Bleeding may require transfusion and repeat endoscopy to achieve hemostasis. Mucosal leaks or dehiscence may heal with conservative management but often require repeat endoscopy and repair with additional clips or suturing. Mediastinitis is treated with antibiotics and may require percutaneous or surgical drainage. Post procedure adverse events in the meta analysis reported by Khan et al for all types of spastic esophageal disorders were 14%. Most of the adverse events (74%) were managed conservatively. Five patients required prolonged hospitalization and/or an intervention for pneumothorax, pulmonary embolism, capnoperitoneum, or bleeding.

CONCLUSION

There is work to be done to the realm of neurohalasia esophageal motility disorders as HRM diagnostics and treatment options evolve. To achieve the best possible outcome, therapeutic options should be considered carefully and individually tailored. Patients should be advised on expectations because treatment outcomes are somewhat unpredictable and may be disappointing in some cases. POEM is a promising, minimally invasive treatment option for hypercontractile and spastic disorders and perhaps will be considered as an early surgical intervention rather than salvage therapy, given its relative success and safety profile. For hypermotility disorders associated with GERD, partial fundoplications remain the gold standard, although Nissen fundoplication also has been shown to be well tolerated in all but the most extreme cases. There also may be a role for newer endoscopic antireflux procedures, although there are insufficient data at this time to define their application for these relatively rare disorders.

ACKNOWLEDGMENT

We acknowledge Lee L. Swanstrom, MD, and Kristin Wilson Bonds, MD, for their comprehensive chapter content in the previous edition of this text.

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Management of Esophageal Cancer

Filippo Filicori, MD, and Lee L. Swanström, MD, FACS, FASGE, FRCSEng

The conceptual approach to esophageal cancer has changed significantly over the past few decades. New treatment modalities have significantly improved the outcomes in this patient population. As an example, neoadjuvant therapy has considerably improved outcomes for patients with advanced locoregional disease; however, the benefits of neoadjuvant treatment in patients with more limited locoregional spread has yet to be proven. Because nodal involvement is the best predictor of long-term survival and an important guide for therapeutic approaches, a thorough staging is mandatory for all esophageal cancers, along with a determination of the functional status of the patient. Another disruptive advance is that of endoscopic resection (ER) of early cancers and premalignant lesions. This has been proven to be a valuable diagnostic and therapeutic tool and is increasingly used as a first-line approach to superficial neoplasms. These changes in treatment algorithms, coupled with decreasing operative morbidity, improved oncologic yields of recent surgical approaches, and enhanced screening and surveillance algorithms for early cancers are the underlying reasons for the improved survival we have witnessed in the last few decades.

STAGING

Staging of esophageal cancers is most often by the TNM classification, which evaluates the local tumor (T), the regional lymph nodes (N) and the distant sites of metastasis (M). Over the past decade, the importance of the number of involved lymph nodes has been recognized and incorporated into the seventh and eighth editions of the American Joint Committee on Cancer (AJCC) Staging System (Table 1 and Figs. 1 to 3). This classification is based on the risk-adjusted random survival factor analysis of data generated from 22,654 patients who were treated with esophagectomy alone or esophagectomy with preoperative neoadjuvant and/or postoperative adjuvant therapy. The eighth edition of the AJCC classification distinguishes three N categories based on the number of lymph nodes involved. The most recent classification also presents separate staging for the clinical, pathologic (pTNM), and postneoadjuvant pathologic groups to increase clarity of treatment algorithms. In addition, pT1 cancers have been further subcategorized in pT1a and pT1b, which allows for a more tailored surgical approach given the higher risk for pT1b lesions to have nodal spread and, by implication, local recurrence after endoscopic treatment. Furthermore, cancers of the esophagogastric junction that have their epicenters within the proximal 2 cm of the gastric cardia (previously classified as Siewert types I and II) are now staged as esophageal cancers. Those with epicenters more than 2 cm distal to the esophagogastric junction (previously classified as Siewert type III), even if the esophagus is involved, are staged as stomach cancers and therefore treated following the gastric cancer guidelines (Fig. 4). Staging should proceed in a methodical fashion to accurately determine the TNM status of the patient and better advise as to the best treatment options.

ESOPHAGOGASTRODUODENOSCOPY AND BIOPSY

Endoscopy and tissue biopsy are the first steps in surgical staging. The location of the tumor, length, extent of circumferential involvement, and presence of associated Barrett's esophagus according to Prague criteria should be accurately recorded. Traditional endoscopic biopsy is the preferred approach for large lesions and those that are suspected of being locally aggressive. Narrow band imaging and newer imaging techniques that allow for real-time detection of dysplastic or neoplastic mucosal, such as confocal laser microscopy or optical coherence tomography, should be used liberally to increase the diagnostic yield of the biopsies. Because ER allows accurate pathologic T staging, it is recommended as a first diagnostic/therapeutic approach for all superficial lesions and especially those that are less than 2 cm and those appearing nodular or ulcerated. Consistent use of ER makes mistaging the depth of invasion of T1a and T1b lesions uncommon. ER techniques are described later in the chapter. When the lesion invades the submucosal layer or if the resection margin is positive, other methods such as endoscopic ultrasound (EUS) can be used to determine the T stage.

EUS is the only tool that allows the clinician to directly visualize the depth of invasion of a neoplasm. Despite technological improvements, T mistaging is still common and occurs in as many as 20% of cases, especially in those with T1 and T2 cancers. Specifically, a recent meta-analysis has shown that EUS accuracy for T1 cancers was 83.5%, 75% for T2 cancers, 89% for T3 cancers, and 89% for T4 cancers. EUS can provide information regarding N status with an accuracy of 77% to 84%, a number that can rise to 95% when this technique is coupled with fine needle aspiration. There is little information on the accuracy of EUS clinical N staging using the AJCC eighth edition staging system. Overall, EUS is a valuable tool when the tumor is too large or deep for endoscopic mucosal resection (EMR) or when EMR yields indeterminate results or positive margins.

CROSS-SECTIONAL IMAGING

Computed tomography (CT) has for a long time been the primary diagnostic imaging modality to determine N and M stage. It is of the utmost importance to rule out metastatic disease, which is present in 35% of the patients at diagnosis. More recently, fused positron emission tomography (PET) CT studies have improved diagnostic performance by combining anatomic and metabolic information. The radiotracer 2-[18F] fluoro-2-deoxy-D-glucose has been reported to accumulate in 92% to 100% of esophageal cancers. Unfortunately, FDG-PET lacks sufficient specificity to determine T staging; other modalities, described previously, are more suitable for the purpose of accurately staging local invasion. Data suggest that PET CT increases accuracy when compared with FDG-PET alone when evaluating N status (92% vs 84%). FDG-PET has also been shown to be more accurate compared with CT to determine the presence of M disease (94% vs 63%). In addition, PET CT also allows detection of the metabolic response of a tumor to neoadjuvant treatment, which has been correlated with survival in several studies. Overall PET CT appears to allow better staging providing additional information in 23% of cases when compared with CT alone. PET CT is therefore the preferred imaging modality in patient with advanced locoregional disease for both initial staging and to determine response to neoadjuvant treatment.

TREATMENT ALGORITHMS

Treatment recommendations are ideally made after joint consultation by a multidisciplinary team including surgical, radiation and medical oncologists, gastroenterologists, radiologists, and pathologists. National Comprehensive Cancer Network guidelines were recently updated in 2018 for both esophageal adenocarcinoma and squamous cell carcinoma and contain several new recommendations compared with their previous versions (Figs. 5 and 6).

TisN0M0, T1aN0M0, and T1bN0M0

Superficial esophageal adenocarcinomas are often cured by resection alone, whether using endoscopic techniques or esophagectomy.

TABLE 1. Staging of Esophageal Cancer, AJCC Manual, 8th Edition

Category	Criteria
T CATEGORY	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a*	Tumor invades the lamina propria or muscularis mucosae
T1b*	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
T4a*	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b*	Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea
N CATEGORY	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to 1–2 regional lymph nodes
N2	Metastasis to 3–6 regional lymph nodes
N3	Metastasis to ≥7 regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
ADENOCARCINOMA G CATEGORY	
GX	Differentiation cannot be assessed
G1	Well differentiated, with >95% of the tumor composed of well-formed glands
G2	Moderately differentiated, with 50%–95% of the tumor showing gland formation
G3*	Poorly differentiated, with tumors composed of neat and sheets of cells with <50% of the tumor demonstrating glandular formation
SQUAMOUS CELL CARCINOMA G CATEGORY	
GX	Differentiation cannot be assessed
G1	Well differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basaloid-like cells, tumor cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing features and pearl formation generally absent
G3*	Poorly differentiated, consisting predominantly of basaloid-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or processes. The arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells
SQUAMOUS CELL CARCINOMA L CATEGORY†	
LX	Location unknown
Upper	Cervical esophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

From Amin MB, ed. *AJCC Cancer Staging Manual*. 8th edition. Chicago: Springer; 2017. Used with permission of the American College of Surgeons.

*Subcategories.

†If further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma (G3).

‡If further testing of "undifferentiated" cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma (G3).

§Location is defined by epicenter of esophageal tumor.

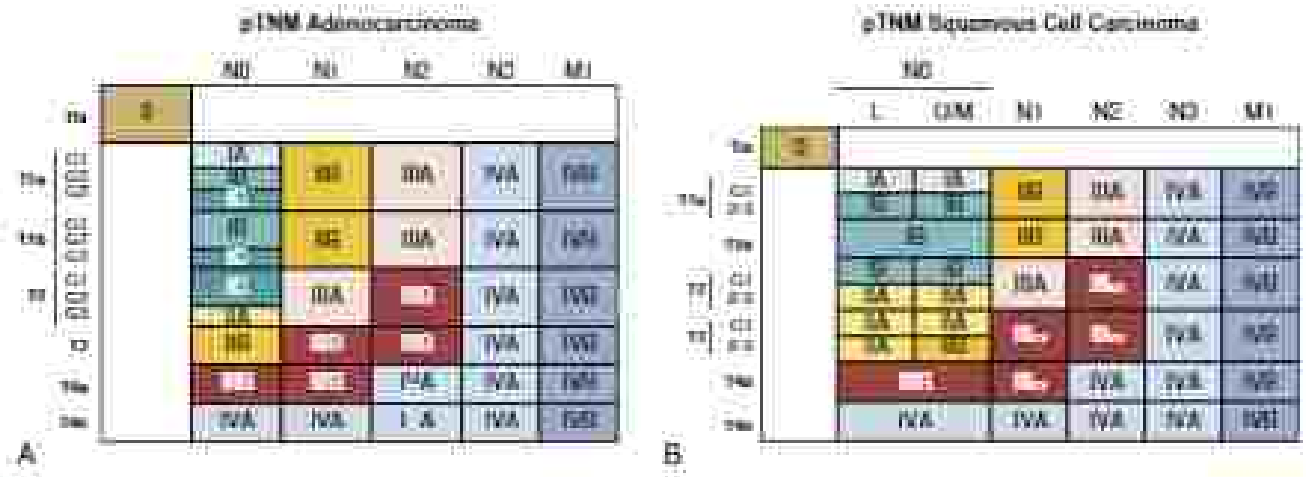

FIG. 1. (A) Pathologic stage groups (pTNM) for (A) adenocarcinoma and (B) squamous cell carcinoma. *From Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thorac Oncol. 2017;12(1):36–42.*

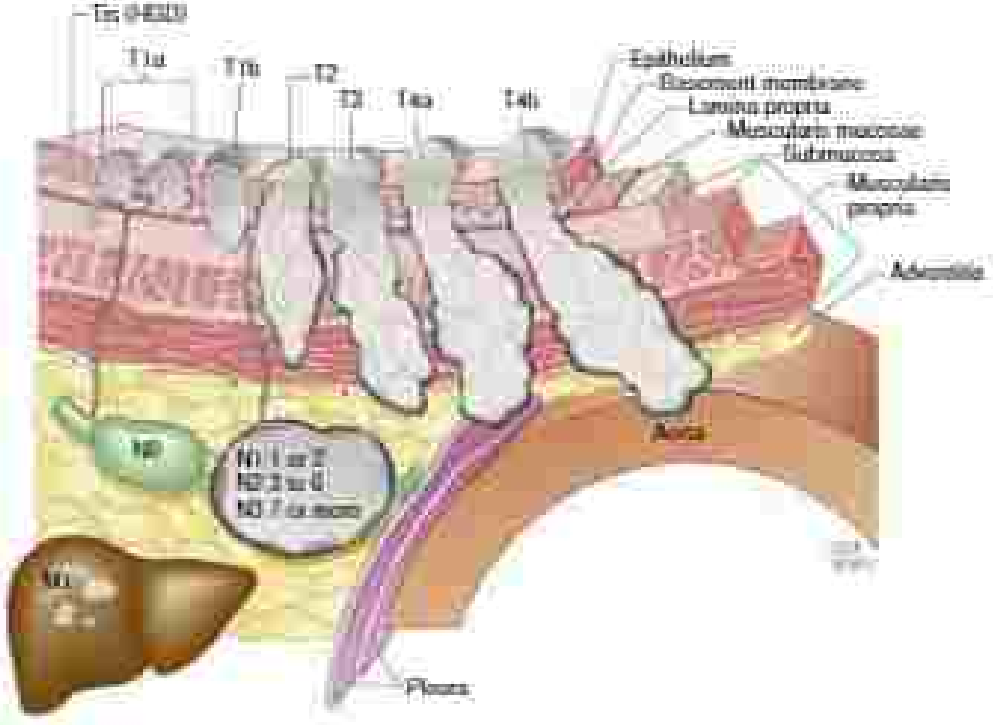

FIG. 2. Eighth edition American Joint Committee on Cancer classification (TNM) anatomy. *From Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thorac Oncol. 2017;12(1):36–42.*

A tumor with stage Tis by definition does not extend beyond the basal membrane and therefore can be treated by endoscopic means such as ER. Radiofrequency ablation (RFA) and cryoablation can also be used on flat lesions but lack the advantage of providing a surgical specimen that might guide further treatment. T1a tumors invade through the basal membrane and into the superficial submucosal space. Local resection is therefore potentially curative. These neoplasms do have a 2% potential to harbor metastases to the regional lymph nodes, but because this is near the operative mortality of surgical resection, it is universally considered the preferable option. Sampling errors might also occur and metachronous neoplasms can potentially surround the biopsied areas and therefore these patients require both endoscopic and radiologic continued surveillance. If the carcinoma is penetrating the muscularis mucosae (T1b), the rate of lymphatic infiltration increases in correlation with the depth of infiltration in the submucosa. The overall chance of nodal spread is directly correlated with the depth of invasion of the three submucosal layers (sm1, sm2, and sm3), tumor differentiation, and presence of lymphovascular invasion (LVI). LVI is the most important prognostic determinant of outcome for locally resected early stage cancer. Risk of nodal involvement has been estimated to increase from 2% for a T1a lesion without LVI to 60% for T1b lesions with LVI with an expected decrease in survival rates. Size of tumor and differentiation are other independent prognostic variables in some studies, with lesions smaller than 2 cm and well to moderate differentiation associated with a low risk of nodal involvement. It is therefore mandatory to obtain lymph node evaluation through CT or EUS in all patients with T1b disease. ER is an ideal minimally invasive treatment

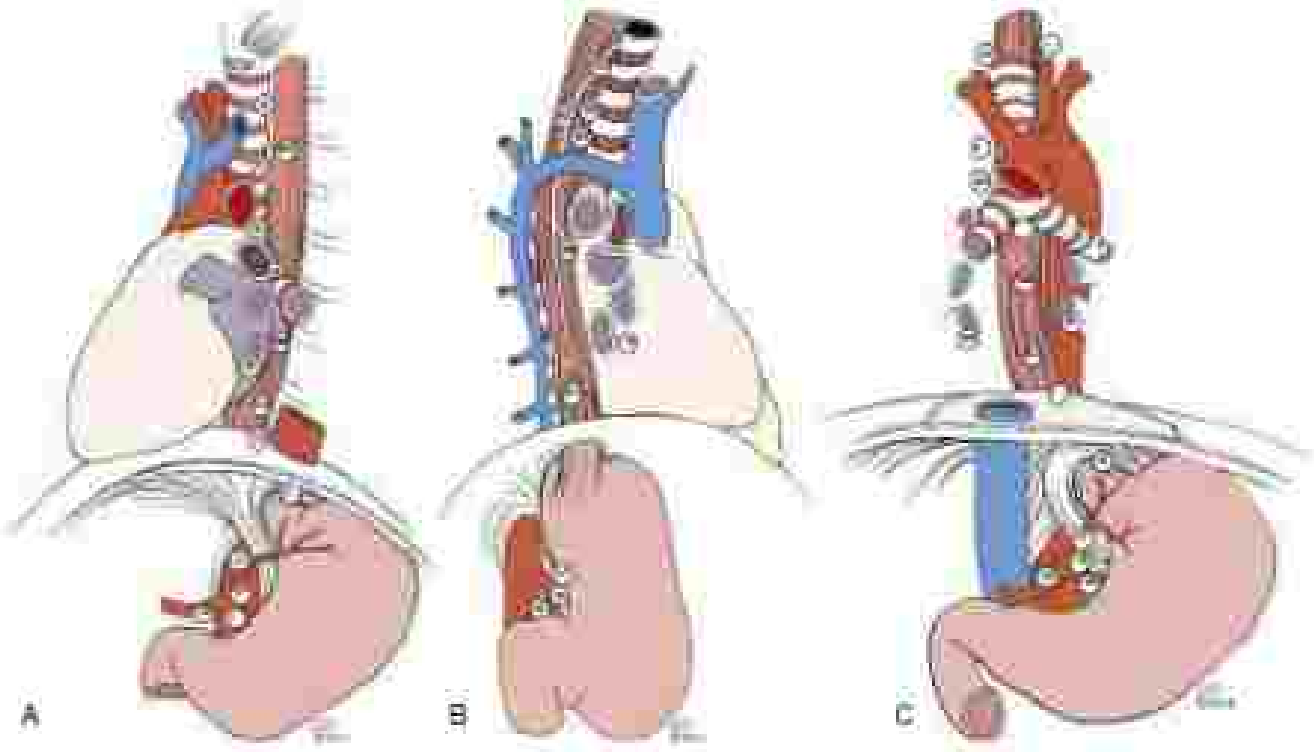

FIG. 3 Lymph node maps for esophageal cancer. Optimal lymph node stations for staging esophageal cancer from the (A) left, (B) right, and (C) anterior. 1, left lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 1R, right lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 2L, left upper paratracheal nodes, between the top of the aortic arch and apex of the lung; 2R, right upper paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and apex of the lung; 4L, left lower paratracheal nodes, between the top of the aortic arch and the carina; 4R, right lower paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and cephalic border of the azygos vein; 7, subcarinal nodes, caudal to the carina of the trachea; 8a, lower thoracic paraesophageal lymph nodes, from the caudal margin of the inferior pulmonary vein to the esophagogastric junction; 8M, middle thoracic paraesophageal lymph nodes, from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein; 8U, upper thoracic paraesophageal lymph nodes, from the apex of the lung to the tracheal bifurcation; 9L, pulmonary ligament nodes, within the left inferior pulmonary ligament; 9R, pulmonary ligament nodes, within the right inferior pulmonary ligament; D, diaphragmatic nodes, lying on the dome of the diaphragm and adjacent to or behind its crura; 14, paracardial nodes, immediately adjacent to the gastroesophageal junction; 17, left gastric nodes, along the course of the left gastric artery; 18, common hepatic nodes, immediately on the proximal common hepatic artery; 19, splenic nodes, immediately on the proximal splenic artery; T , celiac nodes, at the base of the celiac artery. Cervical paraesophageal level VI and level VII lymph nodes are named as per the head and neck map. *(From Ilson DH, Shevanna H, Ferguson MK, Rizkallah TH. Outcome of the esophagus and esophagogastric junction: an eighth edition staging primer. Pract Gastroenterol Nutr. 2017;1[1]:26-47.)*

for tumors that are well differentiated, smaller than 3 cm, within mid and mid-third LVI. Many groups are exploring extended indications for endoscopic treatment (e.g., T1b lesions, larger tumors moderately differentiated, depending on advanced imaging to exclude nodal involvement, but this remains controversial at least for patients who could tolerate esophagectomy. More advanced tumors (T2, poorly differentiated, and with LVI) should undergo esophagectomy if the patient is a good operative candidate based on functional status.

T2, N0-1, M0

Currently, optimal therapy for T2 cancers or tumors with limited locoregional involvement (N0-1) remains controversial. Current dogma that all patients with N1 disease should be offered induction therapy is based on older staging systems in which the number of involved nodes was not taken into account. There is growing evidence that neoadjuvant therapy is not beneficial to node-negative patients and perhaps not even in those with limited (N1) nodal disease. This fits with evidence that less than 50% of patients with N1 lymph node involvement in the current staging system will develop systemic disease and raises questions about the value of toxic systemic therapy for all these patients.

In addition, it is important to bear in mind that understaging represents a major source of suboptimal treatment in up to 20% of patients with T2 disease. The overall survival for these patients is significantly lower than those correctly staged. Understaged patients with advanced nodal disease are at high risk for systemic metastases, and resection alone is inadequate. In a recent study performed at the University of Southern California, three factors were found to be associated with understaging in patients with advanced locoregional disease: dysphagia at presentation, tumor size greater than 3 cm, and poor differentiation. When none of these factors were present, 92% of patients were correctly staged. Conversely, when all three factors were present, 82% of patients were understaged. Patients with dysphagia at presentation, tumor size larger than 3 cm, and poor differentiation should be considered at high risk for advanced nodal disease, despite the objective findings on clinical staging studies, and be recommended to undergo neoadjuvant therapy before resection.

T3-4, N1-3, M0

There is a clear survival advantage to patients with T3+ or N2+ locally advanced disease who undergo neoadjuvant treatment. Recent studies also suggest a benefit of adjuvant therapy in understaged patients

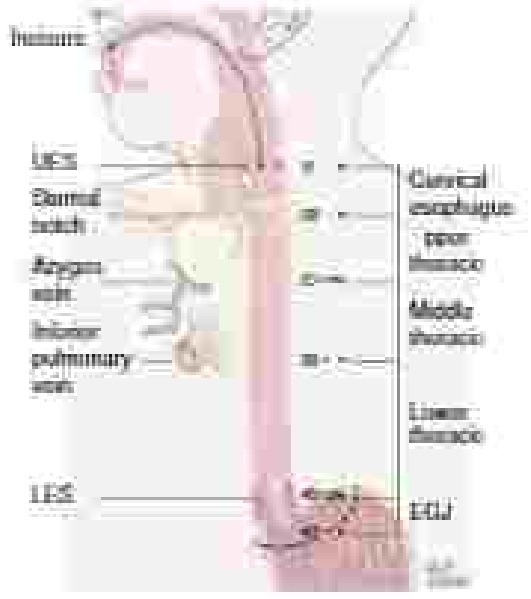

FIG. 6 Location of esophageal cancer primary site, including typical endoscopic measurements at each region measured from the incisors. Exact measurements depend on body size and height. Location of cancer primary site is defined by cancer epicenter. Cancers involving the esophagogastric junction (EGJ) that have their epicenter within the proximal 2 cm of the cardia (Siewert types II/III) are to be staged as esophageal cancers. Cancers whose epicenter is more than 2 cm distal from the EGJ, even if the EGJ is involved, will be staged using the stomach cancer TNM and stage groups. *LES*, lower esophageal sphincter; *UES*, upper esophageal sphincter. (From Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thorac Oncol. 2017;12(1):36–42.)

who undergo primary resection. Chemoradiation has been associated with both a higher rate of R0 resections and a median disease-free and overall survival improvement. The prognostic significance of histologic tumor regression and pathologic complete response in patients with esophageal adenocarcinoma and squamous cell carcinoma has been demonstrated in several studies. The major difference between these two histologic tumors is their response to chemotherapy. Squamous cell carcinoma has a greater response to treatment, and endoscopic surveillance is regarded as a reasonable option when complete clinical response is achieved. Esophageal adenocarcinoma has higher rates of local failure and most centers would still advocate for esophagectomy even in the face of initial complete clinical response. Surgery should be timed at 6 to 10 weeks after completion of neoadjuvant treatment and should aim for an R0 resection with the highest lymph node count possible; current recommendations are for at least 15 lymph nodes.

T4b, Any N or M1

Patients with cancer invading into structures that cannot be resected (aorta, left atrium, and spine) or patients with distant disease are not candidate for curative surgical resection and the focus of their care should be palliation of their disease. This goal is achieved best in the context of a multidisciplinary team that must include an oncologist, psychologists, and palliative care specialists. Chemoradiation can deliver long-term disease control, improve dysphagia, and prolong survival and is therefore indicated in patients with adequate performance status. Although chemotherapy can help to control the growth of disseminated disease, radiation is more effective in controlling dysphagia, pain, and bleeding. Today, HER2 and microsatellite instability analysis is recommended in metastatic disease to evaluate for potential implementation of targeted therapies. Endoscopic stent insertion is effective for dysphagia relief; however, it is associated with a significant number of complications, including perforations and stent migrations. Photodynamic therapy has waned and waxed in popularity for palliating patients with dysphagia and metastatic disease. Despite good results in the short term, there are several associated

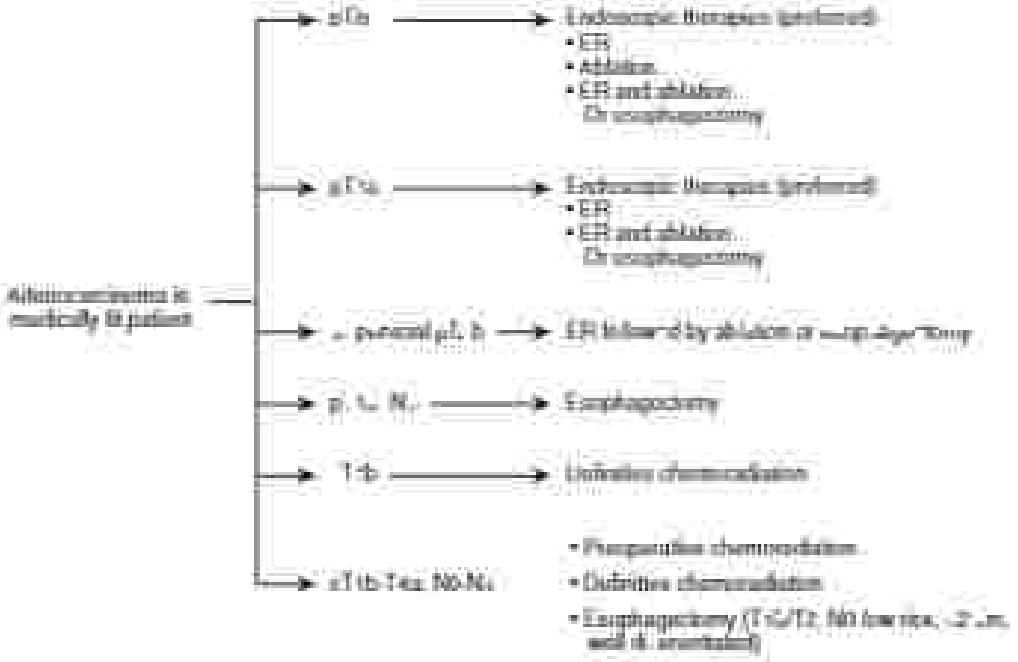

FIG. 8 Treatment algorithm for adenocarcinoma in medically fit patient. *ER*, endoscopic resection. (From from National Comprehensive Cancer Network treatment guidelines, May 2018.)

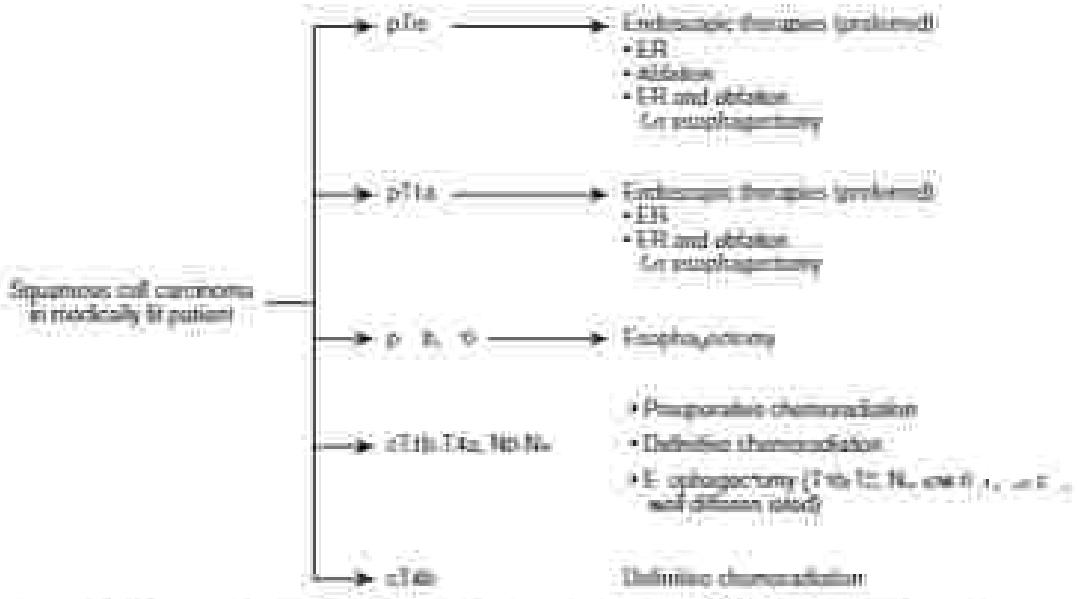

FIG. 6 Treatment algorithm for squamous cell carcinoma in medically fit patients. ER, endoscopic resection. *(Data from National Comprehensive Cancer Network treatment guidelines, May 2018.)*

side effects (photosensitivity being the most bothersome one for patients) and perforations have been reported.

TREATMENT OPTIONS

Endoscopic Resection and Ablation

ER or ablation is useful for both accurately staging and is potentially curative to patients with early esophageal cancer. Determination of which patients should be selected for endoscopic therapy versus esophagectomy in early esophageal cancer should be done on a case-by-case basis. All patients should undergo CT scan and EUS with or without fine needle aspiration of suspicious lymph nodes to rule out metastatic disease. Patients with multifocal and/or long segments of high grade dysplasia, those with poorly differentiated histology or LVI, those with poor esophageal motility, and younger patients in whom continued surveillance may be cumbersome may be better served with an esophagectomy. Multiple endoscopic treatments may be required to attain complete eradication and different treatment modalities should be tailored to the characteristics of the neoplasm. Esophagogastroduodenoscopy (EGD) is usually performed every 8 to 12 weeks until complete eradication of neoplastic and metaplastic tissue is obtained, after which surveillance is continued.

Ablation therapies do not provide a pathologic specimen and are not as effective in treating nodules or ulcerated lesions. However, they are particularly useful in the treatment of mucosa containing long segments of columnar lined esophagus. The two most common techniques described are RFA and cryoablation. These technologies reliably ablate the mucosa down to the lamina propria layer of the esophageal mucosa and normal squamous mucosa regenerates from progenitor stem cells.

Endoscopic Mucosal Resection

EMR is most commonly performed using a cap and suction, either with a band ligation or not, after which a cautery snare is used to resect the artificially created polyp. EMR can be performed under conscious sedation and is indicated for lesions that are smaller than 2 cm. Narrow band imaging should be used liberally before and during the procedure to identify the areas of dysplastic/neoplastic epithelium. Lesions bigger than 2 cm might require piecemeal resection; however, this is not as reliable when determining surgical margins and has a higher local recurrence rate. The main advantages of EMR include a short learning curve, low perforation rate, and the possibility of performing circumferential resections. A combination of resection and ablation can also be used to achieve complete eradication; however, long segments of circumferential resection have the potential to result in stricture formation that can be occasionally difficult to treat.

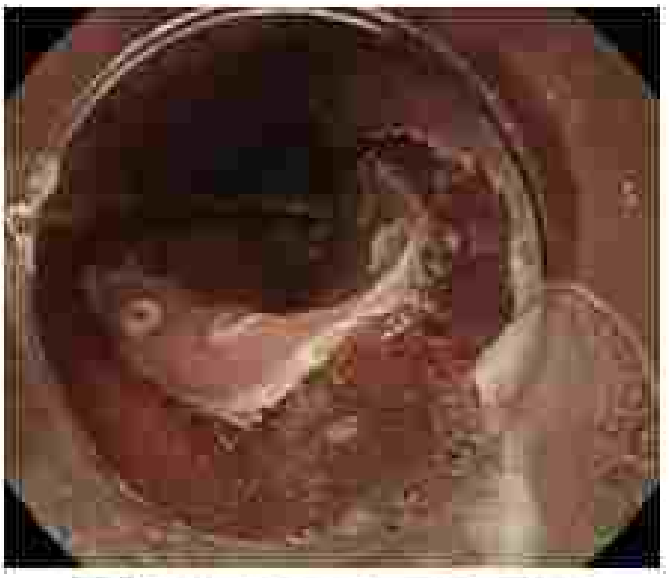

FIG. 7 Endoscopic submucosal dissection resection site.

Endoscopic Submucosal Dissection

Although it is somewhat technically challenging to perform endoscopic submucosal dissection (ESD) in a narrow lumen such as the esophagus, submucosal dissection is particularly useful for flat lesions or lesions that are larger than 2 cm. ESD is associated with a higher R0 resection rate and lower local recurrence rate than EMR. The technology required is widely available and includes high definition endoscopes, beveled dissection caps, and various endoscopic energy sources (Fig. 7). Most complications arising from ESD, including bleeding, stricture formation, and even perforation, can be managed endoscopically.

Radiofrequency Ablation

RFA has become increasingly popular thanks to its ease of use and documented efficacy. It is performed using a high-power radiofrequency generator and a variety of balloon catheters or scope directed ablation catheters. These devices, which apply bipolar energy to the epithelium, consistently ablate the superficial 0.5 mm of mucosa (Fig. 8). Although this modality has been mainly studied for metaplastic and dysplastic changes of the esophageal epithelium, it can also be applied to T1a and even T1a esophageal adenocarcinoma when nodules are not present. The most common complications reported include chest pain lasting less than 1 week, strictures requiring dilation (6% to 8%), and gastrointestinal hemorrhage (1%).

Cryotherapy

Cryotherapy is an ablative technique that causes tissue destruction by application of liquid nitrogen or carbon dioxide gas. Small areas can be treated (2 to 3 cm) while covering approximately one third or one half of the luminal circumference with each application. Multiple areas can be treated in one endoscopic session. On average, three to four endoscopies are needed to completely ablate a long segment of disease, and the procedures can be performed approximately every 6 to 8 weeks. Some small series report complete eradication rates of 75% for superficial lesions and it may be more applicable for irregular surfaces and small nodules.

Surgical Therapy

All patients who are being considered for surgery should be assessed for their fitness to undergo general anesthesia and a major surgical procedure. Definitive chemoradiotherapy should be offered to those patients who would not be able to tolerate major thoracoabdominal surgery. Pretreatment nutritional status should be assessed, especially in patients presenting with dysphagia and weight loss before diagnosis or resulting from neoadjuvant therapy. Enteral nutrition with a feeding tube (jejunostomy tube preferred) should be considered. The type of esophagectomy depends on the location of the tumor as well as the surgeon's expertise. The three most common open operations, transhiatal esophagectomy, two stage Ivor Lewis esophagectomy, or three stage McKeown esophagectomy have low mortality and low morbid minimally invasive alternatives. The choice of procedure should be based on the tumor's location and the surgeon's expertise. Probably more important than the surgical approach is the adequacy of R0 resection and the lymph node harvest. Although no defined number of lymph nodes has been definitively established, National Comprehensive Cancer Network guidelines suggest that at least 15 lymph nodes should be harvested at the time of surgery.

Minimally Invasive Ivor Lewis (2-Stage) Esophagectomy

Ivor Lewis two stage (abdominal, thoracic) esophagectomy is the most commonly performed surgical procedure worldwide for esophageal cancer. Ivor Lewis minimally invasive esophagectomy (MIE) has rapidly become the preferred surgical approach owing to decreased morbidity and faster recovery times compared with its open alternative. Given the optimal intraabdominal and intrathoracic exposure, it is an especially good choice for neoplasms in the middle and distal portions of the esophagus. The patient is positioned supine in a split leg position with moderate reverse Trendelenburg. Five

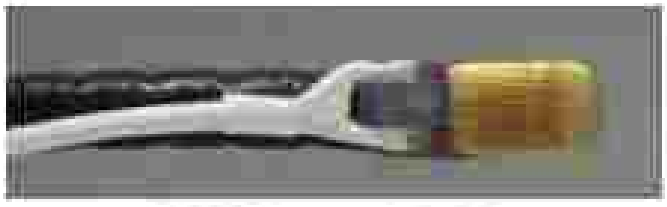

FIG. 8 Radiofrequency ablation device.

intraabdominal ports and an atraumatic liver retractor for the left hepatic lobe are positioned to expose the hiatus. After careful inspection to rule out any metastatic disease, the dissection is started at the gastrohepatic ligament, exposing the right crus. A complete D2 lymph node dissection is performed starting at the celiac trunk and following the hepatic and left gastric artery, the superior margin of the portal vein, and the pretpancreatic tissue. The left gastric vascular pedicle is divided. A thorough node dissection is particularly important for adenocarcinoma of the cardia, which has higher propensity to metastasize to these lymph nodes. Equally important is an en bloc dissection of the distal esophagus, which is easily done from the laparoscopic approach. The gastrocolic ligament is then divided just distal to the gastroepiploic arcade taking care not to injure the gastric vascular structures, which might compromise the blood flow to the newly formed conduit (Fig. 9). The use of fluorescence imaging at this stage can facilitate the identification of the right gastroepiploic artery and determine the adequacy of perfusion at the distal conduit. The dissection is carried out medially to the level of the duodenum and then extended to the fundus by dividing the short gastric vessels and the lateral phrenoesophageal ligament. The stomach is then lifted anteriorly, and the retroperitoneal attachments are divided. Pyloroplasty or botulinum (onto injection of the pylorus is performed at this stage to aid the emptying of the conduit. Transhiatal dissection of the esophagus is then performed dividing the phrenoesophageal ligament and dissecting the paraaortic and lower paraesophageal nodes and dividing the peritoneum from the crurae bilaterally. A Penrose drain is used to encircle the distal esophagus for retraction during both the abdominal and thoracic phase. A 3- to 5-cm wide gastric conduit is then created by dividing the stomach with multiple firings of a purple load linear stapler, starting at the level of the incisura on the medial side all the way proximal to the fundus leaving the last 5 cm of stomach undivided to allow retrieval during the thoracic phase (Figs 10 and 11). A running Lembert suture is then used to reinforce the staple line and a silk suture is placed 5 cm proximal to the incisura to mark the distal end of the conduit during the thoracic phase. As a final step, a 12F feeding jejunostomy tube is inserted in the small bowel.

Thoracic Phase

Traditionally performed with the patient in the left lateral decubitus position, this portion of the procedure is increasingly done with the patient in the prone position. The right lung is collapsed either by use of double lumen ventilation or by positive pressure capnothorax with laparoscopic valved thoracic ports. Four trocars are placed in the thoracic wall in a diamond pattern. After dividing the pulmonary ligament to the level of the inferior pulmonary vein, a fan retractor is placed to provide better visualization of the posterior mediastinal pleura at the level of the azygos vein. The azygos vein is divided with a vascular stapler to allow exposure of the entire esophagus (Fig. 12). Depending on tumor characteristics and patient's comorbidities, we generally perform an en bloc lymph node dissection to maximize local tumor control by resection of the tumor bearing esophagus within a wide envelope of adjoining tissues that includes both pleural surfaces, the thoracic duct, and the azygos vein. This results in a complete mediastinal node dissection from the azygos arch to the esophageal hiatus. The Penrose drain left around the esophagus is retrieved and used to retract the esophagus and facilitate dissection. The esophagus is then divided at the thoracic inlet and the proximal margin is sent for frozen section. The gastric conduit is then gently grasped and pulled up into the chest up to the level of the silk stitch previously placed, making sure no twists are present. A transoral circular stapler (Orvil, Medtronic) is then inserted through the patient's mouth into the esophageal stump. The nasogastric tube connected with the Orvil is passed through a small opening next to the staple line and removed through one of the trocars. At this point, fluoroscopic imaging is once again used to determine appropriate perfusion of the conduit. This can be traumatic to a point of maximal perfusion making sure that excessive tension is avoided. The EEA (Medtronic)

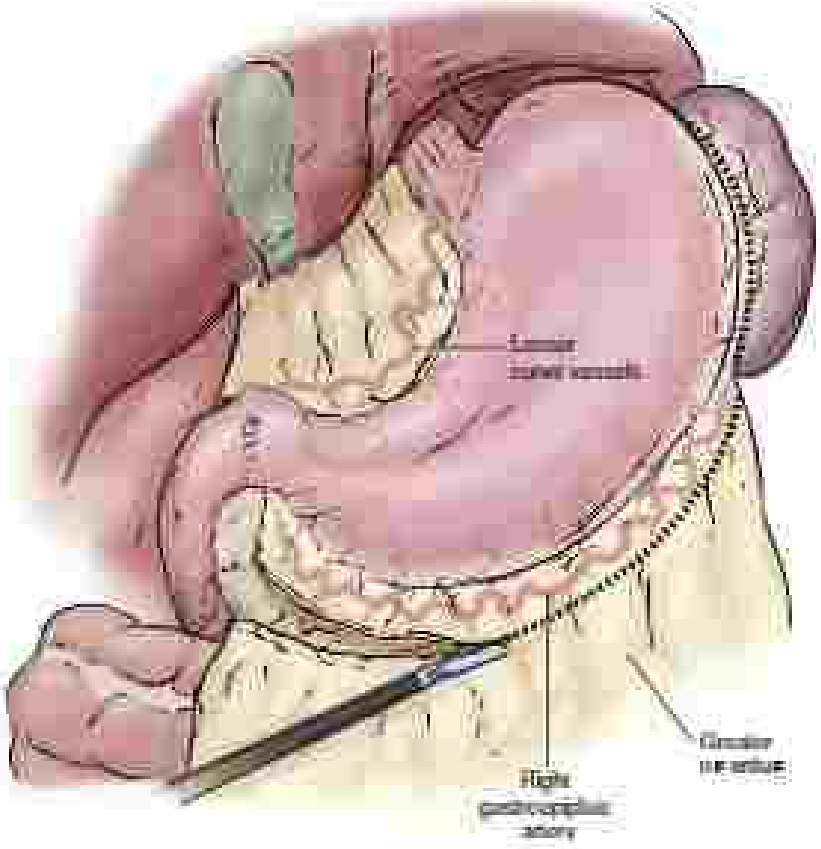

FIG. 9 Division of gastrocolic ligament with preservation of the right gastroepiploic vessels during the abdominal portion of a [illegible] (From Rosen P. Rosen's [illegible]. Philadelphia: Elsevier; 2017.)

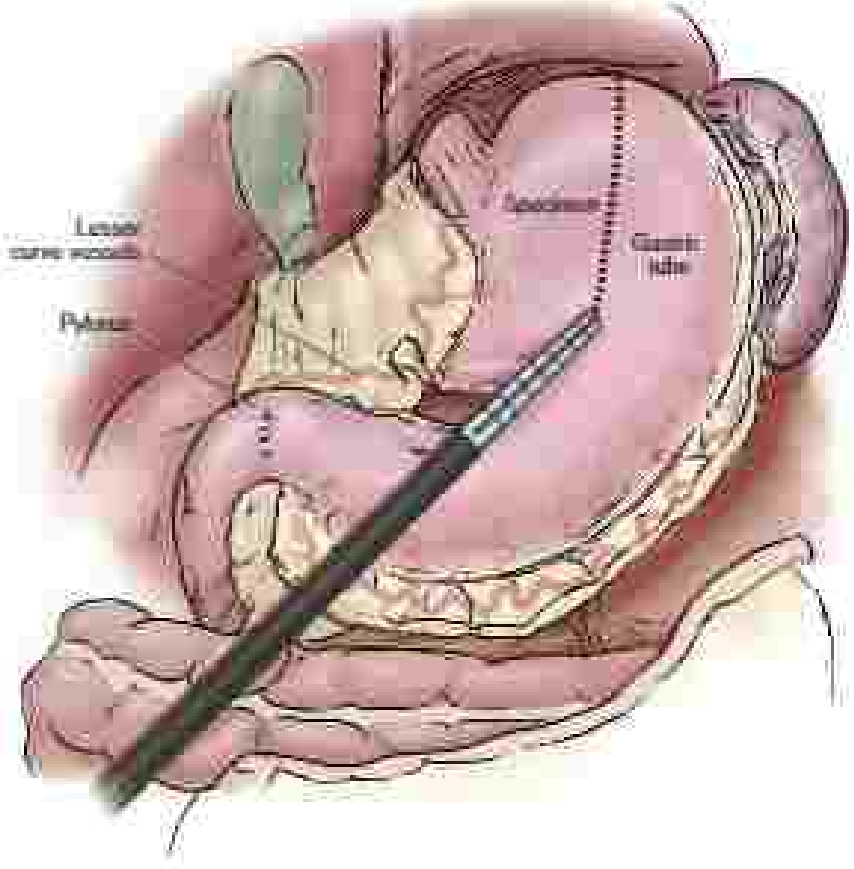

FIG. 10 Creation of the conduit. (From Rosen P. Rosen's Atlas of advanced operative surgery. Philadelphia: Elsevier; 2017.)

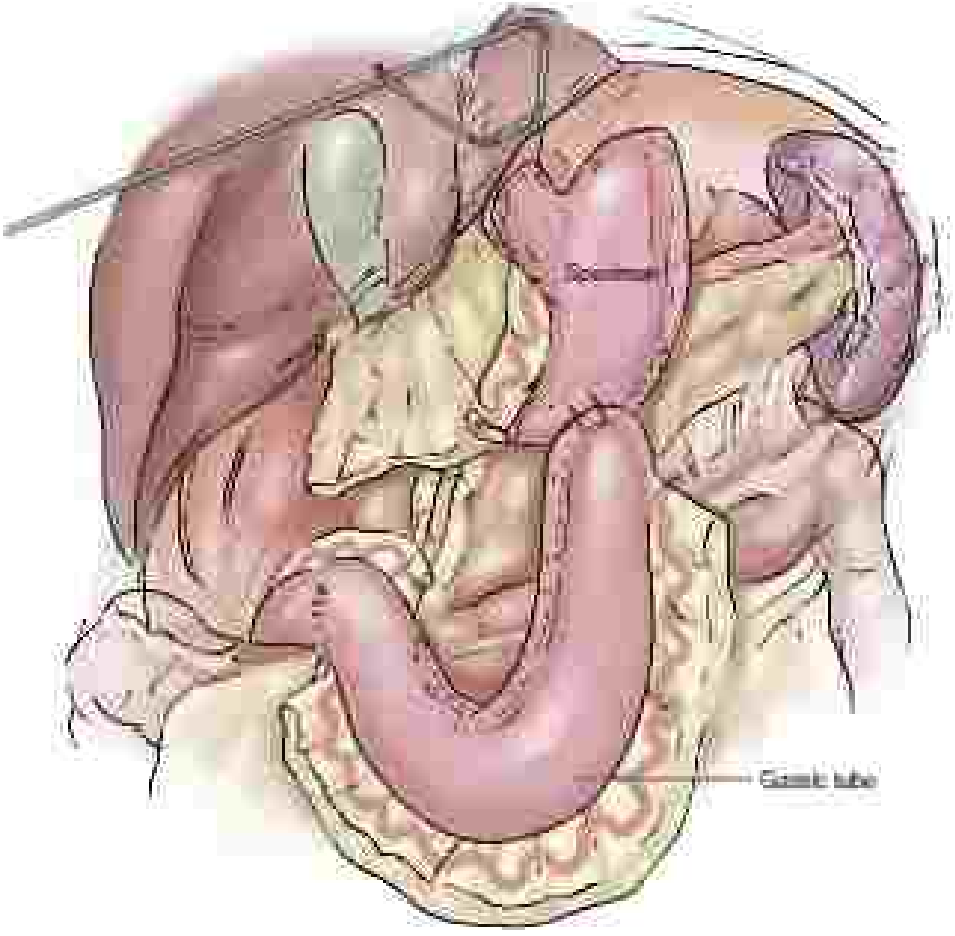

FIG. 11 Creation of the conduit. (From Hölzl P. Atlas of advanced open... in TE. In Pharyngeal Larynx 2017.)

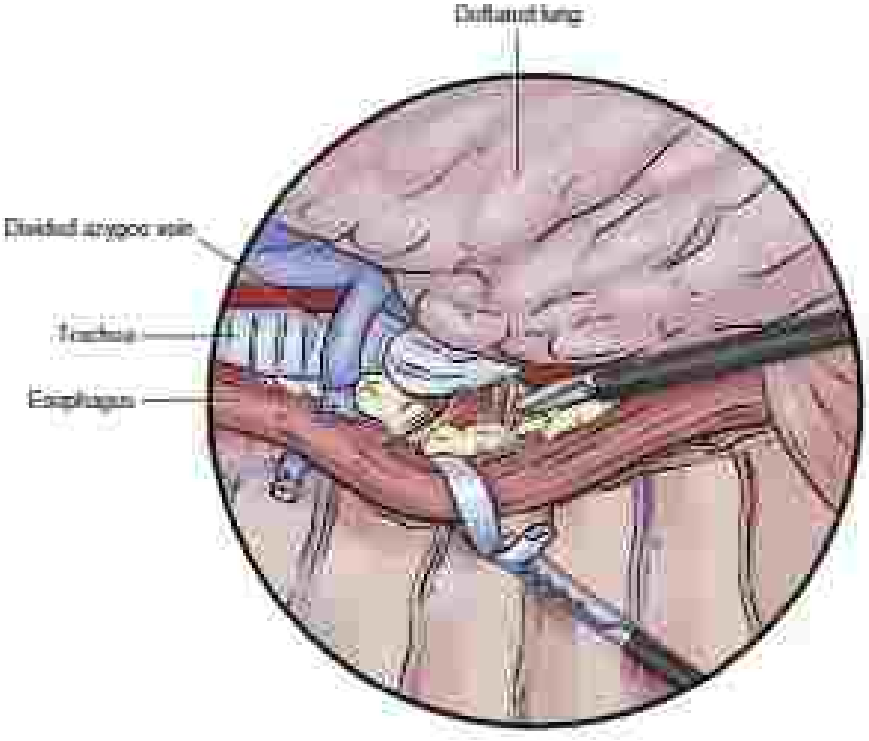

FIG. 12 Thoracic mediastinal exposure after division of the azygos vein. (From Klein F. Atlas of advanced operative surgery. Hölzl Ethics Limited; 2017.)

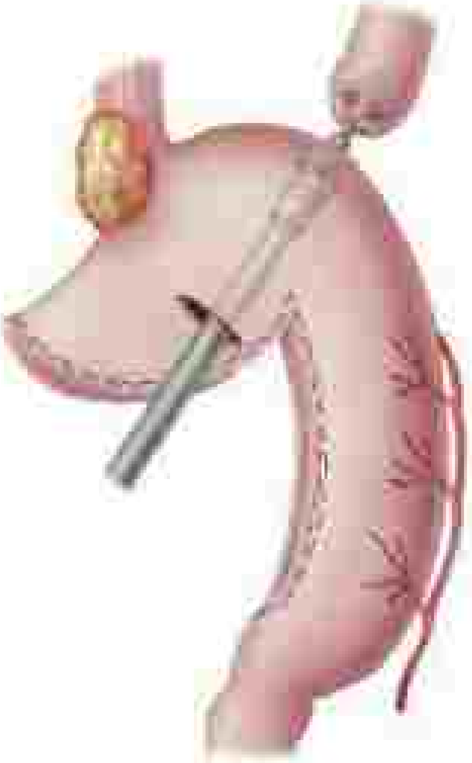

FIG. 13 Insertion of the EEA stapler and creation of the anastomosis. *(From [illegible] Atlas of Thoracic Surgical Techniques. Philadelphia: [illegible]; 2010.)*

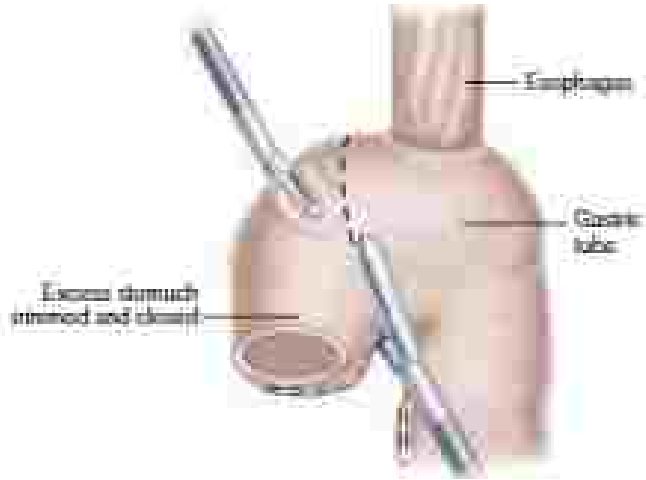

FIG. 14 Trimming of the excess conduit at the esophago-gastric anastomosis. *(From [illegible] Atlas of Thoracic Surgical Techniques. Philadelphia: [illegible]; 2010.)*

stapler is introduced through an opening made in the [illegible] tube [illegible]. The conduit is pulled over the stapler to allow the tube to [illegible] the greater curvature [illegible] the stomach [illegible] the anastomosis ([illegible] Fig. 13). The anvil and the stapler are engaged and the stapler is fired [illegible] the stapler [illegible] to trim [illegible] on the end of [illegible] portion [illegible] protection

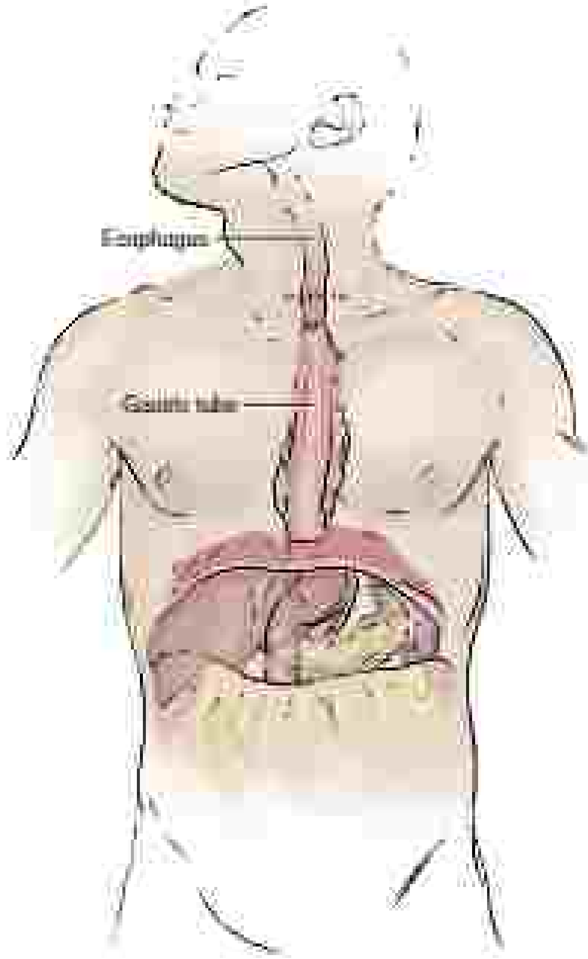

FIG. 15 New configuration after construction of the conduit. *(From [illegible] Atlas of [illegible] surgery. Philadelphia: [illegible]; 2012.)*

[illegible] the gastric [illegible] placed around the [illegible] to decrease the chance of [illegible] anastomosis ([illegible]).

[illegible]

[illegible] sparing the vagus [illegible] when [illegible] the procedure [illegible] stage [illegible] laparoscopic and [illegible] preparation of the gastric conduit [illegible] cervical [illegible] traditional open approach [illegible] and the laparoscopic [illegible] under direct [illegible] the mediastinum [illegible] esophagus [illegible] can be [illegible] through the [illegible] The esophageal specimen can be removed through the [illegible] in the abdomen [illegible] the [illegible] divided and the [illegible] the remaining [illegible] The [illegible] operative [illegible] less operative time [illegible] need not be [illegible] for a [illegible] performed [illegible] in large population [illegible] outcomes after transthoracic and

transhiatal esophagectomy, the latter was associated with higher postoperative survival. Although long-term survival differences have not been demonstrated, many experts believe this operation has a lower oncologic yield, although this has not been analyzed for the laparoscopic approach, where en bloc dissection of the distal mediastinum is possible.

McKeown (Three-Staged) Esophagectomy

For patients with a proximal thoracic tumor located near the airways or with extensive Barrett esophagus or if there is a concern of obtaining a proximal margin free of tumor, a modified McKeown esophagectomy or three-staged esophagectomy with a cervical anastomosis may represent a better option. A leak in the cervical space is generally also easier to manage compared with a thoracic leak and requires opening and packing of the neck wound. The steps of the operation are the same as for an Ivor Lewis esophagectomy. The thoracic inlet is then dissected and the specimen is extracted from an oblique incision anterior to the sternocleidomastoid muscle. A single-layer anastomosis is constructed using a running 3-0 PDS suture.

Surveillance

Most surveillance guidelines are based on retrospective studies and expert consensus rather than being validated by rigorous risk-benefit studies. For asymptomatic patients, follow-up should include a complete history and physical examination every 3 to 6 months for the first 2 years and every 6 to 12 months for the 3 years thereafter together with a comprehensive metabolic and nutritional laboratory work.

More than 90% of recurrences occur within the first 2 years; thus close surveillance for at least 24 months is recommended for these patients. Recurrences even after 5 years from primary treatment have been reported so EGDs should be performed every 1 to 2 years after the first 5 years after EMR. This should be coupled with EUS and CT of the chest/abdomen in patients with T1b disease treated by EMR alone. EGDs should also be performed every 3 to 6 months within the first 2 years after definitive chemoradiation as they provide a useful means to detect local failures. Patients who underwent esophagectomy should undergo CT of the chest/abdomen with contrast every 3 to 6 months for the first 2 years.

CONCLUSION

The science of esophageal cancer, both from the disease and treatment standpoint, has greatly evolved over the past 20 years. There continues to be a migration of squamous cell to adenocarcinoma as obesity and reflux increase in the population. Increased public awareness and improved screening technologies have led to increasingly early diagnosis of the disease, which lends itself to truly minimally invasive treatments such as ablation, EMR, and ESD, which are both patient friendly but also more than 90% curative. Good supportive care has decreased the morbidity and mortality of esophagectomy tremendously and MIE has even further decreased the morbidity to patients at no sacrifice to surgical cure rates. MIE is now more or less the gold standard for surgical treatment in most centers. Better understanding of the patient-specific risk factors for treatment failure as well as patient-specific tumor profiling and treatments, has ushered in an era of minimally invasive and precision therapeutics that holds a promise of improved outcomes for this highly lethal disease.

Suggested Readings

[illegible]

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[illegible]

[illegible]

[illegible]

Multimodality Therapy in Esophageal Cancer

Jonathan Cools-Lartigue, MD, PhD, and
Daniela Molena, MD

For the vast majority of patients, esophageal cancer encompasses two main histologic subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Esophageal adenocarcinoma represents the most common histology in the western world with a rapidly rising incidence. It originates predominantly in a background of Barrett's esophagus (BE) as a result of gastroesophageal reflux disease (GERD), necessitating close surveillance and treatment of the premalignant lesion. Squamous cell carcinoma is the most prevalent subtype worldwide, being more common in patients with significant smoking history and alcohol consumption. Both subtypes frequently present with dysphagia, which portends an advanced stage and poor outcome. Although surgery remains the mainstay of therapy, for patients with locally advanced disease, a multimodal approach has become standard and is necessary to improve survival in this population. Currently, multimodal regimens include preoperative chemoradiotherapy (CRT) or perioperative chemotherapy alone. Although this multimodal approach is associated with a 15% to 30% increase in overall survival, oncologic outcomes remain guarded, with all comers demonstrating 5-year survival on the order of 20%. The poor prognosis highlights the need for additional refinements in treatment paradigms and underscores much of the controversy in the optimal management of this malignancy. This being said, contemporary randomized controlled trials have demonstrated improvements in disease control with the application of multimodal regimens and are the topic of discussion in this chapter.

RATIONALE BEHIND SYSTEMIC THERAPY

When contemplating multimodal treatment for patients with esophageal cancer, it is important to consider the histology-specific characteristics that underlie the behavior of EAC and ESCC, specifically. These include the anatomic location of the tumor and patterns of recurrence. EAC characteristically involves the distal third of the esophagus and gastroesophageal junction (GEJ). This contrasts with ESCC, which demonstrates a predilection for the more proximal intrathoracic and cervical esophagus. These anatomic differences can affect surgical management of the disease, with cervical lesions potentially necessitating concomitant laryngectomy for local control. Lesions of the proximal or mid esophagus may also demonstrate airway invasion, which complicates surgical resection and potentially limits the ability to achieve a complete oncologic R0 resection. Given

transhiatal esophagectomy, the latter was associated with higher postoperative survival. Although long-term survival differences have not been demonstrated, many experts believe that operation has a lower oncologic yield, although this has not been analyzed for the laparoscopic approach, where en bloc dissection of the distal mediastinum is possible.

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Surveillance

Most surveillance guidelines are based on retrospective studies and expert consensus rather than being validated by rigorous risk-benefit studies. For asymptomatic patients, follow-up should include a complete history and physical examination every 3 to 6 months for the first 2 years and every 6 to 12 months for the 3 years thereafter together with a comprehensive metabolic and nutritional laboratory work.

More than 90% of recurrences occur within the first 2 years; thus close surveillance for at least 24 months is recommended for these patients. Recurrences even after 5 years from primary treatment have been reported so EGDs should be performed every 3 to 5 years after the first 2 years after EM. This should be coupled with EUS and CT of the chest/abdomen in patients with T1b disease treated by EMR alone. PET/CT should also be performed every 3 to 6 months within the first 2 years after definitive chemoradiation as they provide a useful means to detect local failures. Patients who underwent esophagectomy should undergo CT of the chest/abdomen with contrast every 3 to 6 months for the first 2 years.

CONCLUSION

The science of esophageal cancer, both from the disease and treatment standpoint, has greatly evolved over the past 20 years. There continues to be a migration of squamous cell to adenocarcinoma as obesity and reflux increase in the population. Increased public awareness and improved screening technologies have led to increasingly early diagnosis of the disease, which lends itself to truly minimally invasive treatments such as ablation, EMR, and ESD, which are both patient friendly but also more than 90% curative. Good supportive care has decreased the morbidity and mortality of esophagectomy tremendously and MIE has even further decreased the morbidity to patients at no sacrifice to survival rates. MIE is now more or less the gold standard for surgical treatment in most centers. Better understanding of the patient-specific risk factors for treatment failure as well as patient-specific tumor profiling and treatments, has ushered in an era of minimally invasive and precision therapeutics that holds a promise of improved outcomes for this highly lethal disease.

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For the vast majority of patients, esophageal cancer encompasses the main histologic subtypes esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Esophageal adenocarcinoma represents the most common histology in the western world with a rapidly rising incidence. It originates predominantly in a background of Barrett's esophagus (BE), as a result of gastroesophageal reflux disease (GERD), necessitating close surveillance and treatment of the premalignant lesion. Squamous cell carcinoma is the most prevalent subtype worldwide, being more common in patients with significant smoking history and alcohol consumption. Both subtypes frequently present with dysphagia, which portends an advanced stage and poor outcome. Although surgery remains the mainstay of therapy, for patients with locally advanced disease, a multimodal approach has become standard and is necessary to improve survival in this population. Currently, multimodal regimens include preoperative chemoradiotherapy (CRT) or perioperative chemotherapy alone. Although this multimodal approach is associated with a 15% to 30% increase in overall survival, oncologic outcomes remain guarded, with all comers demonstrating 5-year survival on the order of 20%. The poor prognosis highlights the need for additional refinements in treatment paradigms and underscores much of the controversy in the optimal management of this malignancy. This being said, contemporary randomized controlled trials have demonstrated improvements in disease control with the application of multimodal regimens and are the topic of discussion in this chapter.

RATIONALE BEHIND SYSTEMIC THERAPY

When contemplating multimodal treatment for patients with esophageal cancer, it is important to consider the histology specific characteristics that underlie the behavior of EAC and ESCC, specifically. These include the anatomic location of the tumor and patterns of recurrence. EAC characteristically involves the distal third of the esophagus and gastroesophageal junction (GEJ). This contrasts with ESCC, which demonstrates a predilection for the more proximal intrathoracic and cervical esophagus. These anatomic differences can affect surgical management of the disease, with cervical lesions potentially necessitating concomitant laryngectomy for local control. Lesions of the proximal or mid esophagus may also demonstrate airway invasion, which complicates surgical resection and potentially limits the ability to achieve a complete oncologic (R0 resection). Given

these features, adjuncts to surgical resection in the form of radiation or chemotherapy may be necessary for the purpose of organ preservation in the case of cervical esophageal lesions, or to facilitate complete tumor resection in the case of close apposition to the airway. More distal lesions, which often characterize EAC, are often more amenable to radical resection by virtue of their location and lack of unresectable structures to surround it.

As previously stated, patterns of recurrence after multimodal therapy demonstrate inherent differences between EAC and ESCC. In general, EAC demonstrates a higher predilection for hematogenous distant metastatic spread to sites such as lung, liver, bone, brain, and peritoneum. Conversely locoregional recurrence, particularly to regional nodes, tends to be marginally more prevalent in ESCC. For example, in the update to the FFCD 9703 trial, in which mixed histology EAC patients harboring stage I and II disease were randomized to receive surgery alone or CRT, Bedi et al demonstrated that patients with EAC more frequently developed distant metastatic disease compared with patients with ESCC, despite improved locoregional recurrence rates compared with patients who received surgery alone in both groups. It is important to note that rates of complete resection were identical in both groups at greater than 90%, suggesting that these observations reflect inherent, histology specific differences and not differences in treatment quality. In keeping with this observation, the time to first distant recurrence was shorter in patients with EAC (patients compared with those with ESCC: 30.9 vs 51 months), and these findings in a cohort of 349 consecutive patients with EC subjected to definitive CRT. Again, this was a mixed histology study comprising mainly patients with EAC (69.2%). Patients with ESCC demonstrated significant improvement in recurrence free survival (RFS) and distant metastasis free survival (DMFS) compared with patients with EAC. Moreover, patients with ESCC demonstrated a marginally increased rate of locoregional recurrence compared with patients with EAC. Given these observations, the ability of a given regimen to improve locoregional and distant recurrence rates needs to be assessed in a histology specific manner.

When assessing the efficacy of a regimen in the management of EC, it is important to evaluate its role with respect to local control and systemic control. These are better measured in terms of disease free survival, DFS, and overall survival (OS), respectively. Regarding local control, the main modalities used in contemporary multimodal regimens include surgery and radiation therapy, either alone or in combination. One of the most important measures of surgical quality is the ability to achieve complete oncologic R0 resection. When radiation or chemotherapy is used, local efficacy is reflected in the degree of pathologic response obtained after surgical resection. Systemic control is a factor through the administration of systemic chemotherapy. Given that the majority of patients with esophageal cancer, and locally advanced disease in particular, die as a result of systemic metastases, considerable focus has been paid to developing novel systemic regimens and optimizing standard ones. Although conceptually simple, the optimal regimen has yet to be determined, and a causal appraisal of the literature to date has the potential to seem contradictory. Similarly, the necessity of adding radiation, a predominantly local therapeutic modality, to contemporary perioperative treatment regimens in patients with EAC has come under question, given the results of recent randomized trials and meta analyses. Thus, when reviewing the available data, it is helpful to assess oncologic outcomes reported in the context of the tumor histology.

MULTIMODAL TREATMENT IN ESOPHAGEAL ADENOCARCINOMA

Chemotherapy Alone

From the standpoint of both locoregional and systemic control, the application of perioperative chemotherapy in patients with locally advanced EAC is associated with improved outcomes. To date, 5 RCTs examining perioperative chemotherapy plus surgery versus surgery alone have been published. These are outlined in Tables 1 and 2.

Locoregional Control

Studies demonstrating the efficacy of perioperative chemotherapy and surgery, compared with surgery alone in the management of patients with EAC are highlighted in Table 1. In the Cunningham (MAGIC) and Ychou trials, accrual was restricted to adenocarcinoma, but on both sides of the diaphragm, with more gastric than esophageal/esophagogastric in the MAGIC and the reverse in the Ychou study. The recently completed FNCLCC trial has yet to be published, but, as in the MAGIC trial, recruitment was restricted to adenocarcinoma, and preliminary results are impressive with respect to survival outcomes. The MRC ST02 trial recruited patients with mixed histology and to

TABLE 1 Randomized Trials Comparing Preoperative Chemotherapy Versus Surgery Alone in Patients with Locally Advanced Esophageal Adenocarcinoma

Study	Year	N	Histology	Regimen	R0	Response Rate	Survival	P Value
Cunningham et al (MAGIC)[3]	2006	503	EAC	Epirubicin, cisplatin, 5FU, 3 cycles before and after resection	79.3% vs 70.3%	NA	5 yr 36% vs 23%	.009
Ychou et al[4]	2011	224	GEJ AC	Cisplatin, 5FU 3 cycles preop, 3 cycles postop	87% vs 73%	NA	5 yr 38% vs 24%	.02
Al Batran (FLOT 4)	2016	716	EAC	FLOT vs ECF/ECX	NR	45% (pCR 9%) vs 36% (pCR 10%)	Median OS 50 mo vs 35 mo 5 yr OS 44% vs 23% median PFS 30 mo vs 18 mo	.004

Denotes statistical significance.

EAC, Esophageal adenocarcinoma; ECF/ECX, 5-FU/cisplatin and epirubicin/ECF vs docetaxel; FLOT, 5-FU, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; pCR, pathologic complete response; postop, after surgery; preop, before surgery.

Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.

Ychou M, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29:1715–1721.

Al-Batran S-E, et al. Histopathological regression after neoadjuvant chemotherapy of resectable gastroesophageal adenocarcinoma (AIO-FLOT3 trial): results from the phase II part of a multicenter, open-label, randomized phase II/III trial. *Cancer Chemother Pharmacol*. 2016;78:1–7.

included here because of the high proportion of patients with EAC and information regarding response rates to chemotherapy (Table 2). Effective therapeutic regimens included cisplatin and 5FU based doublets with the exception of the Cunningham (MAGIC) trial, which administered triplet therapy encompassing an anthracycline in addition to cisplatin and 5FU and TAGET 4, which used a taxane based triplet. Most studies administered chemotherapy in the preoperative and postoperative periods, with the exception is the MRC trial, where chemotherapy was administered in the preoperative setting only.

From the standpoint of local control, reflected by R0 resection rates and R0%, all highlighted studies demonstrated a benefit to the addition of chemotherapy to surgery in patients with locally advanced disease. Tebbe et al randomized patients—of whom 77% had mid or lower esophageal or GEJ tumors—to receive perioperative cisplatin and 5FU versus surgery alone. Patients randomized to preoperative therapy demonstrated improved outcomes with respect to R0 resection rate (87% vs 74%, $P = .04$). R0% was similarly improved with 5-year R0% at 38% in the chemotherapy group, versus 14% in patients randomized to surgery alone ($P = .001$). In the study by Cunningham et al, patients with gastric and lower esophageal/GEJ tumors (27%) were randomized to receive perioperative chemotherapy with 5FU, cisplatin, and epirubicin (ECF). In patients receiving perioperative therapy, an improvement in R0 resection rate (chemotherapy vs surgery alone, 79.3% vs 70.2%, $P = .03$) and a tendency for smaller tumors and less advanced nodal disease were noted. This was associated with improved R0% in patients receiving perioperative chemotherapy compared with surgery alone (hazard ratio [HR] for progression, 0.66; 95% confidence interval [CI] 0.53–0.81; $P < .001$). The trial by Kelsen et al (Table 2), which was a mixed histologic study comprised of roughly equal proportions of patients with EAC and ESCC, demonstrated improved R0 resection rate overall after chemotherapy versus surgery alone (79.3% vs 70.2%, respectively, $P = .008$). Although not broken down by histology, the results of this trial support the use of neoadjuvant chemotherapy to potentially facilitate complete resection. In the MRC study and its subsequent follow up (CT02), perioperative administration of cisplatin and 5FU was associated with a significant reduction in primary tumor size and regional lymph node positivity, compared with spontaneous findings in untreated patients. This was associated with improved R0 resection rates in patients subjected to neoadjuvant chemotherapy (69% vs 58%, $P = .001$) and was similarly associated with improved RFS (HR, 0.882; 95% CI, 0.71–0.95; $P = .003$).

The Cunningham trial formed the basis for the recommendation of ECF in patients with operable esophagogastric cancer. Various randomized studies have cast doubt on the utility of 5FU based triplets with anthracyclins; phase II data have suggested that triplets, including 5FU and a platinum agent in conjunction with a taxane, may provide improved treatment response over standard doublet therapies. The results of the phase III RCT by Al Batran et al appear to confirm these findings. The FLOT-4 trial, which has been published to an abstract to date, randomized patients with locally advanced esophagogastric adenocarcinoma to 3 preoperative cycles of ECF versus 4 preoperative cycles of FLOT (docetaxel, oxaliplatin, 5FU, leucovorin). Although R0 resection rates were not reported, R0% was significantly improved in patients receiving FLOT compared with ECF (median R0% 30 months vs 18 months, $P = .004$). These results mirrored the improved response rates observed in the former regimen from the phase II FLOT-3 trial (35% major response, 20% pathologic complete response [pCR]).

Systemic Control

All the randomized trials using chemotherapy in the perioperative setting exclusively in patients with locally advanced EAC have demonstrated improvements in OS compared with surgery alone. For example, in the trial by Tebbe et al, improved OS after 2 preoperative and 2 postoperative cycles of cisplatin and 5FU was noted in the chemotherapy arm compared with surgery alone (5-year survival CS vs surgery alone, 38% vs 24%; $P < .05$). The MRC/OEO2 trial, using the similar regimen, demonstrated analogous findings with improved OS in patients receiving chemotherapy compared with surgery alone (median survival, 16.8 vs 13.2 months; 43% survival at 2 years vs 34%; $P = .004$). Results after the MAGIC trial were similar, demonstrating a significant survival advantage in patients receiving neoadjuvant chemotherapy versus surgery alone (HR, 0.75; 95% CI, 0.6–0.93; $P = .009$; 5-year survival, 36.3% vs 23%). Finally, the FLOT-4 trial demonstrated an improvement in OS commensurate with an improvement in objective response rates to chemotherapy compared with the older MAGIC trial (median OS, 50 months vs 34 months; $P < .012$; 3-year OS, 57% vs 48%).

The mixed histology trial by Kelsen et al is the only negative study with respect to OS using perioperative chemotherapy consisting of 3 cycles of preoperative cisplatin and 5FU. Although the negative results were related to poor response rates to chemotherapy, with only 7% demonstrating a complete clinical response and 12% demonstrating a partial clinical response, on subgroup analysis, those patients who achieved a major response to chemotherapy did demonstrate a significant survival advantage (HR, 2.85; 95% CI, 1.84–4.38; $P < .001$).

Thus, when taken collectively, the results of the randomized studies to date demonstrate that neoadjuvant chemotherapy in patients with locally advanced EAC improves both locoregional and systemic control, as evidenced by improved R0 resection rates, RFS, and OS, respectively. Furthermore, OS is improved in patients who demonstrate greater a response to neoadjuvant therapy. Accordingly, as chemotherapeutic regimens become more effective, a concomitant improvement in outcomes can be expected.

Chemoradiotherapy

The outcome data outlined above demonstrate that systemic chemotherapy is associated with improved outcomes in patients with EAC

TABLE 2 Randomized Mixed Histology Trials Comparing Chemotherapy to Surgery Alone in Patients With Locally Advanced Esophageal Cancer

Study	Year	N	Histology	Regimen	R0	Response Rate	Survival	P Value
MRC/OEO2	2005/09	802	EAC/GEAC	Cisplatin, 5FU 2 cycles before operation	69% vs 58%*	NA	Median 16.8 mo vs 13.2 mo 2 yr 43% vs 34%	.004
Kelsen et al	2007	440	EAC/GEAC	Cisplatin, 5FU 3 cycles before operation	63% vs 59%	19% (pCR 2.5%)	5 year 19.4% vs 21%	NS

*Denotes statistical significance.

EAC, Esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; pCR, pathologic complete response; SCC, squamous cell carcinoma.

Medical Research Council Oesophageal Cancer Working. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–1733.

Kelsen DP, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007;25:3720–3725.

Furthermore, this improvement, particularly in the context of systemic control, is dependent on the magnitude of the primary tumor's response to preoperative chemotherapy. Response rates, particularly pCR rates on the order of 5% to 10%, have been highlighted as weaknesses of regimens that use chemotherapy alone. Along these lines, CRT regimens have been proposed in part to improve response rates, with the goal of achieving improved disease control, both locally and systemically. What has become clear is that the differential radiosensitivity of EAC and ESCC impacts disease outcome after the application of CRT regimens. Although the addition of radiation to chemotherapy improves pathologic response rates in both histologic subtypes, the benefit in patients with EAC is not as pronounced as in patients with ESCC.

Local Control

To date, only a single positive study examining the utility of CRT exclusively in patients with EAC has been published. The remaining 5 trials included patients with mixed histology and are outlined in Table 1. The Welsh study demonstrated a pCR rate of 25% and a significant down-staging effect, with 42% of patients treated with CRT found to harbor positive lymph nodes at the time of surgery compared with 82% of patients in the surgery-alone arm ($P < .001$).[1]

The CROSS trial is the largest positive trial performed to date comparing neoadjuvant CRT to surgery alone and established it as a standard therapy for both ESCC and EAC in many Western countries. The authors used a slightly different chemotherapeutic approach composed of a weekly regimen of relatively low-dose taxane and carboplatin in conjunction with concurrent radiation at a dose of 41.4 Gy. With respect to local control, a pCR rate of 29% was noted in the adenocarcinoma arm, which is remarkably consistent across studies to date. In fact, the studies by Urba et al, Burmeister et al, and Ilson et al all reported histology specific pCR rates after CRT regimens and found a remarkably consistent pCR rate of 16% to 25% in EAC, suggesting reduced efficacy of radiation in EAC compared with ESCC (see later).

In all the above mentioned trials, R0 resection was achieved in a greater proportion of patients receiving neoadjuvant CRT compared with surgery alone, with the CROSS trial and the trial by Urba et al demonstrating the highest overall rate (92% vs 69% and 96% vs 90% compared with surgery alone, respectively). In the CROSS trial, significantly more patients undergoing surgery alone were found to harbor metastatic lymph nodes compared with patients receiving neoadjuvant CRT (23% vs 11%), despite comparable preoperative clinical staging, suggesting that enhanced resectability was in part due to a primary tumor response to neoadjuvant CRT.

From the standpoint of RFS, the effects of CRT on adenocarcinoma appear less pronounced than what was observed in the chemotherapy alone trials. Histology specific RFS rates were provided in the studies by Burmeister et al and the CROSS trial. Burmeister et al failed to demonstrate any advantage of CRT over surgery alone from the standpoint of RFS. The CROSS trial was a positive study in this regard, with patients with EAC subjected to CRT demonstrating improved RFS compared with patients undergoing surgery

TABLE 1 Randomized Mixed Histology Trials Comparing Chemoradiotherapy to Surgery Alone in Patients With Locally Advanced Esophageal Cancer

Study	Year	Patients	Histology	Regimen	Response Rate	R0	Survival	P Value
Urba et al[1]	2001	100	ESCC/EAC	Concurrent Cisplatin, 5FU, Vinblastine + 45 Gy	pCR 28% pCR SCC: 38% pCR EAC: 25%	96% vs 90%*	Median 19.9 mo vs 17.4 mo 3 year 30% vs 16%	NS
Burmeister et al[2]	2005	257	ESCC/EAC	Concurrent Cisplatin, 5FU + 35 Gy	pCR 16% pCR SCC: 22% pCR EAC: 9%	80% vs 59%*	Median 22.2 mo vs 18.3 mo	NS
Tepper et al[3]	2008	56	ESCC/EAC	Cisplatin, 5FU + 50.4 Gy	pCR 40%	NA	Median 4.48 yr vs 1.79 yr 5 year 39% vs 16%	$P = .002$
Van Hagen[4] Shapiro et al (CROSS)[5]	2011/2015	368	ESCC/EAC	Concurrent Paclitaxel, Carboplatin + 41.4 Gy	pCR 29% pCR SCC: 49% pCR EAC: 23%	92% vs 69%*	Median 48.6 mo vs 24 mo 5 year 47% vs 34%	$P = .003$
Bedi et al[6]	2010	214	ESCC/EAC	5FU, Cisplatin + 50 Gy	pCR SCC: 18% pCR EAC: 25% 20% N+ vs 10% vs alone	NA	Median 23.8 mo vs 15.41 mo	$P < .021$

*Denotes statistical significance.

EAC, Esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; pCR, pathologic complete response; SCC, squamous cell carcinoma.

[1] Urba SG, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19:305–313.

[2] Burmeister BH, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6:659–668.

[3] Tepper J, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26:1086–1092.

[4] Van Hagen P, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–2084.

[5] Shapiro J, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16:1090–1098.

[6] Bedi GA, et al. Chemoradiotherapy with adjuvant surgery for local control confers a durable survival advantage to adenocarcinoma and squamous cell carcinoma of the esophagus. Eur J Cancer. 2010;46:1661–1670.

alone ($P = .01$). This remained true on long-term follow up; a significant reduction in locoregional recurrence was noted in patients with adenocarcinoma after neoadjuvant CRT compared with surgery alone (27% vs 39%; HR, 0.45; CI, 0.3–0.66; $P = .0001$), thus supporting the locoregional benefit of neoadjuvant CRT.

Systemic Control

Similarly to R0 rates, OS improvement after CRT in trials, including mixed histology GEJ, appear to be driven predominantly by the results in ESCC. The trial by Walsh et al, however, which was performed exclusively in patients with EAC, was a positive study from the standpoint of OS. Patients underwent concurrent 40 Gy radiation, with 2 cycles of cisplatin and 5FU, and median overall survival was 16 months versus 11 months in favor of CRT ($P = .01$). The trial by Burmeister et al was a negative trial from the standpoint of OS, as was the CROSS trial when examining only patients with EAC. In patients with EAC, in fact, there was a trend toward improved survival, which did not achieve statistical significance on multivariate analysis (HR = 0.75 [0.57–1.01]).

The trial by Ruo et al randomized patients to receive 2 cycles of cisplatin and 5FU with concurrent 40 Gy radiation or surgical monotherapy. In patients with EAC, a survival advantage was noted, particularly in patients in whom a pCR was achieved. Overall, mean OS in EAC patients was 27 months compared with 23 months after surgical monotherapy ($P < .0001$). In the 25% of patients in whom a pCR was achieved, mean OS was 42 months, higher, albeit without attaining statistical significance, than the 18 months observed in patients with residual disease. Although not broken down along histologic lines, the study by Urba et al similarly demonstrated significant prolongation of OS in patients who attained a pCR.

When considered collectively, the data regarding CRT in patients with EAC suggest that it is effective at improving R0 resection rates, which may translate into improved RFS. However, this is dependent to some extent on the ability to achieve a pCR, which is reduced in EAC compared with ESCC when looking at the same therapeutic regimen.

MULTIMODAL TREATMENT IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Chemotherapy Alone

The rationale for the application of chemotherapy alone to patients with locally advanced ESCC is the same as in patients with EAC, namely, to facilitate complete resection and improve both RFS and OS. To this end, chemotherapy has demonstrated a benefit in patients with ESCC. However, as with EAC, the magnitude of this benefit is related to the magnitude of the response to therapy. Given the enhanced radiosensitivity of ESCC, regimens involving the addition of radiotherapy are most frequently used today.

Locoregional Control

To date, 8 RCTs have been published evaluating perioperative chemotherapy versus surgery alone in patients with ESCC (Table 4). These include the studies by Roth et al, Schlag et al, Law et al, Burmeister et al, Ancona et al, and all three trials by Ando et al. From the standpoint of locoregional control, the data strongly support the notion that neoadjuvant chemotherapy offers some benefit compared with surgery alone. In particular, a neoadjuvant regimen comprising 5FU and cisplatin, which improves R0 resection rates, is associated with significant locoregional down-staging and improved RFS after resection compared with surgery alone.

One of the earlier studies to highlight the local benefit of neoadjuvant chemotherapy in patients with ESCC was conducted by Law et al. Thirteen, 147 patients with esophageal SCC were randomized to receive either 2 preoperative cycles of cisplatin and 5FU, followed by curative intent surgery or upfront surgery alone. The authors found that, in patients who completed preoperative chemotherapy, a curative resection was more likely (R0 resection 67% vs 35%; $P = .0031$). Furthermore, resected tumors from patients subjected to preoperative treatment were significantly smaller and harbored fewer metastatic lymph nodes than those from patients who proceeded immediately to surgery. This is in keeping with the response rates observed with this doublet regimen, which were 38% with a pCR rate of 5%. Accordingly, significantly fewer local recurrences occurred in patients randomized to preoperative chemotherapy (local recurrence 13% after chemotherapy vs 30.8% after surgery alone; $P = .01$).

Similarly, in the 2012 study by Ando et al, patients with SCC underwent 2 cycles of cisplatin and 5FU in either the adjuvant or neoadjuvant setting. Patients who received neoadjuvant chemotherapy demonstrated increased R0 resection rates, compared with patients who received upfront surgery (90% vs 81%; $P = .04$). Along these lines, there was a trend toward improved RFS, supporting the notion that enhanced resectability is associated with improved locoregional control. The overall response rate to chemotherapy in this study was 38%, with a pCR rate of 7%. Finally, the positive study by Ruotsalo et al demonstrated a consistent pCR rate of 7% and major response rate of 30% after administration of a neoadjuvant doublet regimen consisting of cisplatin and etoposide. This was associated with a significantly improved R0 resection rate (from 54% in the surgery alone group compared with 73% in patients who received chemotherapy. This translated to improved RFS at 6 months (55% vs 10%; $P = .05$) in patients who underwent preoperative chemotherapy versus surgery alone, respectively.

Collectively, the data demonstrate pCR rates on the order of 5% to 10%, with improved response rates with cisplatin doublets (about 25% to 30%). Based on the randomized evidence to date, chemotherapy improves R0 resection rates and RFS.

Systemic Control

In the study by Roth et al, survival in patients who demonstrated a major (47%) or complete (3%) response to vinblastine-, cisplatin-, and bleomycin-based chemotherapy exhibited improved survival (median survival 20 months vs 6 months; $P = .0001$), compared with patients who did not. Thus, as expected, patients who demonstrate a response to neoadjuvant chemotherapy demonstrate improved outcomes. Schlag et al similarly showed significant increase in survival for patients with ESCC who demonstrated a response (12% minor, 32% major, 6% complete) to 3 cycles of neoadjuvant cisplatin and 5FU compared with surgery alone. In patients who demonstrated a response to chemotherapy, median and 2-year survival times were improved (CT vs surgery 42.5 months vs 13.8 months; $P = .008$, and 59% vs 33%, respectively). In the study by Ancona et al, the overall survival rate was improved only in the 40% of patients who demonstrated a major response to chemotherapy. In the chemotherapy group, median and 3- and 5-year survival was improved compared with patients undergoing surgery alone (33 months, 38%, 60%, vs 20 months, 6%, 26%, respectively; $P = .01$) and nonresponders to chemotherapy (19 months, 30%, 19%, respectively; $P < .05$). In keeping with this theme, the survival benefit was most pronounced in the 12.8% of patients who demonstrated a complete response. Ruotsalo et al demonstrated a partial response rate of 40% and complete response rate of 7% after neoadjuvant chemotherapy. A significant survival advantage in patients receiving chemotherapy was noted (median and 2- and 5-year survival vs surgery alone: 16 months vs 12 months, 42% vs 30%, and 26% vs 17%; $P = .03$, respectively) and was attributed to the fact that a greater proportion of chemotherapy-treated patients was ultimately found to harbor resectable tumors.

The question about whether chemotherapy should be administered before or after surgery in patients with SCC has specifically been addressed in randomized studies. The rationale for its perioperative administration is that it can be delivered to a tumor with an intact blood supply, thus facilitating drug delivery, tumor response can be assessed in real time, and patients may be more likely to receive their chemotherapy before a prolonged decline in functional status after surgery. Advantages to adjuvant administration include avoidance of

TABLE 1 Randomized Trials Comparing Preoperative Chemotherapy Versus Surgery Alone in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma

Study	Year	N	Histology	Regimen	R0	Response Rate	Survival	P Value
Schlag et al[2]	1992	60	ESCC	Cisplatin, 5FU 3 cycles preop. Restaged after first cycle. If response, 2 additional; if no response, surgery	69% vs 62%	30% (pCR 6%)	Median 8 mo vs 9 mo	NS
Law et al[3]	1997	147	ESCC	Cisplatin, 5FU 2 cycles preop	67% vs 83%*	58% (pCR 7%)	Median 16.8 mo vs 13 mo 2 year 44% vs 21%	NS
Ando et al[4]	1997	206	ESCC	Cisplatin, Vindesine 2 cycles preop	NA	NA	5 year 45% vs 48%	NS
Roth et al[5]	1998	36	ESCC	Cisplatin, Vinblastine, Bleomycin 3 cycles preop; 3 cycles postop	NA	47% (pCR 5%)	5 year 25% vs 5% Median 10 mo vs 10 mo	NS
Apinop et al[6]	2001	86	ESCC	Cisplatin, 5FU 2 cycles preop + 1 additional if response	79% vs 74%	40% (pCR 12.5%)	Median 25 mo vs 24 mo 5 year 44% vs 22%	NS
Ando et al[7]	2003	242	ESCC	Cisplatin, 5FU 2 cycles postop	100% (initial more criteria)	38% (pCR 7%)	5 year 45% vs 55%	.037
Bosset et al[8]	2014	168	ESCC	Bleomycin, cisplatin up to 4 cycles preop	74% vs 57%	25% (pCR 7%)	3 year 44% vs 32% 5 year 26% vs 17%	.003
Ando et al[9]	2012	330	ESCC	Cisplatin, 5FU 2 cycles preop OR postop	96% vs 91%*	NA	3 year 55% vs 43%	.04

*Denotes statistical significance.
ESCC, Esophageal squamous cell carcinoma; pCR, pathologic complete response; postop, after surgery; preop, before surgery; SCC, squamous cell carcinoma.
[2]Schlag PM. Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Arzt Onkologie der Deutschen Gesellschaft fuer Chirurgie Study Group. Arch Surg. 1992;127:1466-1473.
[3]Law S, et al. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg. 1997;114:210-217.
[4]Ando N, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus (the Japan Clinical Oncology Group Study). J Thorac Cardiovasc Surg. 1997;114:205-209.
[5]Roth JA, Pisters PW, Flanagan MM, et al. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. J Thorac Cardiovasc Surg. 1998;96:242-248.
[6]Apinop L, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer. 2001;91:2165-2174.
[7]Ando N, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. J Clin Oncol. 2003;21:4592-4596.
[8]Bosset JF, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable esophageal squamous cell carcinoma: long-term results of a randomized controlled trial. ORE. Cancer. 2011;11:181.
[9]Ando N, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19:68-74.

therapy in patients who do not require it, while avoiding unnecessary delays to surgery. With respect to the latter concern, randomized data support the notion that a multimodal approach is associated with increased harm to patients with early stage resectable disease, highlighting the importance of meticulous staging. Current data support increased efficacy of chemotherapy when administered in the neoadjuvant setting. In 2003, Ando and colleagues published a Japan Clinical Oncology Group multiinstitutional phase III trial investigating postoperative cisplatin and 5FU in patients with completely resected squamous cell carcinoma versus surgery alone. This positive study led to a follow-up study, which compared the same regimen given either before or after surgery. Preoperative versus postoperative chemotherapy was directly compared with surgery alone and highlighted the superiority of the former over the latter. In addition to providing the local benefits associated with neoadjuvant therapy, OS was significantly improved in patients who received preoperative compared with postoperative therapy with 5-year survival rate of 55% versus 43% ($P = .04$).

When collectively assessed, the randomized data published thus far demonstrate that, in patients with ESCC, survival outcomes are improved in patients who demonstrate a response to neoadjuvant chemotherapy. Furthermore, the magnitude of the benefit is related to the magnitude of the response. Thus patients who demonstrate a robust response to neoadjuvant chemotherapy are more likely to derive a substantial survival benefit, with patients who achieve a pCR demonstrating the best survival outcomes overall. This finding is at the heart of why CRT regimens have been adopted, because these regimens, particularly in patients with ESCC, are more frequently associated with a pCR compared with regimens consisting of chemotherapy alone.

Chemoradiation Therapy

Local Control

To date, five RCTs have been conducted exclusively in patients with ESCC comparing neoadjuvant chemoradiation therapy to surgery alone. The studies by Nygaard et al, Le Prise et al, Bosset et al, Cao et al, and Ly et al are outlined in Table 5. As with neoadjuvant chemotherapy, improved local control has consistently been reported, although response rates after CRT are significantly higher than what is observed with chemotherapy. Overall, pCR rates ranged between 10% to 56% across the trials mentioned. The mixed histology studies conducted by Urba et al, Burmeister et al, Van Hagen et al, and Stahl et al (Table 3) all demonstrate pCR rates ranging between 27% to 49%. In fact, the trial by Burmeister et al, which demonstrated the lowest pCR rate of the mixed histology studies at 27%, used a low dose of radiation at 36 Gy in conjunction with concurrent cisplatin and 5FU. This contrasts with other studies using 40 Gy and above and formed the basis of some of the criticisms of this negative study, given the much higher pCR rates ranging between 30% to 49% observed in the other trials. These results demonstrate significantly higher local response rates compared with a pCR rate of 15% to 20% observed in patients with EAC. Not surprisingly, the addition of radiation to perioperative multimodal regimens in patients with ESCC is associated with improved R0 resection rates.

Nygaard et al, Bosset et al, Cao et al, and Ly et al were all able to demonstrate R0 resection rates ranging between 52% to 97.6% after neoadjuvant CRT. When considering the contemporary studies by Cao et al and Ly et al, multimodal therapy was associated with R0 rates of more than 90%. In the study by Cao et al, the addition of 40 Gy to triplet induction chemotherapy consisting of cisplatin, 5FU, and mitomycin was associated with an improvement in R0 resection rates to 95.2% versus 84.6% after triplet induction chemotherapy alone, thus further supporting the utility of radiation therapy in local control in ESCC.

Additional evidence of improved locoregional control in patients with ESCC patients can be further inferred from the results of the studies by Tepper et al, Bosset et al, and Le Prise et al. Both Tepper et al and Le Prise et al demonstrated a reduction in T3 and T4 tumors in patients treated with neoadjuvant CRT compared with those subjected to surgery alone. In the trial by Tepper et al, this translated to improved RFS at 5 years (28% vs 15%, $P < .05$, respectively). In addition, Bosset et al demonstrated a reduction in N+ disease in patients with ESCC after neoadjuvant RT on the order of 50%, which significantly increased RFS compared with surgery alone (HR local recurrence, 0.6; 95% CI, 0.4–0.9; $P = .04$).

As previously stated, the addition of radiation therapy to multimodal regimens appears to be particularly effective in patients with

TABLE 5 Randomized Trials Comparing Preoperative Chemoradiotherapy vs Chemotherapy Alone in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma

Study	Year	Patients	Histology	Regimen	Response Rate	R0	Survival	P Value
Nygaard et al[a]	1992	186 (88 XRT)	ESCC	1. Sx alone 2. 2 cycles cisplatin, bleomycin preop 3. 2× Cis preop 4. Chemo + XRT	NA	(1) 57% (2) 48% (3) 80% (4) —%	3 years 1: 19% 2: 3% 3: 21% 4: 17%; 1+2, 6%; 3+4,19%	Any ...1 vs no RT ... .009
Le Prise et al[b]	1994	104	ESCC	Sequential 5FU,cisplatin + 20 Gy	pCR 10.3%	NA	Median 10 mo in both groups	NS
Bosset et al[c]	1997	282	ESCC	Sequential cisplatin + 18.5 Gy	pCR 26% 25%N+ vs 52% Sx alone	81% vs 69%[d]	Median survival 18.4 mo overall	NS
Cao et al[e]	2009	675	ESCC	Cisplatin, 5FU, mitomycin + Sx 40 Gy + Sx 1 + 40 Gy Sx alone	1.7% 15.2% 22.3%.*	84.6% 95.2% 88.3% 73.3%.*	3 year 37.1% 49.5% 73.3% 33.8%	Any + vs RT P < .05
Ly et al[f]	2010	258	ESCC	Preop cisplatin, paclitaxel + 40Gy vs preop cisplatin, paclitaxel + 40 Gy vs Sx alone	NA	97.8% 78% 80%[d]	Median preop 53 mo vs postop 48 mo vs Sx mo Sx 5 year preop 43.5% vs postop 42.3% vs Sx 34%	P = .008 vs Sx alone

*Denotes statistical significance.

ESCC, Esophageal squamous cell carcinoma; pCR, pathologic complete response; Postop, after surgery; Preop, before surgery; SCC, squamous cell carcinoma; XRT, radiotherapy.

[a]Nygaard HC, et al., Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-1109; discussion 1110.

[b]Le Prise E, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer. 1994;73:1779-1784.

[c]Bosset JF, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med. 1997;337:161-167.

[d]Cao XF, et al., Effects of neoadjuvant radiochemotherapy on pathological staging and prognosis for locally advanced esophageal squamous cell carcinoma. ... Esophagus. 2009;22:477-481.

[e]Ly J, et al. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol. 2010;16:1649-1654.

ESCC compared with EAC. This is apparent in some of the noted histology studies, in which results are broken down according to histology. For example, the CROSS trial, in keeping with improved pCR in ESCC compared with EAC, demonstrated a significant improvement in RFS in patients with squamous histology. Median RFS was 74.7 months in the CRT group compared with 11.6 months in the surgery alone group. Similarly, even in the negative study by Burmeister et al, RFS was significantly improved in patients with ESCC after CRT versus surgery alone (HR, 0.45; 95% CI, 0.25–0.8; $P = .0018$). Thus, when viewed collectively, the data support the addition of radiation therapy to multimodal regimens in patients with squamous histology from the standpoint of locoregional control.

Systemic Control

Neoadjuvant CRT regimens in patients with ESCC have demonstrated efficacy with respect to long-term survival outcomes. All trials listed on Table 5, with the exception of those by Le Prise et al and Nossert et al, have demonstrated a survival benefit on the order of 15% at 3 to 5 years. The two negative trials used very low doses of radiation (18.5–20 Gy), which may have limited their efficacy.

The mixed histologic trials outlined in Table 5 similarly yield valuable information when trying to ascertain the efficacy of neoadjuvant CRT in patients with ESCC from the standpoint of overall survival. The trials by Urba et al and Burmeister et al were negative trials but did demonstrate superior responses to neoadjuvant CRT in patients with ESCC compared with EAC. The trial by Tepper et al was a positive study. Although results were not broken down according to histologic study, the survival difference between the two groups was striking (5-year OS 47% vs 34% in favor of neoadjuvant 5FU, cisplatin, and concurrent 50.4 Gy; $P = .003$). In keeping with the observation that radiation performs particularly well in patients with ESCC, the CROSS trial demonstrated median OS of 81.6 months compared with 21.1 months ($P = .003$) in patients who received neoadjuvant CRT compared with patients who did not, respectively. As previously stated, this was associated with a pCR rate of 49% in patients with ESCC. These results are similar to those of Ilson et al, wherein patients who achieved a pCR exhibited significant improvements in OS compared with patients who underwent upfront surgery (mean OS 61.2 months vs 42.0 months, respectively; $P = .033$). This improvement was not observed in patients who demonstrated residual disease after neoadjuvant CRT. Although this was true for patients with EAC as well, what is notable in this study is the difference in pCR rates between the two histologic entities, with 25% of patients with EAC achieving a pCR compared with 51% of patients with ESCC. Thus, when taken collectively, the magnitude of the response to neoadjuvant CT is predictive of OS outcomes. Furthermore, those patients who achieve a pCR reap the greatest benefit with regard to survival outcomes.

CONCLUSIONS

Patients with locally advanced esophageal carcinoma require a multimodal approach if favorable survival outcomes are to be achieved. However, the two major histologic subtypes represent different entities and specific consideration should be entertained when treating EC. Patients with ESCC present with more proximal tumors, and these tumors demonstrate a proclivity for early locoregional spread and early locoregional recurrence. These tumors are particularly radiosensitive and exhibit dramatic response to concurrent platinum based doublet chemotherapy and external beam radiation. This permits pCR rates on the order of 50%, which, when they occur, are predictive of improved survival outcomes. Patients with EAC tend to present with very distally located tumors and a more resistant response to radiation therapy. Despite changes to concurrent chemoradiation protocols, pCR rates remain stable, on the order of 20% to 25%. Furthermore, the patterns of spread inherent to these tumors are characterized by early distant dissemination and the establishment of distant metastasis. Accordingly, local therapies have demonstrated a more modest effect on overall survival outcomes. Emphasis on effective systemic chemotherapy early in the disease course has been marked with improvements in overall survival. These differences highlight the importance of adopting a targeted approach to the management of EC, taking into consideration a number of factors before application of a given regimen. In this manner, improved outcomes in this vulnerable patient population can be achieved.

SUGGESTED READINGS

Al-Batran SE, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastroesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697–1708.

Dang HX, et al. Neoadjuvant chemoradiotherapy or chemotherapy? A comprehensive systematic review and meta-analysis of the optimal for neoadjuvant therapy for treating esophageal cancer. Eur J Gastrointest Surg. 2017;(1):33421–431.

van Hagen P, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–2084.

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USE OF ESOPHAGEAL STENTS

Nadeige Fadiche, MD, Arthur J. Garner, MD, MPH, Teresa A. Teo, MD, and Malcolm V. Lewis, MD, FACS

First described by French surgeon Leroy D'Etiolles in 1845, esophageal stenting was, at its inception, reserved mainly for the palliation of severe dysphagia in advanced esophageal cancer (EC). Over the years, the use of esophageal stent has steadily increased with an expansion of its indications to include benign disease. Improvement in stent design, endoscopic techniques, and complication rates have made it an attractive therapeutic option for patients with either mechanical or functional dysphagia, perforations, leaks, or fistulas.

Esophageal stenting generally has one of two main goals: (1) to maintain luminal patency and relieve severe dysphagia in the setting of benign or malignant strictures; and (2) to stem off potentially fatal luminal contamination of the mediastinum. For patients with sometimes debilitating disease, esophageal stenting offers the prospect of improved oral intake, symptomatic relief of dysphagia or aspiration, and the avoidance of morbid surgical interventions.

This chapter reviews the evolution of esophageal stenting, currently available stents, most current indications for esophageal stenting, stent placement techniques, and complications.

STENTS THROUGH THE AGES

D'Etiolles' stents, which were made of decalcified ivory, were unfortunately unsuccessful. Over the next 4 decades, several attempts by the likes of Sir Morrell Mackenzie in England yielded similarly disappointing results. The first successful esophageal stent was designed

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Patients with locally advanced esophageal carcinoma require a multimodal approach if favorable survival outcomes are to be achieved. However, the two major histologic subtypes represent different entities and specific consideration should be entertained when treating EC. Patients with ESCC present with more proximal tumors, and these tumors demonstrate a proclivity for early locoregional spread and early locoregional recurrence. These tumors are particularly radiosensitive and exhibit dramatic response to concurrent platinum based doublet chemotherapy and external beam radiation. This permits pCR rates on the order of 50%, which, when they occur, are predictive of improved survival outcomes. Patients with EAC tend to present with very distally located tumors and a more resistant response to radiation therapy. Despite changes to concurrent chemoradiation protocols, pCR rates remain stable, on the order of 20% to 25%. Furthermore, the patterns of spread inherent to these tumors are characterized by early distant dissemination and the establishment of distant metastasis. Accordingly, local therapies have demonstrated a more modest effect on overall survival outcomes. Emphasis on effective systemic chemotherapy early in the disease course has been marked with improvements in overall survival. These differences highlight the importance of adopting a targeted approach to the management of EC, taking into consideration a number of factors before application of a given regimen. In this manner, improved outcomes in this vulnerable patient population can be achieved.

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USE OF ESOPHAGEAL STENTS

Nadege T. Faithche, MD, Matthew Garner, MD, MPH, Tomoaki Ito, MD, and Malcolm V. Brock, MD, FACS

First described by French surgeon Ulrey Dilloffes in 1845, esophageal stenting was, at its inception, reserved mainly for the palliation of severe dysphagia in advanced esophageal cancer (EC). Over the years, the use of esophageal stent has steadily increased with an expansion of its indications to include benign disease. Improvement in stent design, endoscopic techniques, and complication rates have made it an attractive therapeutic option for patients with either mechanical or functional dysphagia, perforations, leaks, or fistulas.

Esophageal stenting generally has one of two main goals: (1) to maintain luminal patency and relieve severe dysphagia in the setting of benign or malignant strictures; and (2) to seal off potentially fatal luminal contamination of the mediastinum. For patients with sometimes debilitating disease, esophageal stenting offers the prospect of improved oral intake, symptomatic relief of dysphagia or aspiration, and the avoidance of morbid surgical interventions.

This chapter reviews the evolution of esophageal stenting, currently available stents, most current indications for esophageal stenting, stent placement techniques, and complications.

STENTS THROUGH THE AGES

Dilloffes' stents, which were made of decalcified ivory, were unfortunately unsuccessful. Over the next 4 decades, several attempts by the likes of Sir Morrell Mackenzie in England yielded similarly disappointing results. The first successful esophageal stent was designed

TABLE 1 Selected Overview of Currently Available Esophageal Stents and Relevant Characteristics for Clinical Practice

Product	Manufacturer	Placement	Material	Diameter Stent: Body (mm)	Length (cm)	Cover
Alimaxx ES	Merit Medical	OTW	Nitinol	CD16/18a/18/22	7/10/12	FC
Choostent	M.I. Tech	OTW	Nitinol	18/20/22/24	6/17	PC
Evolution	Cook	OTW	Nitinol	18/20	8/10/12	FC/PC
HEIGO	HCM	TTSOTW	Nitinol	20/22	10/12/15	FC/PC
Hanarostent	M.I. Tech	TTSOTW	Nitinol	18/20/22/24	6/12	PC
Niti-S single layered	Taewoong Medical	TTSOTW	Nitinol	16/18/20/22/24	6/8/10/12/14/15	FC/PC
Niti-S dic bic layered	Taewoong Medical	OTW	Nitinol	16/18/20/22/24	6/8/10/12/14/15	FC + UC
SX-EsoLA HV	Ella-CS	OTW	Nitinol	18/20	8.5/11/13.5/15	FC
SX-EsoLA BD	Ella-CS	OTW	Biodegradable	18/20/23/25	6/8/10	UC
Ultraflex	Boston Scientific	OTW	Nitinol	18/23	10/12/15	PC
Wallflex	Boston Scientific	OTW	Nitinol	18/23	10/12/15	FC/PC
Polyflex	Boston Scientific		Polyester/silicone			PC

FC, fully covered; OTW, over the wire; PC, partially covered; TTS, through the scope; UC, uncovered.
Modified from Vermeulen BD, Siersema PD. Esophageal stenting in clinical practice: an overview. Curr Treat Options Gastroenterol. 2008;11:269–277.

by Sir Charters Symonds in 1885. Symonds' stent, which was initially inserted, featured an esophageal tube affixed to a hogwood frame by a silver wire and was secured to the ear by a silk thread passing through the mouth or nose. Over the next decades, as interest in plastic polymers grew, stent design evolved. The first stents widely used in the esophagus were constructed from silicon rubber. These early stents were inserted with the assistance of a rigid esophagoscope but had a high rate of stent misplacement and migration. In the late 1950s, Celestin successfully palliated a malignant esophageal stricture using a plastic stent inserted via an open gastrostomy. The next few years would see an evolution in stent placement techniques as endoscopic tools evolved. In the 1970s, Atkinson introduced an endoscopically inserted plastic prosthesis. Unfortunately, a significant drawback of the Atkinson stent was its small internal diameter, which proved rate limiting when patients resumed a regular diet. High complication rates plagued many of these early plastic endoprostheses. Because of their rigidity and fixed internal as well as external diameters, most stents required endoscopic dilation, which invariably led to perforations. Additionally their inability to conform naturally to the structural morphology caused frequent stent migrations requiring intervention. In 1985, the modern era of esophageal stent innovation was ushered in when Ishibiger published the first description of the endoscopic placement of a self-expanding metal stent (SEMS) for a patient with a malignant esophageal stricture. In the 1990s, SEMS grew in popularity, in part fueled by the results of a series of trials conducted by Kozarek et al., which demonstrated that SEMS had higher patency rates, successful placement rates, and a better safety profile than available rigid plastic endoprostheses. Over the next few years, stent design and materials would continue to evolve. The modern esophageal stent is self-expanding and made of either plastic, Nitinol (a metal alloy), or biodegradable material. It may also come fully or partially covered. Table 1 reviews currently available stents and their characteristics.

STENT SELECTION

Selecting the appropriate stent for a given lesion, a critical step in preprocedural planning and a significant determinant of outcome, requires an understanding of the mechanical and physical properties of the various stents available (Fig. 1).

FIG. 1 Self-expanding metal stent.

The majority of SEMS are made of Nitinol, a nickel titanium alloy, that has super elasticity and shape memory. This property allows a metal's shape to be easily modulated by small temperature variations, but there is also a spontaneous return to the original shape when the temperature is outside of the transformative range. These unique characteristics are exploited in SEMS as they expand at body temperature to fit the morphology of a given lesion. Nitinol is also

resistant to corrosion and hypoallergenic. Although biologically inert, it triggers a mild inflammatory response with resulting fibrosis that is useful in reducing stent migration. Unfortunately, this same property can be a major drawback of uncovered SEMS, fostering stent stenosis by allowing fibrotic tissue regrowth through the openings in the mesh material. To counter this phenomenon, fully covered and partially covered stents were developed. These stents feature proximal and distal cuffs that remain bare and uncovered to provide additional luminal anchorage. Covered stents are believed to have less tumor ingrowth, but can potentially be more susceptible to stent migration, especially in high risk areas such as at the distal esophagus.

Self expandable plastic stents (SEPS) are double layered, featuring polyester mesh on their external surface with an embedded silicon inner lining creating a smooth inner surface. To prevent migration, flared distal and proximal ends facilitate luminal anchorage. Considering that their internal diameter tends to decrease under tension, SEPS are easily retrieved endoscopically, making them ideal for short term stenting.

Introduced in the mid 2000s, biodegradable stents (BDS) are mainly used in the setting of benign strictures, as they negate the need for retrieval. These are made of plated polydioxanone, a monofilament, which undergoes hydrolytic degradation over 8 to 12 weeks. These maintain their mechanical strength for 4 to 6 weeks.

PATIENT SELECTION

Careful clinical evaluation and characterization of the lesion of interest are necessary to optimize clinical outcome in patients receiving esophageal stenting. Baseline assessment of dysphagia, nutritional status, and quality of life (QOL) will provide a reference point from which the efficacy of the intervention can be measured. The Dysphagia Scoring Scale by Ogilvie et al. (Table 2) is a simple and effective tool to assess dysphagia in patients with strictures. Combining radiographic modalities such as esophagram, positron emission tomography computed tomography, and endoscopy can provide invaluable information about the lesion's location, size, morphology, and relationship to adjacent intrinsic structures, and thus inform stent selection.

INDICATIONS

The Food and Drug Administration (FDA) has approved esophageal stenting for the preservation of luminal patency in the setting of intrinsic or extrinsic malignant strictures, and the occlusion of concurrent esophageal fistula. In practice, however, the list of lesions amenable to esophageal stenting has increased, owing to better stent design, improved safety profile, and sophisticated endoscopic techniques. In the United States and other developed nations, stenting for malignant esophageal strictures has decreased because of improved outcomes with single dose brachytherapy. Conversely, esophageal stenting for the management of various benign conditions, such as refractory benign esophageal strictures (RBES), esophageal perforations, variceal bleeding, postsurgical anastomotic leaks, and achalasia has increased by over 50% in the past decade.

TABLE 2 Dysphagia Scoring Scale

Class	Dysphagia Scoring Scale
0	Able to consume normal diet
1	Dysphagia with certain solid foods
2	Able to swallow semisolid foods
3	Able to swallow liquids only
4	Unable to swallow saliva (complete dysphagia)

Data from Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative endoscopic management of oesophagogastric neoplasms at thoracoscopy. Gut. 1993;34:1163–1167.

Malignant Esophageal Disease

Malignant Esophageal Strictures

Malignant esophageal dysphagia results from luminal narrowing either by intraluminal growth of primary esophageal tumors, or by extrinsic compression from mediastinal and airway tract neoplasms. Primary HC remains one of the most lethal cancers of the aerodigestive tract. Because of its insidious course, clinically apparent disease is typically synonymous with advanced stage. In these patients, relief of dysphagia and resumption of oral intake provides an invaluable improvement in QOL, and in some cases, survival prospects. Since its inception, esophageal stenting has been regarded as the first line therapy for the palliation of malignant dysphagia. SEMS provides prompt relief and the opportunity to optimize patients' nutritional status. Interest in regionally targeted radiation modalities such as brachytherapy has transformed the clinical approach to malignant dysphagia. A randomized controlled trial (RCT) comparing SEMS to single dose brachytherapy demonstrated that although stenting resulted in earlier relief of dysphagia, brachytherapy provided longer lasting relief, higher QOL scores, and significantly less morbidity, as evidenced by a rate of major complication of 12% compared to 25% for SEMS. Despite these findings, the initial enthusiasm for brachytherapy is fading due to frequently noted need to insert rescue stents. Brachytherapy may be considered for carefully selected patients with mild to moderate dysphagia who have a longer life expectancy. Esophageal stenting thus remains the first line of intervention for patients with moderate to severe dysphagia who are not candidates for other modalities or patients with recurrent dysphagia after brachytherapy. Fully covered SEMS (fcSEMS) are the stents of choice for the management of malignant strictures. In recent studies, these have demonstrated a lower rate of tumor ingrowth compared with uncovered SEMS and a lower risk of stent migration when compared with covered SEPS. Although there is no difference in outcomes between fcSEMS and partially covered SEMS (pcSEMS), the latter is often subject to tumor ingrowth at its uncovered distal and proximal ends, thus making for challenging endoscopic retrieval.

Malignant Esophageal Fistulas

Malignant esophageal fistulas result primarily from esophageal tumor infiltration into surrounding structures, such as the trachea, mediastinum, pleura, and proximal abdominal cavity and less commonly from extrinsic infiltration of respiratory tract tumors, or cholecystoduodenal tumor necrosis. Regardless of the mechanism, temporary suspension of oral intake, drainage of involved spaces, and endoscopic insertion of an fcSEMS are frequently recommended. Currently, successful fistula closure rates are over 70%, and recent evidence suggests a modest survival advantage once closure is achieved. The early appeal of concurrent stenting of the tracheobronchial tract (Fig. 7), or "dual stenting," has been largely overshadowed by a higher risk of highly lethal pulmonary and vascular erosions due to aggressive pressure necrosis. Despite the scarcity of data available regarding the most appropriate stent for malignant fistulas, fcSEMS are the modality of choice by consensus.

Gastroesophageal Junction Tumors

Palliation of gastroesophageal junction (GEJ) strictures by endoscopic means is technically challenging, owing to intrinsic anatomic peculiarities. Unlike the upper and middle esophagus, the GEJ features an acute angle and varying luminal diameters, which may interfere with satisfactory stent fixation. Esophageal stenting at this location is frequently associated with an increased risk of acid reflux, distal migration, and ineffective palliation. The higher rate of complications is often compounded by the overall poorer survival ascribed to GEJ tumors and has long been a basis for an argument against stenting of these lesions. In clinical practice, pcSEMS are considered the stent of choice for GEJ strictures, as their flare ends allow for better anchorage

The introduction of modified ESEMS featuring progressive flaring of the distal end (anchoring lumen to the gastric opening) and one-way reflux valves at the distal end theoretically favors improved treatment of GJO lesions. A recent RCT by Persson et al. comparing modified ESEMS with pcSEMS in 95 patients with malignant GJO strictures showed no difference in stent migrations, although there was a trend toward better relief of dysphagia with ESEMS.

Bridge to Surgery

Preoperative esophageal stenting in patients with locally advanced EC undergoing neoadjuvant therapy may allow for nutritional optimization before surgical resection. Although several small studies have demonstrated improved oral intake, weight stabilization, and QOL when SEMS, SEPS, or BDS were used as a bridge to surgery in a neoadjuvant setting, a retrospective study by Markakis et al. reported worse oncologic outcomes with SEMS. A lower rate of complete resection (71.0% vs 85.3%; $P = .041$), shorter disease free interval (6.5 vs 9.0 months; $P = .040$), and worse 3-year overall survival (25% vs 48%; $P = .023$) were noted in the preoperative SEMS group. One possible explanation resides in the fact that SEMS-induced mural inflammation may distort the tissue planes and interfere with the complete rate of resection. There is currently no evidence regarding oncologic outcomes with preoperative stenting during neoadjuvant therapy for SEPS and BDS. Of note, although stent migration rates in this setting are upward to 50%, they may represent a favorable response to neoadjuvant therapy.

Benign Esophageal Disease

Benign Refractory Esophageal Strictures

The mainstay in the treatment of benign esophageal strictures is peri-orifice endoscopic balloon dilation. However, for a subset of patients, dysphagia will persist despite repeated dilation, thus requiring more aggressive interventions. BSEMS are most commonly encountered after caustic injuries, radiation to the chest or mediastinum, postsurgically after esophagogastric anastomosis, or after endoscopic interventions such as per oral endoscopic myotomy and endoscopic mucosal resection. Although no study has, to date, evaluated the impact of dilation time on outcomes, proponents of temporary stenting for BSEMS purport that continued radial pressure on the esophageal lumen may result in sustained luminal patency. The challenge in selecting a stenting modality for BSEMS resides in the transient nature of the intervention. The ideal stent needs to be easily retrievable, and yet resistant to migration. To this end, ESEMS are the most commonly used. Although initially showing great efficacy, Polyflex, the only FDA-approved SEPS for BSEMS was discontinued in the United States owing to a disappointing safety profile. Its insertion resulted in migration rates up to 50% and a rate of severe stent-related complication nearing 25%. There are currently no RCTs evaluating outcomes for various stent designs in the management of BSEMS. A recent meta-analysis by Thomas et al. examined the performance of ESEMS in 199 patients with BSEMS. The efficacy of ESEMS for palliation was 86.2% with a migration rate of 24.4% and a successful retrieval rate of 87%. BDS has shown similar efficacy to ESEMS and has the added advantage of not requiring retrieval. However, BDS has a higher rate of stent-related complications such as retrosternal pain and bleeding. In brief, esophageal stenting with either ESEMS or BDS is an intervention of last resort in benign esophageal strictures, reserved for carefully selected patients with BSEMS.

Benign Perforations, Anastomotic Leaks, and Fistulas

Benign esophageal perforations (BEP) can be classified as spontaneous, such as in Boerhaave's syndrome, iatrogenic or traumatic. As for fistulas, contamination of surrounding mediastinal or pleural spaces by esophageal luminal contents can have dire consequences, triggering highly lethal inflammation and infection. For the practicing surgeon, early determination of the etiology and severity of the leakage is crucial, as these considerations will guide therapeutic management and determine outcomes. A contained perforation or anastomotic leak in an otherwise clinically stable patient may be successfully treated with conservative measures. In these patients, nil per os, intravenous hydration, nasogastric drainage, and broad-spectrum antibiotics are the mainstays of therapy. In patients with noncontained leaks, esophageal stenting may allay the potential morbidity of surgical intervention and is now increasingly used (Figs. 3 and 4). As with traditional surgical approaches, the goal of therapy in using stents in these patients remains complete drainage of the contaminated spaces, successful sealing of the leak, possible diversion of oral secretions, and prevention of widespread infection. In a recent meta-analysis comparing SEMS to surgical intervention in patients with esophageal leakage, Persson et al. reported a higher success rate (88% vs 8%)

FIG. 3 Left to right: Self-expandable plastic stent, partially covered self-expanding metal stent (SEMS), and "all-age" fully covered SEMS. Early removal SEMS.

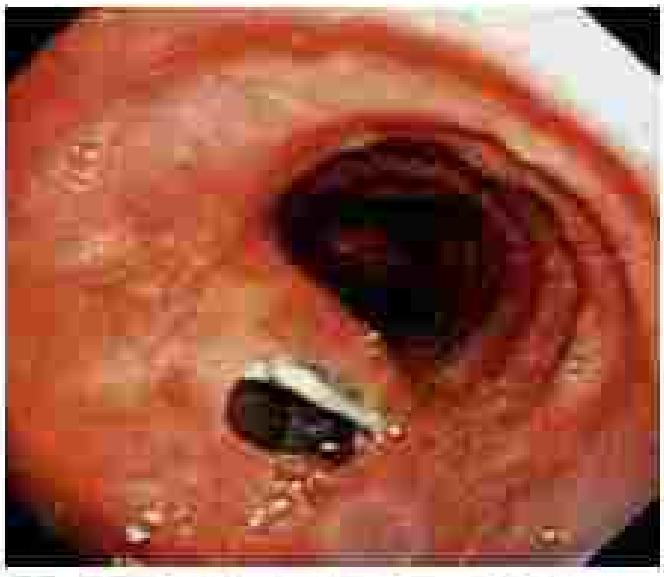

FIG. 4 Acquired tracheoesophageal fistula. (Courtesy Dr. Richard K. Freeman, MD.)

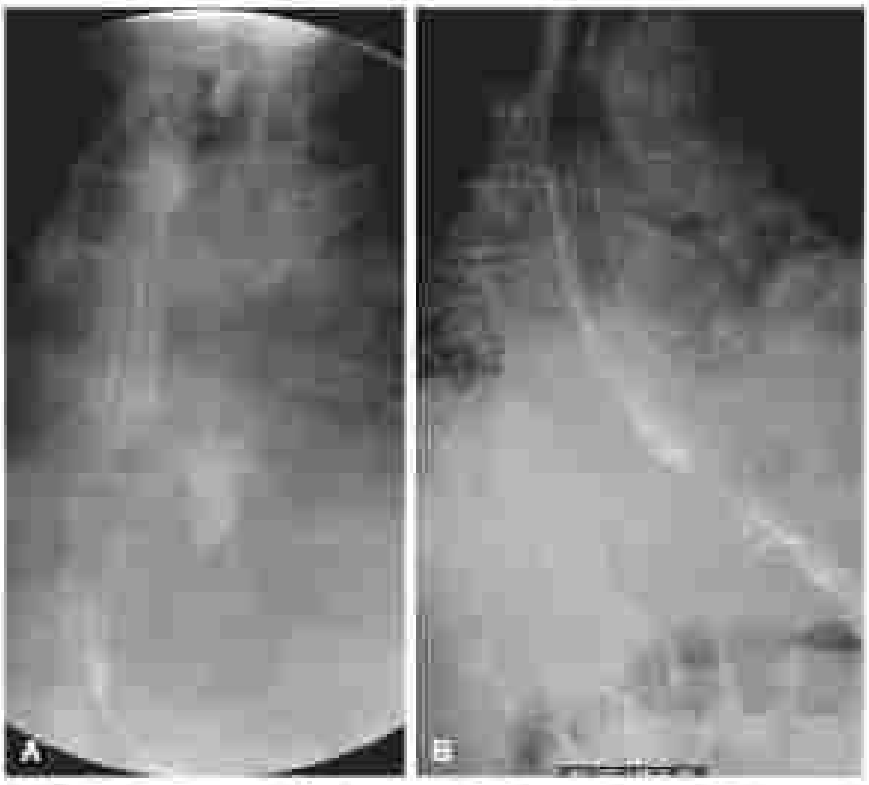

FIG. 4 (A) Upper gastrointestinal (GI) series with water-soluble oral contrast medium demonstrating contralateral conveyance of contrast medium from the left side of the esophagus approximately 2 cm below the level of the cervical constriction, with esophageal perforation. (B) Repeat upper GI series with water-soluble oral contrast medium in the same patient as in Fig. 4A demonstrates a distal esophageal stent in good position, there is no evidence of contrast medium extravasation to suggest a persistent leak.

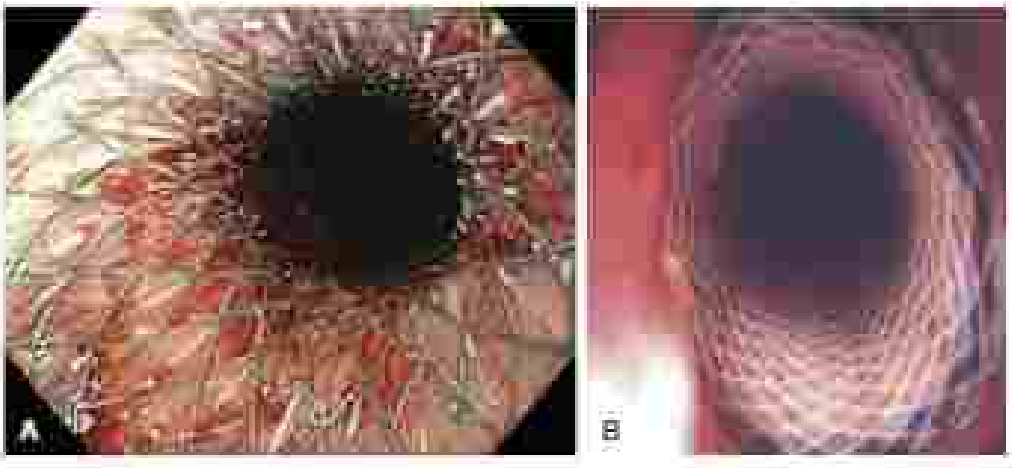

FIG. 5 Endoscopic view of duplicate self-expanding metal stent (A) and self-expands in plastic stent (B).

and a lower mortality rate (7.5% vs 17%) when SEMS were used. We recommend the use of covered stents—either ASEMS or pcSEMS—for the management of hemodynamically stable patients with SEP. Concurrent drainage of the involved space, broad-systemic antibiotic therapy, intravenous fluid administration, and temporary diversion of oral secretions are often employed to optimize clinical outcomes.

Achalasia

The role of esophageal stenting in the treatment of achalasia is evolving. Over the last 3 decades, the introduction of temporary stenting using retrievable SEMS has renewed interest in this modality. In 2018, a long-term follow-up of a prospective comparison of pneumatic dilation and SEMS of various diameter in 120 patients with achalasia showed a higher clinical remission rate at 15 years (83.3% vs 9) when 30-mm SEMS were used compared to pneumatic dilation. Although surgical and endoscopic interventions such as Heller myotomy and per oral endoscopic myotomy are the mainstays of definitive therapy for achalasia, temporary retrievable stenting with SEMS may be an option for the surgically unfit patient (Fig. 5).

PROCEDURE

Meticulous planning is necessary when considering esophageal stenting. Although both conscious sedation and general anesthesia are

comparable, the latter would best serve a patient at high risk for aspiration. Preprocedural endoscopic evaluation of the lesion should be comprehensive. The luminal diameter, location, and size of the lesion of interest must be carefully assessed and documented. Evaluating the friability of the luminal tissue is equally as important, as it could portend a greater risk than usual of bleeding, pressure necrosis, or mural erosion after the procedure. Endoscopic debridement of the lesion is no longer routinely performed but could be considered for the small subset of patients in whom the severity of the stenosis might prevent stent insertion. Particular attention should be paid to stent size. The internal diameter of the stent should be slightly larger than the lesion of interest, thus allowing for adequate radial force to be applied. An inadequately small stent diameter may increase the risk of migration, whereas an oversized stent may lead to perforation and excessive pressure necrosis. The length of a stent should be at least 4 cm longer than that of the lesion, overlapping it both proximally and distally by at least 2 cm. Esophageal stenting can be achieved using either fluoroscopic or endoscopic guidance. We use a Seldinger technique to advance a guidewire endoscopically into the esophagus 2 to 3 cm past the distal end of the lesion. Next, the endoscope is removed, and the stent delivery system is advanced over the guidewire. The endoscope is then reinserted, and the stent positioned and deployed under direct visualization. Caution should be used to ensure that the stent is not fully deployed until satisfactory positioning has been achieved. Using fluoroscopy, the guidewire is inserted using a catheter. Once a satisfactory position has been secured, a small amount of water soluble contrast medium is injected through the catheter to delineate the structure. Radiopaque markers are then used to delineate the location and length of the structure on the patient's skin. Next, after the catheter is removed, the delivery system is advanced over the guidewire and the stent is deployed under continuous fluoroscopic monitoring. Repeat endoscopy or an upper gastrointestinal series 24 to 36 hours postdeployment is often performed before the resumption of oral intake is permitted.

COMPLICATIONS

Close to 30% of patients undergoing an esophageal stent placement experience complications (Table 3). These events are often classified as early or late (Table 4). Events of mild to moderate severity such as retrosternal pain or reflux symptoms typically resolve within 1 or 2 weeks postprocedure. Persistence of retrosternal pain beyond 2 weeks may indicate the need for endoscopic removal of the stent. Recent studies have shown improvement of reflux symptoms with the use of stents equipped with a distal reflux valve, especially in patients with GOJ lesions. Tumor ingrowth is most commonly seen with uncovered or partially covered stents, but now can be successfully managed with a stent-in-stent technique (Fig. 6). This chapter focuses on the major complications of stent migration and vascular and aerodigestive erosions.

Tissue Erosion

Stent erosion into neighboring mediastinal structures such as the big vessels and the airway is rare but highly lethal when it occurs. Tissue necrosis resulting from high radial pressure exerted on the esophageal wall is often compounded by poor tissue perfusion and impaired wound healing secondary to malnutrition or radiation exposure. Indeed, a history of radiation to the chest or mediastinum increases the risk of tissue erosion up to tenfold. Similarly, distal stenting of the esophageal and tracheal is also associated with an increased risk of tissue erosion.

Vascular Erosion

Vascular erosion is rare but highly lethal. Although aortoesophageal fistula is perhaps the most common, vascular erosion involving the retroesophageal subclavian and common carotid arteries have been reported. One must always have a high degree of suspicion as to its possibility. For example, an abrupt sentinel hematemesis associated with retrosternal chest pain in a patient with a history of esophageal stent placement should prompt immediate evaluation and intervention before a potential catastrophic exsanguination. Emergent management of an aortoesophageal fistula involves prompt control of the potentially fatal hemorrhage, followed by timely vascular repair (Fig. 7). Concurrent activation of the massive transfusion protocol and airway protection may be necessary. In such an emergent setting, endoscopic balloons can often be used to control the bleed, and stent surgeons have even successfully used Sengstaken-Blakemore tubes for this purpose. Temporary intravascular occlusion and emergent surgery are also options. Once control is obtained, it can be followed with endovascular repair of the aortic defect. After the patient is stabilized, attention can then be turned to the esophageal defect. Following removal of the offending stent, a small defect may be primarily repaired with muscle interposition. An esophagectomy may be necessary for larger defects. Alternatively, in moribund patients, a conservative approach involving diversion of esophageal contents and palliative care may be more appropriate.

TABLE 3 Overview of Adverse Events Related to Esophageal Stent Placement for Different Indications

Complications	Malignant Dysphagia (n = 1017)	Benign Dysphagia (n = 73)	Esophageal Leakage (n = 339)
SERIOUS ADVERSE EVENT (%)			
Major bleeding	8.0	3.0	1.3
Aspiration pneumonia	5.0	1.5	10.7
Perforation	2.0	1.5	1.8
ADVERSE EVENTS (%)			
Retrosternal pain	30.0	6.5	8.5
Reflux symptoms	7.0	2.6	8.5
Recurrent dysphagia: case	31.0	26.0	20.0
Stent migration	11.0	21.5	16.5
Tissue ingrowth/ overgrowth	14.0	2.3	2.7
Food obstruction	7.0	2.3	1.1

Modified from Vermeulen BG, Siersema PD. Esophageal stenting in clinical practice: an overview. Curr Treat Options Gastroenterol. 2010;13:260-273.

TABLE 4 Common Early and Late Complications After Esophageal Stent Placement

Early Complications (<2 weeks), 10%–25%	Late Complications (>2 weeks), 15%–17%
Retrosternal pain	Migration
Minor hemorrhage	Stent fracture
Aspiration	Obstruction/tumor ingrowth
Gastroesophageal reflux disease	Erosion
Migration	Airway stenosis/compression
Occlusion	Vascular erosion
Airway stenosis/compression	
Vascular erosion	

Modified from Vermeulen BG, Siersema PD. Esophageal stenting in clinical practice: an overview. Curr Treat Options Gastroenterol. 2010;13:260-273.

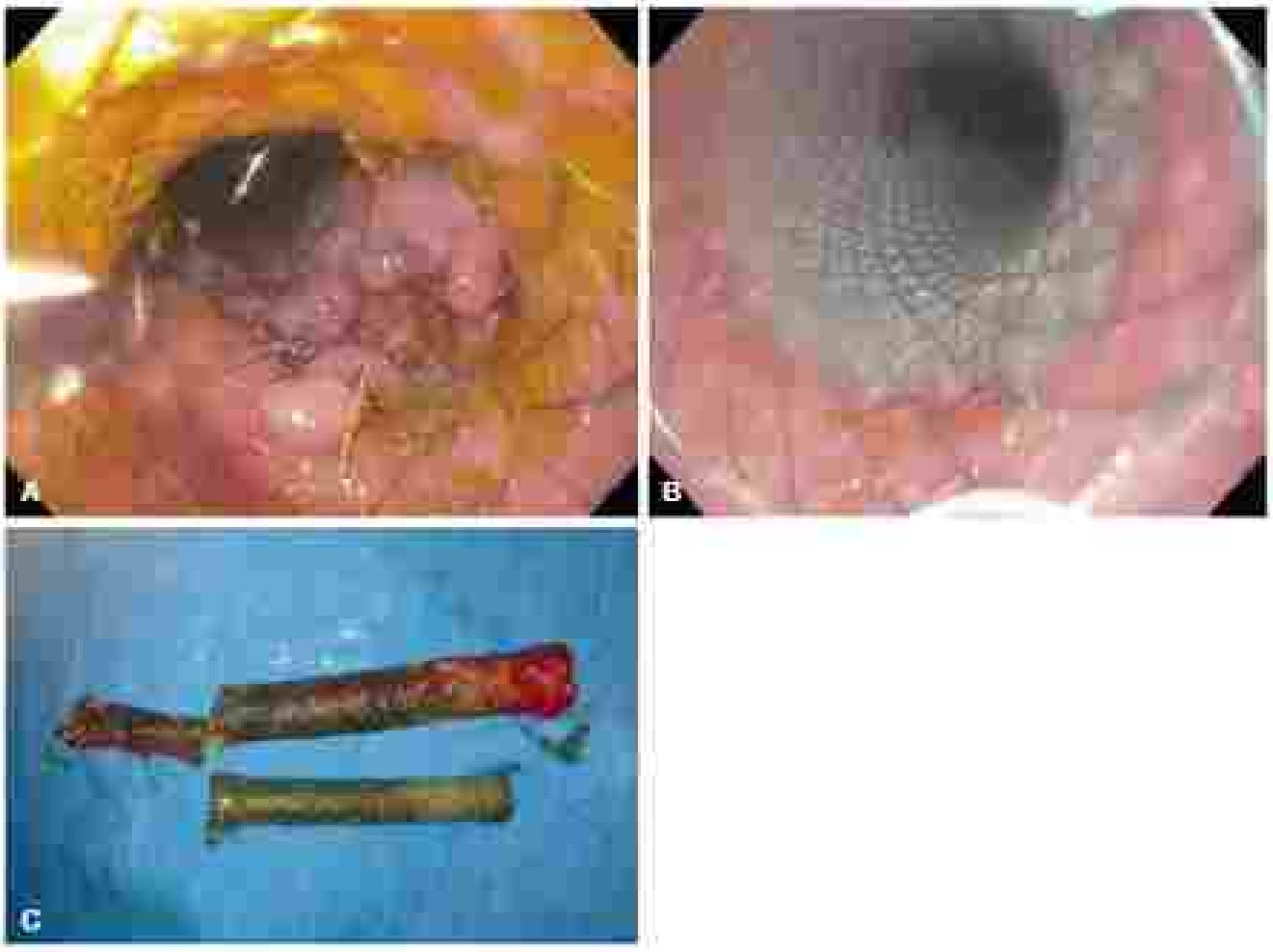

FIG. 6 (A) Endoscopic view of a fractured self-expanding metal stent (SEMS) with exposed struts of esophageal mucosa. (B) Internal placement of an SEMS within the lumen of the pre-existing fractured SEMS to facilitate retrieval. (C) Successful extraction of both fractured SEMS (top) and intact SEMS (bottom).

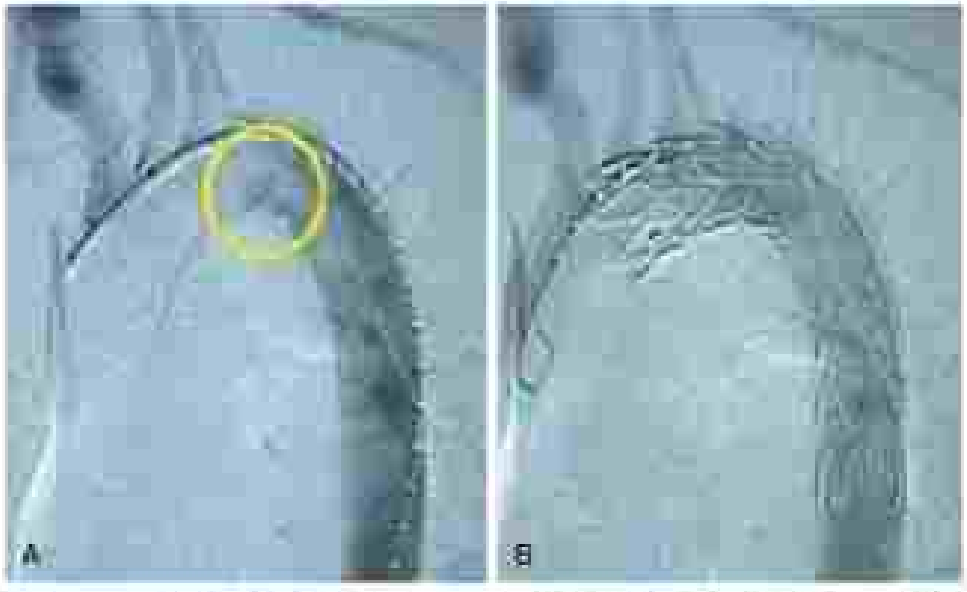

FIG. 7 Thoracic endovascular aortic repair of aortic defect after an esophageal fistula. (A) Contrast and stool-stained mixture leaking from the aortic defect. (B) Arch aortogram showing the endovascular stent graft. (From Song H, Shim J, Jo W, et al. Definitive treatment of esophageal fistula by endovascular stent graft. Indian J Surg. 2013;75:114–116.)

FIG. 8 Endoscopic view of an esophageal clip that outlines the proximal aspect of an esophageal stent.

FIG. 9 Endoscopic view of the Apollo Overstitch device and the suture fixation of the proximal aspect of an esophageal stent to the esophageal mucosa.

Aerodigestive Erosion

Tracheoesophageal erosions have been reported in 6% to 9% of patients after esophageal stenting (Fig. 8). Unlike the dramatic presentation seen with vascular erosion, patients often present with nonspecific symptoms such as dyspnea and frequent pulmonary infections. Although a chest computed tomography scan may help identify the lesion of interest, bronchoscopic and endoscopic evaluations are often necessary to characterize the extent and size of the defect. The management of tracheoesophageal fistulas depends on the patient's hemodynamic status and on the underlying pathology that led to esophageal stricture. In a patient that presents in extremis, securing the airway must be the priority. One should maintain spontaneous ventilation if possible, but the patient should be promptly intubated if there is an inability to ventilate. A variety of intubation methods can be used if ventilation is difficult including controlled exposure intubation, use of a double lumen tube, employing a bronchial blocker, or isolating the patient to ventilate. In some cases, tracheal stenting and esophageal diversion may be needed, and definitive management may be delayed. Stable patients with good functional status and with good esophageal tissue integrity can undergo either a primary repair with muscle interposition or an esophagectomy. Otherwise, tracheal stenting, esophageal diversion, and palliative care should be considered.

Stent Migration

Stent migration is perhaps the most common complication of esophageal stricture, occurring in 11% to 25% of cases. Over the last 2 decades, various interventions aimed at reducing the frequency of migrations, such as anchoring the stent to the esophageal wall, have been introduced. Endoclips are used to secure the proximal stent end to the esophageal wall, but a high migration rate persists (Fig. 8). Endoscopic suturing using the only FDA-approved suturing device Apollo Overstitch (Fig. 9) has also shown some potential benefit in small studies; however, high-quality evidence is not available. The best treatment of migration is probably prevention. A study by Freeman et al. evaluating the impact of stent indwelling time in 162 patients treated with esophageal stenting showed a significant reduction in stent-related complications in patients who had a shorter indwelling time (Table 5). In patients with anastomotic leaks, a 30% ($P = .04$) reduction in stent migration rates was noted with a stent duration of fewer than 14 days. Patients with acute perforation experienced a 34% reduction in stent migration when the indwelling time was fewer than 28 days.

CONCLUSIONS

Esophageal stenting remains a mainstay in the palliation of advanced malignant strictures. Although its indications have greatly expanded to include various benign esophageal disease, complications associated with this procedure mandate thorough preprocedural evaluation of the patients as well as an individualized therapeutic approach.

TABLE 5 Rates of Complication Based on Stent Indwelling Time in the Management of Esophageal Leaks and Perforations

	Anastomotic Leak			Perforation		
	<2 Weeks	>2 Weeks	P Value	<4 Weeks	>4 Weeks	P Value
Number	28	36		36	22	
Migration	4 (14%)	7 (44%)	.04	9 (9%)	9 (41%)	.0007
Dysphagia	5 (17%)	8 (28%)	.38	4 (4%)	6 (29%)	.0022
Hemorrhage	0	1 (4%)	.4	0	2 (10%)	.03
Stent fracture	3 (10%)	4 (28%)	.05	5 (5%)	7 (35%)	.002
Airway compromise	1 (3%)	2 (13%)	.3	3 (3%)	2 (10%)	.2

Data from Freeman RK, Ascioti AJ, Dake M, Mahidhara RS. An assessment of the optimal time for removal of esophageal stents used in the treatment of an esophageal anastomotic leak or perforation. Ann Thorac Surg. 2011;92:411-418.

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Management of Esophageal Perforation

Eric Lambright, MD

Esophageal perforation is an ominous disease process and is universally fatal without appropriate and optimal management. Even with prompt diagnosis and optimal management, mortality rates are significant and have consistently ranged from 15% to 20%. There are multiple options related to the management of esophageal perforation, and a definitive uniform recommendation for treatment has not been established. Esophageal perforation and physiologic sequelae are related to the extravasation of oral and gastric secretions into the mediastinum with resultant intense and rapidly progressing inflammatory process. This process quickly overwhelms the body's defensive capacity, resulting in life-threatening impacts. The first clinical description of esophageal perforation was presented by Herman Boerhaave in 1720. He described the events of a Dutch Naval Grand Admiral who developed acute chest pain after an episode of vomiting after a gluttonous meal who had rapid clinical decline with profound chest pain, fever, and ultimately death. Postmortem analysis documented a distal esophageal perforation. The cause of esophageal perforation has evolved over time, and iatrogenic causes have become the most common cause (▶ Box 1). The principles of care for the patient with esophageal perforation reflect basic and classical surgical management. Prompt diagnosis, source control, eradication of sepsis, and optimal intensive care management are required to achieve and maximize survival. These principles will be reviewed.

ETIOLOGY

Anatomically, the most common site for esophageal perforation remains within the thoracic esophagus. Greater than 80% of perforations occur in that location. A small percentage occurs within the cervical esophagus and only rarely are perforations confined to the intraabdominal segment of the esophagus. The most common cause of esophageal perforation is iatrogenic related to esophageal instrumentation. Perforations will occur in areas of normal anatomic narrowing such as proximal to the cricopharyngeus or within the distal esophagus. Interruption of manipulations of pathologically abnormal esophagus by endoscopy may also cause perforation. Iatrogenic perforation accounts for approximately 20% of esophageal perforations. Less common causes of perforations include traumatic injury, ingestion of either foreign body or caustic material, suppurative necrotizing infection, or surgical intervention within the neck or chest in juxtaposition to the esophagus.

Patient symptoms at the time of presentation will be dependent on multiple factors, but fundamental issues are anatomic location of perforation, time from inciting event, and patient comorbidities. Provided a presenting patient has no changes to his or her baseline sensorium or mental status, pain remains a near-uniform complaint. Esophageal perforation must be suspected in any patient who has recently undergone esophageal instrumentation who has atypical neck or chest discomfort. Appropriate evaluations are required. Individuals who have suffered from iatrogenic esophageal perforation will infer complaints of excruciating and burning chest or upper abdominal discomfort. At times, clinicians may pursue an alternative diagnosis such as myocardial infarction or aortic dissection before entertaining the possibility of esophageal perforation. Patients will also describe some degree of dysphagia, odynophagia, or dysphonia. Signs on physical examination are typically very nonspecific in the setting of esophageal perforation. Subcutaneous crepitus is rarely identified. Findings such as decreased breath sounds or pleural rubs can be identified but do not provide for diagnostic clarification.

BOX 1 Causes of Esophageal Perforation

Iatrogenic
- Esophagoscopy with dilation, biopsy, or stent placement
- Transesophageal echocardiography
- Esophageal ultrasonography

Iatrogenic: Boerhaave syndrome

Traumatic
- Blunt
- Penetrating
- Surgical intervention: cervical intervention or mediastinal surgery

Ingestion: caustic or foreign body

Neoplastic
- Primary esophageal malignancy
- Mediastinal malignancy with esophageal involvement and erosion

Infectious—mediastinal necrotizing process

Suggested Readings

Bick BL, Song I, MWK, Sellor MS, et al. Risk associated esophagojejunostomy leakage: incidence and risk factors. Gastrointest Endosc. 2012;75:181–188.

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Ingestion: caustic or foreign body

Neoplastic
- Primary esophageal malignancy
- Mediastinal malignancy with esophageal involvement and erosion

Infectious—mediastinal necrotizing process

Tachycardia related to presence of the profound inflammatory process is typically present. Hypotension usually suggests a significant interval from inciting event to presentation. As with other acutely life threatening disease processes, clinical suspicions require appropriate and prompt diagnostic evaluations. Thus a low threshold for additional interrogation is warranted.

Radiographic diagnostic assessments are typically required for not only diagnostic confirmation but also for anatomic clarification with reference to location of perforation, disease associated with the esophagus, and any abnormality that would be identified distal to the area of perforation. Plain films of the chest offer nonspecific findings such as pleural effusion, subcutaneous emphysema, pneumomediastinum, or hydropneumothorax. However, chest radiographs in individuals with esophageal perforation are not consistently normal. A contrast swallow test remains the gold standard for evaluation of esophageal perforation. It is our practice to perform barium esophagography because these evaluations consistently have lower rates of false negative testing results when compared with water soluble contrast material. Additionally aspiration of barium is rarely associated with pneumonitis in contrast to water soluble materials. In patients who have been intubated, evaluations can be done through nasoenteric tubes. Cross sectional imaging with chest computed tomography (CT) can also complement contrast swallow evaluations and can provide useful diagnostic information, such as pathologic changes within the esophagus, clarification of the status of the pleural spaces, and other unsuspected anatomic findings. Endoscopy can also be useful for diagnostic clarification and does not appear to add any significant risk even in the setting of a possible esophageal perforation. Again, false negative assessments are not infrequent. Liberal use of endoscopy should be considered because additional information that could potentially impact therapeutic planning, such as anatomic location of the injury, associated pathologic changes of the esophagus, such as stricture or neoplasm, and assessment of the esophagus distal to the area of perforation can also be obtained. After diagnoses of esophageal perforation, standard and optimal medical care should be implemented. Broad spectrum antibiotics, including antifungal therapy, should be initiated. Appropriate physiologic support and interventions for relief of pain will be needed. Essential information, including cause of perforation, exact anatomic location, duration from inciting event, and knowledge of any underlying esophageal disease, is required to formulate an optimal therapeutic plan. Patients' underlying comorbid states must also be considered.

TREATMENT

Regardless of anatomic location, basic principles of management are control of leak, drainage of infection, eradication of sepsis, and, optimally, maintenance of gastrointestinal continuity. The combined expertise of surgeon, anesthesiologist, and intensivist is required for successful management. Typically, operative therapy is required for treatment of esophageal perforation. In unique situations, Cameron described criteria for nonoperative treatment of esophageal perforation, including contained perforation, free drainage of contrast back into the esophageal lumen, and minimal symptoms. Rigorous attention to all these details is required, should nonoperative management be considered. Clinical deterioration or changes would necessitate appropriate interventions. Additional observations have been made that further clarified and reinforced the principles of conservative management. Classically, nonoperative therapy consists of nasogastric decompression, broad spectrum antibiotics, and nutrition support. Intensive care unit monitoring would typically be necessary.

With the increasing use of CT imaging in the evaluation of patients in the emergency department with chest discomfort, surgeons are often asked to evaluate individuals with pneumomediastinum of unclear clinical importance. Not uncommonly, patients will present after a vomiting episode with these CT findings without any evidence of clinical deterioration. Our practice is to manage these individuals with appropriate esophagography and, provided this is normal, support with a brief period of cessation of oral intake, antibiotics, and clinical observation. Within a day or so, symptoms resolve, and patients will require no further evaluations or follow up. Active management and thoughtfulness are required when considering nonoperative therapy for esophageal perforation because most clinicians favor definitive interventions for a defined life threatening surgical disease process.

OPERATIVE TREATMENT

There are several different approaches from a technical perspective to achieve the goal of esophageal leak control and drainage of infection and debridement of devitalized soft tissue. Most commonly, primary buttressed repair of the perforation is performed. At times, based on underlying esophageal disease, esophageal resection with either primary reconstruction or diversion may be necessary. Perforations within the cervical esophagus are typically approached through the left neck. A right thoracotomy is chosen for injuries to the midesophagus. Distal esophageal perforation would typically be managed through a left thoracotomy approach through the seventh intercostal space. The use of stenting with appropriate mediastinal debridement has been involving. Operative intervention for management of esophageal perforation typically includes use of the following: primary repair, diversion and exclusion, closure over a T tube, and esophageal resection with immediate or staged reconstruction.

When approaching cervical esophageal perforation, a left neck incision just anterior to the sternocleidomastoid would be favored. After division of the omohyoid and thyroid vein, excellent exposure to the cervical esophagus can be achieved with retraction of the carotid sheath and contents laterally. The esophagus can be mobilized from the prevertebral fascia. Appropriate debridement of any infected material can be achieved. If the mucosal abnormality can be identified, primary repair is performed. However, exhaustive evaluation of the esophagus is not recommended because, typically, drainage of the area provides for appropriate management with ultimate esophageal healing. Nutrition support and antibiotics would be used as adjunctive management. The surgeon must ensure that all areas of contamination are drained. A low threshold to enter the mediastinum by an alternative access such as right thoracotomy must be maintained. Appropriate use of closed suction drain is necessary. Perforations within the thorax, esophagus cannot be managed with drainage alone because survival rates with this management strategy are unsatisfactory.

Regardless of anatomic location and exposure via either a right thoracotomy or left thoracotomy, principles of primary operative repair of esophageal perforation are standard, meticulous closure of the esophageal defect, debridement of devitalized tissue with evacuation of all infected material, and wide drainage. A buttressed repair is typically used. An intercostal flap can be promptly mobilized on entering the chest. Pleural debris and contamination are promptly evacuated. The mediastinal pleura is opened, and exposure of the esophagus is achieved. Esophageal perforation is identified. Provided there is no underlying esophageal structural disease such as neoplasm or achalasia, it is rare that primary repair of the esophageal defect cannot be considered, even when there is significant time delay from inciting event to therapeutic intervention. Complete exposure to the full extent of the esophageal perforation is required. Typically, the mucosal defect will extend more superficially than the esophageal muscularis disruption. Esophageal musculature is opened to identify the full extent of the injury. A meticulous mucosal approximation is achieved. We will typically use an absorbable monofilament suture in an interrupted fashion. A running repair is also appropriate. Esophageal musculature can be mobilized to achieve a second layer of closure to reinforce the primary mucosal repair. A running absorbable braided suture can achieve this goal. Additional buttressing of the repair should be performed. Options for reinforcement include intercostal muscle flap or pleural parietal flap. We have found that the integrity of pleural flap reinforcement is often inadequate

Although less rarely used, intercostal flaps of the diaphragm or gastric fundus reinforcement may be helpful. While mediastinal drainage, nasogastric decompression, and nutrition are adjuncts to care. Other techniques that are used in the management of esophageal perforation include esophageal dilatation and exclusion or closure over T tubes. This technique is less commonly implemented but is technically very straightforward, and interventions can be completed in an efficient manner in physiologically unstable patients. Exclusion and diversion involves the creation of a cervical esophageal fistula with gastrostomy tube placement with stapling of the distal esophagus and appropriate mediastinal drainage. Biliary T tubes can be used to create a controlled esophageal fistula. The tube is positioned within the perforation and brought out through the chest wall. The T tube can then be slowly removed over multiple months.

Management of esophageal perforation in the setting of underlying esophageal disease such as malignancy, benign stricture, or achalasia is very challenging. Attempts at primary repair in the setting of a diseased esophagus or any evidence of distal obstruction (either anatomic or functional) will fail. If esophageal perforation is sustained during an esophageal dilation for achalasia, primary repair of the perforation, as well as myotomy to relieve the distal obstruction, will be needed. Typically, the perforation is repaired, and, on the contralateral side of the esophagus, a myotomy extending onto the stomach is performed. Perforation sustained in the setting of a dilation for benign or malignant strictures is very challenging. Primary repair cannot be achieved, and resection may be required. On the basis of a patient's physiologic stability, primary esophageal reconstruction can be considered; however, esophageal diversion with end cervical esophagostomy may be required. In a patient who has a newly diagnosed esophageal cancer who sustained an iatrogenic perforation, we would typically consider esophageal stenting and mediastinal drainage as optimal initial intervention to achieve initial control of the sepsis and leak and subsequently allow for appropriate oncologic staging assessments. Esophageal stents achieve the goal of sealing the leak, as well as relieving any potential distal obstruction.

With advances in stent technology, stenting of esophageal perforations has become another tool to assist in the management of this life-threatening disease process. Even with optimal surgical intervention, persistent leak after Boerhaave's injury is not uncommon. Options for management of the fistula, depending on patient's clinical status, would include surgical intervention or esophageal stenting. Thus stenting can be considered as relevant in the initial management of iatrogenic esophageal perforation, as well as in the setting of iatrogenic perforation. If esophageal perforation is recognized at the time of endoscopy, esophageal stenting can be performed in a straightforward way and may limit any mediastinal contamination. Again, basic principles of esophageal management must be followed with leak control and drainage. Options for drainage would include percutaneous or thoracoscopic intervention.

When dealing with diagnosis of esophageal perforation and the options for therapeutic management, prompt intervention is necessary with minimal time for preparation. Basic understanding of the multiple technical options for management, experience in using the different technical interventions, with adherence to the fundamental principles for esophageal perforation, is required for successful patient-centered outcomes.

POSTOPERATIVE CARE

The perioperative management after surgical treatment for patients with esophageal cancer requires ongoing active management. Hemodynamic instability with septic physiology is expected and will likely take a period of days to improve. Mechanical ventilatory support is often necessary. Ongoing optimal antibiotic and antifungal care is required. Nutritional support is used as an adjunct. Rigorous surveillance for residual septic foci will be needed. As the patient's physiology improves, discussions regarding enteral tube placement will be necessary. Nutrition can be supported with either feeding gastrostomy tube or jejunostomy tube. Typically, we would perform a contrast evaluation of the repair approximately 1 week after surgery. Provided this is satisfactory, slow reinitiation to normal regular diet over a week would be implemented. The exact frequency of esophageal stricture after primary repair of esophageal perforation is unknown; however, should patients develop symptomatic stricturing, standard dilation would typically provide for resolution.

RESULTS

Esophageal perforation remains a highly morbid disease. Overall mortality rate remains approximately 20%, with spontaneous perforations having a mortality rate approaching 30% and instrumental perforation approximately 10%. Cervical esophageal perforations have the lowest rate mortality with thoracic perforations having the highest rate. Delay in diagnosis with implementation of treatment beyond 24 hours significantly increases the mortality rate. Primary emergency repair has a mortality rate of approximately 12%. Esophageal resection and exclusion have higher event rates. Although the exact frequency of postoperative complications is unclear, morbidity is very common, including pneumonia, prolonged ventilatory support, multisystem organ dysfunction/failure, and persistence of esophageal leak.

Esophageal perforation remains a significant and potentially daunting clinical challenge. Fundamental surgical principles of prompt diagnosis, effective control of leak, eradication of mediastinal sepsis, optimal adjunctive supports, and rigorous surveillance for postprocedural issues must be followed. Multiple technical options are considerations for management. However, primary reinforced repair and wide drainage remains the standard consideration. Esophageal stenting appears to have an expanding role in the management of esophageal perforation; however, standard guidelines continue to evolve.

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STOMACH

BENIGN GASTRIC ULCER

Daniel T. Dempsey, MD, MBA

Benign gastric ulcer is a disc[illegible] and surface [illegible]

[illegible]

TYPES OF BENIGN GASTRIC ULCER

Johnson initially defined [illegible] gastric ulcer [illegible] ulcers are the most common [illegible] gastric ulcer. They typically occur at or near the angularis incisura on the lesser curvature [illegible]

gastric ulcers are not associated with gastric acid hypersecretion, and thus vagotomy has not traditionally form part of the surgical treatment. Type 2 ulcers usually occur in the distal stomach and are associated with duodenal ulcer disease, either active or chronic. Type 3 ulcers occur in the prepyloric region. Pathophysiologically, type 2 and 3 gastric ulcers are believed to resemble duodenal ulcers, and thus truncal vagotomy to ameliorate acid hypersecretion has been part of the surgical treatment. Recently two additional types of gastric ulcer have been described, resulting in a "modified Johnson classification" (Table 1). Type 4 gastric ulcer occurs high on the lesser curvature near the gastroesophageal (GE) junction. Excision of type 4 ulcers may get close to the esophagus, requiring [illegible] reconstruction (Csendes operation). Type 5 gastric ulcers are believed to be drug induced and typically occur toward the greater curvature, making them amenable to simple wedge resection. Neither type 4 nor 5 gastric ulcers are believed to be associated with acid hypersecretion, so vagotomy is probably unnecessary.

SURGICAL OPTIONS FOR GASTRIC ULCER

When operating on a patient with gastric ulcer, the choice of operation depends on a variety of technical and clinical factors, which will be discussed further below. Fundamentally, operations for gastric ulcer fall into two categories: those that excise the ulcer and those that do not (Table 2). If the ulcer is not excised, it must be biopsied to rule out cancer. Formal gastric resection with anastomosis is avoided in unstable patients. Before embarking on resection, it is prudent to assess during surgery whether the ulcer involves the pancreas, portal triad, or celiac artery or branches. For low risk patients with distal gastric ulcers, distal gastrectomy with (type 2 and 3 ulcers) or without (type 1 ulcers) truncal vagotomy is the treatment of choice. Reconstruction consists of Billroth 1 gastroduodenostomy or Billroth 2 gastrojejunostomy (Fig. 1). The latter may be preferred when there is concomitant duodenal ulcer disease (type 2 gastric ulcer). With both types of reconstruction, we prefer to do the anastomosis to the greater curvature side of the gastric remnant. Roux reconstruction is much preferred with small gastric remnants when the gastrojejunostomy is close to the GE junction, but it should be avoided with large gastric remnants. For low risk patients with high gastric ulcers (type 4), distal subtotal gastrectomy and in continuity excision of the high lesser curvature ulcer can be considered, with reconstruction via Roux-en-Y esophagogastrojejunostomy (Csendes procedure) if resection encroaches on the gastric cardia (Fig. 2). For type 4 ulcers that are more distally located (or type 1 ulcers that are unusually proximal), a more limited distal gastric resection and lesser curvature extension can be performed, with reconstruction by gastrojejunostomy (Billroth 2 or Roux) (Pauchet procedure). Simple wedge resection is a good option for type 5 gastric ulcers, but it is difficult to perform for prepyloric ulcers (type 2 and 3), juxtacardial ulcers (type 4), and

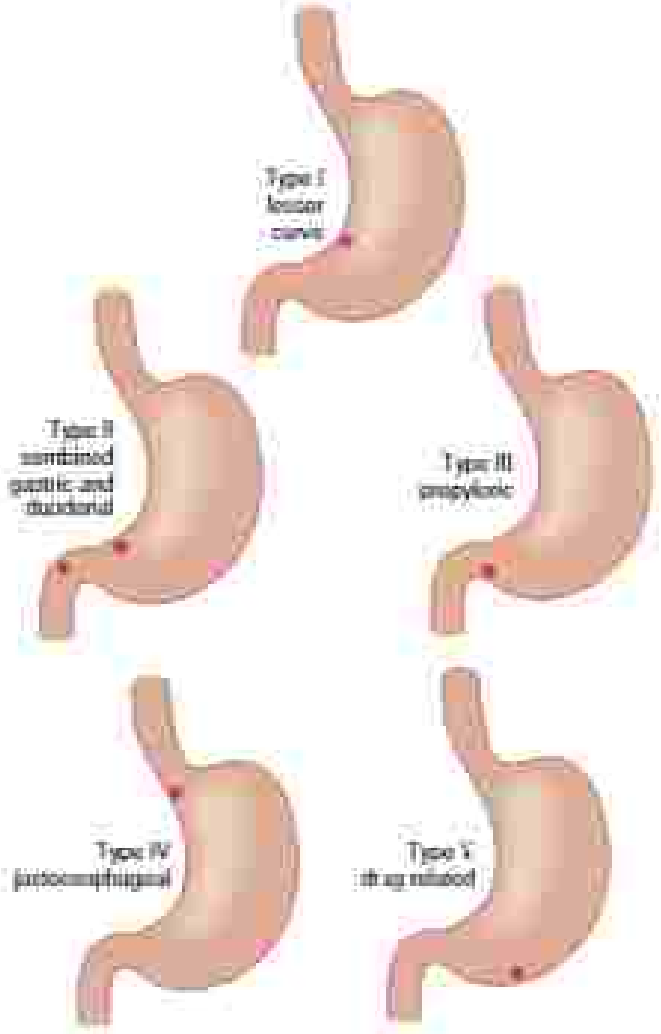

FIG. 1 Types of gastric ulcer [illegible]

TABLE 1 Modified Johnson Classification

Type	Location	Acid Hypersecretion
I	Lesser curvature; incisura	No
II	Body of stomach, incisura, and duodenal ulcer (active or healed)	Yes
III	Prepyloric	No
IV	High on lesser curve, near gastroesophageal junction	No
V	Anywhere (medication induced)	No

ulcers on the lesser curvature. For type 2 and 3 gastric ulcers that are left in situ, truncal vagotomy and gastrojejunostomy (with ulcer biopsy) may be a reasonable alternative to distal gastric resection. Similarly, for type 4 gastric ulcers, distal gastrectomy without ulcer excision (but with ulcer biopsy) can be considered (Billroth-Mikulicz operation).

TABLE 2 Choice of Operation for Gastric Ulcer by Type*

Ulcer Type	Option 1 (Remote Ulcer)	Option 2 (Biopsy Ulcer)
Type 1	Distal gastrectomy	[illegible] gastrotomy and drainage (with or without wedge excision)
Type 2	Distal gastrectomy and vagotomy	[illegible] gastrotomy and drainage
Type 3	Distal gastrectomy and vagotomy	Vagotomy and drainage
Type 4	Camalot or Pyeloplasty procedures	Kelling-Madlener procedure, or vagotomy and drainage
Type 5	Wedge resection	Patch/oversew

* Ulcer patch or oversew with biopsy is [illegible]

INDICATIONS FOR OPERATION

Most patients with benign gastric ulcer never see a surgeon. They present to primary care or gastrointestinal (GI) practices or emergency departments, with complaints of upper abdominal pain, nausea, vomiting, or iron deficiency anemia. These complaints are evaluated with upper endoscopy with or without upper GI radiology. If a gastric ulcer is diagnosed, it is appropriately biopsied to rule out gastric cancer. If biopsy and cytology specimens are benign, the patient is treated with acid suppression, and the causative factors discussed above (*H. pylori*, NSAIDs, smoking) are eliminated if possible. Then the upper endoscopy is repeated in 2 to 3 months to document ulcer healing and to perform repeat biopsy. With this approach, the likelihood of misdiagnosing a gastric adenocarcinoma or lymphoma as a benign gastric ulcer is low.

If helicobacter is eradicated, NSAID and aspirin use is stopped, and smoking is eliminated, almost all gastric ulcers will heal with a 2- to 3-month course of proton pump inhibitor therapy, and recurrence or nonhealing is unusual. But, if helicobacter infection, NSAID or aspirin use, or smoking persists, recurrent gastric ulcer is the rule, as the condition of acid suppression. It is doubtful that definitive operation can completely nullify this fact, although recurrence of peptic ulceration (gastric or marginal ulcer or both) may be delayed after operation. For optimal results after operation for gastric ulcer, it is very important to screen for and document after surgery the absence of helicobacter infection, NSAID use, and smoking. Vagotomy or long-term acid suppressive medication may prevent recurrent peptic ulcer in some patients, and clearly patients having operation for gastric ulcer who cannot stop long-term NSAIDs or aspirin should receive long-term acid suppressive medication. Selective COX-2 inhibitors should be considered in patients with ulcers requiring NSAIDs because these may have a lower risk of peptic ulceration.

PERFORATED GASTRIC ULCER

The most common indication for operation in benign gastric ulcer is perforation. Patients with gastric ulcer perforation present with acute abdominal pain and tenderness, usually with signs of peritoneal irritation (ie, rebound tenderness and referred rebound tenderness). Because of the severity and acuteness of the symptoms, these patients must commonly present to the emergency department where computed tomography (CT) scanning reveals free intraperitoneal air, usually with free fluid as well. If water-soluble oral contrast has been administered, the scan often reveals oral extravasation

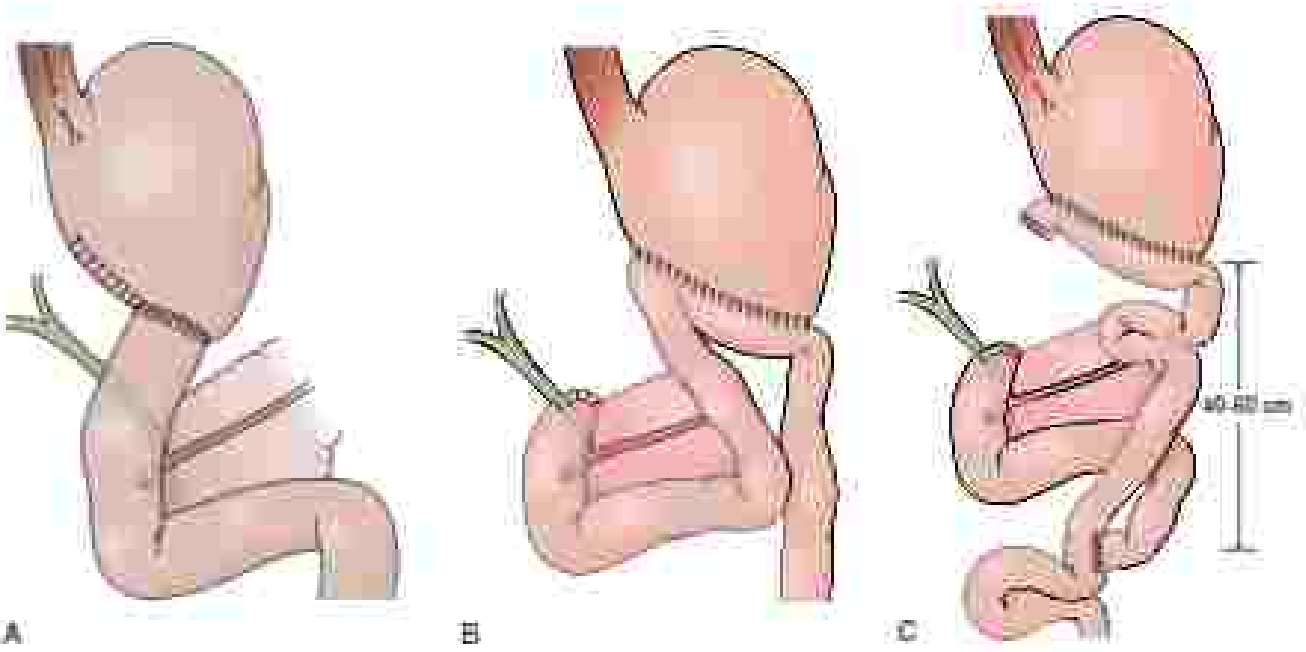

FIG. 2 These types of reconstruction after distal gastrectomy. (A) Billroth I (A gastroduodenostomy) is performed to avoid the greater curvature. (B) Billroth II (A gastrojejunostomy is created to reattach to the alimentary circuit. Several variations may be observed in this type of reconstruction.) (C) Roux-en-Y prevents duodenogastric reflux. Here the stomach is connected to the stomach of the Roux limb. Typically 40 to 50 cm of the Roux limb is used.

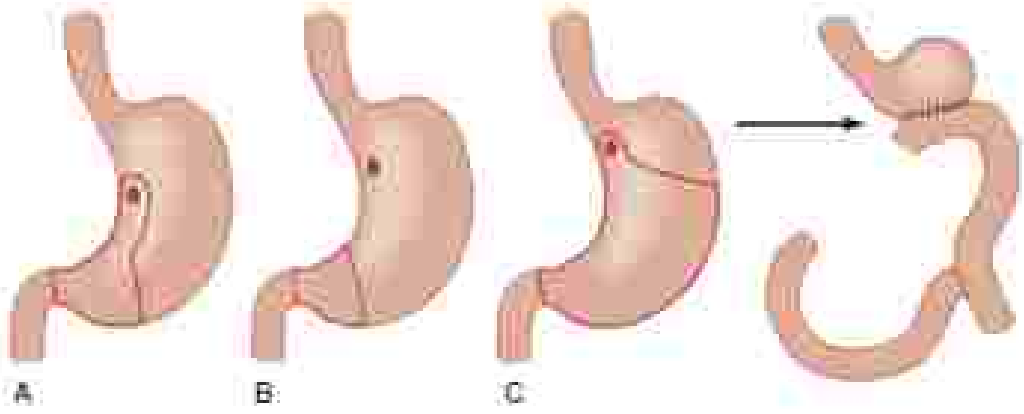

FIG. 3 Operations for a type IV gastric ulcer. (A) Partial procedure. (B) Billroth I without procedure. (C) Combined procedure (sleeping gastrojejunostomy).

from the stomach. Gastric wall thickening is difficult to evaluate on CT if the stomach is collapsed. Simple upright chest radiography usually shows free air under the diaphragm, but this classic radiologic finding may be absent in 20% of patients with perforated gastric ulcer.

Intravascular volume depletion is the rule, so fluid resuscitation begins with 1 to 2 L of isotonic fluid. Induction of general anesthesia in the patient with severe hypovolemia may result in cardiovascular collapse and cardiac arrest. Intravenous antibiotics (cefazolin and flagyl, if unstable) are administered. Careful insertion of a nasogastric (NG) tube before surgery for gastric decompression is prudent, especially if water-soluble oral contrast has recently been administered or if imaging shows gastric distention. Operation is planned to occur usually within 2 hours of presentation. Rarely, nonoperative treatment is indicated if the patient is clinically stable, without signs and symptoms of sepsis, and with good radiologic evidence that the perforation has sealed.

Operation may be done open or laparoscopically. Copious irrigation of the soiled peritoneal cavity is performed with 5 to 10 L of warm saline. The entire anterior surface of the stomach is inspected. If no perforation is seen, the lesser sac is entered through the gastrocolic omentum and retained and the posterior stomach inspected. If still no perforation is found, it may be along the greater or lesser curvatures. If the patient is hemodynamically unstable or a poor operative risk, the perforated gastric ulcer should be biopsied and closed, either with a Graham (omental) patch or with a wedge resection of the ulcer

TABLE 3 Choice of Operation for Gastric Ulcer by Indication

Indication	Option 1	Option 2	Option 3
Perforation	Patch or wedge excision	Patch or wedge excision with vagotomy and drainage	Distal gastrectomy[a]
Bleeding	Oversew or wedge excision	Oversew with vagotomy and drainage	Distal gastrectomy[a]
Obstruction	Vagotomy and distal gastrectomy	Vagotomy and gastrojejunostomy	
Nonhealing/Intractability	Distal gastrectomy (with vagotomy for type 2 and 3)	Wedge excision with vagotomy and drainage	

[a] Consider addition of vagotomy for type 2 and 3 gastric ulcer.

TABLE 4 Rockall Score to Assess Rebleeding and Mortality Risk in Upper Gastrointestinal Bleeding

Variable	0 Points	1 Point	2 Points	3 Points
Age (yr)	<60	60–79	≥80	
Shock	None	HR >100, SBP >100 systemic	SBP <100 systemic	
Comorbidity	None	[illegible]	[illegible]	Renal or liver failure, metastatic cancer
Diagnosis	Mallory-Weiss	All other	GI cancer	
Bleeding stigmata	None		Visible vessel/active bleeding	

[illegible] HR, heart rate; SBP, systolic blood pressure; GI, gastrointestinal; Mallory-Weiss, Mallory-Weiss tear; mm Hg, millimeters of mercury; min, minute.

(Table 3). The latter is appropriate for perforations that occur along the lesser curvature, on the anterior or posterior surface of the proximal stomach in the low-risk patient who is hemodynamically stable. The operative choice for a chronic, stable gastric ulcer is controversial. Some surgeons still perform a wedge excision of the ulcer with the goal of removing the ulcer crater and the surrounding inflammatory tissue. Others advocate the addition of vagotomy and drainage with the goal of decreasing the acid secretion that seems to be the most significant factor in the pathogenesis of peptic ulcer disease. Whether the ulcer is excised or left in place, the surgeon must be certain by appropriate preoperative evaluation that the ulcer is benign. Ulcers that are refractory to medical therapy, that recur after simple excision, or that are associated with a large mass should be resected with a wide margin, and frozen section examination should be performed to exclude malignancy. Ulcers that are confirmed to be benign by frozen section should be managed as described above. Ulcers that are associated with a mass, but are found to be benign on frozen section, may be managed by a wide excision of the ulcer and the surrounding mass. Ulcers that are associated with a mass and are found to be malignant on frozen section require a gastrectomy with a wide margin of resection and a lymphadenectomy. Ulcers that are associated with a mass and are found to be malignant on frozen section require a gastrectomy with a wide margin of resection and a lymphadenectomy. Ulcers that are associated with a mass and are found to be malignant on frozen section require a gastrectomy with a wide margin of resection and a lymphadenectomy.

[illegible] GASTRIC ULCER

Although still a common cause for hospitalization, bleeding gastric ulcer is no longer an indication for operation in most cases, due to the increasing effectiveness of medical therapy for bleeding gastric ulcer. The most common cause of bleeding is hospital- or patient-related peptic ulcer disease. Small, [illegible] ulcers in the duodenum or stomach are the most common peptic ulcer bleeding. Most [illegible] patients with bleeding peptic ulcer disease will stop bleeding spontaneously. Only a small percentage of patients will need to undergo operation for bleeding peptic ulcer disease. Risk assessment tools have been developed to help predict which patients are at high risk for rebleeding and death. One of the most widely used is the Rockall score (Table 4). Most of these tools can predict with reasonable accuracy who does and does not have a life-threatening ulcer bleed, but they are useful as guides. Patients with a low score of 0 to 2 are very unlikely to have a life-threatening bleeding ulcer, whereas patients with a score of 5 or more may be at high risk of rebleeding or death. In general, patients at high risk present with hematemesis, hypotension, or tachycardia, or have multiple units of blood transfusion. These patients require early surgical consultation. Urgent upper endoscopy, even those with high-risk endoscopic features, such as active bleeding or visible vessel in the ulcer crater, should be performed. Endoscopic hemostasis, in the form of cautery, injection, or epinephrine and application of clips, is common and is successful in most cases. Surgical intervention is required in patients who continue to bleed despite endoscopic therapy and a transfusion. Those patients with persistent hypotension should also be considered for surgical intervention. Patients who have had multiple bleeding episodes, are elderly, or have other medical problems may also be considered for operation for bleeding gastric ulcer even if they have had more than one transfusion. Those who have recurrent or rebleeding ulcers, or those who have ulcers extending to a large area, such as the lesser curvature or upper antrum, have a higher mortality rate if treated nonoperatively. The operative mortality rate is around 5%.

Biopsy is a crucial part of the bleeding ulcer operation. Although the appropriate operation for a clinically or hemodynamically unstable patient with a bleeding ulcer is a wedge resection, a suitable alternative for bleeding ulcers in the greater curvature or fundus of the stomach is a vagotomy and antrectomy. Antrectomy is used because it is not only curative for the ulcer but also removes the area of the stomach that is most likely to contain gastrin-producing cells. Gastrin is a hormone that stimulates acid secretion. Removal of the antrum, which contains the majority of gastrin-producing cells, decreases the amount of acid secretion. Vagotomy is also curative for the ulcer because it decreases the amount of acid secretion. Vagotomy and antrectomy is the most common operation performed for bleeding gastric ulcer. Vagotomy and pyloroplasty is also a common operation performed for bleeding gastric ulcer. Vagotomy and gastrojejunostomy is also a common operation performed for bleeding gastric ulcer. Vagotomy and gastrojejunostomy is also a common operation performed for bleeding gastric ulcer.

OBSTRUCTING GASTRIC ULCER

The most common cause of gastric outlet obstruction in the adult patient is cancer (pancreatic, duodenal or gastric). So, when considering operation for obstructing distal gastric ulcer, the surgeon must ask whether the patient might have malignant obstruction. Whereas upper endoscopy, biopsy, contrast radiography, endoscopic ultrasound, CT, or magnetic resonance imaging may all be suggesting that the obstruction is benign, malignancy, although rare, remains a real possibility. The classic operation for obstructing gastric ulcer is vagotomy and distal gastrectomy, but vagotomy and gastrojejunostomy may be an acceptable alternative. The latter procedure has a lower operative mortality risk, and, in the event of severe dumping, the gastrojejunostomy is potentially reversible if gastric outlet patency can be maintained. However, distal gastrectomy confirms the absence of cancer. Vagotomy should be performed because obstructing gastric ulcers are likely to be Johnson type 2 or 3 lesions.

NONHEALING GASTRIC ULCER (INTRACTABILITY)

Operation for nonhealing gastric ulcer should be unusual today because our understanding of ulcer pathophysiology is more complete than ever. Acid suppression, eradication of helicobacter, cessation of NSAIDs, and smoking cessation should heal the ulcer. So why would the gastric ulcer persist. Could it be cancer? Is the patient noncompliant? Is there unrecognized gastric stasis or emesis/gastric reflux? Are there important factors in ulcer pathogenesis that we haven't discovered yet? These are all important questions for the surgeon to consider before operating on a patient for nonhealing gastric ulcer. Furthermore, it must be recognized that patient noncompliance and unknown pathophysiologic factors may predispose to ulcer recurrence or poor functional results after gastrectomy for nonhealing ulcer. This may be particularly problematic in thin patients who are easy to operate on but who have minimal nutritional reserves in the event of a poor functional outcome.

In the event that operation for nonhealing ulcer is necessary, the ulcer should be excised either with distal gastrectomy or wedge resection. This both excludes cancer and resects the vulnerable part of the stomach. If distal gastrectomy, the classic operation, is performed, then vagotomy should be added for type 2 and 3 gastric ulcers. If the ulcer is wedged out, then vagotomy and drainage should be added.

MARGINAL AND RECURRENT ULCER

Ulcers that occur at or near the gastroenterostomy are termed marginal ulcers. They may occur on either side of the anastomosis, where on the distal side, they are generally believed to be due to acid peptic injury to small bowel mucosa, which is ill equipped to defend itself against unbuffered gastric juice. This occurs most commonly in Roux gastrojejunostomy because the anastomosis is devoid of the buffering effects of duodenal contents, which fully protect a Billroth 2 anastomosis. When on the proximal side of the anastomosis, the ulcer is generally thought to be due to ischemia, stasis, foreign body (suture), bile reflux, or the circumstances that led to the gastric ulcer in the first place (recurrent ulcer). Marginal ulcer complicates Roux or Y gastric bypass in about 8% of patients, and presently this is the most common cause of marginal ulcer, which may also complicate gastrojejunostomy for cancer or ulcer.

The medical treatment of marginal ulcer is identical to gastric ulcer: acid suppression, eradication of helicobacter, cessation of NSAIDs, and smoking cessation. Indications for operation are also identical to those for gastric ulcer: perforation, bleeding, obstruction, and intractability. The realization that reoperation for recurrent or marginal ulcer puts the patient at increased risk (and closer to total gastrectomy) underscores the importance of patient education and good management after the first ulcer operation, which includes minimizing the risk factors for ulcer recurrence. In addition to elimination of helicobacter, NSAIDs, and smoking, we consider every patient who has had an operation for gastric ulcer a candidate for lifelong acid suppression, unless the patient has had a vagotomy.

Perforated marginal ulcer may be treated with simple patch closure, which is certainly appropriate in high-risk and unstable patients. It may also be the preferred treatment in patients with Roux-en-Y gastric bypass because resection may necessitate esophagojejunostomy, be risky in high-risk patients with perforated gastrojejunostomy after distal gastric resection, resection of the anastomotic region (segmental jejunal resection with additional gastrectomy) is preferred. The addition of truncal vagotomy may be considered. If the remaining gastric remnant is 50% or less, reconstruction should be Roux gastrojejunostomy to avoid bile reflux esophagitis. If the remaining remnant is larger than 50%, reconstruction should be via Billroth 1 or 2 technique to minimize recurrence of marginal ulceration. If the original operation was a simple loop gastrojejunostomy, consideration may be given to reversal (if the gastric outlet is patent) or distal gastrectomy with Billroth 1 or 2 reconstruction.

Bleeding marginal ulcer can usually be managed without surgery with the help of endoscopic hemostatic techniques or angiographic embolization, unless the ulcer has eroded into a named visceral vessel such as the splenic, left gastric, or middle colic artery. Those patients requiring emergency operation may have torrential bleeding and often present with a less impressive "herald bleed." Whereas gastrotomy and transluminal oversewing of the bleeding vessel may prove adequate, resection of the anastomotic region may be expeditious and safer. Perioperative angiographic embolization might complement the operation. Marginal ulcers associated with obstruction or intractability should be treated with discise resection of the anastomosis, followed by Roux or Billroth reconstruction, depending on how close the anastomosis is to the GE junction.

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MANAGEMENT OF DUODENAL ULCERS

F. Charles Brunicardi, MD, [illegible] F. Kamran Qasim, MD, MPH

In the past 30 years, we have seen a remarkable decline in the incidence of duodenal ulcers (DUs) and peptic ulcers overall. This is due to wide acceptance and availability of proton pump inhibitors (PPIs) and selective histamine blockers, and from eradication efforts against *Helicobacter pylori*. Despite the reductions in incidence of DU, the morbidity and mortality for patients hospitalized with DU remains unchanged. For those patients requiring surgery, the 30-day postoperative mortality rate has been a steady 10% since the early 2000s. Although medical management of DUs is now well established, challenges remain; for example, poor patient compliance may result in ulcer recurrence and rebleeding, whereas the long-term use of PPIs has recently been associated with dementia, *Clostridium difficile* colitis, and osteoporosis. In addition, disparities in social determinants of health and economic health are associated with poor access to acid-reducing medications, increased rates of *H. pylori*, and increased rates of complicated DU. Finally, increased societal burdens related to obesity, diabetes, cardiovascular disease, and an aging population mean that patients presenting with DU today are sicker than those presenting in previous decades. For surgeons, the most common presentation of DU is in the setting of bleeding, perforation, and obstruction; therefore, proficiency in the surgical management of DU remains a critical skill for general surgeons.

There have been few high-quality, published studies on the incidence of DUs in the past 10 years. Systematic reviews in the late 2000s concluded that, in the developed world, 1 to 2 people out of every 1000 will be diagnosed with peptic ulcer disease each year. A total of 95% of DU are attributable to *H. pylori*, use of nonsteroidal antiinflammatory drugs (NSAIDs), or both. Less common causes of DU include gastrinoma (Zollinger–Ellison syndrome, 1% to 3% of ulcers), smoking, steroid or cocaine use, and dysmotility. Of patients hospitalized for duodenal ulceration, 10% will require surgery, most commonly resulting from persistent hemorrhage, with a 30-day postoperative mortality rate of 10%. DUs develop as a result of suprapeptic acid secretion despite normal serum gastrin levels. In response to increased acid burden, columnar cells from Brunner glands migrate and replace the duodenal epithelium. Normal duodenal epithelium is susceptible to *H. pylori* colonization; however, this metaplastic tissue facilitates colonization and impairs mucosal defense. *H. pylori* infection is associated with a vigorous local immune response, mediated by macrophages, neutrophils, and lymphocytes, and local release of interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-12, and tumor necrosis factors. A positive feedback loop between *H. pylori* infection and further acid secretion via histamine *N*-methyltransferase hastens and sustains the inflammatory process. Together, these effects result in the development of the DU.

Patients with DU classically present in one of four ways. Uncomplicated DU is diagnosed based on a presentation of dyspepsia, presence of ulcer risk factors such as NSAID and tobacco use, and epigastric pain beginning 2 to 3 hours after meals. Pain that radiates to the back should be concerning for ulcer erosion to adjacent structures and pending perforation. Patients with perforated ulcer present with peritonitis and an acute abdomen, typically can state the exact timing of symptom onset, and are often visibly uncomfortable and will lay still in bed. Tachycardia is the most common initial finding with fever, hypotension, and tachypnea representing late findings. Bleeding ulcers may present as melena or upper gastrointestinal (GI) hemorrhage. Hematemesis is associated with higher mortality rates because it typically represents a higher rate of ulcer bleeding. Ulcer should also be considered in patients undergoing workup for signs of gastric outlet obstruction, including vomiting, loss of appetite, and weight loss. Upper GI endoscopy is indicated in the workup of non-perforated ulcers. More than 90% of ulcers are visualized in the first portion of the duodenum, may be hidden in the duodenal bulb, and ulceration in the more distal portions should raise concern for gastrinoma. In contrast to gastric ulcers, routine biopsy of DUs is not supported by evidence because the complication rate for biopsy is much higher than the rate of malignancy. Biopsy should be done for DU in the setting of obstruction, giant ulcer (>2 cm), or known high malignancy risk.

MEDICAL MANAGEMENT OF DUODENAL ULCERS

Medical management of DU is centered around the eradication of *H. pylori* infection and protection of the intestinal wall from acid damage. While physicians treat the ulcer, ultimately, the patient's body is responsible for healing; therefore, optimal nutrition and a healthy lifestyle (i.e., tobacco cessation) are critical. The initial diagnosis of DU by endoscopy should be supplemented by testing for *H. pylori* via serology, stool antigen test, breath test with carbon-labeled urea, or endoscopic biopsy of the ulcer (not routinely recommended). Although any of these are appropriate for diagnosis of *H. pylori* and some have more than 95% sensitivity or specificity, only carbon-labeled urea breath testing or fecal antigen testing are appropriate for proving eradication after treatment. We recommend therapy against *H. pylori* be initiated in the presence of DU regardless of testing results, because the recurrence and rebleeding rates associated with a false-negative test are unacceptably high compared with the relative safety of combination therapy. Eradication of *H. pylori* significantly reduces rates of ulcer recurrence and bleeding.

Traditional "triple therapy" has been associated with 80% eradication rate, whereas "quadruple therapy" has been associated with a slightly higher rate, but this difference in large meta-analyses is not statistically significant. Recommended regimens are listed in Table 1. NSAIDs and aspirin should be avoided; however, patients with a cardiovascular indication for low-dose aspirin use should continue to use it. Smoking cessation is essential, and patients should be considered for a formal cessation program. Patients who have uncomplicated DU disease should be managed with short-term antisecretory drugs, such as PPIs, for 2 to 4 weeks, whereas patients with complicated DU disease should receive long-term PPI therapy.

SURGICAL MANAGEMENT OF DUODENAL ULCERS

Operative management of DUs is indicated in the setting of perforation, recurrent or refractory hemorrhage, and persistent obstruction; therefore, the ulcer operation should be designed toward the indication. Typically, the modern surgeon is presented with an ulcer operation only in the urgent/emergent setting. Deciding whether to operate in the first instance is the main, if an operation is indicated, the next step is categorizing the patient as either stable or unstable to determine which operation should be performed. Elective ulcer surgery on stable patients is an uncommon occurrence. Unstable patients should be managed using damage control techniques and with a goal of restricting anesthesia time to less than 1 hour if possible. For example, it would be unsafe to perform a concurrent acid-reducing procedure, such as a vagotomy and drainage, in an unstable patient.

TABLE 1 Treatment for *H. pylori* as Recommended by 2017 American College of Gastroenterology

Regimen	Duration	Considerations*
First-line triple therapy: PPI, clarithromycin, amoxicillin, metronidazole	14 days	Known local clarithromycin resistance rates <15%; no history of macrolide exposure
First-line quadruple therapy: PPI, bismuth, tetracycline, metronidazole	10–14 days	Ideal for patients with penicillin allergy or previous macrolide use. May be used as initial therapy or if patient fails triple therapy
Levofloxacin salvage regimen: PPI, levofloxacin, amoxicillin	10–14 days	May use if patient does not respond to either triple or quadruple therapy

*Always consider the patient's unique history of previous antibiotic use, renal and hepatic function, and local resistance patterns in selecting regimen.
PPI, proton pump inhibitor
Modified from Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112:212.

Perforated Duodenal Ulcer

Perforated duodenal ulcer is a surgical emergency. Patients present with an acute abdomen, peritonitis, epigastric pain, tachycardia, and leukocytosis. The 30-day mortality risk of perforated duodenal ulcer in the literature ranges from 3% to 40%; however, a plurality of studies agree that true risk is in the 2% to 10% range. Advanced age, higher American Society of Anesthesiologists classification, elevated body mass index, and perforation diameter are all nonmodifiable risk factors associated with increased mortality. The only modifiable risk factor associated with mortality is time to operation, wherein a delay of 3 hours is associated with a doubling of mortality risk. Shock is associated with a nearly threefold increase in mortality. Although fluid resuscitation is essential, the surgeon must be aware that time to operation is an important consideration. Patients may rarely present with a contained perforation and no signs of peritonitis. This subset of patients can be cautiously managed nonoperatively.

Before surgery, the patient should receive broad-spectrum antibiotics, including antifungal coverage. Surgical approach may be either laparoscopic or via upper midline incision, according to surgeon preference and proficiency with the goal of short operative time. Fluid in the peritoneum should be sent for culture and sensitivity. Liberal irrigation after benign perforation (5 to 10 L warm saline) was previously the standard of care. Recent research has questioned whether a liberal irrigation strategy spreads contamination to distant areas, worsening infection risk. At this time, we recommend suction and irrigation to control visible contamination. Routine biopsy is not necessary for perforated DU but should be performed in patients with giant ulcer (> 2 cm) or suspicion of malignancy.

Closure of Ulcer Perforation

Most perforated DU ulcers are small in diameter, typically 0.5 cm or smaller. Benson Graham is credited with the first description of omental patch closure with his publication of 51 successful cases in 1008, and the Graham patch remains the most durable repair for a small perforated ulcer. A well-vascularized, sessile, free pedicle of omentum is mobilized to cover the perforation. Interrupted sutures are placed on either side of the perforation through healthy portions of the duodenum but left untied. There should be no attempt to repair the primary defect, as suture material is likely to either tear the friable tissue surrounding the ulcer or to cause stricture of the intestinal lumen. Next, the omental flap is laid on the defect and the sutures are gently tied down (Fig. 1). The seal is tested for air leak by submerging the repair under saline and insufflating the stomach through a nasogastric tube. In the setting of air leak, additional interrupted sutures may be placed circumferentially around the patch. Drains are optional, however there is no evidence to support their routine use.

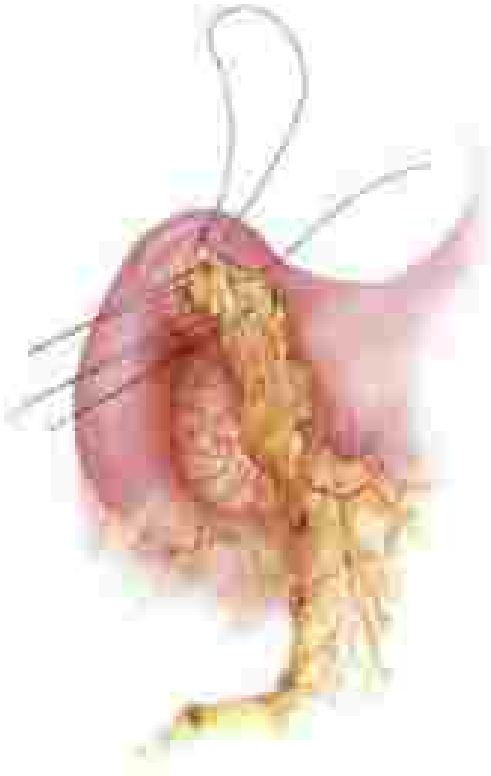

FIG. 1 The omental patch repair. (From Llorente JL, Sánchez C. Atlas of Gastroenterological Surgery, 2nd ed. Online CD-ROM. Houston, Methodist DeBakey Heart; 2007.)

Giant ulcers (>2 cm) should not be managed with a patch repair because of a risk of leak, undertaking, and stricture. The goals of an operation for giant perforation are to (1) control GI outflow, (2) provide the patient with nutrition, and (3) avoid creating a difficult duodenal plump in a hemodynamically unstable patient. "Damage control" surgical technique with tube duodenostomy is recommended. In this procedure, the duodenum is knuckled and the ulcer well freshly debrided. A Malecot catheter is placed directly into the ulcer defect and a purse-string absorbable stitch closes the ulcer defect around the malecot. A pedicle of omentum is mobilized and placed around the purse-string at the base, and a closed suction drain is placed nearby (Fig. 2). Combined, the omental pedicle and closed suction drain serve to control an expected small volume of leakage. Consideration should be given for placement of both a decompressive

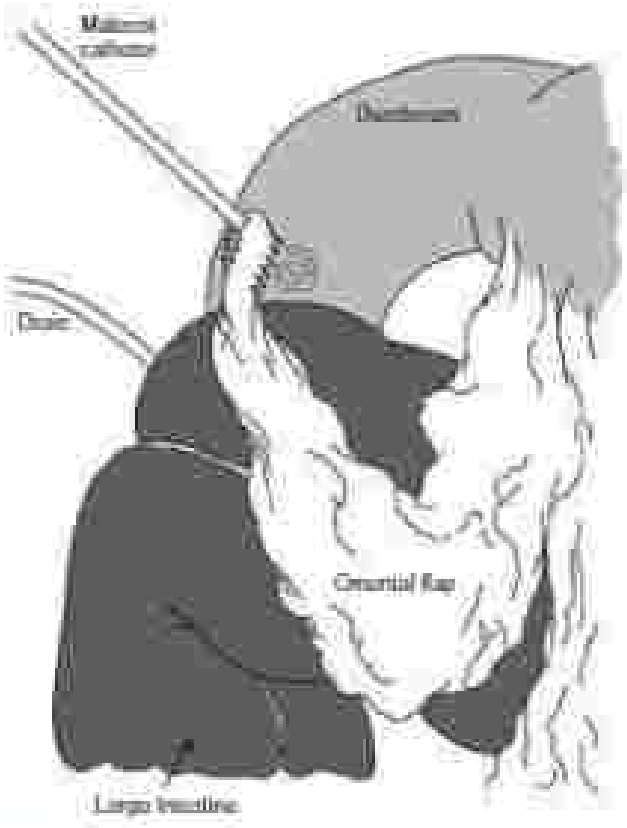

FIG. 2 Omental tube duodenostomy for giant perforated duodenal ulcer. *Modified from Kudo SE, Ogawa S, Hosokawa S. The rationale use of a wide tube duodenostomy in large duodenal perforations that cause shock. Br J Surg Case Rep 6: pp 205–214 2017.*

tube gastrostomy and feeding jejunostomy. Although both decompress the stomach and control gastric outflow, tube gastrostomy is superior to nasogastric decompression for postoperative respiratory outcomes, such as pneumonia. The peritoneum should be liberally irrigated and the abdomen closed.

Postoperatively, the patient is managed in the intensive care unit with the Malecot tube placed to gravity drainage and left in place for a minimum of 6 weeks to allow for tract formation. Enteral feeding is begun through the tube jejunostomy as soon as postoperative ileus resolves. Oral feedings are initiated at postoperative day 5 or 6 at the earliest and should begin conservatively with a liquid diet. Before removal of the Malecot drain, a 2- to 3-day champ trial should be initiated. Routine imaging of the drain before removal is optional. After removal, a dry gauze dressing should be placed until the tract closes.

Variability in ulcer location, patient condition, adhesions, and inflammation necessitate adaptability in managing perforated, giant ulcers. In a hemodynamically stable patient with giant, perforated DU, the preferred option is mobilization of the duodenum via kocherization, debridement of the ulcer edge to fresh, viable tissue, and then Roux-en-Y reconstruction between the ulcer edge and a limb of jejunum. Additional options include a loop of jejunum sutured to the ulcer or an antrectomy and Billroth II reconstruction with truncal vagotomy. If performing truncal vagotomy, nerve specimens should be sent to pathology for confirmation and documentation. Each of these procedures is associated with increased operative time and risk of leak in the postoperative period.

Minimally Invasive Treatment

As mentioned previously, the choice of laparoscopic versus open approach for a stable patient with perforation should be made based on surgeon experience. Multiple studies have demonstrated equivalence in the two approaches among experienced surgeons. We recommend an open approach for surgeons who do not routinely perform laparoscopic foregut surgery. The principles of laparoscopic repair of perforated duodenal ulcer are the same as those for open surgery.

There are several reports, predominantly from 2009 through 2014, on the use of natural orifice transluminal endoscopic surgery with or without laparoscopic guidance to repair small perforated DUs. This technique has been hypothesized to represent a lower physiologic insult. The proposed technique begins with diagnostic laparoscopy to confirm perforation. Once the perforation is identified, an endoscope is advanced transorally to the site of perforation. Either a small tongue of omentum or the falciform ligament is pulled into the defect. The endoscope is then used to place clips attaching the omental or falciform plug to the duodenal wall. This technique is best suited for small perforations, with the most ambitious studies estimating 50% of small perforations can be ultimately managed in this manner. Because there have been no recent reports or randomized trials of the natural orifice transluminal endoscopic surgery technique published to date, we cannot recommend this technique.

Postoperative and Long-Term Management

Postoperative care for patients with perforated DU is standardized. Sepsis protocols should be followed. In accordance with the 2015 *STOP-IT Multicenter Study of Duration of Antibiotics for Intra-abdominal Infection* trial, antimicrobials should be continued for 4 to 7 days postoperatively and then stopped. Nasogastric tube removal and oral feeding decisions are made on clinical grounds, typically after upper GI radiographic studies. The placement of a decompressive gastrostomy tube during surgery allows the patient to be managed without a nasogastric tube and decreases postoperative respiratory complications. Typically, we recommend against routine placement of closed suction drains because of a lack of supporting evidence; if placed, the drains should be removed 24 hours after the patient tolerates oral feeding.

BLEEDING DUODENAL ULCER

Although the most common indication for operation in DU is perforation, the most common indication for hospitalization of DU is bleeding. A total 75% of cases of upper GI bleeding due to DU will respond to medical management alone. The Glasgow Blatchford score has been validated to predict which patients may be safely managed as an outpatient and which will need endoscopic management. The full Rockall score (which takes into account endoscopic findings) is best at predicting mortality after hospitalization and first endoscopy. A multitude of techniques exist for endoscopists, including epinephrine injection, bipolar cautery, endoclipping, and thrombin/thrombin application. Epinephrine injection should always be accompanied by another modality. If the first endoscopy is unsuccessful or the patient exhibits persistent shock, a second attempt at endoscopic management is indicated. With modern endoscopy, only 5% to 10% of patients with bleeding DUs will require an operation.

For patients who continue to bleed after two endoscopies or who are hemodynamically unstable, catheter directed angioembolization or surgical exploration is mandated. Whether surgery or angiography is the first modality of choice is highly dependent on physician experience and protocols at the hospital level. Rather than recommend surgery versus angioembolization, we believe that each hospital should establish protocols for patients who fail endoscopic management. If possible, teams should drill, simulate, and train in a multidisciplinary fashion for these patients because these cases represent a challenge to time and logistics.

Operative morbidity and mortality for bleeding DUs is high; however, the majority of these patients succumb to multiorgan failure rather than exsanguination. Early identification of patients who are likely to fail endoscopic management is a critical decision

point that will affect survival. Transfusion of six or more units of packed red cells is a commonly accepted indication for operation. Once this threshold is hit, operative intervention should not be delayed because these patients likely have large bleeding vessels destined to fail other management modalities. Prompt surgery to avoid blood loss and shock and minimize the total transfusion required will affect postoperative mortality. The gastroduodenal artery, located in the posterior and proximal duodenum, is commonly involved and is amenable to both angioembolization and surgical oversewing.

Operation for Bleeding Duodenal Ulcer

Preoperative endoscopic evaluation identifies the site of bleeding in 80% of cases. An upper midline incision is performed and the duodenum is kocherized. The surgeon's nondominant hand can compress the gastroduodenal artery at this time, limiting hemorrhage. For cases in which the site of bleeding is known, a limited incision of the anterior duodenal wall at the site of the bleeding is appropriate. In cases in which the bleeding site has not yet been identified, the duodenum is opened with a longitudinal incision, and extended into the pylorus to examine the duodenal bulb and gastric antrum. Bleeding at the ulcer bed is controlled locally using a combination of "U" stitches and figure-of-8 stitches proximal and distal to the actual bleeding site. Suture ligation of the gastroduodenal artery has been shown to decrease rebleeding, but surgeons should be aware of variant anatomy, including a 8.5% incidence of accessory right hepatic artery arising from the gastroduodenal artery.

Once bleeding has been controlled, consideration is made between closing the duodenotomy and ending the operation or performing a definitive acid reducing operation. Previously, a definitive acid reducing surgery was mandated because of high rebleeding rates; however, in the modern era of PPIs, *H. pylori* testing and eradication, and avoidance of NSAID therapies, these operations are no longer required. In the rare instance of a stable patient who is unlikely to be compliant with postoperative medical management or who has a giant (>2 cm) bleeding ulcer, there are options for definitive ulcer management: antrectomy with vagotomy, truncal vagotomy with pyloroplasty, or a vagotomy can be combined with a gastrojejunostomy for drainage.

GASTRIC OUTLET OBSTRUCTION

Of all indications for ulcer operation faced by the modern surgeon, operation for relief of gastric outlet obstruction is the least frequent and most likely to be planned. DU may present as gastric outlet obstruction resulting from edema and dysmotility associated with obstruction. These patients typically complain of nausea, emesis, weight loss, early satiety, epigastric pain, and distention. The patient's history in combination with upper endoscopy remains the diagnostic modality of choice, and an obstructing mass must be excluded via computed tomography scan and biopsy of the ulcer. This acute obstruction is typically reversible with bowel rest, PPIs, and *H. pylori* diagnosis and eradication.

If an ulcer is allowed prolonged time without treatment, chronic DU may form, and can lead to obstruction via scar formation. Compared with acutely obstructed patients with DU, chronically obstructed patients may additionally complain of weight loss and should be examined for signs of underlying GI malignancy, such as jaundice and adenopathy. The malignancy rate in this patient population is significantly higher compared with all other presentations of DU, ranging from 10% to 40%. Endoscopic dilations and medical ulcer treatment can delay operation for months or years in at least one half the patients with benign gastric outlet obstruction from duodenal ulcer or serve as a palliative operation in the malignant setting. Malignancy presenting as DU should be managed according to oncologic guidelines such as those of the National Comprehensive Cancer Network. The decision to operate for benign gastric outlet obstruction resulting from chronic duodenal ulcer should not be undertaken lightly because each operation is prone to complications. If required, antrectomy with vagotomy, loop gastrojejunostomy, and Billroth II are all potential options. The procedure of choice should take into account surgeon experience and the patient's unique anatomy.

DIFFICULT DUODENAL STUMP

During resection, careful consideration must be made for the duodenal stump. Leak from the duodenal stump is associated with significant morbidity and mortality. This complication is most associated with the Billroth II procedure. Tissue edema, technical error, infection, local blood clot formation, overuse of sutures leading to ischemia, and concurrent pancreatitis are known contributory factors.

To prevent creation of a difficult duodenal stump, the ulcer bed, if not resected, should have secure hemostasis because it will be unreachable postoperatively by endoscopy should bleeding occur. Whenever possible, the duodenal stump should be closed with a stapler and reinforced with Lembert sutures. If stapled closure cannot be accomplished because of inflammation, adhesions, or scarring, then interrupted suture closure in two layers can be used. The closure should be tested by immersing it in saline and observing for air bubbles. Next, healthy omentum is sewn over the closure and closed suction drain placed in close proximity. Should leak from the duodenal stump occur, it is managed conservatively except in the setting of peritonitis or sepsis. Primary repair of the leak is typically not successful, thus Roux-en-Y reconstruction, end-to-side duodenojejunostomy, or catheter drainage and controlled fistula creation are recommended.

CONCLUSION

Modern general surgeons still face challenges in the management of DUs. Few indications exist for a planned operation addressing DUs; therefore, younger surgeons are no longer able to build of a repertoire of experience in elective ulcer operations. Surgeons today operate in the face of life threatening hemorrhage, perforations resulting from perforation, and obstruction is typically older, more acutely ill patients with chronic diseases. The modern surgeon needs to treat DUs in a team-based setting, working closely with endoscopists, intensivists, interventional radiologists, anesthetists, and emergency physicians. Success depends on the recognition of complications of DU (bleeding, perforation, and obstruction) and mobilization of the team to find the optimal treatment. To maximize survival, complicated cases must proceed through presentation, resuscitation, receipt of medications, endoscopy, and angiography, and if all else fails, to the operating room for emergency surgery. The surgical time should be kept as short as possible by performing the most straightforward operation that the patient can tolerate.

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MANAGEMENT OF ZOLLINGER-ELLISON SYNDROME

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Zollinger Ellison syndrome (ZES) is a medical condition characterized by severe and refractory peptic ulcer disease that may or may not be associated with diarrhea. It was first described in 1925 by Zollinger and Ellison, who reported two cases of ulcer diathesis associated with jejunal ulcerations and required total gastrectomy after multiple failed ulcer operations. In both of the initial patients, non-beta islet cell tumors were identified in the pancreas. Zollinger and Ellison postulated that these tumors were possibly secreting a hormone that caused acid secretion and the peptic ulcer disease. In the discussion of the paper presented at the American Surgical Association in 1935, Lester Dragstedt, the father of vagotomy, commented that the cells in these tumors identified in the pancreas could be similar to the cells in the gastric antrum that produce gastrin. The syndrome name was suggested by Ben Eiseman at the Society of University Surgeons meeting in 1956. Subsequent investigation by a group at the University of Liverpool in 1960, led by Rodney A. Gregory and Hilda J. Tracy, found that tumors from patients with ZES contained high amounts of a gastrin like substance by using a bioassay on extracts of the tumors. Before the early 1970s, diagnosis of the condition required astute clinical assessment and a high index of suspicion because there were no blood and or imaging tests to help establish the diagnosis.

In 1966, the gastric radioimmunoassay (RIA) was described by James H. McGuigan and became readily available in the early 1970s. This now serves as the mainstay of diagnosis. In early reports, before gastrin RIA, patients usually had multiple gastric operations before establishing the diagnosis. Multiple reports showed that total gastrectomy was the foundation of successful treatment and reduced the mortality of the syndrome because the cause of death was usually related to complications of the ulcer diathesis, such as perforation or bleeding. Fortunately, advances in pharmacology, control of acid secretion with histamine 2 (H_2) antagonists and proton pump inhibitors (PPIs) have obviated the need for total gastrectomy. Total gastrectomy is no longer part of the management of ZES except in highly unusual cases. Today, it is established that ZES is caused by the secretion of gastrin from neuroendocrine tumors that arise in the pancreas, duodenum, or ectopic sites. The tumors are called gastrinomas. The syndrome is associated with multiple endocrine neoplasia type I (MEN-1) in 20% to 25% of cases. Surgical treatment today is focused on resection of gastrinoma and reliance on long-term pharmacologic suppression of acid secretion for control of the peptic ulcer disease and management of the hyperparathyroidism and other endocrine conditions that may be associated with MEN-1.

CLINICAL PRESENTATION

Gastrinoma is the second most common functional neuroendocrine tumor with an annual incidence reported as 1 to 3 cases per million people. Gastrinoma is the underlying cause of peptic ulcer disease in approximately 0.1% to 1% of patients and, as such, it is the cause of all causes of ulcer disease.

ZES is usually diagnosed in the fifth decade of life. Although it may occur in children, adolescents, or the elderly, it is diagnosed between ages 30 and 60 years in 90% of patients. ZES most commonly occurs as a sporadic disease; however, in 20% to 25%, it is associated with MEN-1. Indeed gastrinoma is the most common functional neuroendocrine tumor in MEN-1 occurring in 50% of patients. Hence, in the workup of patients with suspected gastrinoma, MEN-1 must be excluded. In addition, patients with MEN-1 should be screened for gastrinoma. Patients with MEN-1 have onset of the disease at a younger age. The 50th percentile of the age of onset of ZES was 33.2 years for patients with MEN-1 compared with 43.5 years for sporadic gastrinoma. In addition, gastrinoma may occur in association with Von Hippel Lindau syndrome and Von Recklinghausen's disease.

Importantly, ZES is not the initial diagnosis in 97% of patients. The symptoms at presentation for this disease have changed little despite more effective pharmacologic treatment of gastric hypersecretion and widespread use of these agents for symptoms of dyspepsia and other digestive complaints. The clinical presentation is not specific for gastrinoma and there is overlap of symptoms associated with this illness and other more common gastrointestinal conditions accounting for the high frequency of misdiagnosis and delay in diagnosis. In reported series, abdominal pain and diarrhea were the most common symptom occurring in more than 70%, followed by heartburn (40%), nausea (30%), vomiting (25%), and weight loss (17%). Only 11% of patients had a single symptom.

Although there is an increased awareness of ZES, multiple authors have noted that the diagnosis is more difficult today given the common use of PPIs. The diagnosis can usually be established by measurement of fasting serum gastrin levels when off PPIs, yet the average time from onset of symptoms to diagnosis remains between 6 and 8 years. Contributing to the delay in diagnosis is that many patients with ulcer disease are effectively treated with H_2 antagonists or PPIs without excluding the possible diagnosis of ZES. Such treatment controls the acid secretion and related symptoms and hence may further delay the diagnosis if gastrinoma is not considered in the initial differential diagnosis.

CLINICAL PATHOLOGIC CORRELATION

Gastrinomas are usually found in the pancreas or duodenum within the region known as the gastrinoma triangle which includes the head of the pancreas and duodenum (Fig. 1). This imaginary triangle is bounded by the cystic duct, the second and third portion of the duodenum and the neck and body of the pancreas. Two-thirds of primary gastrinomas occur in this region. In addition, gastrinomas may occur in ectopic locations such as the stomach, bile duct, periportal lymph nodes, ovaries, lungs, and heart. In contrast to the original studies of ZES, most gastrinomas are now found in the duodenum and not the pancreas. It has been estimated that 50% to 70% of gastrinomas occur in the duodenum. These are usually most common in the first portion of the duodenum with a descending incidence as one goes more distally. Duodenal gastrinomas tend to be very small and can be difficult to identify preoperatively and during operation. In patients with MEN-1, both pancreatic and duodenal gastrinomas occur. Patients with MEN-1 are more likely to have multiple tumors in the pancreas or duodenum.

Most gastrinomas are malignant. Yet, gastrinomas are characteristically slow growing and well differentiated and have a low proliferative rate with a Ki-67 of 1% to 2%. Hence, the disease is usually more indolent and slow growing than other gastrointestinal malignancies. Gastrinomas are associated with lymph node metastasis in 50% to 80% of patients, but unlike most cancers, lymph node metastases have minimal impact on survival. Liver metastases occur in about 25% of patients and are more common with pancreatic primary tumors, particularly those occurring to the left of the superior mesenteric vessels. Unlike lymph node metastases, liver metastases portend a poor prognosis. The extent of liver involvement is an important predictor of survival. In patients with diffuse

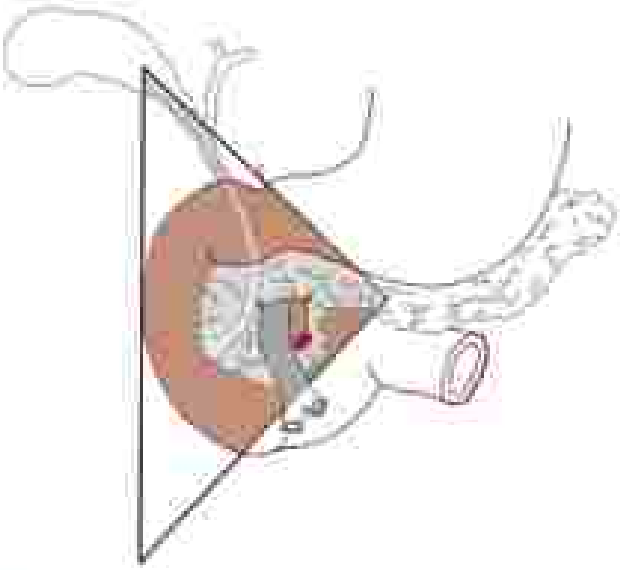

FIG. 1 The gastrinoma triangle is an imaginary space marked by the cystic duct, the duodenum, and the junction of the neck and body of the pancreas. (From University of Cincinnati Surgical Associates, Inc., and Ariel Surgical Handbook. ... on Philadelphia: Elsevier 2003.)

liver metastases, the 10-year survival is 10% to 12% compared with 97% in the absence of liver metastases. In addition, the prognosis is better in patients with single liver lobe metastases with a 10-year survival of nearly 60%. Regardless of location, the primary tumor size is predictive of distant metastasis (Table 1).

A staging system for neuroendocrine tumors of the pancreas, stomach, and duodenum has been proposed by a multidisciplinary international group at the Frascati Consensus Conference in 2006 (Rindi et al.) and the reader is referred to that article for the suggested readings.

DIAGNOSIS

Although ZES is rare, a patient should be referred for prompt workup for the presence of refractory peptic ulcer disease, longstanding diarrhea, ulcer disease in the absence of *Helicobacter pylori* infection, or failure to improve after treatment for established *H. pylori* and acid suppression therapy. In addition, the presence of hypercalcemia and hypercalciuria should raise suspicion of possible MEN-1; these patients should be screened for gastrinoma and MEN-1. The algorithm for the diagnosis of gastrinoma is shown in Fig. 2. The diagnostic steps include measurement of gastric acid, baseline fasting gastrin levels, and secretin-stimulated serum gastrin levels as well as imaging.

Fasting serum gastrin is the appropriate initial diagnostic test for patients with suspected ZES; however, it is not sufficient alone to establish the diagnosis as several medical conditions may cause hypergastrinemia. Most commonly, pernicious anemia, atrophic gastritis, and pharmacologic acid suppression may cause achlorhydria, which can cause hypergastrinemia resulting from the absence of acid suppression of gastrin secretion from the G cell in the gastric antrum. Other conditions that may cause fasting hypergastrinemia associated with increased acid hypersecretion include *H. pylori* infection, gastric outlet obstruction associated with peptic ulcer, antral G-cell hyperplasia, retained antrum, short bowel syndrome, and renal failure. Pernicious anemia and atrophic gastritis and the associated achlorhydria are the most common causes of hypergastrinemia. In these patients, it is not unusual for the fasting gastrin level to exceed 1000 pg/mL. Hence, a fasting serum gastrin level greater than 1000 pg/mL is not diagnostic for ZES unless it occurs in association increased gastric acid secretion (gastric pH <2).

TABLE 1 Primary Tumor Size and Frequency of Distant Metastases

Tumor Case	Diameter Range (cm)	No. of Patients	% (Mean) Metastases
T0 (no tumor)	0	18	0
T1	0.8–1.9	23	48
T2	1.2–2.6	22	14
T3	2.2–7.6	16	12
T4	3.3–8.5	29	59

Modified from Ellison EC, Johnson LK. *Zollinger-Ellison syndrome: a comprehensive review of historical, scientific, and clinical considerations.* Curr Probl Surg 2006;44:13–106.

It is important to emphasize that determination of gastric pH and verification of acid production is essential to confirm the diagnosis of ZES. If there is no acid in the stomach of a patient not being treated with H_2 antagonists or a PPI, then the patient is unlikely to have the diagnosis of ZES; no acid, no ZES!

Serum gastrin is measured by RIA, a readily available technique. It is preferable to send properly collected specimens to a reference laboratory for determination of serum gastrin levels. The director of your hospital laboratories will have access to an appropriate reference laboratory. The patient should be off pharmacologic acid suppression with PPI for a minimum of 72 hours (ideally, 7 days) before testing. H_2 receptor antagonists should be prescribed during this time to control acid secretion. In ZES, a normal fasting gastrin is very rare, occurring in only 4% to 5% of patients. This renders serum gastrin measurement a very good screening test for ZES, with a sensitivity that approaches 99%. If the fasting gastrin is normal and the clinician continues to suspect ZES, then a referral to medical center with expertise in gastrinoma is warranted.

Patients with suspected ZES whose have fasting hypergastrinemia and measurement of a gastric pH showing the presence of gastric acid should undergo confirmation with provocative stimulation of gastrin with secretin. Following an overnight fast, patients are given an intravenous bolus injection of secretin of 0.4 μg/kg of body weight. Blood drawn for determination of gastrin levels are collected and analyzed at 0, 2, 5, 10, 20, and 30 minutes following secretin administration. In our experience, it has not been necessary to discontinue PPIs or H_2 blockers for this test. Minimal side effects of intravenous secretin administration may include flushing and nausea.

Multiple definitions for a positive secretin test exist based on the absolute change in gastrin concentration. The most common threshold used is an increase in gastrin of 110 pg/mL over baseline, as proposed by Deveney. We have found this threshold to be accurate in nearly 100% of patients. Rarely, false negative or false positive tests may occur. The false positive rate is 0% in patients without achlorhydria when an increase over baseline of more than 110 pg/mL is used.

Once the biochemical diagnosis of gastrinoma is confirmed, the patient should be screened for MEN-1 with measurement of serum calcium, parathyroid hormone, and prolactin.

TUMOR LOCALIZATION

In patients considering surgical exploration, imaging is required to localize the gastrinoma. The initial localization test should be cross-sectional imaging with computed tomography (CT) scan of the abdomen and pelvis, with fine cuts through the pancreas, or magnetic resonance imaging (MRI). Neuroendocrine tumors are hypervascular and therefore demonstrate a greater degree of enhancement than the normal pancreas during the arterial and capillary phases of the

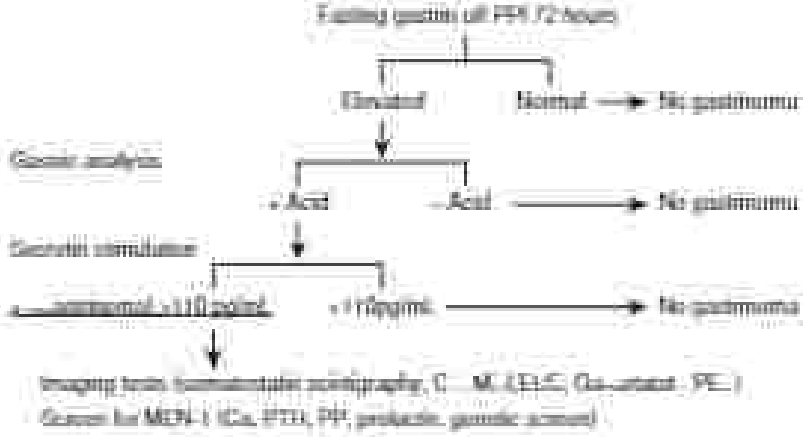

FIG. 2 Diagnostic algorithm for Zollinger-Ellison syndrome. *Ca*, calcium; *CT*, computed tomography; *EUS*, endoscopic ultrasound; *MEN-1*, multiple endocrine neoplasia type 1; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *PPI*, proton pump inhibitor; *PTH*, parathyroid hormone.

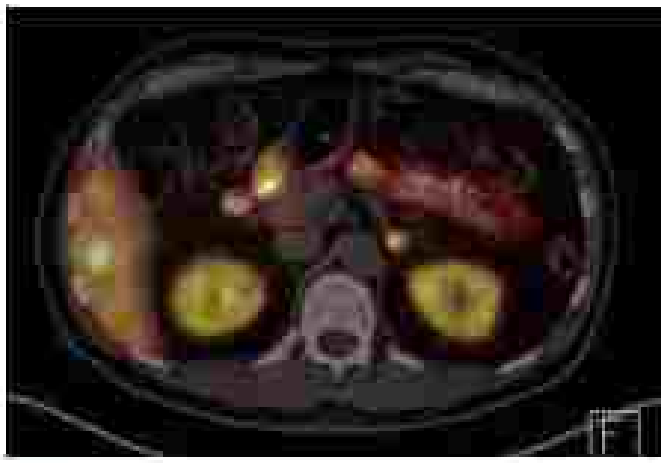

FIG. 3 ^{68}Ga-dotatate positron emission tomography showing duodenal gastrinoma and liver metastases.

contrast bolus. This is helpful in identification and differentiation of pancreatic neuroendocrine tumors (PNETs) from pancreatic cancer. Dual-phase MRI of the abdomen with delayed images may be helpful in delineating the primary tumor or metastases to the liver. Somatostatin receptor scintigraphy (SRS) can also be helpful in the preoperative localization of gastrinoma. SRS has been reported to be significantly better than all of the conventional imaging methods in the identification of gastrinomas later found at surgery, but SRS will still miss 20% of gastrinomas.

In most countries, ^{68}Ga dotatate positron emission tomography (PET)/CT has replaced SRS for localization of neuroendocrine tumors, including those causing ZES (Fig. 3). Gastrinomas are slow growing tumors. ^{99}In-diethylenetriamine PET/CT is not commonly used for initial evaluation. Because of the slow metabolic activity of gastrinomas in initial stages, they are not typically avid on ^{18}F-fluorodeoxyglucose PET/CT. In contrast to FDG PET/CT, ^{68}Ga Dotatate PET demonstrates a high uptake because neuroendocrine tumors express significant somatostatin 2 receptors. ^{68}Ga Dotatate PET identified significantly more lesions than ^{111}In DTPA octreotide scintigraphy. The National Comprehensive Cancer Network guidelines has added ^{68}Ga Dotatate PET/CT as an appropriate test in the management of neuroendocrine tumors.

Endoscopic ultrasound (EUS) is an invasive alternative to be considered when cross-sectional imaging and ^{68}Ga Dotatate PET have not identified the location of the gastrinoma. In addition, a biopsy can be accomplished at the time of EUS. The sensitivity of EUS to localize small PNETs is excellent (as high as 97%) compared with CT (86%) or MRI (79%).

Alternatively, a selective secretin stimulation test may be performed with direct secretin injection into the hepatic, splenic, gastroduodenal, and superior mesenteric artery with sampling from the right hepatic vein for measurement serum for gastrin. Very small doses of secretin are selectively administered intraarterially with sampling at 0, 20, 40, and 60 seconds. A step-up in hepatic vein gastrin will indicate the dominant blood supply of the tumor and its likely location.

To minimize costs, one may consider the following sequence to imaging: Cross-sectional imaging with CT or MRI followed by ^{68}Ga dotatate PET. If these studies are negative, then EUS should be considered.

INDICATIONS FOR SURGERY IN GASTRINOMA

After the diagnosis of gastrinoma is established, then the surgeon should consider whether an operation is indicated. In sporadic patients, exploration is warranted in the presence of a positive imaging study. In addition, sporadic gastrinoma patients with negative imaging warrant exploration as tumors in the duodenum, pancreas, or lymph node primaries may be very small and not detectable by imaging. Exploration by an experienced gastrinoma surgeon will identify a tumor in 80% to 90% of patients with negative imaging. Survival in patients that have negative imaging studies or who have no tumors identified at operation is exceedingly high, approaching 99% 20 year disease free survival without later stage progression.

In the MEN-1 patient, surgical treatment of the associated parathyroid hyperplasia is essential. This typically involves a 3½ gland parathyroidectomy or a total parathyroidectomy, followed by transplant of parathyroid tissue in to the forearm. Control of hyperparathyroidism with normalization of serum calcium will reduce baseline gastrin levels and may reduce the medication requirements to control gastric acid secretion. This has been reported to be done at the same time as abdominal exploration; however, our preference is to perform parathyroidectomy as the first procedure and the exploration for gastrinoma at a later date.

The role of resection of gastrinoma in MEN-1 patients is less clear. Some groups recommend pancreaticoduodenectomy or total pancreatectomy for gastrinoma with MEN-1. From one studies, those of the National Institutes of Health, and in the current European Neuroendocrine Tumor Society and North American Neuroendocrine Tumor Society guidelines for treatment of ZES MEN-1 patients, however, these aggressive resections are not routinely recommended. First, without aggressive resection, these patients may survive up to 30 years; hence, the benefit of such surgery has been difficult to establish. Second, the metabolic sequelae, including diabetes and pancreatic insufficiency, may worsen the quality of life for these patients.

In our institution, the decision to remove the gastrinoma in a patient with MEN-1 is determined by imaging. (1) Image negative patients are observed and do not undergo exploration given the low cure rates with surgery; (2) image positive patients with no distant metastases undergo exploration for local surgical resection because resection has been shown to improve survival independent of a medical cure.

GOALS OF SURGERY

Tumor control is the primary goal of surgery in ZES. First, removal of the primary tumor or tumors is accomplished to reduce the possibility of metastatic disease at a later date. Second, removal of all tumors can potentially correct the hypergastrinemia that causes ZES and reduce the need for long term PPI use. It is agreed that gastrinomas have a greater potential to metastasize to the liver even when they are small (<2 cm). Size is clearly related to distant metastases; therefore, surgical tumor control is beneficial. Norton and colleagues showed ZES patients having surgery have improved long term survival and were less likely to develop metastases. Ellison showed a long term survival advantage in both sporadic and MEN-1 patients having a BI or BII resection compared with those having an R2 resection in which BII is defined as complete surgical excision with normal postoperative serum gastrin levels, R1 is defined as residual microscopic disease or complete tumor excision and persistent hypergastrinemia, and R2 is defined as gross residual disease with persistent hypergastrinemia.

TECHNIQUE OF SURGICAL EXPLORATION AND RESECTION OF GASTRINOMA

Preoperative Management

Before the operation, the serum gastrin levels, secretin provocative test, and imaging should be reviewed. If there is any question to the accuracy, they should be repeated. The surgeon should consider whether special equipment may be necessary including intraoperative ultrasound, an endoscope, and cart if endoscopy is planned as part of the procedure to identify duodenal tumors, and indocyanine green for intravenous injection, and a near infrared light source that may aid in tumor localization.

The morning of surgery, the patient should receive the routine administration of a proton pump inhibitor, the anesthesiologist should have this available because redosing may be necessary.

Operative Management

General endotracheal anesthesia is preferred. A nasogastric tube should be inserted. A gastric pH should be determined at the beginning of the case to determine the effectiveness of acid pharmacologic acid suppression. The pH should be greater than 5; if it is not, an additional dose of PPI may be necessary. The anesthesiologist should monitor the nasogastric tube output because, in ZES, large volumes of gastric secretion may occur.

Laparotomy is performed through a midline incision. Although there are reports of laparoscopic exploration and there will likely be reports of robotic exploration, an open approach provides the surgeon with the best exposure and tactile feedback to help identify very small tumors. No gastric procedure should be planned unless there are specific complications of ZES that may require surgical treatment such as gastric outlet obstruction, a bleeding ulcer, perforation, and, in patients with previous gastric surgery, marginal ulceration or gastrojejunocolic fistula.

The essential steps in surgical exploration for gastrinoma include:

1. Midline laparotomy.
2. Palpation of the intraabdominal organs, including running the small intestine, is necessary to exclude secondary tumors or tumors in an ectopic location. Masses in the liver may be further examined by ultrasound and should be biopsied by excision or needle biopsy depending on the size. Given the extensive preoperative imaging in gastrinoma, the surgeon will rarely be surprised by unsuspected metastatic disease, but this may occur, particularly with small miliary (<1 mm) lesions over the surface of the liver that we have observed in 2% of patients.
3. Exposure.
   a. A wide Kocher maneuver is performed to the extent that the surgeon can visualize the left renal vein. This will facilitate bimanual palpation of the head of the pancreas and possible use of intraoperative ultrasound.
   b. Division of the gastrocolic omentum to widely open the lesser sac for exposure of the body and tail of the pancreas.
4. Intraoperative localization may be facilitated by the intravenous administration of indocyanine green 0.1 mg/kg and within 1 minute of injection examination of the pancreas and duodenum with near infrared fluorescence visualization (Fig. 6).
5. Assessment of the pancreas.
   a. Bimanual palpation of the head of the pancreas, taking note of any masses for later excision.
   b. Bimanual palpation of the body and tail of the pancreas is facilitated by incising the peritoneum overlying the inferior edge of the body and tail of the pancreas.
   c. Use of intraoperative ultrasound to map the head, uncinate process, body, and tail of the pancreas, noting any hypoechoic masses for later excision.
6. Palpation of the hepatoduodenal ligament and removal of any enlarged lymph nodes, which are sent for standard histology unless no primary gastrinoma is identified in the typical locations, in which case, they are sent for frozen section because these represent an ectopic lymph node primary.
7. Excision of suspicious pancreatic nodules and frozen section.
   a. In the head of the pancreas and uncinate process, local excision of tumors less than 2 cm in diameter and not involving the pancreatic duct as determined by intraoperative ultrasound. These tumors are hypervascular and use of bipolar coagulation aids in the dissection. Larger tumors may require a pancreaticoduodenectomy.
   b. In the body and tail of the pancreas, the tumors usually are near the pancreatic duct and, as such, distal pancreatectomy and splenectomy are preferred to avoid injury to the pancreatic duct. Because the majority of gastrinomas are malignant, splenectomy is warranted, as is distal pancreatectomy to remove lymph nodes in the splenic hilum.
8. Examination of the duodenum and removal of duodenal nodules in the same stage. This requires a longitudinal duodenotomy and internal palpation of the duodenum. Most of the tumors are in the first portion of the duodenum with descending incidence the further distal in the duodenum. Use of external palpation or ultrasound will only identify 20% to 30% of these tumors. Although intraoperative endoscopy and transillumination of the duodenum may also be helpful in some cases to identify, a duodenal gastrinoma false negative results are not infrequent. Suspected duodenal gastrinomas may be locally excised and do not require duodenal resection. The tumors are submucosal, and closure of the mucosal defect created by the excision is warranted. For lesions on the anterior or lateral wall of the duodenum, full thickness excision is possible. The duodenum is closed longitudinally with a single layer of 3-0 interrupted silk sutures. We have not found an advantage to transverse closure.
9. A closed suction drain is placed near any sites in the pancreas in which a tumor was locally excised or the transected pancreas if a pancreatectomy was performed.

Postoperative Management

The nasogastric tube is removed at the discretion of the attending surgeon. PPI treatment is continued by intravenous administration

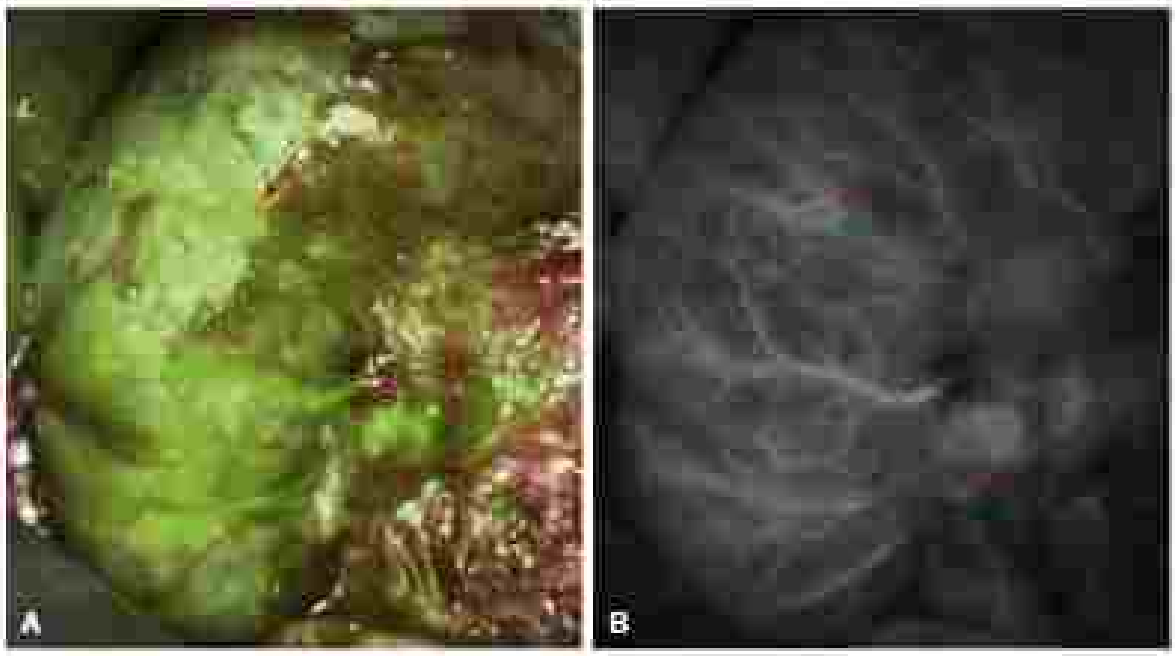

FIG. 4. Near-infrared fluorescence of pancreatic head and duodenum 30 seconds after intravenous (A) indocyanine-green injection (overlay and (B) grayscale overlay. A portaduodenal metastatic lymph node (arrowhead) and a duodenal wall gastrinoma 2 cm medial to the major papilla (arrow) are visible. (From Hartwig W., Jimeno A, Wilson J, et al. Indocyanine-green near-infrared fluorescence visualization of the duodenal gastrinoma in a patient with Zollinger–Ellison syndrome. Surgery. 2010;148(1):8-14.)

TABLE 2 Surgical Cures in Patients With Zollinger-Ellison Syndrome

Author, Year	No. of Patients	Median Follow-up (yr)	Multiple Endocrine Neoplasia Type 1 (%)	Tumor Resected (%)	Initial Tissue Cure Survival (%)	Disease-free Cure at Last Follow-up (*)
Ellison, 2008	106	15	25	72	30	25
Norton, 2006	148	12	24	94	59	41
McArthur, 1994	22	6a	14	41	18	Not available

until the patient is taking liquids orally, he or she then may be switched to an oral form. Partial cell hyperplasia induced by the hypergastrinemia may take 3 months or more; as such, PPI treatment should be continued for 3 months in a patient with normal postoperative fasting gastrin. A fasting gastrin level is drawn on day 3 and repeated at the first clinic visit. In a patient with established ZES, we have not seen postoperative false-positive elevations of gastrin caused by continued PPI therapy. If postoperative fasting gastrin levels are elevated, then PPI therapy should be continued and repeat imaging completed at 6 months after surgery with consideration of reoperation if there is positive imaging.

Results of Treatment

Biochemical cure of sporadic gastrinoma is reported in 30% to 50% of patients (Table 2); however, recurrence has been documented in nearly one-third of patients. The average time to recurrence is 5 to 10 years. Regardless of achieving biochemical cure, complete resection of all gross tumors is associated with improved survival. The 10-year disease-specific survival in patients having R0/R1 resection of sporadic gastrinoma is 85%, compared with 40% for patients having R2 resection and 25% for those having no resection. Pancreatic gastrinoma survival fares well when compared with other PNETs (Table 3).

TABLE 3 Median Survival of Pancreatic Gastrinoma Compared with Other Pancreatic Neuroendocrine Tumors

Tumor Type	Median Survival (yr)
Insulinoma	12.7
Gastrinoma	10.2
VIPoma	2.7
Mixed tumors	5.9

Modified from Krueger KM, Hilsabeck N, Kelebow E. Malignant functioning neuroendocrine tumors of the pancreas: a survival analysis. Surgery. 2010;148(3):580-589.

In our experience of MEN 1 patients operated on with a curative intent, cure was achieved in only 6% of patients; others report similar results (Table 4). The 10-year survival with gastrinoma in MEN 1 with R0/R1 resection was 90%, compared with only 42% for patients having an R2 resection or no resection. Because R2 resections do not increase survival, MEN 1 patients with extensive metastatic disease or locoregional spread that precludes complete resection rarely benefit from surgical resection, and these patients are typically not offered surgery.

TABLE 4 Surgical Cures in Patients With Zollinger-Ellison Syndrome With Multiple Endocrine Neoplasia Type 1

Author, Year	No. of Patients	Median Follow-up (yr)	Tumor Resected (%)	Disease-Free Survival at 5 Years (%)
Metz-Flamant, 2009	12	18	92	0
Ellison, 2006	26	15	81	38
Norton, 2001	40	7	94	0

BOX 1 Treatment Options for Metastatic Disease

Liver resection
Liver transplant
Transarterial chemoembolization
Ablation (radiofrequency or microwave)
Chemotherapy
- Doxorubicin ± streptozotocin
- 5-[illegible]
- 5-[illegible]
Targeted therapy
- [illegible]
- Somatostatin analog, [illegible]
- Somatostatin receptor [illegible]
Short-acting octreotide
Long-acting octreotide
- [illegible]
- Lanreotide (Somatuline Depot)

Recurrent Gastrinoma

Norton and colleagues reported 223 patients in a prospective database that had an initial operation for ZES and then were subsequently managed with serial cross-sectional imaging (CT, MRI, ultrasound, and somatostatin scintigraphy). They reported that 52 patients (23%) underwent reoperation a mean of 6 years after the initial surgery for recurrent ZES with gastrinoma on imaging. Of the 52 reoperated patients, 12 had ZES with MEN 1. They found that, after reoperation, 18 of 52 patients were initially free of disease (35%), after a mean follow-up of 8 years, 13 of 52 remained disease free (25%). During follow-up, 30/52 (57%) of the reoperated patients died, of whom 7 died of disease (13%). The overall survival from first surgery was 84% at 20 years and 68% at 30 years.

These findings are important and suggest that ZES patients should have systematic imaging after curational surgery, and if gastrinoma recurs or is persistent, be given the option for reoperation. Patients with persistent or recurrent gastrinoma with negative imaging are unlikely to benefit from reoperation. Data concerning reoperation for recurrent image positive gastrinoma in MEN 1 are less clear; we are less likely to recommend reoperation in this situation.

Management of Metastatic Disease

Patients with malignant gastrinoma of the pancreas and duodenum not infrequently present with liver metastases. In these situations, it is essential for the surgeon to work collaboratively with a multidisciplinary team. The extent of disease burden in the liver often dictates the quality and length of survival. Surgical excision of both the primary tumor and liver metastases has been reported in the literature; however, its use should be considered carefully. Some authors suggest that select patients may see a survival benefit if a complete or near complete (90% or more) resection of hepatic metastases can be achieved. In addition, there are reports of long-term survival with liver transplantation for metastases from PNETs including gastrinoma.

A variety of options for the treatment of metastatic disease is shown in Box 1. The decision to proceed with treatment depends on the rate of disease progression and the patient's symptoms. Because gastrinoma is a rare condition, it is recommended that clinical trials be considered to help elucidate the best treatments in the future.

SUMMARY

In conclusion, ZES is a syndrome caused by gastrinoma. Two-thirds of cases are located within the gastrinoma triangle and associated with symptoms of peptic ulcer disease and diarrhea. The diagnosis of ZES is established by measuring fasting levels of serum gastrin, gastric pH, and secretin provocative gastrin stimulation. ZES is frequently associated with MEN 1; hence, this must be excluded in all patients. Treatment of ZES consists of medical control of symptoms with PPIs and evaluation for potentially curative surgery. Preferred preoperative imaging studies include cross-section MRI or CT and Octreotate PET/CT scans. EUS may be performed to further evaluate primary tumors if other testing is negative. All patients with resectable sporadic gastrinoma should undergo surgical exploration. The goal of surgery is tumor control. Two-thirds of the primary tumors are located within the gastrinoma triangle. Intraoperative tumor localization requires methodical exposure of the pancreas and duodenum for possible duodenal gastrinoma. In patients with MEN 1, surgical resection should be pursued only if there is a tumor located on imaging in the absence of metastatic disease. Patients with sporadic ZES and negative imaging should undergo surgery. In those patients who have synchronous or metachronous liver metastases, surgery should be performed if all visible tumor can be removed safely. Patients with recurrent ZES should be restaged and operation considered if localized tumor is identified. Patients with liver metastases benefit from coordinated care with a multidisciplinary team and not infrequently will have survival prolonged by surgical resection.

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MANAGEMENT OF MALLORY-WEISS SYNDROME

Yu Liang, MD, and David W. McFadden, MD

Mallory Weiss syndrome was first described by G. Kenneth Mallory and Soma Weiss in 1929. They described 15 patients with a history of alcohol use who developed violent vomiting or retching followed by massive hemoptysis. Four of the 15 patients were found to have vertical gastric mucosal lacerations at the gastroesophageal junction (GEJ); Mallory Weiss tears (MWTs). In 1932, Mallory and Weiss reported six more cases of massive hemoptysis following forceful vomiting. It became clear to Mallory and Weiss that vomiting was the primary predisposing factor. For the next 40 years, there were sporadic case reports of Mallory Weiss syndrome in the literature.

The proliferation of flexible endoscopy in 1970s and 1980s transformed the diagnosis and treatment of upper gastrointestinal (UGI) hemorrhage. MWTs were found in about 10% of UGI bleeding (3%–15%) compared with ulcers being found in 50% of UGIB. Although forceful vomiting remains the most common cause of MWT, other associating factors have been reported in case studies or small case series. These precipitating factors include esophagogastroduodenoscopy, straining during defecation, lifting, blunt abdominal injury, epileptic convulsions, coughing, and hiccups under anesthesia. Before the advent of flexible endoscopy, UGIB from MWT treatment consisted of supportive observation or laparotomy for surgical hemostasis.

PATHOPHYSIOLOGY, INCIDENTS, AND RISK FACTORS

There are two possible scenarios for pathophysiology of MWT during emesis. During forceful vomiting, there is a sudden increase in pressure gradient between the abdominal and thoracic cavity. The pylorus closes while the lower esophageal sphincter, the gastric cardia, and the diaphragmatic hiatus relax. At the same time, the abdominal wall, the diaphragm, and the distal gastric wall contract to forcefully propel gastric content retrograde. This leads to retrograde prolapse of the proximal stomach into the esophageal lumen with tearing of the gastric and, occasionally esophageal, mucosa. Alternatively, the sudden increase in intragastric pressure and relaxation of gastric cardia leads to sudden dilation of gastric cardia and distal esophagus. This abrupt dilation may also lead to tissue laceration of the GEJ mucosa. For patients without hiatal hernia, MWTs tend to be located at the GEJ. For patients with hiatal hernia, MWTs tend to be located at gastric cardia. Isolated esophageal mucosal tears are unusual. The most common location for MWT is at the lesser curve (Fig. 1).

Wuerth and Richey recently published a nationwide analysis of UGI hemorrhage admissions from 2002 to 2012 in the United States. Their report showed a 21% decrease in all UGI hemorrhage. Because treatment of *Helicobacter pylori* and the use of proton pump inhibitors (PPIs), bleeding from gastritis and peptic ulcer decreased by 35% and 30%, respectively. MWTs accounted for about 7% of all UGIB. The hospitalization rate for MWT was essentially unchanged between 2002 and 2012. The mortality from UGIB decreased by 28%, whereas mortality from MWT decreased by 36% (Tables 1 and 2).

The majority of patients with gastrointestinal bleeding are males in their 50s and 60s. There are some distinct differences in the characteristics of patients bleeding from MWT compared with patients bleeding from ulcers (Table 3). About one half of the patients with MWT bleeding have a history of alcohol use, compared with 20% of patients with bleeding ulcers. Patients with liver disease have more severe MWT bleeding compared with those without. The prevalence of MWT in the cirrhotic population is comparable to the prevalence of MWT in the general population. Patients with bleeding from MWT are less likely to be in shock compared with patients with bleeding ulcer, 14% versus 6.7%, respectively. Patients with MWT bleeding have higher American Society of Anesthesiologists risk score compared with patients with bleeding ulcers. Endoscopic treatment was successful in 90% of patients with MWT bleeding and 95% successful in bleeding from ulcers.

Multiple small case series in the past demonstrated that 20% to 90% of patients with MWT have a hiatal hernia. Some consider hiatal hernia as a necessary predisposing factor; however, case series by Sugawa et al. found only 20% of the patients with Mallory Weiss syndrome have a hiatal hernia. A recent matched case control study reviewed more than 2000 cases of MWT and found hiatal hernia in only 26% of patients compared with 22% in the non-MWT controls (not significant). An association between hiatal hernia and MWT remains unanswered.

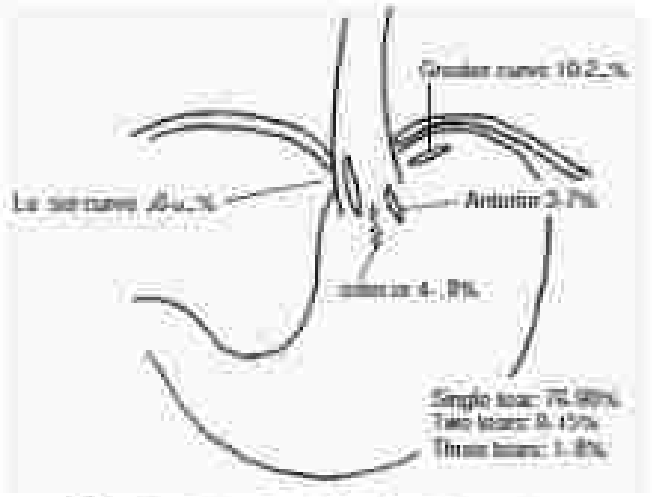
Diagnosis

Patients with UGIB from MWT usually present with a history of forceful nonbloody emesis follow by hematemesis. Only about 10% report a history of melena. Abdominal pain is uncommon. Association with alcohol is variable. Definitive diagnosis of MWT is impossible without direct visualization by flexible endoscopy or surgery.

Flexible endoscopy is the standard diagnostic and therapeutic modality for treatment of UGIB. Resolution is essential for visualization of the Mallory Weiss lesions at the cardia mucosa. About 75% of the lesions will have no active bleeding at the time of endoscopy. Most lesions are 0.5 to 2.5 cm but lesions up to 5 cm have been reported. Complete evaluation of the UGI track is also essential because coexistence of bleeding from varices, gastritis, duodenitis, or ulcer are seen in up to 10% of the patients with MWT. During flexible endoscopy, lesions are also classified based on their risk of rebleeding using the Forrest classification (Table 4). Other diagnostic modalities for GIB include tagged red blood cell scan, angiography, and multidetector computed tomography (MDCT) angiogram. For patients bleeding from MWT, angiography of the left gastric or inferior phrenic artery may show a tissue contrast collection at the GE junction. MDCT angiogram is now considered equivalent to angiography. Triphasic MDCT (precontrast, arterial and portal phases) provides better results than computed tomography angiograms especially in patients with portal hypertension or patients with concern for bleeding from within the liver.

Treatments: Endoscopy, Angiography, Surgery

Patients with UGIB need to be treated for hemodynamic instability prior to diagnostic or treatment intervention. The treatment outline is summarized in Fig. 2. If the patient is obtunded from shock, intubation for airway protection is essential. Initial laboratory studies should include hematocrit, type and cross match, coagulation parameters, and liver function tests. Any derangement in coagulation should be corrected quickly. Platelet transfusion should be considered for patients with thrombocytopenia or for patients on dual antiplatelet therapy for cardiovascular disease. However, platelet transfusion may not be effective in patients on dual antiplatelet therapy. If unable to place InG or IJG venous access, large central venous access should be placed for resuscitation with crystalloids or whole blood. Organ perfusion status should be monitored by blood pressure, heart rate, and urine output.



F G . Distribution of tear(s) in allory-Weiss syndrome.

TABLE 1 Hospitalization Rate by Etiology

	Hospitalization Rate (Cases per 100,000 Population)			
	2002	2012	% Change	P Value
Peptic ulcer disease	43	30	-30	<.01
Gastritis	17	10	-55	<.01
Esophagitis	10.6	12.2	26	<.01
Angiodysplasia	4	5	32	<.01
Mallory-Weiss	4.9	5.3	8	.28
Neoplasm	2.2	3.2	50	<.01
Esophageal varices	4.5	3.8	-5	.26
Dieulafoy	1.0	1.2	33	<.01
UGIH (total)	89	67	-21	<.01
Non-UGIH	7438	6807	-8	<.01

UGIH, upper gastrointestinal hemorrhage.
Modified from Wuerth BA, Rockey DC. Changing epidemiology of upper gastrointestinal hemorrhage in the last decade: A nationwide analysis. Dig Dis Sci. 2016;61(5):1288–1295.

TABLE 2 All-Cause Mortality Rate of UGIH by Etiology

	Mortality (Deaths per 100 Cases)			
	2002	2012	% Change	P Value
Esophageal varices	7.3	6.1	-17	.08
Neoplasm	4.9	5.1	3	<.05
Dieulafoy	3.8	2.9	-24	<.05
Peptic ulcer disease	2.8	2.0	-32	<.01
Mallory-Weiss	2.0	1.3	-34	<.01
Esophagitis	2.0	1.4	-30	<.01
Gastritis	1.6	1.2	-23	<.05
Angiodysplasia	1.5	1.0	-26	<.01
UGIH (total)	2.6	1.9	-28	<.01
Non-UGIH	3.2	2.5	-23	<.01

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Antiemesis medication should be started for all patients with persistent nausea and vomiting. High-dose PPIs by continuous infusion or intermittent dosing has shown to decrease need for endoscopic intervention and transfusion. It is recommended to continue PPI for at least 2 weeks after bleeding stops to promote healing and hemostasis. For massive UGIH, erythromycin can be administered 20 to 90 minutes before endoscopy to facilitate clearing of blood from the stomach and improve endoscopy visualization.

Initial UGIH bleeding workup should include nasogastric tube placement and gastric lavage with 500 mL of saline to assess for the presence of blood. Gastric lavage may also be needed during endoscopy to remove blood in the stomach that may obscure visualization. Retrograde view of the GEJ is essential for diagnosis and treatment. At the time of initial endoscopy, between 30% and 70% of MWTs will have no bleeding. These can be treated with PPI alone and do not need repeat endoscopy for proof of healing. Endoscopic treatment modalities available during endoscopy include hemoclip, banding, thermal coagulation, injection of sclerosing, or vasoconstricting agents. Each modality has its own advantages and disadvantages. There is no good study to advocate one modality over another, and the choice of modality is often dependent on the preference of the endoscopist.

Endoscopic Treatment

Injection of 15 to 20 mL of epinephrine leads to tamponade and local vasoconstriction to stop the bleeding. Sclerosing agents injected into the bleeding site causes tissue necrosis and subsequent thrombosis; however, the use of sclerosing agents is limited due to concern for extensive necrosis leading to perforation. In general, monotherapy with injection of epinephrine or a sclerosing agent has a high risk of rebleeding and should be combined with another modality such as hemoclip or banding.

Thermal coagulation can be applied by monopolar, bipolar, multipolar, or argon plasma coagulation (APC). Bipolar is considered safer than monopolar. Thermal coagulation should not be used repeatedly at the same location out of concern for perforation. This is especially true in the esophagus because it lacks serosa. In APC, an electric current travels through ionized argon gas released from the tip of a probe and heats up the nearby target. APC should be avoided in patients with portal hypertension because it may increase bleeding from varices.

An endoscopically placed clip and fund powder mechanical closure of the bleeding vessel. Blood vessels larger than 2 mm are more difficult to control using a traditional "through the scope" clip. Clip and fund placement are angle and location dependent and some lesions may require a newer technology called over the scope (OTS) clip. The lesion is first suctioned into an opening of the scope; the OTS clip is then placed over the lesion. This allow for precise placement of the clip onto its target. OTS clips are much less location or angle dependent because the suction stabilized the lesion before clip placement. The suction step also allows for clip placement on a lesion that cannot be visualized in a head on fashion. This device can place clips on a lesion that is visualized tangentially. Multiple studies showed OTS clips are more effective for hemostasis compared with through the scope clips. Some studies suggest OTS clips are successful at MWT bleeding and are becoming the first line treatment for UGIH.

TABLE 3 Clinical Characteristics of Patients With Bleeding MWS and PU Bleeding

	MWS	PU	P Value
No. patients	281	1570	
Age, n (%), years			
<65	135 (48.0)	673 (42.9)	
≥65–80	94 (33.5)	590 (38.6)	.2e4
>80	52 (18.5)	267 (17.5)	
Gender, n (%), M/F	211 (75.1)/70 (24.9)	1020 (64.7)/550 (35.3)	.005
Clinical presentation, n (%)			
Gastric content			
Blood	157 (55.8)	647 (41.2)	<.001
Coffee ground	89 (31.6)	883 (57.7)	<.001
Shock	9 (3.4)	103 (6.7)	<.001
Hb level, median (range), g/L	100 (32–160)	94 (27–195)	<.001
Overall comorbidities, n (%)			
Mild disease (ASA class 2)	72 (25.6)	504 (32.9)	.015
Moderate severe (ASA class 3–4)	174 (62.4)	258 (16.8)	<.001
Drugs on presentation, n (%)			
Without	193 (68.7)	736 (48.1)	
NSAIDs	38 (13.5)	457 (29.9)	
Aspirin	28 (8.5)	239 (15.6)	<.001
Amphicillin	10 (3.6)	23 (1.5)	
Anticoagulants	16 (5.7)	75 (4.9)	
History, n (%)			
Alcohol consumption	153 (87.5)	525 (34.2)	<.001
Smoking	53 (18.9)	346 (22.6)	.1e3
Previous GI bleeding	55 (19.6)	327 (21.4)	.494

ASA, American Society of Anesthesiologists; GI, gastrointestinal; HB, hemoglobin; MWS, Mallory-Weiss syndrome; NSAID, nonsteroidal antiinflammatory drug; PU, peptic ulcer.
Modified from Lubrick N, Redstone I, Kerin V, et al. Mortality in high-risk patients with bleeding mallory-weiss syndrome is similar to that of peptic ulcer bleeding: results of a prospective database study. Scand J Gastroenterol. 2014;49(4):458–464.

TABLE 4 Forrest Classification

Forrest Classification	Description	Prevalence (n = 2481), %	Further Bleeding Rate (n = 2 [a]), Mean Rate (Range), %*	Mortality (n = 1187), Mean Rate (Range), %*
Ia	Spurting hemorrhage	11	55 (11–100)	11 (0–23)
Ib	Oozing hemorrhage			
IIa	Nonbleeding visible vessel	8	43 (0–81)	11 (0–21)
IIb	Adherent clot	8	22 (14–36)	7 (0–16)
IIc	Flat pigmented spot	16	10 (0–13)	3 (0–10)
III	Clean ulcer	56	5 (0–10)	2 (0–3)

*Figures in prospective trials without endoscopic therapy.
Modified from Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107(3):345–360.

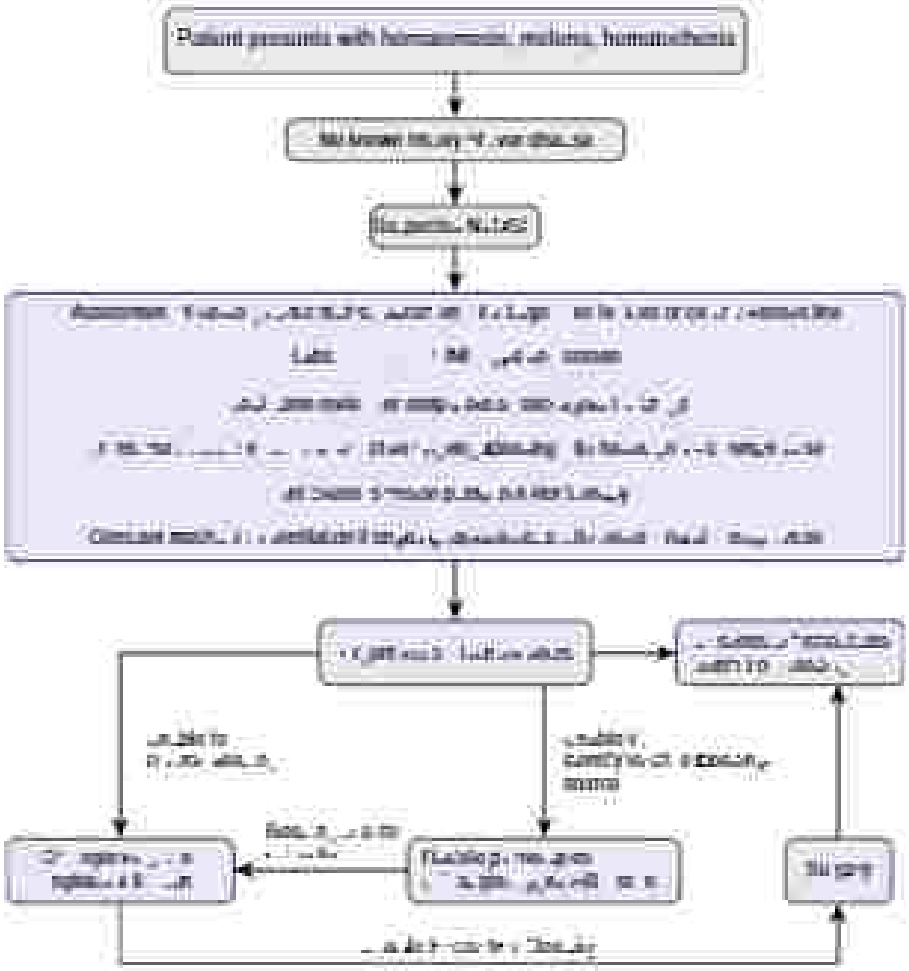

Fig. 1 Initial evaluation and management of nonvariceal gastrointestinal bleeding. CBC, complete blood count; CMP, comprehensive metabolic panel; CT, computed tomography; EGD, esophagogastroduodenoscopy; Hb, hemoglobin; IMR, international normalized ratio; IR, interventional radiology; IV, intravenous; NVUGIB, nonvariceal upper gastrointestinal bleeding; PRBC, packed red blood cells. (Modified from Yamout S, Lee M. Approach to Category 1/1 bleeding and management of nonvariceal upper gastrointestinal bleeding. Clin Hem 2018;64(2):113–9.)

Topical hemostatic agents (e.g., Hemospray, EndoClot) can also be used to treat UGIB. These agents concentrate coagulation factors and create a plug to stop bleeding at injured blood vessels. Intermittently, Hemospray is being used as a first-line agent or as a bridge to surgery. In one study that looked at the use of Hemospray on lesions at high risk of rebleeding (Forrest class IIa or IIb), primary hemostasis was 95% with a 15% rebleeding rate in 7 days. A French study with 202 subjects showed Hemospray was easy to use and created primary hemostasis in 97%, with a rebleeding rate of 25% at 8 days. Multiple studies showed Hemospray and EndoClot can be used as a bridge to surgery for high-risk lesions.

New, innovative strategies to treat UGIB are emerging. Potential future endoscopic modality includes ultrasound-guided angiography, new hemostatic agents, new mechanisms of delivery for hemostatic agents to wider area, and endoscopic suturing devices.

Angiography

Transcatheter arterial embolization or infusion of vasopressin is a treatment option for patients who are poor surgical candidates and who have failed endoscopic treatment. Vasopressin infusion has been replaced by embolization because of a 40% risk of recurrence and risk of major complications using vasopressin. Choice of embolization agent includes autologous clot, microspheres, and glue. UGIB is often sporadic because of vasoconstriction from hypovolemia or temporary clot formation. At the time of angiography, only about 50% will have active extravasation. Provocative angiography injects vasodilator, anticoagulant, or a thrombolytic agent to induce bleeding and can double the detection rate. The left gastric artery accounts for 80% of UGTB involving the stomach. Bleeding from an MWT usually involves either the left gastric artery or inferior phrenic artery. Empiric embolization of these arteries based on endoscopic localization may be necessary if angiography is unable to identify any extravasation. When compared with surgical treatment, embolization has a higher rebleeding rate, more than 50% in some reports. Embolization is usually a last resort for patients who are poor surgical candidates.

Surgical Treatment

Endoscopic therapy is successful in 90% of UGIB caused by MWT. Unlike endoscopy, there has been minimal change to the surgical treatment of MWT. Since the widespread use of endoscopy and enteric innovation in endoscopic tools, less than 5% of patients with MWT will require surgical intervention. Patients who fail initial endoscopic treatment usually get a second endoscopy before proceeding to surgery.

Surgical treatment for MWT usually requires laparotomy. Before surgery, the bleeding source and location is identified by endoscopy. A high anterior longitudinal gastrotomy will allow visualization of the lesion at the GE junction. The MWT is oversewn using absorbable sutures. If the lesion cannot be visualized because of massive hemorrhage, packing of the gastric lumen will compensate any active bleeding and allow time for resuscitation. The packing is then sequentially removed to find the active bleeding and repair. The surgeon should

look for other bowel injury as part of MWT because up to 80% of MWT will coexist with other lesions. The anterior gastrotomy is closed using staples or two layer sutures. Care must be taken to not narrow the gastric lumen or the GE junction. If a hiatal hernia exists and it is difficult to see the bleeding MWT, one trick the senior author has used is to insert a Foley catheter through the gastrostomy and up to the distal esophagus. Gently inflation of the balloon combined with gentle downward traction will usually reduce the GE into the operative field.

There are a lack of data for laparoscopic assessing of MWT using endoscopic guidance. Laparoscopic ports are placed similar to standard hernia surgeries. Endoscopy is used to guide the laparoscopic placement of full thickness sutures to close the MWT through an anterior gastrotomy. There are not enough data in the literature to comment on this strategy and it poses multiple potential problems. First, there is no good way to control bleeding if gastric blood interferes with visualization. Second, patients with MWT who end up in the operating room usually have failed another modality and are unstable. These patients require quick access of the gastric lumen and control of the bleeding vessel, for which laparoscopy and endoscopy are not suited.

Sengstaken-Blakemore Tubes

The use of Sengstaken-Blakemore tubes for control of Mallory-Weiss bleeding has been reported with varying degrees of success. Its use is controversial and considered an act of desperation. Concern about their usage in patients with Mallory-Weiss syndrome centers on the risk of extending the mucosal tears into full thickness tears of the esophagus or stomach. The presence of a hiatal hernia is also a contraindication to the use of such tubes because the asymmetric pressure gradient generated by the gastric balloon may lead to necrosis and perforation of the herniated portion of the stomach.

SUMMARY

MWT is a linear laceration of the mucosa at the GEJ. The mucosal tear is most commonly associated with violent emesis. The UGIB caused by MWT is self limiting in 80% to 90% of cases. Initial treatment of unstable patient must start with resuscitation and stabilization. Endoscopy is the main stay for diagnosis and treatment. Fewer than 10% of patients will require surgical treatment of UGIB for MWT.

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MANAGEMENT OF GASTRIC ADENOCARCINOMA

Aslam Ejaz, MD, MPH, Bradley T. Baxman, MD, MS, and Farhan Zaheer, MD, MHS, FACS

In the United States, gastric adenocarcinoma will be responsible for an estimated 26,240 new cases, resulting in 10,800 deaths in 2018. Although the incidence and mortality of gastric cancer has been decreasing for several decades, it remains the 6th leading cause of digestive tract cancer in the United States. The worldwide incidence of gastric cancer, however, varies greatly, with more than 70% of gastric cancers occurring in the developing world and approximately 50% occurring in East Asia. Because of the high incidence seen in these populations, screening programs are common and have likely contributed to a decrease in mortality from this disease. However, because of the lower incidence observed in the United States, screening for gastric adenocarcinoma is not routinely performed and no reliable biomarkers currently exist for this disease.

As with many cancers, chronic inflammation appears to play a vital pathogenic role in the development of gastric adenocarcinoma. Among known infectious causes, the most identifiable and common are chronic *Helicobacter pylori* infection and Epstein-Barr virus infection. Other risk factors include gastric polyps, exposure to nitrosamines and pickled foods, low consumption of fruits and vegetables, high salt intake, tobacco use, previous gastric surgery, pernicious anemia, and obesity.

Approximately 10% to 15% of gastric cancer cases occur in patients with a family history of gastric cancer. Inherited gastric cancer syndromes include hereditary diffuse gastric cancer (E-cadherin/CDH1 mutation), familial adenomatous polyposis, and Lynch syndrome (hereditary nonpolyposis colorectal cancer). Genetic counseling and screening should be offered and discussed with all patients with an inherited gastric cancer syndrome. For patients with a CDH1 mutation, prophylactic total gastrectomy is recommended in family members older than 20 years of age. Furthermore, females with hereditary diffuse gastric cancer are at increased risk for the development of breast cancer and should receive appropriate surveillance.

PATHOLOGY/HISTOLOGY

More than 90% of malignant gastric tumors are classified as adenocarcinoma (glandular in origin); however, gastric adenocarcinoma can be highly heterogeneous. The most commonly used classification scheme is the Lauren classification, in which gastric adenocarcinoma is divided into two main histologic subtypes: diffuse (poorly differentiated) and intestinal (well differentiated). The diffuse subtype is more common in patients with an inherited syndrome and often carries a much poorer overall prognosis. The intestinal subtype is often seen in high-risk populations and the elderly, with a strong association with *H. pylori* infection.

In 2014, the Cancer Genome Atlas Network published the results of a comprehensive molecular evaluation of 295 primary gastric adenocarcinomas. As part of this genomic profiling, gastric cancer was divided into four subtypes: tumors positive for Epstein-Barr virus (EBV); microsatellite unstable tumors (22%); genomically stable tumors (20%); and tumors with chromosomal instability (50%). These classifications may serve as the basis for future targeted therapies and treatments.

DIAGNOSIS AND STAGING

Symptomatology related to gastric cancer is often vague and nonspecific. These symptoms, if present, often mimic other gastrointestinal disorders and may include epigastric pain, nausea, vomiting,

look for other lesions after repair of MWT because up to 80% of MWT will coexist with other lesions. The anterior gastrotomy is closed using staples or two layer sutures. Care must be taken to not narrow the gastric lumen or the GE junction. If a hiatal hernia exists and it is difficult to see the bleeding MWT, one trick the senior author has used is to insert a Foley catheter through the gastrotomy and up to the distal esophagus. Gently inflation of the balloon combined with gentle downward traction will usually reduce the GEJ into the operative field.

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Aslam Ejaz, MD, MPH, Bradley N. Reames, MD, MS, and Fabian Johnston, MD, MHS, FACS

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DIAGNOSIS AND STAGING

Symptomatology related to gastric cancer is often vague and nonspecific. These symptoms, if present, often mimic other gastrointestinal disorders and may include epigastric pain, nausea, vomiting,

dyspepsia, postprandial fullness, anorexia, and weight loss, among other symptoms. As previously discussed, screening for gastric adenocarcinoma is not routinely performed in the United States. Diagnosis is often achieved after the onset of symptomatology (and subsequent investigation) or incidentally through staging performed for other causes. Because of this, the majority of gastric cancers found in the United States are often found at advanced stages of disease, with more than 50% of patients having regional or distant spread of disease at the time of diagnosis. Furthermore, physical examination for patients with gastric cancer is unremarkable in its early stages. Late stages of the disease may include a palpable abdominal mass, the presence of a periumbilic (Sister Mary Joseph's) or left supraclavicular (Virchow's) lymph node, or a pre-rectal mass resulting from tumor deposition in the rectovesical or retrouterine pouch (Blumer's shelf).

Endoscopy with biopsy of any suspicious manifestation is the first diagnostic modality used when gastric cancer is suspected. Endoscopic ultrasound (EUS) is used as an adjunct to further characterize the depth of tumor (T stage) as well as the presence of any suspicious or involved perigastric lymph nodes (N stage). Biopsy of suspected nodal metastasis may also be performed during EUS. EUS accuracy is operator dependent with wide ranging reported accuracies between 66% and 75%.

In the United States, reported utilization of EUS is around 25%. This is likely because of the increased reliance on high-quality cross-sectional computed tomography (CT) to characterize tumor depth and nodal involvement, as well as the presence or absence of any metastatic spread. EUS, however, may be most useful in the early stages of disease, to guide decisions regarding neoadjuvant therapy. Reported accuracy of CT scan versus EUS appears to be equivalent for locoregional staging for patients with gastric cancer; however, CT scans perform poorly in the detection of peritoneal disease because up to 50% of patients may have microscopic or macroscopic peritoneal disease despite a negative CT scan. As such, additional modalities such as positron emission tomography (CT and magnetic resonance imaging may all be diagnostic but are currently not routinely used in the diagnostic workup for patients with gastric adenocarcinoma.

Staging is most commonly based on the American Joint Committee on Cancer and International Union Against Cancer system that uses a traditional TNM system (Table 1). An eighth edition of this staging system was published in 2017 and was modified from the seventh edition based on Japanese and Korean data from the International Gastric Cancer Association. Compared to the seventh edition, patients with pN0s (0 to 1% regional metastatic nodes) and pN3s (16 or more regional metastatic nodes) were separated into different pathologic TNM stages to further improve the stratification of survival by stage of disease.

MULTIMODALITY THERAPY

Systemic Therapy

Even among patients with early stage disease, recurrence is common following resection alone. Based on several randomized clinical trials, neoadjuvant, adjuvant, and combined (neoadjuvant and adjuvant) systemic therapies are often used, and have been shown to provide a disease free and overall survival benefit. One of the most commonly used systemic therapy regimens originates from the British Medical Research Council's *MAGIC* (Adjuvant Gastric Infusional Chemotherapy) trial. This randomized trial compared perioperative epirubicin, cisplatin, and 5-fluorouracil (5-FU) with surgery alone for patients with stage II/III gastric or esophageal cancer (T3 or greater, N1 or greater). Chemotherapy given in the neoadjuvant setting offers the theoretic benefit of improved patient tolerance to therapy, ability to assess disease response in vivo, tumor downstaging/downstaging, improved resectability rates, and elimination of micrometastatic and asymptomatic disease. In this trial, perioperative chemotherapy resulted in an improvement in both progression-free and overall survival compared with the surgery alone group; however, only 42% of patients in the chemotherapy arm completed the full course of prescribed therapy. More recently, the *FLOT4-AIO* (Haustumoraff and Leucovorin versus Epirubicin, Cisplatin, and Fluorouracil or Capecitabine in Patients with Resectable Gastric or Gastro-esophageal Junction Adenocarcinoma) phase III trial showed an improvement in progression-free and overall survival among patients who received 5-FU, leucovorin, oxaliplatin, and docetaxel chemotherapy regimen versus epirubicin, cisplatin, and 5-FU or epirubicin cisplatin and Xeloda/capecitabine, as well as increased rates of pathologic complete regression, and completion of all intended therapies.

Chemoradiotherapy

In 2001, the Intergroup 0116 trial showed an improved overall and relapse-free survival among patients who received adjuvant 5-FU, leucovorin, and external beam radiation compared with patients who underwent resection alone. This study, however, has been criticized for poor standardization of surgical technique among study centers, with only 10% of patients undergoing a formal D2 lymphadenectomy (see the following section). Opponents of the trial argue that the benefit seen in the chemoradiation group may be due to "inadequate" surgery and suboptimal local control. Furthermore, only 64% of patients were able to complete the chemoradiation regimen because of intolerance and toxicity. To further evaluate the effect of adjuvant chemoradiation, the recently published *CRITICS* (Adjuvant Chemotherapy or Chemoradiotherapy in Resectable Gastric Cancer) trial compared perioperative chemotherapy (epirubicin, cisplatin or oxaliplatin, and capecitabine) versus preoperative chemotherapy (similar to that previously described) and adjuvant chemoradiation (external beam radiation, capecitabine, cisplatin) in patients who underwent curative-intent gastrectomy. The addition of chemoradiotherapy to the perioperative chemotherapy regimen did not improve overall survival. Moreover, roughly 60% of patients completed adjuvant therapy in both groups, potentially emphasizing the importance of neoadjuvant therapy in gastric cancer. Similarly, the *ARTIST* (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial evaluated postoperative chemotherapy (capecitabine and cisplatin) with or without radiation and found no benefit in disease free or overall survival with the addition of adjuvant chemoradiation. A subgroup analysis of patients with nodal metastasis, however, did show an improvement in disease free survival among the patients who received adjuvant radiation.

Targeted Agents

Several targeted therapeutic agents have and are continually being developed for use among patients with advanced gastric cancer. These agents include monoclonal antibodies against PD-1/PD-L1 antibodies (nivolumab, pembrolizumab), anti-HER2 receptor therapy (trastuzumab, pertuzumab), anti-extracellular glomerular filtration rate antibodies (panitumumab), and antivascular endothelial growth factor antibodies (bevacizumab, ramucirumab), and to date have all shown mixed results among patients with advanced gastric cancer.

Surgery

Diagnostic Laparoscopy

As previously stated, a substantial proportion of gastric cancer patients who appear to have organ confined disease based on CT imaging may actually have peritoneal metastases despite a negative CT scan. Currently, diagnostic laparoscopy with biopsy and peritoneal washings for cytology provide the only modality to accurately assess the presence or absence of metastatic peritoneal disease, and has been found to change management in up to 40% of patients. As

TABLE 1 Eighth American Joint Committee on Cancer Staging System for Gastric Adenocarcinoma

Primary tumor	TX	Primary tumor cannot be assessed		
	T0	No evidence of primary tumor		
	Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia		
	T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa		
	T1a	Tumor invades the lamina propria or muscularis mucosae		
	T1b	Tumor invades the submucosa		
	T2	Tumor invades the muscularis propria		
	T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures		
	T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures		
	T4a	Tumor invades the serosa (visceral peritoneum)		
	T4b	Tumor invades adjacent structures/organs		
Regional nodes	NX	Regional lymph node(s) cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Metastasis to one or two regional lymph nodes		
	N2	Metastasis to three to six regional lymph nodes		
	N3	Metastasis to seven or more regional lymph nodes		
	N3a	Metastasis to 7 to 15 regional lymph nodes		
	N3b	Metastasis to 16 or more regional lymph nodes		
Metastasis	M0	No distant metastasis		
	M1	Distant metastasis		
Stage groupings (pathologic)	0	Tis N0 M0	IIIB	T1 N3b M0
	IA	T1 N0 M0		T2 N3b M0
	IB	T1 N1 M0		T3 N3a M0
		T2 N0 M0		T4a N3a M0
	IIA	T1 N2 M0		T4b N1 M0
		T2 N1 M0		T4b N2 M0
		T3 N0 M0	IIIC	T3 N3b M0
	IIB	T1 N2a M0		T4a N3b M0
		T2 N2 M0		T4b N3a M0
		T3 N1 M0		T4b N3b M0
		T4a N0 M0	IV	Any T Any N M1
	IIIA	T2 N2a M0		
		T3 N2 M0		
		T4a N1 M0		
		T4a N2 M0		
		T4b N0 M0		

Modified from Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging Manual, 8th edition. Chicago: Springer; 2017. Used with permission of the American College of Surgeons.

such, diagnostic laparoscopy with cytology is indicated for all patients with a clinical stage T1b or higher.

If cytopathologic evaluation reveals malignant cells (indicating cytologic M1 disease), laparoscopy with cytology may be repeated following the completion of *pre-operative systemic* therapy to assess whether cytologically positive metastatic disease resolves. If no gross or cytologic peritoneal disease remains present, the patient should be treated with curative-intent gastrectomy. However, even in the presence of limited peritoneal disease and no solid organ involvement, recent data suggest an association with survival for resection combined with cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC), as discussed in the following section.

Primary Resection

Complete surgical resection is the only curative therapy for patients with gastric adenocarcinoma. Though no randomized data exist to guide management, retrospective studies suggest that gross margins of 2 to 4 cm are needed to increase the likelihood of microscopically negative margins. Numerous analyses suggest that positive margins independently predict worse outcomes following resection. Currently, National Comprehensive Cancer Network guidelines suggest a minimum gross margin of 4 cm. Management of a microscopically positive margin on final pathology remains controversial because literature evaluating outcomes following resection is limited. Currently chemotherapy, chemoradiation, or resection may be considered in this situation, depending on the type of preoperative therapy received. The extent of stomach

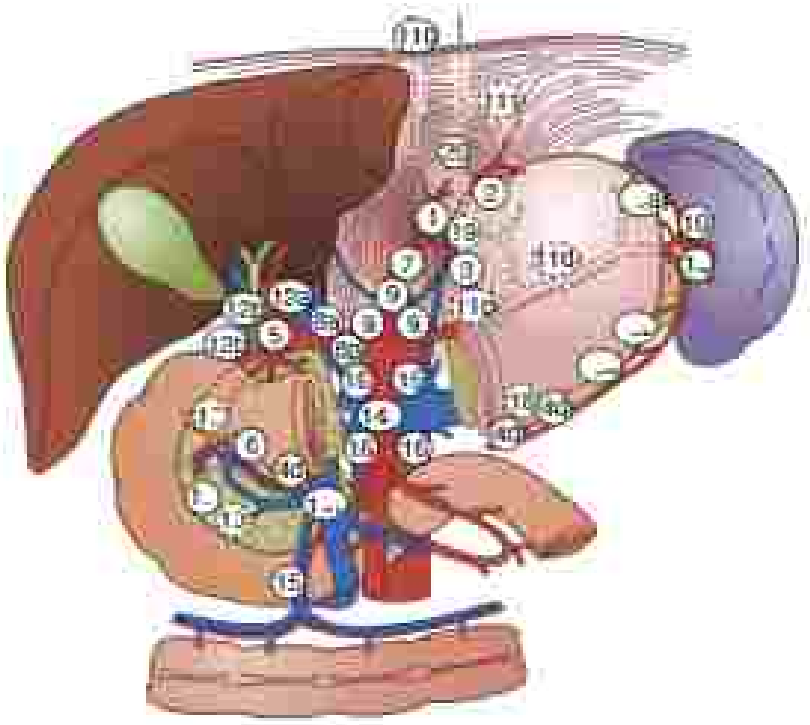

FIG. 1 Distribution of lymph node stations in gastric cancer

resection is determined by tumor location because a total or subtotal gastrectomy may each be used in the appropriate circumstances to achieve a microscopically negative margin. In select cases, consideration may be given to multivisceral resection, if safe and feasible.

Minimally Invasive Approaches

Advances in surgical technique, perioperative care, and operative technique have led to the increasing use of minimally invasive approaches in gastric cancer. Laparoscopic gastrectomy was first reported in 1994. Numerous observational studies and randomized trials have since evaluated the outcomes of laparoscopic and open approaches. In experienced hands, the laparoscopic approach has been reported to result in lower blood loss, quicker return of bowel function, shorter hospital stay, and fewer overall morbidity with comparable rates of operative mortality and total lymph nodes examined, at the expense of prolonged operative times. Although observational data suggest oncologic outcomes are equivalent, several ongoing trials are expected to address this question. The surgeon's level of experience is critical to successful outcomes following laparoscopic gastrectomy because studies suggest that 50 to 60 cases are required before proficiency may be achieved.

Robotic assisted gastrectomy was first reported in Japan in 2003 and has become increasingly used in specialized centers. Advantages of the robotic platform over laparoscopy include a three dimensional camera and magnification for improved visualization, and articulating instruments for improved dexterity and precision. Early literature suggests that in experienced hands, a robotic approach may achieve short term outcomes similar to laparoscopy, at the potential expense of prolonged operative times and increased costs. Current data suggest the learning curve for robotic gastrectomy is 20 to 25 cases in surgeons already proficient with advanced laparoscopy.

Lymphadenectomy

The extent of lymphadenectomy performed at the time of resection remains controversial. A standardized lymphadenectomy for gastric cancer was first published by the Japanese Research Society for Gastric Cancer in 1973 and was translated to English and more widely accepted in 1981. Lymph nodes are classified into 16 stations by their location (Fig. 1). The type of lymphadenectomy performed is defined by the proximity of harvested nodes to the stomach. A D1 lymphadenectomy includes perigastric nodes (stations 1 through 6), whereas a D2 lymphadenectomy also includes stations of the celiac axis (7 through 11), and a D3 lymphadenectomy includes celiac and paraaortic stations (7 through 16). Although a D2 lymphadenectomy was originally described to include a distal pancreatectomy and splenectomy, this led to significantly increased perioperative morbidity and mortality, and has largely been abandoned in favor of pancreas and spleen preserving approaches.

Historically, a more extensive lymphadenectomy has been performed in eastern countries, whereas western countries have favored more conservative approaches. To date, eight randomized trials have evaluated this topic: three comparing a D3 with D2 lymphadenectomy and five comparing D2 with D1 lymphadenectomy. None of the trials evaluating a D3 lymphadenectomy has reported a benefit in overall, disease specific, or disease free survival. Initial reports of trials evaluating a D2 versus D1 lymphadenectomy reported similar long term oncologic outcomes, largely influenced by the increased morbidity associated with pancreatectomy and splenectomy. However, recently published 15 year data from the Dutch Gastric Cancer Trial reported a significantly improved disease specific survival in patients receiving a D2 lymphadenectomy, and these findings have been confirmed by a Cochrane systematic review of published trials to date. Although numerous retrospective studies have reported associations between survival and increased number of resected nodes, these findings may in part be due to a reduction in understaging, or stage migration (i.e., the Will Rogers phenomenon). Currently, National Comprehensive Cancer Network guidelines recommend retrieval of at least 15 lymph nodes.

Operative Technique

Regardless of surgical approach, the core principles of operative technique remain constant. If a minimally invasive technique is planned, pneumoperitoneum is established in the standard fashion, via Hasson or Veress needle technique. For both laparoscopic

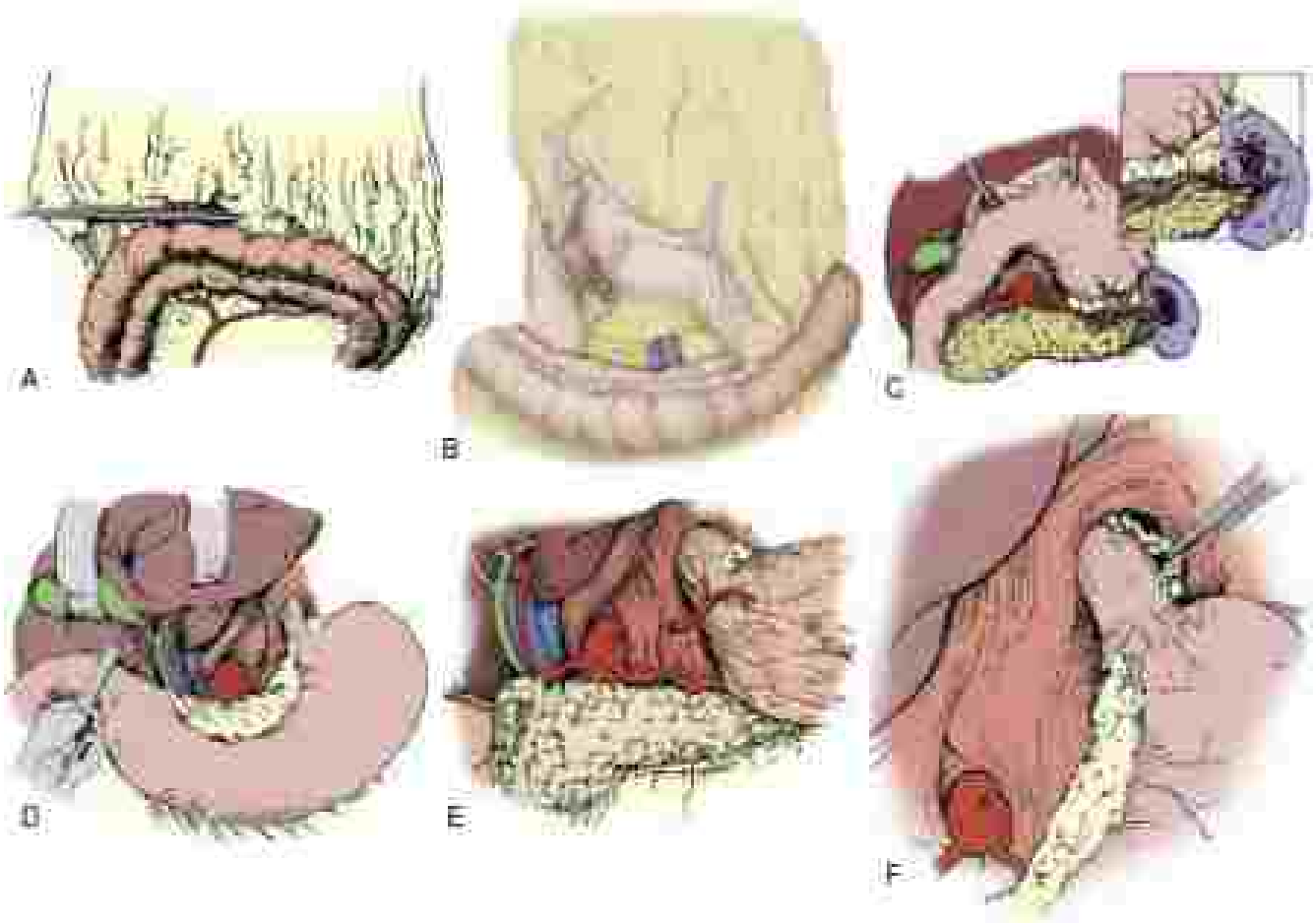

FIG. 2 (A) The avascular plane between the greater omentum and transverse mesocolon is defined. (B) The greater omentum is dissected off the colon along the avascular plane between the anterior and posterior sheaths of the transverse mesocolon. Resection is carried down to the level of the pancreas. (C) The lateral attachments of the stomach and short gastric vessels are divided. First, the splenic artery is dissected along the superior border of the pancreas. Next, these is dissected down to the level of the splenic hilus. (D) The duodenum is identified and divided with the gastrointestinal anastomosis linear stapler. (E) Distal dissection proceeds from the porta hepatis toward the celiac axis along the superior border of the pancreas. The left gastric artery is divided at its origin. (F) Final dissection continues along the right diaphragmatic crus and esophageal hiatus. The left pericardial nodes are taken during total gastrectomy.

and robotic approaches, five ports are most commonly used, with a central umbilical port and two ports right and left of the midline, although the sizes and configurations of ports vary by surgeon and technique.

Any operation should begin with a thorough exploration of the peritoneal cavity to evaluate for metastatic disease. Once the absence of metastatic disease is confirmed, the resection begins with dissection of the greater omentum off the transverse colon (gastrocolic ligament) (Fig. 2). The anterior sheath of the transverse mesocolon is dissected down to the pancreas. Left lateral omental attachments to the abdominal wall, splenic flexure, and spleen are divided, and the short gastric vessels are ligated and divided with ties or an energy device. The superior extent of dissection along the greater curvature toward the left crus is determined by the extent of stomach resection planned. Dissection of the greater omentum is continued rightward, separating the omentum from the hepatic flexure and mesocolon while controlling the gastroepiploic veins, keeping the omentum intact with the specimen. The duodenum is isolated and divided 1 cm distal to the pylorus. The left gastric artery is identified and ligated at the take-off from the celiac axis, and the associated lymph nodes are dissected en bloc with the lesser omentum and stomach, toward the right crus of the diaphragm. For tumors that are distally located on the greater curvature, the left gastric artery may be preserved. The lymph node bearing fibroadipose tissue of the porta hepatis, common hepatic artery, celiac axis, splenic artery, and superior pancreas is dissected, completing a D2 lymphadenectomy.

For a total gastrectomy, the esophagus is encircled and controlled, and the specimen is divided at the gastroesophageal junction. For a subtotal or distal gastrectomy, the stomach is divided transversely with a linear stapler at a site that allows for an adequate proximal margin. Frozen sections of the proximal and distal transection lines may be sent to confirm microscopically clear margins. For a total gastrectomy, gastrointestinal continuity is restored through creation of a Roux-en-Y esophagojejunostomy, often with roux limb of 50 to 60 cm in length to prevent bile reflux gastritis. If a subtotal gastrectomy is performed, reconstruction may be performed via a Roux-en-Y or Billroth II technique. Depending on the nutritional and functional status of the patient as well as any planned postoperative therapy, placement of a feeding tube may be considered.

Heated Intraperitoneal Chemotherapy

Even after curative intent gastrectomy, previous data suggested that patients with cytologic positive M1 disease carry a prognosis similar to patients with other forms of stage IV disease. In recent years,

however, several studies suggest that a select group of patients with limited peritoneal only disease, as well as an absence of solid organ metastasis, may achieve a survival benefit by undergoing aggressive cytoreductive surgery and HIPEC. Following cytoreductive surgery/HIPEC, a complete cytoreduction (minimal to no visible disease remaining) appears to be the most important factor in survival among gastric cancer patients with peritoneal disease. Furthermore, ongoing trials in Asia and Europe have evaluated intraperitoneal chemotherapy in the neoadjuvant and adjuvant settings with promising results.

Palliation

In western countries, one third of all patients with gastric cancer are found to have stage IV disease at the time of initial diagnosis. The prognosis of metastatic gastric cancer is poor, with median survival ranging from 4 months with best supportive care, to 12 months with palliative chemotherapy. As such, the management of this population must be individualized for a patient's symptoms, functional status, and prognosis. In appropriately selected patients, options for management in this population include best supportive care, palliative gastrectomy or bypass, chemoradiation, and systemic therapy.

In metastatic gastric cancer patients with aggressive tumor histology or poor functional status, the focus of care should be on symptom control and optimizing quality of life. Nausea may be addressed with antiemetic medications. Pain should be controlled through a multimodal approach. Bleeding is common and may be treated by endoscopy, angiography, or radiotherapy. Obstructive symptoms may be managed with endoscopic stent placement, venting gastrostomy, or radiotherapy, and, in select patients, palliative gastrectomy or gastrojejunostomy may be considered.

In patients demonstrating favorable tumor biology and good performance status, more aggressive treatments may be offered. Although controversial and subject to selection bias, recent retrospective studies and a systematic review suggest palliative gastrectomy may be associated with improved survival, particularly in younger patients with a single site of metastasis. Chemoradiation may also be considered in select patients who are radiotherapy naïve. Systemic therapeutic options include cytotoxic chemotherapy and targeted agents. Although two-drug chemotherapy combinations are preferred for a lower toxicity profile, three-drug regimens may be considered in medically fit patients with a robust performance status. Frequently used agents include 5-FU or capecitabine, cisplatin or oxaliplatin, docetaxel or paclitaxel, and epirubicin. Targeted agents shown to be effective in advanced gastric cancer include trastuzumab (anti-HER2; Trastuzumab for Gastric Cancer trial), ramucirumab (antivascular endothelial growth factor receptor 2), and panitumumab (anti-EGFR).

SUMMARY

Curative intent resection remains the mainstay of treatment for patients with operative gastric adenocarcinoma. A microscopically negative resection and an extended D2 lymphadenectomy provide the best outcomes for long term survival. Given the aggressive nature of the disease, management of patients with gastric adenocarcinoma necessitates a multidisciplinary approach so optimal treatment may include cytotoxic chemotherapy and possibly radiotherapy and/or targeted agents. Ongoing research will further help define the optimal regimen and timing of systemic therapy in combination with surgical resection in patients with locoregional disease and even limited metastatic disease.

Suggested Readings

Cancer Genome Atlas Research, N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513(7517):202–209.

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Familial Gastric Cancer

Alex B. Blair, MD, and Mark D. Duncan, MD, FACS

Gastric cancer is a common cause of cancer worldwide, with more than 700,000 cancer related deaths yearly. Late diagnosis and limited effective therapeutic options are two prominent causes for a high associated mortality. As with most cancers, gastric adenocarcinoma is most commonly observed as sporadic disease with a multifactorial etiology. Multiple risk factors have been extensively studied, including gastroesophageal reflux disease, obesity, smoking, *Helicobacter pylori* infection, long term inflammation, and smoked foods. In addition to extrinsic environmental factors, emerging evidence supports a growing effect of inherited genetic predispositions in a subset of gastric cancers. *Familial gastric cancer* is a term used to describe families with two first- or second-degree relatives with gastric cancer before the age of 50 years or three first- or second-degree relatives independent of age. This aggregation of disease within families occurs in roughly 10% of gastric cancer cases.

There are many reports of presumed familial gastric cancer from as early as the famed French military leader Napoleon Bonaparte at the turn of the nineteenth century. Napoleon, his grandfather, father, four sisters, and a brother all died of gastric cancer, strongly suggesting familial clustering of disease. In 1998, Guilford *et al.* reported a high incidence of multigenerational diffuse gastric cancer affecting individuals at a young age within the indigenous Māori people of New Zealand. Germline mutations within the gene coding for the calcium dependent E-cadherin cell cell adhesion molecule (CDH1) was identified as a central mutation within this family responsible for their inherited gastric cancers (Fig. 1). A thorough knowledge of the molecular profile specific for familial gastric cancer is useful for clinicians in identifying individuals and family members at high risk who may benefit from early or preventative surgical intervention.

PATHOLOGY OF GASTRIC CANCER

The three most common primary gastric malignancies are adenocarcinoma (90%), lymphoma (4%) and gastrointestinal stromal tumor. Other primary malignancies such as carcinoid, squamous cell carcinoma, and angiosarcoma rarely occur. Gastric adenocarcinomas are then divided into broad histologic subtypes per the Lauren classification: intestinal and diffuse. The intestinal subtype is more commonly associated with extrinsic environmental risk factors and inflammation than the more aggressive diffuse form. Diffuse type

however, several studies suggest that a select group of patients with limited peritoneal only disease, as well as an absence of solid organ metastasis, may achieve a survival benefit by undergoing aggressive cytoreductive surgery and HIPEC. Following cytoreductive surgery/HIPEC, a complete cytoreduction (minimal to no visible disease remaining) appears to be the most important factor in survival among gastric cancer patients with peritoneal disease. Furthermore, ongoing trials in Asia and Europe have evaluated intraperitoneal chemotherapy in the neoadjuvant and adjuvant settings with promising results.

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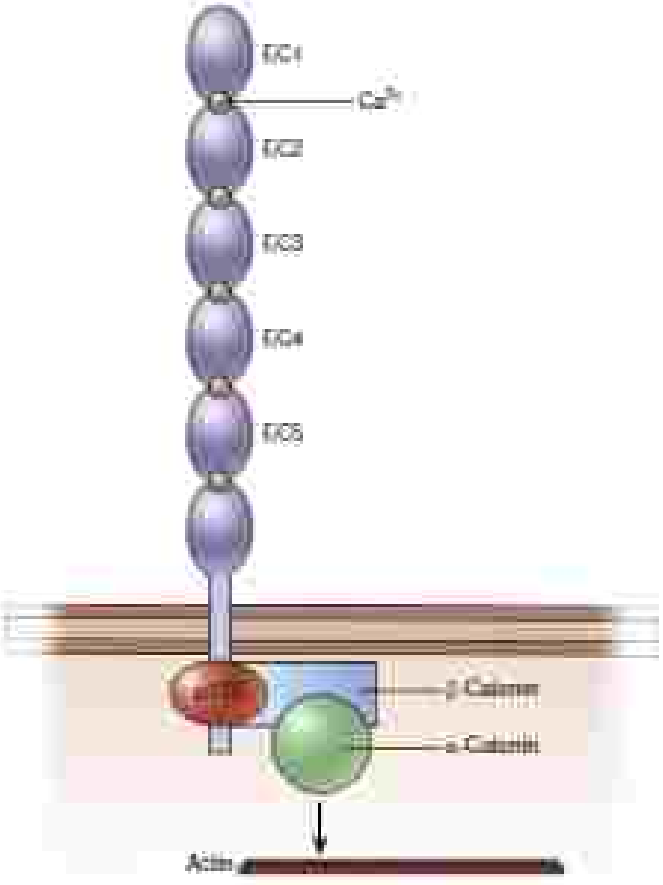

FIG. 1. Loss of E-cadherin gene disrupts cell-cell adhesion.

TABLE 1 Candidate Genes Associated With Familial Gastric Cancer

Associated Syndrome	Candidate Gene
Hereditary diffuse gastric cancer	*CDH1*
Hereditary nonpolyposis colorectal cancer	*MSH2, MLH1*
Li-Fraumeni syndrome	*P53*
Familial adenomatous polyposis	*APC*
MUTYH-associated polyposis	*MUTYH*
Peutz-Jeghers syndrome	*P53, STK11*
Gastric adenocarcinoma and proximal polyposis of the stomach	Unknown

gastric cancer is more likely to be a poorly differentiated, ulcerating, transmural lesion with higher lymphatic spread and is often associated with younger patients.

Genetic alterations are involved in all cancers as normal cells are transformed into a malignant state. A selection of genes is altered and leads to malignant transformation. In the majority of cases, these genes are altered at the tissue level by random errors in cellular processing. A proposed multistep model of carcinogenesis requires the accumulation of additional downstream genetic mutations to achieve the full neoplastic phenotype. Familial syndromes offer an inherited initial hit to this neoplastic process, thus markedly increasing the likelihood of eventual gastric cancer development (Table 1).

BOX 1 International Gastric Cancer Linkage Consortium Criteria for *CDH1* Genetic Testing

- Family with ≥2 or more cases of gastric cancer, with at least 1 being diffuse gastric cancer diagnosed before the age of 50 years
- 1 affected individual diagnosed with diffuse gastric cancer at age <40 years from a low-incidence population
- Personal or family history of both diffuse gastric cancer and lobular breast cancer, with 1 affected person age <50 years at the time of diagnosis
- Three confirmed diffuse gastric cancer cases in first- or second-degree relatives independent of age

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer is an autosomal dominant cancer predisposition syndrome associated with mutations in *CDH1* on chromosome 16q characterized by an increased risk of diffuse gastric cancer and lobular breast carcinoma. This was first identified in two large Maori families in New Zealand. *CDH1* has an important role in cell–cell adhesion; thus, the loss of function increases invasiveness and epithelial to mesenchymal transition. Individuals with a *CDH1* mutation are more likely to develop diffuse, aggressive, signet ring gastric adenocarcinoma and lobular breast carcinoma at an early age.

CDH1 testing is recommended based on the international gastric cancer linkage consortium (IGCLC) (Box 1). Their guidelines suggest testing in (1) patients with two family cases of gastric cancer with at least one being the diffuse subtype before the age of 50 or (2) one case of diffuse gastric cancer in an individual <40 or (3) a personal or family history of gastric cancer and lobular breast cancer in an individual <50 or (4) three confirmed diffuse gastric cancer cases in first- or second-degree relatives independent of ages. The IGCLC recommends against genetic testing in children; therefore, the earliest recommended age is 18, with qualifying asymptomatic family members typically undergoing testing in the second decade and at least 5 years before the earliest age of diagnosed familial gastric cancer. Familial testing is important because penetrance is quite high, with >80% of men and women developing gastric cancer and a 60% probability of developing lobular breast cancer in women. A family pedigree of a young patient with *CDH1* and gastric cancer treated at our institution is shared with their permission (Fig. 2).

An average age of 38 is reported for the development of gastric cancer; therefore, treatment for these individuals extends beyond increased surveillance to recommended prophylactic total gastrectomy. In those that decline surgery, annual endoscopic surveillance is offered starting at age 20 with multiple biopsies of any visible lesion and at least five random biopsies to each of the anatomical zones of the stomach. Unfortunately, endoscopy does a poor job of screening for tumor because of the difficulty identifying early disease of the diffuse gastric cancer subtype, which can infiltrate without endoscopically visual lesions.

Advanced hereditary diffuse gastric cancer presents as poorly differentiated diffuse carcinoma with signet ring cells invading widely and involving the entire thickness of the gastric wall. These ultimately have poor prognosis; thus, early prophylactic intervention is imperative and offered even if the carriers are asymptomatic. Prophylactic gastrectomy is a risk reduction gastrectomy given the high prevalence of microscopic carcinoma. Those that undergo prophylactic gastrectomy have excellent prognosis. The stomach of asymptomatic *CDH1* mutation carriers nearly always seem normal to the naked eye because of an absence of a mass lesion. Following prophylactic gastrectomy, however, close pathologic inspection reveals multiple foci of intramucosal (T1a) diffuse signet ring cell carcinoma ranging from 0.1 to 10 mm to the overwhelming majority of cases. A T1M0 malignancy was found in 92% of patients with *CDH1* mutations in a prospective series of prophylactic total gastrectomy. Of these patients, only 56% had a diagnosis preoperatively despite adequate endoscopic surveillance.

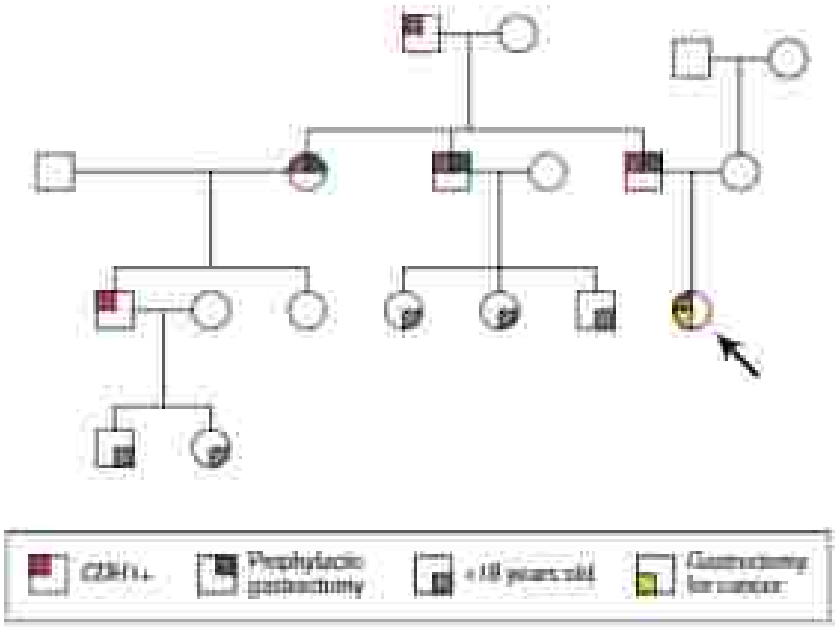

FIG. 2. Family pedigree of CDH1+ gastric cancer patient. The proband (arrow) developed diffuse gastric cancer at age 20 and underwent total gastrectomy at our institution. Subsequently family members underwent genetic counseling and testing with two prophylactic gastrectomies ultimately performed. At 15 yr. 3C months, all postgastrectomy individuals including the proband are alive and cancer free. Pedigree reproduced with patient permission.

Although distal gastric cancer was most common in the initial report of the Maori families, the identified diffuse foci are not restricted to any topographic region of the stomach and can be identified from cardia to the prepyloric region without specific clustering.

Because of the high lifetime risk of also developing lobular breast cancer, women with *CDH1* mutations are also encouraged to undergo yearly mammography and breast magnetic resonance imaging from age 35 onwards. Prophylactic mastectomy may also be an option, although data are insufficient. Although not meeting official IGCLC criteria, genetic testing for *CDH1* should be considered in cases of bilateral lobular breast cancer or a family history of two cases of lobular breast cancer at less than 50 years of age. Because of their shared risk, adequate knowledge of familial gastric cancer syndromes is imperative to not just the gastrointestinal surgeon, but those physicians managing breast malignancy as well. Although a *CDH1* mutation is only identified in 3% to 6% of lobular breast cancer patients, this still represents a significant number of individuals who would be counseled for prophylactic gastrectomy.

Hereditary Nonpolyposis Colorectal Cancer

Henry T. Lynch initially discovered two families predisposed to develop colorectal cancer (CRC) in the 1960s and deemed it hereditary nonpolyposis colorectal cancer (HNPCC). The development of cancers other than CRC, including gastric cancer, has been identified and thus the term Lynch syndrome has gained popularity. This is a highly penetrant, dominantly inherited familial cancer syndrome with a molecular phenotype of DNA microsatellite instability and accumulated DNA mismatch alterations resulting in carcinogenesis in several organs including the colon, rectum, uterus, ovaries, stomach, and hepatobiliary systems. Germline mutations in mismatch repair genes *MSH2* on chromosome 2p and *MLH1* on chromosome 3p cause 90% of the microsatellite instability observed in CRC from HNPCC families and are believed to play a role in inherited gastric cancers.

The Bethesda criteria are used to establish a diagnosis of HNPCC but do not include gastric carcinoma as a defining criterion. The criteria include (1) CRC diagnosed in an individual younger than 50 years of age; (2) presence of synchronous or metachronous CRC or other HNPCC related tumors, irrespective of age; (3) CRC with high microsatellite instability histology diagnosed at less than 60 years of age; (4) individuals with CRC with at least one first degree relative with CRC or HNPCC related tumor diagnosed at less than 50 years of age; and (5) individuals with CRC with at least two first or second degree relatives with CRC or HNPCC related tumor, irrespective of age. If an individual meets these criteria, they are referred for molecular and immunohistochemical testing for microsatellite instability because some individuals may meet the clinical criteria but are microsatellite stable on testing, which is an exclusionary characteristic.

Gastric cancer is found in carriers of Lynch syndrome at approximately 4% to 8% in patients with mutations in *MLH1* and 9% in those with mutations in *MSH2*. Gastric cancer with HNPCC is more commonly intestinal than the diffuse histologic subtype. Surveillance is recommended with upper gastrointestinal screening in individuals with HNPCC for whom a family history of gastric cancer is present or carriers of the *MLH1* or *MSH2* gene. Eradication of *H. pylori* infection in HNPCC patients is important to help reduce additional carcinogenic risk factors. Similar to familial adenomatous polyposis (FAP) and MUTYH associated polyposis (MAP), there is not a role for prophylactic gastrectomy and surgical intervention is restricted to the presence of confirmed gastric cancer.

Li-Fraumeni Syndrome

The gene *TP53* on chromosome 17p is a commonly studied tumor suppressor gene in many types of cancer. DNA damage to normal cells results in *TP53* mediated arrest and cell apoptosis; however, knock out of *TP53* prevents this and permits malignant transformation. Deletion or suppression of *TP53* is the most common genetic abnormalities found in more than two thirds of both inherited and noninherited forms of gastric cancer. Li Fraumeni syndrome (LFS) is associated with *TP53* mutations, thus encompassing several tumor types that generally develop before age 45 years. Malignancy risk with this mutation includes sarcoma, breast carcinoma, leukemia, and other neoplasms. Sarcoma before 45 years of age plus a first degree relative with cancer before this same age or another first or second degree relative with any cancer before this age or relative in this age with sarcoma at any age are the defining criteria of LFS. Gastric carcinoma is reported in 3% to 3% of LFS carriers and reported as early as 12 years of age with a median age of diagnosis of 36 years. Forty percent of families with *TP53* mutations present with at least one gastric cancer at ages significantly younger than sporadic gastric cancer.

The phenotypic diversity of LES complicates effective screening strategies. Periodic screening gastroscopy of LES carriers with at least one family member affected by gastric cancer should be considered. Early onset screening should be initiated at an early age.

Polyp-Associated Gastric Cancer Syndromes

Familial gastric cancer syndromes can be subclassified broadly into those prominently associated with polyps and those without. Benign neoplasms and polyps of the gastric mucosa are made up of multiple components including adenomatous, fundic gland, hyperplastic, inflammatory, and hamartomatous polyps. In general, the inflammatory, hyperplastic and hamartomatous polyps are considered benign, although occasionally malignant potential is appreciated. Gastric adenomatous polyps and fundic gland polyps are uncommon outside of familial syndromes and are more likely to behave as premalignant lesions. Despite displaying relatively modest rates of neoplastic development, these subsets of polyps are associated with a significantly increased life time risk of developing gastric adenocarcinoma and are thus approached with greater caution. A number of inherited cancer syndromes are characterized by a higher frequency of these polypoid lesions yielding an increased risk of gastric cancer.

FAP

FAP is an autosomal dominant disorder associated with the inactivation of the *APC* gene on chromosome 5q. APC is a gatekeeper gene for chromosomal instability and has many roles in development and carcinogenesis. Polyposis is a prominent phenotypic of this inherited mutation with more than 100 colonic and rectal adenomatous polyps a defining criterion. Adenomatous polyps are also manifested in the upper gastrointestinal tract in 50% to 80% of FAP cases. Gastric polyposis (>20 gastric polyps) may also be identified. In cases of gastric polyposis, the polyps are predominately located in the body/fundus, with adenomatous change most frequently identified near the body/antrum junction. Of interest, fundic gland polyps are more frequently observed in patients with attenuated FAP or confirmed *APC* mutation with less than 100 colonic polyps and later CRC disease onset. Although the overall risk of carcinoma is low (2%), individuals with familial polyposis have a much higher incidence of harboring dysplasia than sporadic gastric polyps (25%–40% vs <1%), with dysplasia risk directly proportional to polyp size. Dysplasia can be found in both adenomatous polyps and fundic gland polyps.

FAP patients are recommended to undergo prophylactic total proctocolectomy with ileal pouch anal anastomosis because of the high penetrance of early CRC cancer. No standard guidelines currently exist for gastric surveillance. The age of gastric manifestations is variable in FAP patients, although gastric adenocarcinoma is typically developed long after their colectomy. Current data suggest upper endoscopy initiated at 25 to 30 years of age and performed at intervals of 3 to 5 years with a decreased interval following finding of adenomatous polyps or dysplasia. Polyps larger than 1 cm should be removed to confirm the diagnosis and diminish the risk of malignant degeneration. If dysplasia is identified, low grade dysplasia is most common and the overall risk of carcinoma is low. Surgical intervention is typically reserved for patients with severe polyposis causing symptoms (i.e., bleeding) or in the case of confirmed malignancy on endoscopy. Hence, Prophylactic gastrectomy can be discussed for patients with FAP or attenuated FAP and displaying diffuse fundic gland polyps, large, or high grade dysplasia polyps.

MAP

MAP is an autosomal recessive polyposis syndrome phenotypically similar to attenuated FAP but demonstrating wild type APC. Mutations are identified in the *MUTYH* gene at chromosome 1p, a DNA glycosylase that excises misincorporated bases from DNA damage. Thus, loss of this protein function results in increased accumulation of DNA damage. Similar to FAP, MAP predominately affects the colon, but is also associated with CRC, breast, ovary, skin, and bladder carcinomas.

Gastric polyps are noted in just 11% of MAP cases at a median age of diagnosis of 49 years. These polyps include both adenomas and fundic polyps. The risk of cancer in these polyps is low, seen in just 2% of cases but diagnosed at a median age of 38. Duodenal polyps and malignancy are observed at higher rates, with malignancy in 12% of cases.

Endoscopic surveillance is the mainstay of treatment. Surveillance guidelines for families with MAP recommend upper endoscopy at age 25 to 30 years and then subsequently at intervals of 3 to 5 years. Screening and testing in minors are not recommended because of the low risk of gastric conversion to malignancy. Surgical intervention is reserved for cases of confirmed malignancy or symptomatic polyps. In patients with FAP or MAP, there is a significant risk of duodenal polyps and malignancy and thus continued surveillance following resection is required. Consideration of duodenal surveillance is prudent when undertaking reconstruction after gastrectomy in these patients. The authors have recommended a wider Roux en Y anastomosis with a deliberately shorter biliary pancreatic limb to facilitate subsequent endoscopic surveillance of the duodenal stump. We recognize this may lead to increased risk of bile reflux.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by an association of multiple hamartomatous gastrointestinal polyps with mucocutaneous pigmentation and increased cancer risk, particularly for gastrointestinal and breast cancers. Polyps are found throughout the gastrointestinal tract, most commonly in the small bowel, colon, and stomach (70%, 80%, 69%, and 25%, respectively). Gastric polyps can involve the antrum and pylorus and can grow to large sizes, mimicking carcinoma. Because of their size, these polyps are occasionally associated with symptoms including bleeding, abdominal pain, intussusception, and even obstruction.

PJS is associated with *STK11* on chromosome 19p. Seventy percent of individuals with PJS also have germline mutations of the tumor suppressor gene *STK11* on chromosome 19p, providing a potential secondary driver for the typically benign hamartomas to the progression of adenocarcinoma. The role of these genes as initiators of gastric cancer is poorly defined but the association of gastric polyps and cancers implicates a potential role. Individuals with *STK11* mutations are more likely to develop gastric polyps and malignancies than the wild type counterparts. Gastric polyps are reported as early as 2 years of age with a median age of onset of just 16 years. Despite these early findings, gastric carcinoma transformation is rare and usually develops slowly after a long latency period of greater than 20 years. As a whole, gastric cancer is reported in 2% to 3% of Peutz-Jeghers families at a median age of approximately 40 years. Individuals with PJS are also at increased risk of developing cancer in multiple locations including the pancreas, breast, uterus, cervix, testis, ovary, and lung.

Because of their young age of development, endoscopic surveillance should be initiated early, with baseline endoscopy as early as 8 years with screening interval tailored based on the findings of the first endoscopy. In the absence of polyps, screening is reinitiated at 18 years of age with more rigorous yearly screening after the age of 30. Surgical intervention is uncommon and reserved for a confirmed finding of gastric cancer or symptomatic polyps refractory to conservative treatments.

GASTRIC ADENOCARCINOMA AND PROXIMAL POLYPOSIS OF THE STOMACH

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal dominant syndrome with incomplete penetrance. The precise associated genetic mutation remains unknown at this time. Although FAP and MAP are defined primarily by their

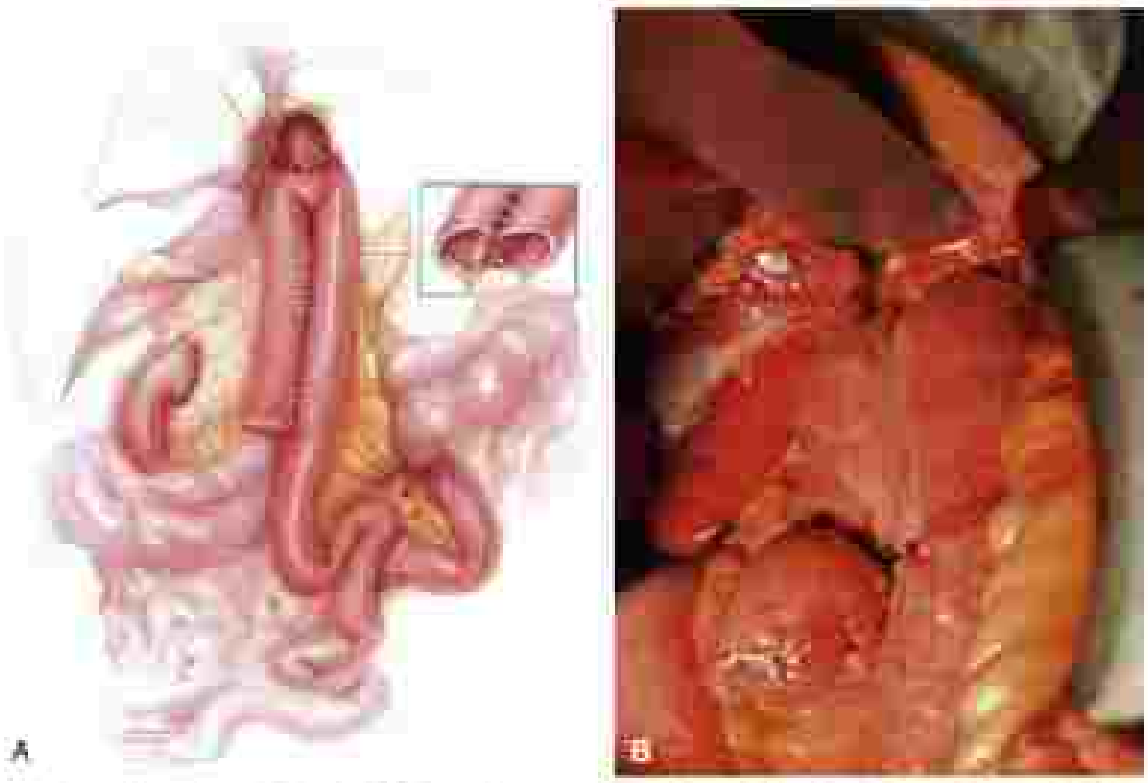

FIG. 3 Reconstruction and formation of jejunal pouch following total gastrectomy (from Cameron JL, Sandler C, Pitt HA, et al. Gastrointestinal Surgery, 6th ed. Philadelphia, PA: Elsevier; 2020).

CBC phenotype. GAPPS is associated with fundic gland polyposis with more than 100 polyps carpeting the proximal stomach while sparing the antrum, duodenum, and colon. Exclusion of other hereditable gastric polyposis syndromes and the use of proton pump inhibitors (which can induce benign gastric polyp formation) is necessary to confirm the diagnosis of this syndrome. GAPPS can also be diagnosed in cases of more than 30 gastric polyps in a first degree relative of another case. These polyps are predominately smaller than 1 cm and typically spare the lesser curvature of the stomach. Occasional hyperplastic and adenomatous polyps can be detected, although fundic gastric polyps represent the majority. These polyps can also display dysplasia and the development of intestinal type gastric adenocarcinoma. Dysplastic lesions have been described in those affected individuals as young as age 10, with adenocarcinoma occurring as early as age 30 years. Endoscopic surveillance can prove to be challenging with the large number of polyps and thus prophylactic gastrectomy should be considered. Considerations for gastrectomy timing are based on the limitations of endoscopic surveillance and patient specific risk of morbidity with prophylactic surgery.

Surgical Intervention

In patients with familial cancer predisposition syndromes in which gastric cancer is identified, surgical resection offers the only curative treatment. Initial workup is similar to that described in the previous gastric adenocarcinoma chapter. In short, following dedicated staging and patient selection, operative intervention is pursued with a goal for complete resection with margins of at least 5 cm from gross tumor. The most important prognostic indicators are lymph node involvement and depth of tumor invasion. The diffuse type are more common in familial gastric cancer; this histologic subtype is quite infiltrative and the cells can extend well beyond the tumor mass, thus margins beyond 5cm are typically recommended with frozen sections to confirm complete extirpation. More than 15 resected nodes are necessary for adequate staging, and a D2 or extended lymphadenectomy is then performed.

Prophylactic total gastrectomy is recommended for patients with *CDH1* mutations and other select familial cancer predisposition patients. The entire stomach must be excised to remove all at risk tissue. With total gastrectomy, we recommend the formation of an intestinal pouch if anatomically permitted (Fig. 3). This, in our opinion, leads to improved functioning in both the short and long term. The pouch functions as a reservoir, and ultimately, many patients eat almost normally (Fig. 4). Total gastrectomy should ideally be performed at high-volume centers with achievable low perioperative mortality rates, especially in these prophylactic patients. Radical lymph node dissection is not deemed necessary when gastrectomy is performed for prophylaxis, as lymph node metastases are highly unlikely. A D1 lymphadenectomy is considered adequate. Prophylactic gastrectomy can be performed laparoscopically or via a small upper midline incision based on the surgeon's preference, taking into consideration comfort with constructing an intestinal pouch.

Timing of prophylactic gastrectomy must be discussed in detail with at risk patients because personal preferences, family history, and age of diagnosis with cancer in relatives will all affect the decision. Because approximately 5% of clinically diagnosed diffuse gastric cancer in *CDH1* carriers occurs before the age of 30, preventive gastrectomy is typically recommended before the age of 30 in patients with *CDH1* mutations and at least 5 to 10 years before earliest age of gastric cancer in relatives.

Postoperative Physiologic Recovery

Although offering a cure, treatment is not completed with the surgical extirpation of disease. Physiologic postsurgical recovery must be taken into consideration. This important part of the surgical patient experience includes eating difficulty, weight loss, and potential postoperative complications and infections. Within the first month, all patients have difficulty with eating; thus, appropriate expectations of initial postoperative difficulties are imperative. It is not uncommon for these initial struggles to be associated with "buyer's remorse" in patients having prophylactic surgery who are normally without

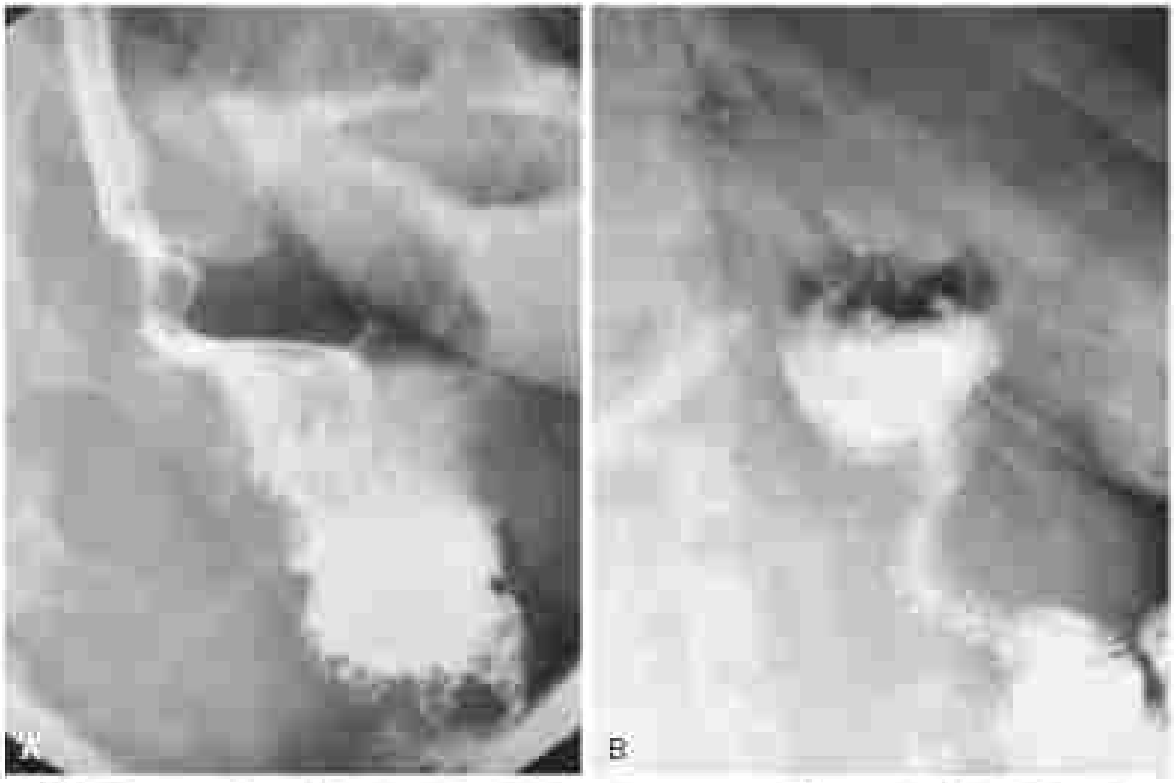

FIG. 4 Contrast swallow study in patient with prophylactic total gastrectomy now dilatory capacity of an inverted pouch.

symptoms and had no clinical disease. It is important to include a nutritionist in the treatment team counselling patients. Fortunately, there is usually improvement, particularly in the first 4 months but continuing throughout the first year. In our institutional series of prophylactic resections for *CDH1*, an initial 6-month weight loss of 12.5 kg was noted, which remained stable at 1 year. The majority of patients are eating well at 1 year and some patients report completely normal long term eating, including weight gain.

Gastric surgery changes how the stomach and intestines work, with different amounts and types of foods potentially causing nausea, diarrhea, or other symptoms. Dietary modifications and vitamin supplementation are necessary to maximize postoperative function and patient experience. Eating approximately six small meals and snacks throughout the day and drinking 30 to 60 minutes after, instead of with meals, can greatly improve tolerance. In the early postoperative period, our nutritionists recommend that meals should be made up of tender, soft, well cooked foods, high in protein and prepared without added fat. Foods high in sugar content, caffeine, dried beans, nuts, raw vegetables, and raw fruits should be limited, or avoided if particularly problematic. In patients who are doing better, a more liberal approach of eating smaller amounts of their own typical diet generally works well.

Because of changes in absorption, additional supplementation is necessary to meet daily requirements. This includes taking one to two multivitamins (including vitamin E) daily to provide iron, folic acid, thiamine, trace elements, and calcium. Calcium can be included in the multivitamin, or calcium citrate may be preferred at 1500 mg per day divided in three doses. Chewable and liquid vitamins are absorbed better than swallowed capsule or gummy forms. Vitamin B12 absorption is affected through loss of intrinsic factor, thus patients need regular supplementation after gastrectomy. This can be given either as a daily pill (1000 μg sublingually), or as a monthly injection (1000 μg intramuscularly), or rarely as a nasal spray (500 μg) weekly.

Other Malignancy Risks

It is crucial to recognize that gastric cancer is not the only malignancy with increased observed frequency for the majority of these syndromes and genetic mutations. For example, it is well recognized that HPNCC is associated with increased risks of colon cancer and thus appropriate colonoscopic surveillance is necessary. As previously mentioned, a *CDH1* mutation is associated with high rates of lobular breast cancer in women. It is important to identify these other malignancy risks on both sides of presentation and appropriately monitor and prevent malignancy of all types.

Appropriate Family Testing

Finally, these discussed syndromes are all inherited disorders, meaning the index patients directly cared for are not the only ones at risk. Appropriate genetic testing for family members is necessary to ensure that preventive care and surveillance are offered to all at risk. Genetic counseling is highly encouraged. Genetic counselors, working as part of the health care team, present and explain the often complex and confusing information about genetic risks, testing, and diagnoses. They also serve as patient advocates offering both pre- and positive counselling services to prepare patients and their families for testing results and implications. The advent of new, fast, and inexpensive, massive, parallel sequencing technologies is expected to increase the identification of potential oncogenes. With the growing availability and performance of genetic testing, mutations such as *CDH1* may be identified incidentally on a multigene panel in an individual without a relevant history of gastric cancer or lobular breast cancer. The true risks of these incidentally identified mutations are unknown. It is difficult to know the best recommendations; however, close surveillance is warranted and offering prophylactic surgery to appropriate candidates is reasonable.

As our understanding of familial gastric cancer and the associated putative genes improves, more at-risk patients will be identified earlier with an opportunity to offer surgical prevention of cancer.

Suggested Readings

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Management of Gastrointestinal Stromal Tumors

Michael G. Heinz, MD, FACS

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract and the most common sarcoma subtype overall; thus, a general surgeon should be familiar with the unique principles of management for this disease. Knowledge of the pathophysiology of GISTs has advanced rapidly over the past 2 decades. The cell of origin for GIST is the interstitial cell of Cajal, and in most cases, development of tumor appears to require oncogenic activation of a tyrosine kinase. Approximately 75% of GISTs bear activating mutations in *KIT*, with *PDGFRα* mutated in another 10%. The remaining group of wild-type *KIT* GISTs has continued to shrink because alterations have been discovered in *BRAF* and *NF1* genes in other patients. Since the description of a gain of function mutation in the *KIT* proto-oncogene in 1998, targeted therapy against GIST has been studied extensively. Imatinib mesylate (Gleevec), a tyrosine kinase inhibitor (TKI) of ABL, BCR-ABL, *KIT*, and platelet-derived growth factor receptor (PDGFR), has become a major component in the multidisciplinary management of patients with GIST.

Treatment of GIST with imatinib has been studied extensively. In patients with metastatic disease, imatinib prolongs median survival to more than 5 years from a historical median of 18 months. In the adjuvant setting, imatinib prolongs recurrence-free survival (RFS), and neoadjuvant imatinib therapy may improve resectability for tumors that are locally advanced or located in anatomically difficult areas (e.g., pelvis). Neoadjuvant imatinib may also downsize a tumor to permit an organ-preserving resection. Imatinib therapy has also expanded the role of surgical therapy for metastatic GIST. The ability to estimate the risk of recurrence in GIST patients increasingly is refined. In addition to traditional stratification using tumor size, mitotic index, and organ site, specific mutations in *KIT* have a significant bearing on tumor behavior and sensitivity to TKIs. Although targeted therapy plays a major role in the management of patients with GIST, surgery remains the only potentially curative therapy for GIST.

CLINICAL PRESENTATION

GIST is typically a disease of adults, with a median presenting age of approximately 60 years, with a slight male predominance. The incidence of GIST is estimated to be approximately 6000 new cases per year in the United States. According to autopsy studies, the incidence of occult micro GISTs, smaller than 1 cm, is much higher. Although GIST may arise anywhere from the esophagus to the rectum, the stomach is the most common site (~50%), followed by small bowel (25% to 35%). The majority of small bowel tumors are found in the jejunum and ileum, with a minority (<10%) arising in the duodenum. Rare sites of GIST include the rectum, colon, esophagus, and extraintestinal/indeterminate locations. The median size of GIST at presentation is 5 to 7 cm, although tumors may grow to excess of 30 cm. GISTs may produce clinical symptoms (e.g., early satiety, nausea, weight loss, postprandial pressure, bloat) induced by a large space occupying tumor. Often, GISTs are discovered incidentally by endoscopy or imaging during the workup for other conditions or at the time of unrelated surgery. Patients with large GISTs may experience pain or a palpable mass. Although GIST is not a mucosa-based tumor and grows from the muscular layer of the gut wall, it still may be accompanied by occult or overt gastrointestinal bleeding in up to one-quarter of patients as a result of direct tumor erosion of the underlying mucosa. Careful endoscopy is necessary to reveal small punctate areas of mucosal ulceration resulting from GIST. Bleeding from tumor rupture into the peritoneal cavity is rare, but is a negative prognostic factor and may lead to life-threatening hemorrhage. Metastasis typically involves the liver or peritoneal cavity. Lymph node involvement, occurring less than 5% of patients, is rare in adult GIST and usually reflects direct tumor extension.

Pediatric GIST, often associated with succinate dehydrogenase deficiency, exhibits a different biology compared with adult GIST. This disease is indolent and shows female predominance with multifocal disease, frequent lymph node metastasis, and imatinib resistance. Familial GIST involving germline mutation of *KIT* or *PDGFRα* mutations is rare. Typically, the tumors are multifocal and indolent. GIST can occur rarely in association with the Carney triadakis syndrome (GIST and paraganglioma), Carney's triad (GIST, paraganglioma, and pulmonary chondroma), or neurofibromatosis type 1 (GIST, neurofibroma, glioma, and malignant peripheral nerve sheath tumor).

Workup

Computed tomography (CT) of the abdomen and pelvis with oral and intravenous contrast is the imaging test of choice for the initial evaluation of GIST. A typical GIST appears as an enhancing mass arising in the wall of the stomach or intestine. GISTs may be grossly categorized as exophytic, endophytic, or mixed dumbbell shape (Fig. 1). Large masses may exhibit heterogeneous enhancement resulting from necrosis or areas within the tumor. Small GISTs may not be visible on CT, depending on the distention of the bowel or stomach and whether oral contrast was administered. A large hypervascular GIST arising from the lesser curvature of the stomach may be misinterpreted as a primary liver tumor. Determining whether adjacent structures are involved by large tumors can be difficult because of a loss of plane interfaces on CT; however, most GISTs are found to be mobile

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Treatment of GIST with imatinib has been studied extensively. In patients with metastatic disease, imatinib prolongs median survival to more than 5 years from a historical median of 18 months. In the adjuvant setting, imatinib prolongs recurrence-free survival (RFS), and neoadjuvant imatinib therapy may improve resectability for tumors that are locally advanced or located in anatomically difficult areas (e.g., pelvis). Neoadjuvant imatinib may also downsize a tumor to permit an organ-preserving resection. Imatinib therapy has also expanded the role of surgical therapy for metastatic GIST. The ability to estimate the risk of recurrence in GIST patients increasingly is refined. In addition to traditional stratification using tumor size, mitotic index, and organ site, specific mutations in *KIT* have a significant bearing on tumor behavior and sensitivity to TKIs. Although targeted therapy plays a major role in the management of patients with GIST, surgery remains the only potentially curative therapy for GIST.

CLINICAL PRESENTATION

GIST is typically a disease of adults, with a median presenting age of approximately 60 years, with a slight male predominance. The incidence of GIST is estimated to be approximately 6500 new cases per year in the United States. According to autopsy studies, the incidence of occult micro GISTs, smaller than 1 cm, is much higher. Although GIST may arise anywhere from the esophagus to the rectum, the stomach is the most common site (~50%), followed by small bowel (25% to 35%). The majority of small bowel tumors are found in the jejunum and ileum, with a minority (<10%) arising in the duodenum. Rare sites of GIST include the rectum, colon, esophagus, and extraintestinal/indeterminate locations. The median size of GIST at presentation is 5 to 7 cm, although tumors may grow to excess of 30 cm. GISTs may produce clinical symptoms (e.g., early satiety, nausea, weight loss, postprandial pressure, bloat) induced by a large space occupying tumor. Often, GISTs are discovered incidentally by endoscopy or imaging during the workup for other conditions or at the time of unrelated surgery. Patients with large GISTs may experience pain or a palpable mass. Although GIST is not a mucosa-based tumor and grows from the muscular layer of the gut wall, it still may be accompanied by occult or overt gastrointestinal bleeding in up to one-quarter of patients as a result of direct tumor erosion of the underlying mucosa. Careful endoscopy is necessary to reveal small punctate areas of mucosal ulceration resulting from GIST. Bleeding from tumor rupture into the peritoneal cavity is rare, but is a negative prognostic factor and may lead to life-threatening hemorrhage. Metastasis typically involves the liver or peritoneal cavity. Lymph node involvement, occurring less than 5% of patients, is rare in adult GIST and usually reflects direct tumor extension.

Pediatric GIST, often associated with succinate dehydrogenase deficiency, exhibits a different biology compared with adult GIST. This disease is indolent and shows female predominance with multifocal disease, frequent lymph node metastasis, and imatinib resistance. Familial GIST involving germline mutation of *KIT* or *PDGFRα* mutations is rare. Typically, the tumors are multifocal and indolent. GIST can occur rarely in association with the Carney triadakis syndrome (GIST and paraganglioma), Carney's triad (GIST, paraganglioma, and pulmonary chondroma), or neurofibromatosis type 1 (GIST, neurofibroma, glioma, and malignant peripheral nerve sheath tumor).

Workup

Computed tomography (CT) of the abdomen and pelvis with oral and intravenous contrast is the imaging test of choice for the initial evaluation of GIST. A typical GIST appears as an enhancing mass arising in the wall of the stomach or intestine. GISTs may be grossly categorized as exophytic, endophytic, or mixed dumbbell shape (Fig. 1). Large masses may exhibit heterogeneous enhancement resulting from necrosis of areas within the tumor. Small GISTs may not be visible on CT, depending on the distention of the bowel or stomach and whether oral contrast was administered. A large hypervascular GIST arising from the lesser curvature of the stomach may be misinterpreted as a primary liver tumor. Determining whether adjacent structures are involved by large tumors can be difficult because of a loss of plane interfaces on CT; however, most GISTs are found to be mobile

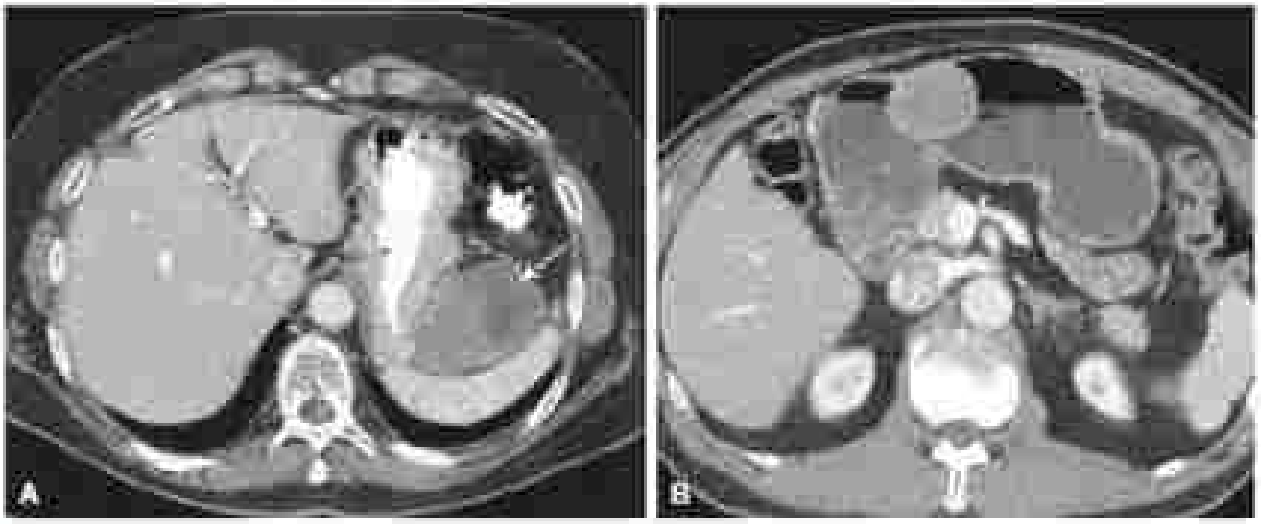


FIG. 1 Contrast-enhanced computed tomography scan of a patient with a gastrointestinal stromal tumor (GIST). (A) The most common appearance on neoplastic on axial imaging. (B) Endophytic GISTs of the stomach are less common but may be associated with higher rates of intestinal erosion and bleeding.

at the time of operation and do not require multivisceral resection. Although GISTs are typically glucose avid on [^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography, this test is not necessary in the initial evaluation and should be reserved for assessment of metastatic disease when there is heterogeneity of response to TKIs.

Some GISTs are detected initially by endoscopic evaluation by the presence of a submucosal mass or a small punctate mucosal ulceration. Endoscopic ultrasound with fine needle aspiration (FNA) is highly sensitive and will reveal a population of spindle cells that stain positive for CD117 (KIT) on immunohistochemistry. Endoscopic ultrasound FNA may help differentiate GIST from other tumors involving the stomach or duodenum such as leiomyoma, lymphoma, or adenocarcinoma that would require different treatment considerations. For indeterminate tumors that would require potentially morbid operations (e.g., tumors involving the gastroesophageal junction, periampullary duodenum, or rectum), several biopsy attempts to establish an accurate diagnosis may be necessary to recommend the optimal sequence of intended treatments with resection and targeted therapy. If the radiologic appearance of a tumor involving the stomach or small bowel is typical of GIST, biopsy is not necessarily required. Percutaneous biopsy of a small bowel GIST is never recommended as it risks peritoneal dissemination.

Risk Stratification

Three clinicopathologic parameters have been shown to independently predict risk of recurrence after complete resection of primary GIST: tumor size, mitotic rate, and tumor site. Size greater than 5 cm; tumors larger than 5/50 high powered fields; and nongastric site are poor prognostic variables. Several different risk stratification systems have been developed based on these variables (Table 1). A nomogram that incorporates all three criteria (Fig. 2) provides an individualized estimate of 3- and 5-year RFS after complete resection of a primary GIST and can provide selection criteria for adjuvant imatinib.

Identification of the specific *KIT* or other gene (e.g., *PDGFR*, *SDH*) mutation in GIST, either after resection or even preoperatively from FNA cytopathology, provides useful information regarding responsiveness to targeted therapy and progression free survival after resection. Specific mutations are associated with tumor biology and most importantly tumor response to imatinib therapy. Three-quarters of tumors harbor a *KIT* mutation, and mutations of exon 11 are the most common, encompassing 67% of all GISTs. Among exon 11 mutations, codons 557 and 558 are hot spots for mutation, and tumors with deletions of this part of the gene are more likely to metastasize or recur as compared with point mutations or insertions in this area. *KIT* exon 9 mutations (about 10% of all GISTs) typically arise in nongastric tumors and carry unfavorable biology. Meta-analysis of two large trials of imatinib in metastatic unresectable GIST showed that patients with exon 9 mutations require higher dose imatinib for response (800 mg vs 400 mg daily). PDGFRα mutant tumors, representing 10% of GISTs, are almost always gastric based and display comparably indolent biology. However, the most common PDGFRα mutation to exon 18 (D842V) imparts imatinib resistance.

SURGERY FOR PRIMARY DISEASE

Indications

Resection is the mainstay of treatment for the majority of patients with GISTs. National Comprehensive Cancer Network guidelines recommend that GISTs larger than 2 cm *should* be resected in patients who are *otherwise* acceptable candidates for surgery. Asymptomatic, uncomplicated small GISTs smaller than 2 cm may be observed with surveillance imaging.

General Technical Aspects

At the time of surgical exploration, whether open or laparoscopic, the peritoneal surface and liver should be surveyed for metastatic disease. Exophytic anterior and greater curvature gastric tumors are immediately apparent. Posterior gastric tumors require mobilization of the stomach, which is facilitated by retracting the left lobe of the liver to the right and entering the lesser sac thru the greater omentum or gastrocolic ligament. Small intramural, or intraluminal gastric tumors that are not easily identified externally during laparoscopy, can be localized with intraoperative endoscopy with a gastroscope. Duodenal tumors beyond the first portion require an extensive Kocher maneuver and possibly mobilization of the ligament of Treitz. Ileal and jejunal tumors are identified best by carefully running the small bowel from the ligament of Treitz to the terminal ileum.

After the primary tumor is identified, all manipulations should be done with great care because these tumors are friable, especially after neoadjuvant treatment. During laparoscopic surgery, manipulation is achieved best by handling only tissue adjacent to the tumor (i.e., no touch technique). Tumor rupture, whether spontaneous or iatrogenic, is associated with almost inevitable peritoneal recurrence. Likewise, GISTs recruit large arterial and venous collateral blood

TABLE 1 Risk Classification for Primary GIST According to Mitotic Index, Tumor Size, and Tumor Site

Tumor Parameters			Risk of Disease Progression (% of Patients)		
Mitotic Index	Size	Stomach	Duodenum	Jejunum or Ileum	Rectum
≤5 per 50 HPF	≤2 cm	None	None	None	None
	>2 to ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.3%)
	>5 to ≤10 cm	Low (3.4%)	Insufficient data	Moderate (24%)	Insufficient data
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None	Insufficient data	High	High (54%)
	>2 to ≤5 cm	Moderate (3.4%)	High (50%)	High (73%)	High (52%)
	>5 to ≤10 cm	High (52%)	Insufficient data	High	Insufficient data
	>10 cm	High (85%)	High (86%)	High (90%)	High (71%)

Data based on long-term follow-up of 1055 patients, 629 small intestinal, 144 duodenal, and 111 rectal (1.8%).
GIST, gastrointestinal stromal tumor; HPF, high-powered field.
From Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23(2):70–83.

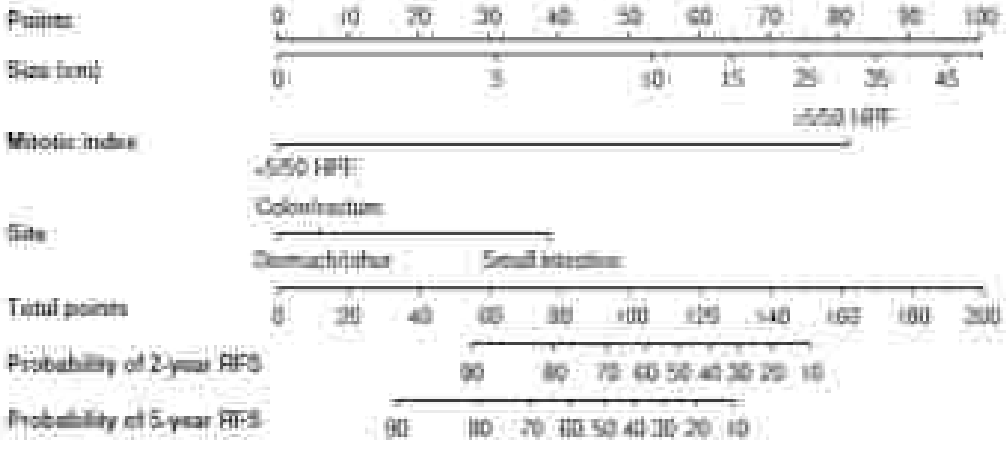


FIG. 2 Nomogram for predicting 2- and 5-year recurrence-free survival (RFS) after resection of primary gastrointestinal stromal tumor. Points are assigned based on tumor size, mitotic index, and site by drawing a vertical line from each row to the "points" row. The sum is then located in the "total points" row, and a vertical line is drawn to the "probability" rows to estimate RFS. HPF, high-powered field. (Modified from Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009;10(11):1045–1052.)

wounds, and careful dissection is required to prevent the potential for significant blood loss. During laparoscopic surgery, retrieval of the specimen should be done with a plastic specimen retrieval bag to prevent tumor seeding. Although GISTs usually displace and do not invade adjacent organs, any tissue surface that is densely adherent to the tumor should be at least partially resected en bloc.

Site-Specific Considerations

Several fundamental principles and site-specific considerations exist for the resection of GIST. Complete resection of GIST does not require wide margin clearance or formal lymphadenectomy. Complete (R0) resection is the goal, but data from 819 primary GISTs 3 cm or larger resected in the American College of Surgeons Oncology Group Z9000 and Z9001 trials showed no difference in RFS in the 72 (8.8%) patients who had microscopically positive (R1) margins compared with those who underwent R0 resection. Gross circumferential resection margins of 1 cm will ensure an R0 resection.

Exophytic tumors with a narrow stalk or those on the greater curvature or fundus of the stomach can be removed easily by laparoscopic wedge partial gastrectomy using surgical staplers without compromising the lumen of the stomach.

A unique technique of tumor excision with a small negative margin (usually 1 cm) under direct visualization using cautery is useful for gastric GISTs (Fig. 3). Direct visualization and excision facilitate safe resection while preserving gastric capacity and minimizing luminal narrowing in more difficult areas, such as the pyloric antrum, incisura, lesser curvature, or gastroesophageal junction (GEJ). GISTs involving the GEJ should attract attention for neoadjuvant imatinib for tumor downsizing before resection, and open surgery is preferred for tumors along the posterior aspect of the GEJ (Fig. 4). Tumor resections from the lesser curvature of the stomach will require careful dissection to preserve vagal nerve integrity. When the vagal trunks cannot be preserved, pyloroplasty or pyloromyotomy should be performed.

Total gastrectomy or esophagogastrectomy is rarely necessary but may be required for sizable tumors involving a large area of the lesser gastric curvature or GEJ, respectively. Massive tumors may be adherent to the spleen, distal pancreas, or colon, necessitating en bloc resection. When neoadjuvant preoperatively preferred lies with

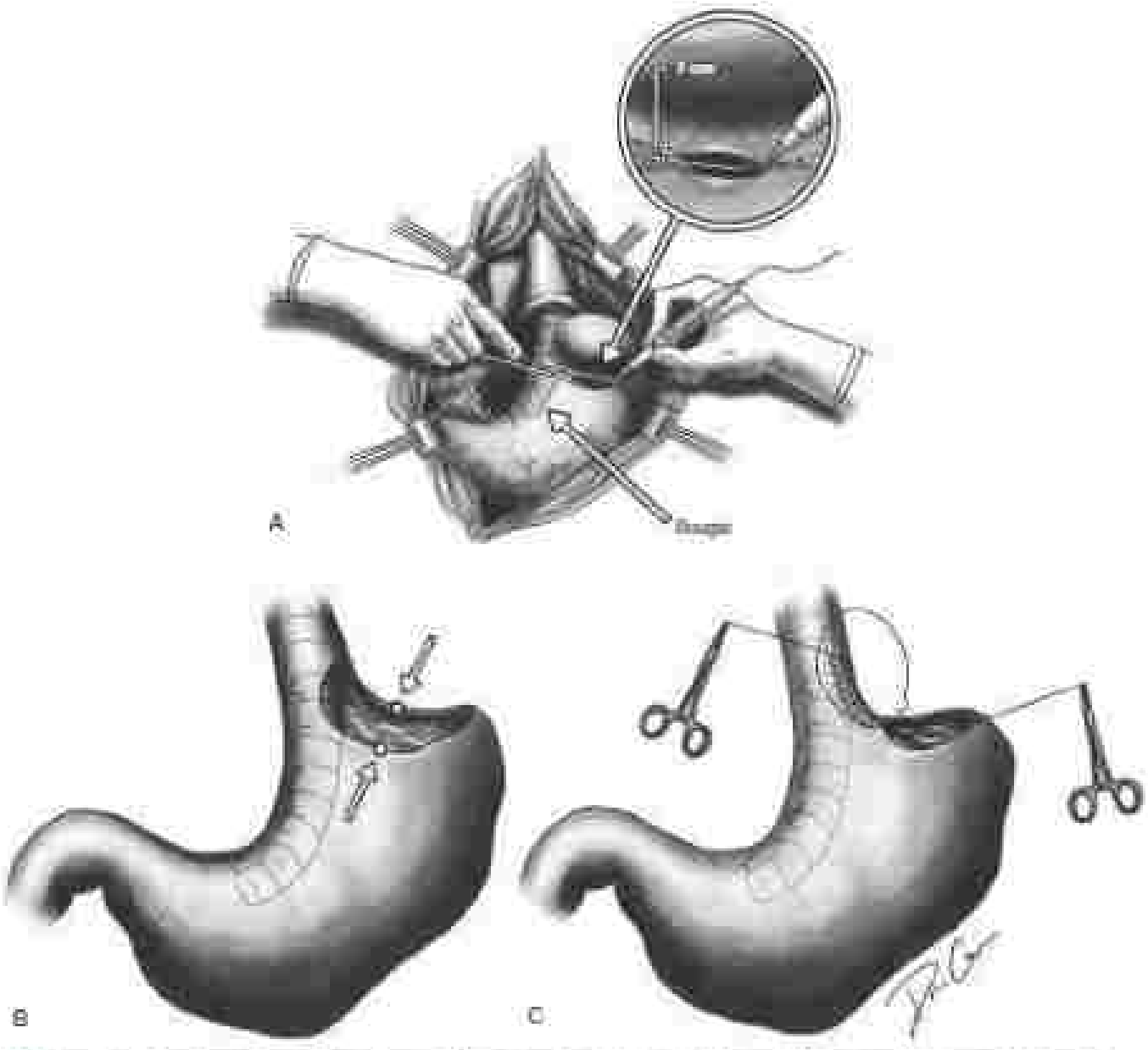


FIG. 3. Resection of a large gastrointestinal stromal tumor at the gastroesophageal junction. (A) After making a gastrotomy with marking the tumor is resected with a 1–cm margin. (B) The defect is then sewn closed (C) over a large bougie placed in the esophagus to prevent narrowing. (Courtesy Cleveland Clinic)

neoadjuvant imatinib to accomplish tumor downsizing and demarcation before an attempt at organ preserving resection.

The next most common site of GIST is the small bowel. Jejunal and ileal tumors can be removed easily with either open or laparoscopic techniques. Management of duodenal GISTs may be complicated because of relationships with the pancreas and bile duct. Consideration for neoadjuvant imatinib should occur for any duodenal GIST where pancreaticoduodenectomy is deemed necessary for complete resection. Small GISTs not involving the peri-Vaterian duodenum can be resected without pancreatectomy. Periampullary GISTs involving the medial duodenal wall usually require pancreaticoduodenectomy even after neoadjuvant imatinib. Small GISTs arising from the lateral wall of the second portion of duodenum can usually be excised. The duodenal defect can be closed with suture duodenorrhaphy without compromising luminal caliber. Alternatively, the duodenal defect can be anastomosed to a Roux limb. Tumors in the third or fourth portion of the duodenum can be managed with segmental duodenectomy followed by primary duodenojejunostomy.

Rectal GISTs are rare but are much more common than colonic GISTs. Neoadjuvant imatinib treatment should be offered to patients with large rectal GISTs to accomplish tumor downsizing and sphincter preservation. Small GISTs involving the lower rectum can be excised transanally with possible need for transanal endoscopic proctoscopic surgery.

NEOADJUVANT IMATINIB

For nonmetastatic GISTs, neoadjuvant imatinib treatment should be considered for tumors that are locally advanced and require major multivisceral resection. Neoadjuvant imatinib may also allow tumor downsizing that could facilitate operative resection. Although change in metabolic activity is evident by [18F] fluoro-2-deoxy-D-glucose

positron emission tomography imaging within days of imatinib exposure, objective tumor downsizing may take many weeks or even several months on imatinib treatment. Treatment response is more reliably assessed by comparing tumor density and dimensions, particularly when evaluating early tumor response (Fig. 5). After initiation of neoadjuvant imatinib, a follow up contrast enhanced CT should be obtained within 8 weeks. Surveillance imaging is typically obtained at 3 month intervals thereafter. Beyond 6 months of neoadjuvant imatinib therapy, further tumor downsizing is unlikely to be observed. Unlike most cytotoxic chemotherapy regimens used in the neoadjuvant setting, neoadjuvant imatinib and other TKIs can be continued up until the time of surgery without compromising wound healing or causing immunosuppression.

ADJUVANT IMATINIB

The initial large-scale studies of imatinib in metastatic unresectable GIST were highly successful. These studies realized a dramatic improvement in survival from a historical median of 18 months to beyond 5 years. However, demonstrating similar improvement in survival from adjuvant imatinib after complete surgical resection has been more difficult. Randomized adjuvant trials designed with crossover treatment arms have demonstrated that placebo-treated patients who develop recurrence are usually salvaged with imatinib therapy and resection and survive for extended periods. The American College of Surgeons Oncology Group Z9001 study was a phase III multicenter prospective randomized trial of imatinib compared with placebo for 1 year after resection of primary GISTs of at least 3 cm size regardless of mitotic index. The study was stopped early at interim analysis when significantly improved RFS survival was noted in the imatinib group (98% vs 83% at a median follow-up of 19.7 months). Long-term follow-up of these patients revealed that relapse occurred within 5 years after completing the 1 year of prescribed imatinib (Fig. 6). After 54 months of follow-up, the RFS curves of the placebo and imatinib treatment arms converged. Imatinib seems to be effective in controlling but not eradicating residual microscopic disease. Interestingly, the majority of improvement in RFS from imatinib was observed primarily in the patients with exon 11 deletions, but not other mutations.

The SSG XVIII study was a phase III randomized study designed to compare the benefits of 1 versus 3 years of adjuvant imatinib.

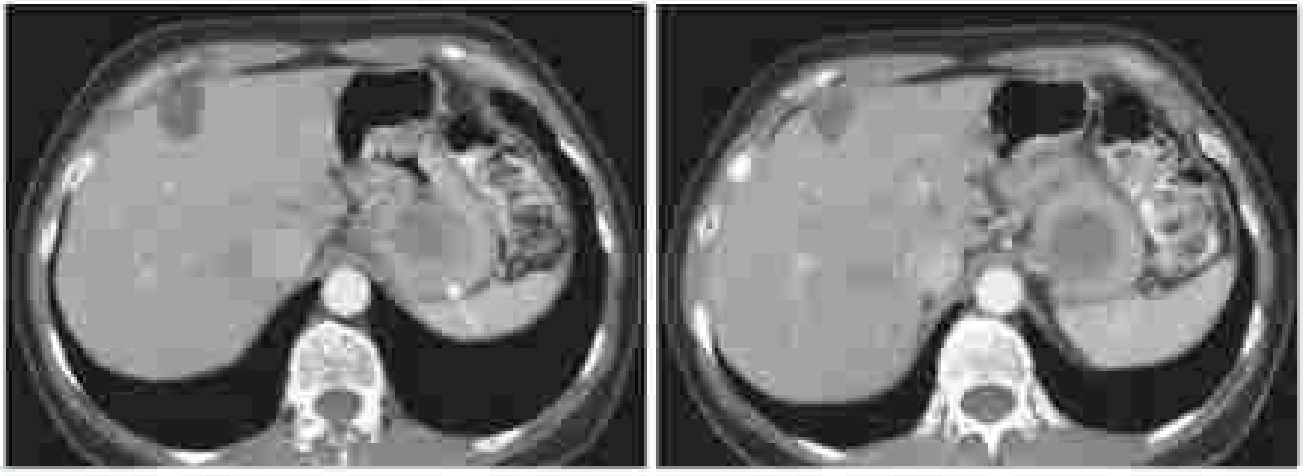


FIG. 4 Contrast-enhanced computed tomography scan of a patient with a gastric gastrointestinal stromal tumor that is endophytic in nature and located along the posterior aspect of the gastric cardia just 3 cm beyond the gastroesophageal junction (arrow). Open excision with nature gastrectomy is recommended for tumors in this location.

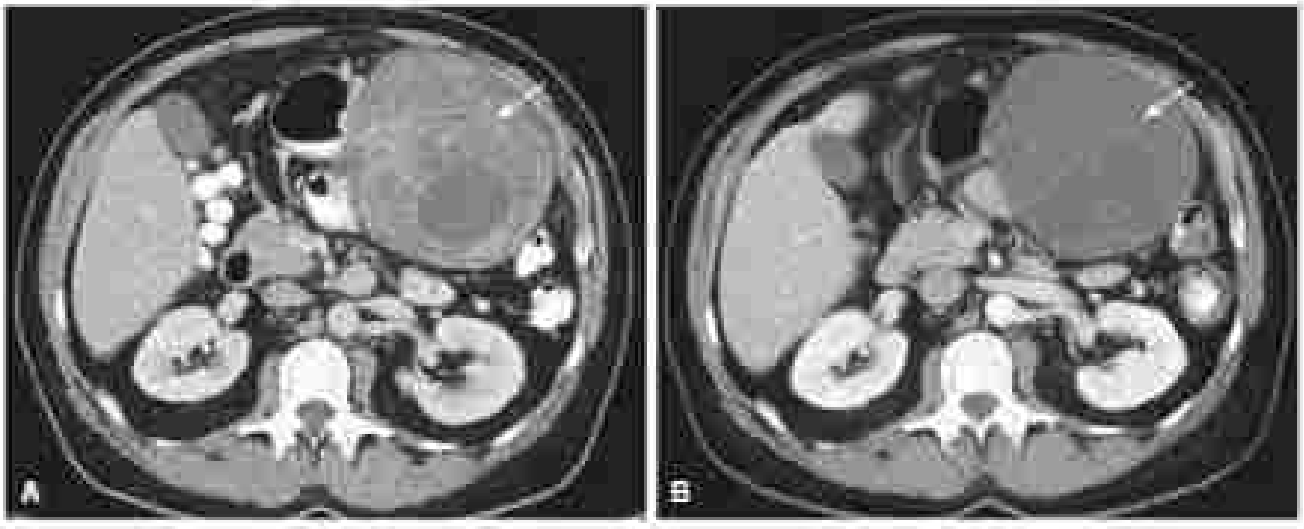
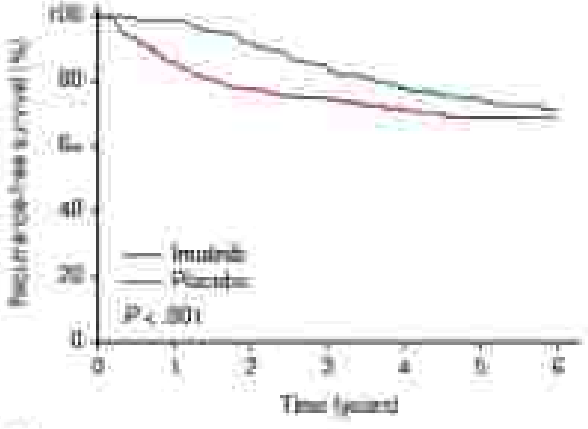


FIG. 5 Initial tumor response to neoadjuvant imatinib is best assessed by changes in tumor density. (A) A large gastric gastrointestinal stromal tumor was treated with imatinib for 8 weeks. (B) After treatment, computed tomography showed similar size (maximal dimension 12.6 cm pretreatment, 11 cm post-treatment), but decreased density. The patient eventually underwent an uncomplicated wedge partial gastrectomy and pathology showed RECIST treatment response.

this study showed improved 5-year RFS (90% vs 69%), with a slight improvement in overall survival (92% vs 82%). The PERSIST-5 (Efficacy Study of Imatinib Therapy for the Treatment of Myelofibrosis Irrespective of Baseline Cytogenetics-5) trial was a phase II single-arm study of 5 years of adjuvant imatinib after resection of primary GISTs at high risk for recurrence (any site ≥2 cm with ≥6 mitoses/50 high-powered fields or any nongastric GIST ≥5 cm). Five years of imatinib treatment for this group of GIST patients was effective in preventing recurrence in those with sensitive *KIT* gene mutations.

RECURRENT, METASTATIC, AND RESISTANT DISEASE

First-line imatinib therapy will usually induce an objective partial tumor response in the majority of patients who develop recurrent disease after resection for GIST. However, the median time to disease progression with imatinib therapy alone is on the order of 24 months



No. at risk							
Imatinib 400 mg	359	256	151	230	199	143	74
Placebo	354	278	243	218	186	132	64

FIG. . Recurrence-free survival in patients with primary gastrointestinal stromal tumor of 3 cm or greater after complete resection, randomized to 1 year of adjuvant imatinib versus placebo. (*Modified from* Corless CL, Ballman KV, Antonescu CR, et al: Pathology and molecular biology correlates with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32:1563.)

and often reflects the development of secondary mutations in *KIT*. Resistance to imatinib may be detected during radiographic surveillance with the appearance of an enhancing nodule(s) within a previously lucent tumor. Despite accumulation of further *KIT* mutations, treated GISTs that have become resistant to imatinib will often show partial response to second lines of TKIs (e.g., sunitinib, regorafenib). However, second- and third-line TKI therapy affords smaller benefits with regards to progression-free survival on the order of 3 to 6 months.

Patients with recurrent or metastatic GIST should be imaged on a 3-month basis. Operative resection can be considered when tumor resistance becomes apparent. Survival benefit from surgical therapy in these two situations is realized only in carefully selected patients with limited burdens of disease. Patients with partially responsive GISTs after TKI therapy will experience improved survival after surgery compared with patients who develop either rapid or multifocal tumor resistance patterns. Patients with multifocal sites of tumor resistance during TKI therapy should be referred for clinical trials.

Resection or ablation of hepatic GIST metastases should be planned to clear all detectable sites of tumor with attention to parenchymal preservation of the liver remnant. Resection of peritoneal GIST metastases may require removal of adjacent organs. After resection of hepatic or peritoneal metastases, adjuvant TKI therapy should be continued indefinitely or until tumor recurrence develops.

CONCLUSIONS

GISTs most commonly arise from the stomach or small intestine and are caused by activating mutations in the *KIT* or *PDGFRα* genes. GIST is a heterogeneous disease that may present as a clinically indolent micrometer or a rapidly progressive malignancy with widespread metastases. Surgery for GIST requires a no-touch technique to avoid tumor rupture and spillage. Tumor locations along the alimentary tract dictate the specific aspect of surgical therapy that will provide complete tumor clearance. Operative resection of larger tumors and tumors located at difficult anatomic locations may be facilitated by neoadjuvant imatinib therapy. Risk for tumor recurrence is independently predicted by tumor size, mitotic rate, and site of disease. Specific mutations of *KIT* help to predict responsiveness to TKI therapy. Adjuvant imatinib should be used in patients at high risk for disease recurrence predicted by individualized nomograms. Resection of recurrent or metastatic GIST should be considered for patients with limited burdens of disease who are responding to TKI therapy or demonstrate only focal tumor resistance. An algorithm for multimodality therapy of GIST is shown in Fig. 7.

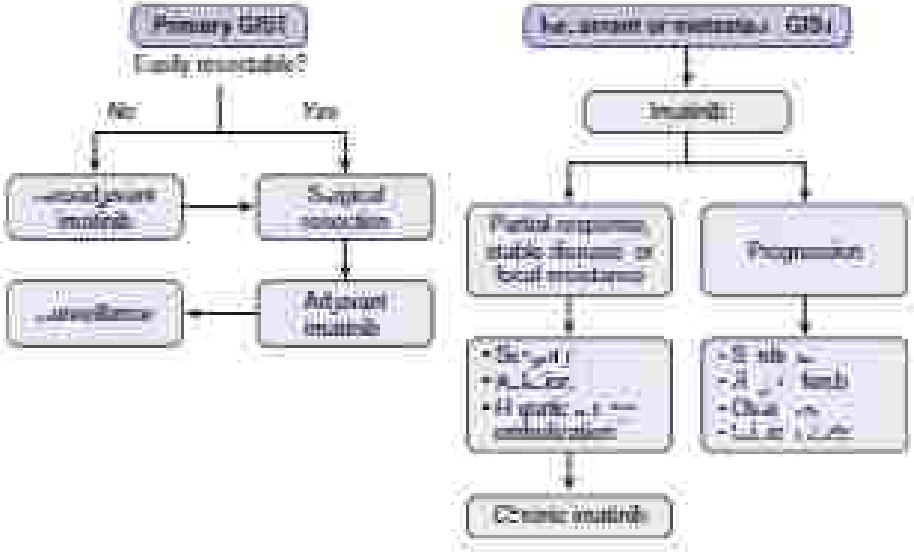


FIG. 7 Schematic approach to patients with gastrointestinal stromal tumor (GIST). For locally advanced primary tumors treated with adjuvant imatinib, tumor assessment should be performed by computed tomography (CT) at 4 weeks to document response to therapy. If GIST nomogram predicts a high or intermediate risk of recurrence, adjuvant imatinib (*) should be continued for at least 3 years; possibly chronically. Surveillance after resection of GIST should include a CT of abdomen and pelvis every 3 or 6 months for 3 to 5 years and then annually. TKI, tyrosine kinase inhibitor. (*Modified from* Corless CL, Heinrich MC: Gastrointestinal stromal tumors. Surg Clin North Am 2008;88:1495.)

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Management of Morbid Obesity

Andrew P. Rogers, MD, and Anne O. Lidor, MD, MPH

The prevalence of morbid obesity continues to increase in the United States and throughout the world. In the United States, >5% of adults are classified as either overweight or obese, up 10% in the past generation. The majority of that increase is in the obese population (body mass index [BMI] >30 kg/m^2), with more than 6% being severely obese (BMI >40 kg/m^2). This trend is seen across the age spectrum, as the prevalence of obesity (>95% BMI for age and sex) in children and adolescents has tripled since 1970.

Although initial forays into weight loss surgery had high complication rates and poor long-term results, advances in technology and technique have led to a surge in surgical interventions for morbid obesity. Recent studies have shown bariatric surgery to be superior to intensive medical management for both weight loss and all-cause mortality for the morbidly obese patient, even when perioperative morbidity and mortality are included. As of 2014, more than 200,000 surgical weight loss procedures are performed annually in the United States. The majority of these are sleeve gastrectomy (58.2%), with Roux-en-Y gastric bypass (18.2%) and revisions (13.9%) comprising most of the rest. Gastric bands have greatly fallen out of favor (3.4%, down from 35.4% 5 years prior), owing to their poor outcomes and higher complication rates.

Surgical intervention may achieve weight loss either by restriction of caloric intake (gastric band and sleeve gastrectomy), intestinal malabsorption of calories (duodenal switch), or a combination of restriction and malabsorption (gastric bypass). Weight loss surgery also has been demonstrated to have significant metabolic and neurohormonal effects (independent of restriction and malabsorption), which also may play an important role in the beneficial effects of these procedures.

Patient Selection

The National Institutes of Health issued a consensus statement in 1991 regarding the effectiveness of bariatric surgery and patient selection criteria. A patient is considered a candidate for bariatric surgery if his or her BMI is 40 kg/m^2 or greater or between 35 and 40 kg/m^2 if an obesity-related comorbidity (i.e., diabetes, hypertension, sleep apnea) is present. Candidates should demonstrate prior unsuccessful attempts at nonsurgical weight loss, including dietary intervention, pharmacologic therapy, or behavioral modification. Realistic long-term outcomes and expectations should be set before surgical intervention, and the patient should be an appropriate operative candidate from a perioperative perspective. Relative contraindications include inability to comply with postoperative requirements, active alcohol or substance abuse, and uncontrolled psychiatric disease.

Preoperative evaluation should involve a multidisciplinary team, including a dietician and a mental health professional familiar with bariatric surgery. It is critical to obtain a complete history of prior weight loss attempts and behavior history around food intake. Preparation for postoperative behavior modifications and examination of social support is also important to success. Patients should be required to attend a multidisciplinary preoperative education program. Participation in postoperative support group meetings also is encouraged. As experience builds, the age for which surgical intervention is appropriate continues to grow; adolescents and those older than age 70 are now routinely undergoing bariatric surgery.

Operative Procedures

Most bariatric surgical procedures are performed laparoscopically, with a hospital length of stay of 48 hours or less. Open surgery may be necessary and planned for patients who undergo revision surgery, those with prior extensive abdominal operations, or patients with a high BMI (>70).

Perioperatively, all patients should receive appropriate antibiotics as well as subcutaneous unfractionated or low molecular weight heparin to help minimize venous thromboembolic complications. Patients are typically in steep reverse Trendelenburg position and must be supported with a footboard and arms and legs secured. Initial laparoscopic entry to a morbidly obese patient can be difficult. We have found that the safest way to enter is to the left upper quadrant with direct vision, using a device that allows visualization of the abdominal wall layers during entry with a 0-degree laparoscope. Once proper placement is confirmed, the abdomen then can be insufflated and the remaining laparoscopic trocars placed.

Laparoscopic Vertical Sleeve Gastrectomy

Laparoscopic vertical sleeve gastrectomy (LVSG) is the most recent of the bariatric surgery procedures to be introduced (Fig. 1) and is the most commonly performed weight loss operation in the United States. The LVSG is restrictive; the lateral aspect of the stomach is removed to create a sleeve-like tube or reservoir. Because the fundus produces the pro-appetite hormone ghrelin, its removal also gives this procedure a neurohormonal mechanism of action. Although not

Suggested Readings

Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 2014;32:1563–1570.

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Management of Morbid Obesity

Andrew P. Rogers, MD, and Anne O. Lidor, MD, MPH

The prevalence of morbid obesity continues to increase in the United States and throughout the world. In the United States, >5% of adults are classified as either overweight or obese, up 10% in the past generation. The majority of that increase is in the obese population (body mass index [BMI] >30 kg/m^2), with more than 6% being severely obese (BMI >40 kg/m^2). This trend is seen across the age spectrum, as the prevalence of obesity (>95% BMI for age and sex) in children and adolescents has tripled since 1970.

Although initial forays into weight loss surgery had high complication rates and poor long-term results, advances in technology and technique have led to a surge in surgical interventions for morbid obesity. Recent studies have shown bariatric surgery to be superior to intensive medical management for both weight loss and all-cause mortality for the morbidly obese patient, even when perioperative morbidity and mortality are included. As of 2014, more than 200,000 surgical weight loss procedures are performed annually in the United States. The majority of these are sleeve gastrectomy (58.2%), with Roux-en-Y gastric bypass (18.2%) and revisions (13.9%) comprising most of the rest. Gastric bands have greatly fallen out of favor (3.4%, down from 35.4% 5 years prior), owing to their poor outcomes and higher complication rates.

Surgical intervention may achieve weight loss either by restriction of caloric intake (gastric band and sleeve gastrectomy), intestinal malabsorption of calories (duodenal switch), or a combination of restriction and malabsorption (gastric bypass). Weight loss surgery also has been demonstrated to have significant metabolic and neurohormonal effects (independent of restriction and malabsorption), which also may play an important role in the beneficial effects of these procedures.

Patient Selection

The National Institutes of Health issued a consensus statement in 1991 regarding the effectiveness of bariatric surgery and patient selection criteria. A patient is considered a candidate for bariatric surgery if his or her BMI is 40 kg/m^2 or greater or between 35 and 40 kg/m^2 if an obesity-related comorbidity (i.e., diabetes, hypertension, sleep apnea) is present. Candidates should demonstrate prior unsuccessful attempts at nonsurgical weight loss, including dietary intervention, pharmacologic therapy, or behavioral modification. Realistic long-term outcomes and expectations should be set before surgical intervention, and the patient should be an appropriate operative candidate from a perioperative perspective. Relative contraindications include inability to comply with postoperative requirements, active alcohol or substance abuse, and uncontrolled psychiatric disease.

Preoperative evaluation should involve a multidisciplinary team, including a dietician and a mental health professional familiar with bariatric surgery. It is critical to obtain a complete history of prior weight loss attempts and behavior history around food intake. Preparation for postoperative behavior modifications and examination of social support is also important to success. Patients should be required to attend a multidisciplinary preoperative education program. Participation in postoperative support group meetings also is encouraged. As experience builds, the age for which surgical intervention is appropriate continues to grow; adolescents and those older than age 70 are now routinely undergoing bariatric surgery.

Operative Procedures

Most bariatric surgical procedures are performed laparoscopically, with a hospital length of stay of 48 hours or less. Open surgery may be necessary and planned for patients who undergo revision surgery, those with prior extensive abdominal operations, or patients with a high BMI (>70).

Perioperatively, all patients should receive appropriate antibiotics as well as subcutaneous unfractionated or low molecular weight heparin to help minimize venous thromboembolic complications. Patients are typically in deep reverse Trendelenburg position and must be supported with a footboard and arms and legs secured. Initial laparoscopic entry to a morbidly obese patient can be difficult. We have found that the safest way to enter is to the left upper quadrant with direct vision, using a device that allows visualization of the abdominal wall layers during entry with a 0-degree laparoscope. Once proper placement is confirmed, the abdomen then can be insufflated and the remaining laparoscopic trocars placed.

Laparoscopic Vertical Sleeve Gastrectomy

Laparoscopic vertical sleeve gastrectomy (LVSG) is the most recent of the bariatric surgery procedures to be introduced (Fig. 1) and is the most commonly performed weight loss operation in the United States. The LVSG is restrictive; the lateral aspect of the stomach is removed to create a sleeve-like tube or reservoir. Because the fundus produces the pro-appetite hormone ghrelin, its removal also gives this procedure a neurohormonal mechanism of action. Although not

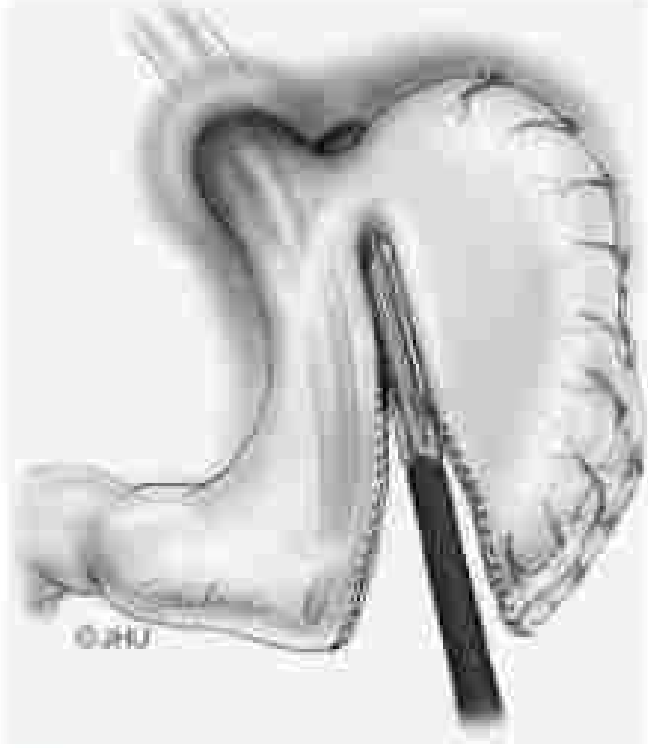

FIG. 1 Creation of the gastric sleeve. (Courtesy Carlos Jacobo, copyright Johns Hopkins University)

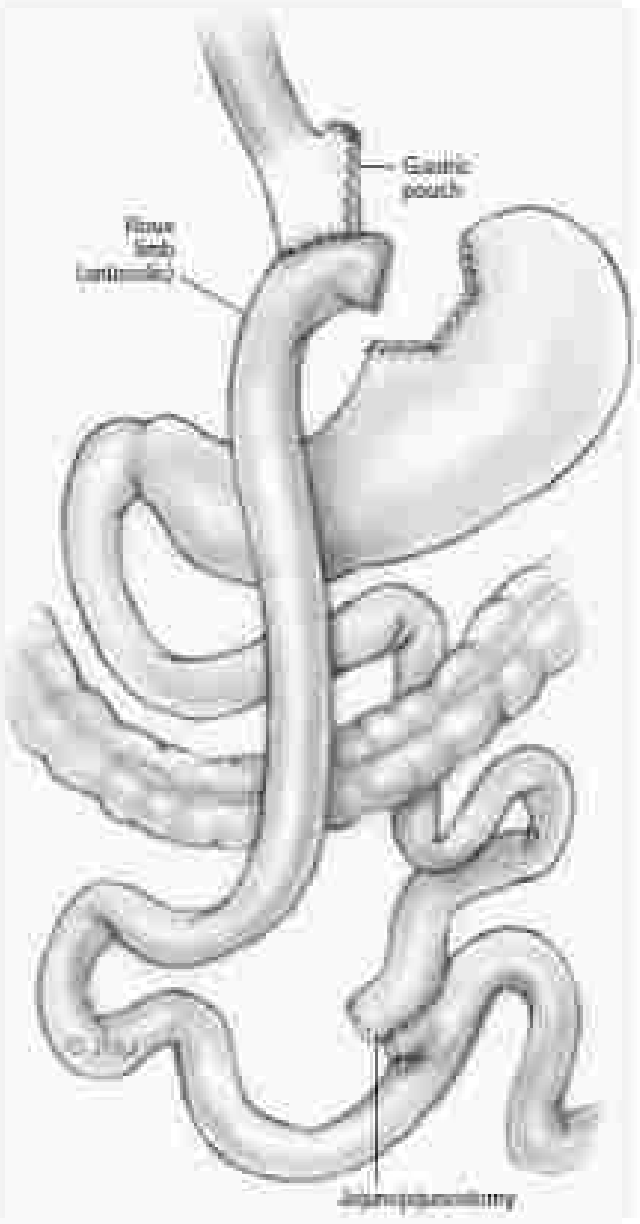

FIG. 2 Antecolic antegastric Roux-en-Y gastric bypass. (Courtesy Carlos Jacobo, copyright Johns Hopkins University)

roversible, LVBG; can be converted into a Roux-en-Y gastric bypass or duodenal switch if greater weight loss is desired.

The LVBG typically is performed with four trocars (various combinations of 5, 12, or 15 mm). With the liver retracted with the Nathanson retractor (Cook Medical), the short gastric vessels are divided along the greater curve of the stomach. An energy sealing device (such as a LigaSure or Harmonic scalpel) (Covidien) typically is used to accomplish this. A 40F bluntly tip bougie is placed in the stomach and directed along the lesser curve. The stomach is divided at the greater curvature, beginning 4 cm proximal to the pylorus. Appropriately sized staple loads are used adjacent to the 40F bougie and extending to the angle of His. The staple line is oversewn or an absorbable buttress material can be used with the staples to assist with hemostasis. To test the integrity of the staple line, an endoscopic air leak or liquid dye infused through an orogastric tube can be used.

The partial gastrectomy specimen is removed through one of the larger trocar sites. Care should be taken to repair the fascial opening of this enlarged trocar site to prevent postoperative herniation. An upper gastrointestinal contrast study is performed only if clinically indicated.

Laparoscopic Roux-en-Y Gastric Bypass

Gastric bypass (Fig. 2) is the second most common bariatric procedure performed in the United States. Numerous reports have shown that gastric bypass results in durable long-term weight loss and remission of metabolic disease with a reasonably low complication rate.

A 45-degree angled laparoscope is inserted above the umbilicus, and the operation is performed using a total of five laparoscopic trocars (three 12 mm and two 5 mm). The omentum and transverse colon are retracted cephalad until the ligament of Treitz is visualized. The jejunum then is transected approximately 40 cm distal to the ligament of Treitz with an appropriately sized stapler cartridge. The mesentery is divided with either a stapler or an energy sealing device. The proximal biliopancreatic limb of jejunum then is anastomosed to the distal segment of jejunum 75 to 100 cm distal to the point of division. We perform this anastomosis in a side-to-side fashion using linear stapler cartridges. The resulting mesenteric defect is closed with a running permanent suture to help minimize the risk of internal hernia.

The patient is then placed in steep reverse Trendelenburg position, and the gastric pouch is created. The left lateral segment of the liver is retracted using a Nathanson through a subxiphoid 8 mm puncture. The peritoneal attachments at the angle of His are dissected to expose the left crus, followed by the base area of the gastrohepatic ligament to allow entry the lesser sac. Division of the neurovascular bundle on the lesser curve side of the stomach just distal to the left gastric artery and vein is accomplished using a gray vascular cartridge. Multiple appropriately sized 45-mm stapler cartridges then are used to transect the stomach up to the angle of His, creating a vertically oriented, 20 mL proximal gastric pouch. Any bleeding staple lines are controlled easily with clips or suture ligation.

We typically bring the Roux limb up to the gastric pouch in an antecolic antegastric orientation. This has been shown to reduce the incidence of internal hernias and is simpler to perform than a retrocolic retrogastric approach. The side of the Roux limb is sutured to the gastric pouch staple line. A small enterotomy is made just proximal to the end of the Roux limb, a similarly sized gastrotomy is made in the pouch for the placement of the linear stapler. The stapler is loaded with a 45-mm cartridge to create the gastrojejunostomy, using only the first 30 mm of the staple cartridge. After the stapler is fired, a stay suture is placed on the lesser curve (right) side of the opening, and the suture then is used to retract the anastomosis to the left and anterior, thereby exposing the posterior side. A running 2-0 suture is placed posterior on the left side and commonly ran to the stay suture on the right side to which it is tied.

A 32F, blunt, round and bougie then is passed from the mouth through the gastrojejunal anastomosis and into the Roux limb. The bougie can be seen through the opening that was formed after the stapler was removed. A stay suture is placed at the halfway point of the opening between the end stay sutures. This stay suture and the stay suture on the left (angle of His side) are used to elevate the tissue so that the 45-mm length blue load cartridge can be used to close the openings. The stapler is brought down on tip of the bougie while the tissue to be transected is retracted. This firing will close most of the opening, and the small remaining defect on the right side is closed readily with a 2-0 suture. The gastrojejunostomy is completed by running a 2-0 suture to cover the entire anterior portion in a second layer. The resultant anastomosis is approximately 15 mm in diameter. A leak test can be performed by clamping the Roux limb just distal to the anastomosis and insufflating air (via endoscope or stapler's tube), whereas the gastric pouch and anastomosis are submerged in saline. The use of a circular stapler to create the gastrojejunostomy is also an acceptable and widely used method by many bariatric surgeons.

The mesenteric defect then is closed between the Roux limb mesentery and the transverse mesocolon, up to the transverse colon (Petersen's defect). If clinically indicated, a Gastrografin swallow study is performed on postoperative day 1 or 2 to check for leakage or obstruction.

Laparoscopic Adjustable Gastric Band

The laparoscopic adjustable gastric band (LAGB) has seen a decrease in the frequency of use since the advent of the sleeve gastrectomy. Although the band is reversible and does not carry a risk of anastomotic or staple line leak, it has fallen out of favor as more data have been collected regarding complications. In addition, the sleeve gastrectomy is comparably easy to complete. In addition, the band requires multiple postoperative adjustments in the first year after surgery and success depends more on patient compliance than the durability of the bypass. Studies have suggested inferior long-term weight loss compared with other operative options.

The LAGB procedure (Fig. 3) is performed routinely via the pars flaccida technique, with four various-sized trocars. The liver is retracted with a Nathanson retractor. Dissection is performed bluntly at the angle of His, freeing up attachments for later insertion of the band. The gastrohepatic ligament adjacent to the lesser curve of the stomach is then divided with electrocautery. The right crus is identified, and the anterior peritoneal tissue is divided. If a hiatal hernia is identified, reinforcement of the hiatus is important, either anteriorly or posteriorly, to discourage further herniation once the band has been placed. Two graspers are used to carefully dissect the plane of tissue posterior to the gastroesophageal junction to provide a tunnel for the LAGB.

An articulating dissector then is placed from the right crus toward the angle of His. The dissector arm then is flexed to create a right angle and locked into place. The adjustable band is placed into the abdomen through the 15-mm trocar in the left upper quadrant. The band is secured to the articulating dissector and brought around the

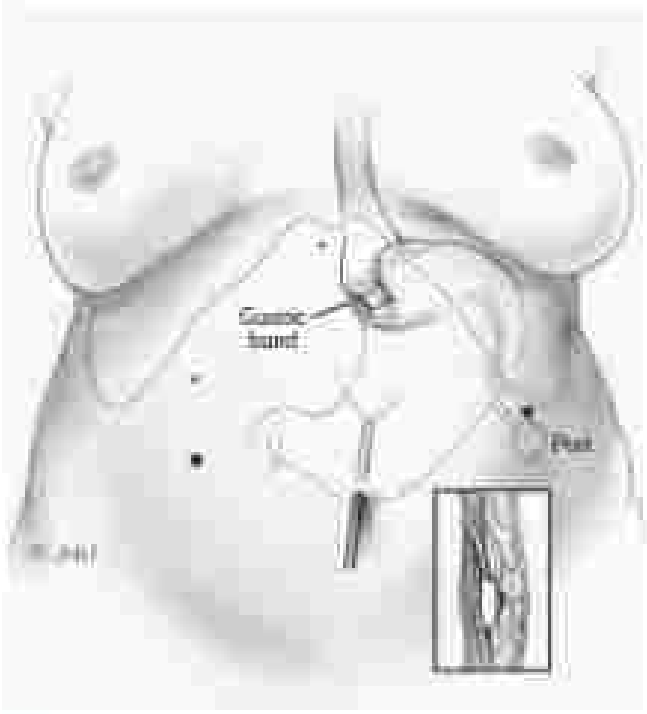

FIG. 3 Laparoscopic adjustable gastric band (courtesy Ethicon Endosurgery, Cincinnati, Ohio). (Adapted from Nguyen NT, Slone JA: Laparoscopic bariatric surgery: current perspectives and new developments, *Adv Surg* 43:1–30, 2009.)

stomach while the instrument is withdrawn. The band then is locked into place with an approximate 45-degree angle toward the patient's left shoulder. A minimum of two sutures then are placed from the fundus to the proximal gastric tissue around the band to secure the band into place. This reduces the possibility of band migration or herniation. It is important to ensure that the balloon portion of the band has not been compromised while either placing the band or suturing it into position.

The band tubing is brought out through the left upper quadrant port and secured externally to the subcutaneous injection port. When securing the port to the fascia, the surgeon must clear a sufficient space along the rectus sheath. After hemostasis has been achieved in the pocket, the port can be sutured or deployed into position while care is taken to leave the majority of the tubing in the abdomen. Finally, the port can be tested via Hubert needle to ensure that the tube and band are functional and not kinked or malpositioned.

Though the band has fallen out of favor, it is still important to maintain familiarity with the procedure because revision is increasingly necessary. If planning to remove the band, it is necessary to remove the band, tubing, and subcutaneous port. Conversion from a laparoscopic band to either a gastric bypass or sleeve gastrectomy is relatively straightforward and may be done at the time of the band removal or at a subsequent operation if scarring at the time of the initial operation is not severe.

Laparoscopic Duodenal Switch With Biliopancreatic Diversion

The laparoscopic duodenal switch with biliopancreatic diversion (DS-BPD) is primarily a malabsorptive operation that involves gastrectomy of the pylorus and creation of a short, 100-cm final "common channel" (Fig. 4). The DS-BPD is the least common bariatric procedure performed because of its surgical complexity and potential for severe malabsorptive nutritional deficiencies.

This procedure can be performed in a single operation or in two stages if the patient has a high BMI (>70). The first stage is similar to LSG, with the creation of a gastric sleeve. After approximately a

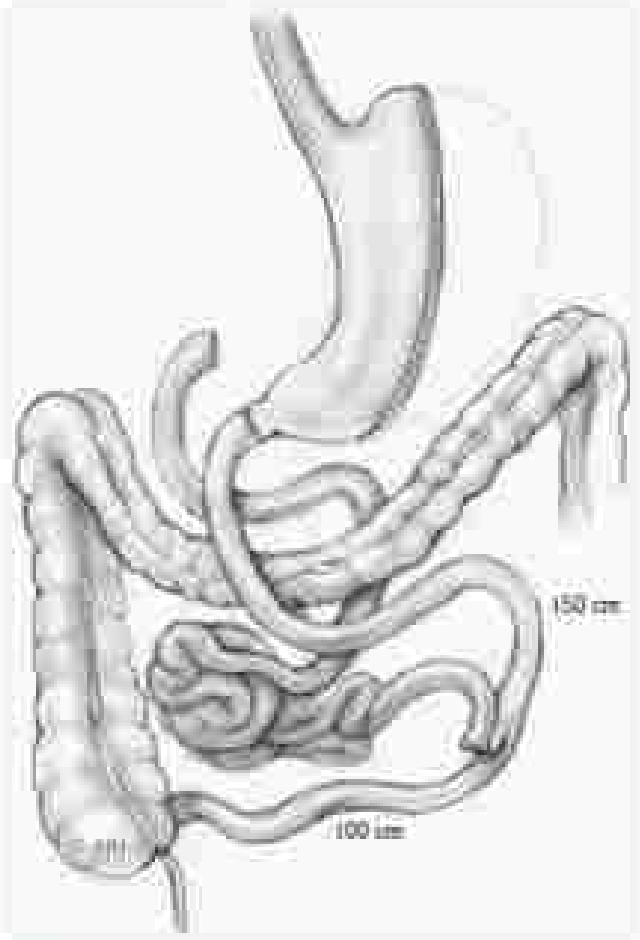

FIG. 4 Ascending duodenal switch with biliopancreatic diversion. (Courtesy Carmen Lorenzo, copyright John Hopkins University)

1-year period of weight loss, the patients can be converted to DS BPD and the malabsorptive second stage performed. This is performed by dividing the small bowel 250 cm from the ileocecal valve. The proximal end of bowel then is anastomosed to the distal ileum 100 cm from the cecum.

The patient then is placed in steep reverse Trendelenburg position and the liver is retracted. If the sleeve gastrectomy portion has not been performed previously, then partial gastrectomy proceeds as previously described. The duodenum is then divided approximately 3 to 4 cm distal to the pylorus with a 60 mm linear stapler. The Roux limb is directed in an antecolic fashion, and a side-to-side anastomosis is performed with the duodenum. An air leak or dye test can be performed to check for leaks at the stomach staple line and new duodenal jejunal anastomosis. Finally, the mesenteric defect then is closed between the Roux limb mesentery and the transverse mesocolon.

POSTOPERATIVE CARE AND SHORT-TERM OUTCOMES

After any of the bariatric procedures, patients are seen in follow-up at 2 weeks to ensure that they are well hydrated, tolerating oral intake, and without wound complications. They are then seen at 3, 6, 12, 18, and 24 months and annually thereafter to follow weight loss and nutritional issues. Patients are encouraged to meet with dietitians and remain with their support groups indefinitely.

For 1 month after surgery, patients are all maintained on a high-protein puree consistency diet; after that, they gradually are advanced to solid food. They also receive multivitamins, calcium, and vitamin B12 supplements. This is especially important for patients with gastric bypass and DS BPD who are at higher risk for malabsorption and possible malnutrition. Supplemental iron always is considered for menstruating women.

Weight loss after gastric bypass and DS BPD occurs primarily in the first to 18 months after surgery and averages approximately 70% and 80% excess weight loss, respectively. Sleeve gastrectomy typically has less excess weight loss, on average 50% over a 2- to 3-year period. Recent 5-year follow-up data suggest that this difference may decrease over time and ultimately may not be clinically significant.

Overall complication rates after bariatric surgery are less than 15% in most reports. As with most surgeries, there are early and late complications for bariatric surgery. Early or perioperative complications include bleeding, anastomotic leakage, and deep venous thrombosis. The mortality rate is less than 1% and is usually attributable to a pulmonary embolus or sepsis from anastomotic leak. Persistent unexplained tachycardia higher than 120 beats/min may be an early sign of sepsis; an appropriate workup should be considered.

Vitamin B12, calcium, iron, vitamin D, and protein deficiencies can occur within the first year or longer after surgery. Rigorous monitoring of nutrition status is necessary. Vitamin B1 deficiency also can occur in patients with protracted vomiting after surgery; these patients may experience extremity paresthesias and confusion. Lower extremity weakness and paresthesias also can be seen with vitamin B12 deficiency. Anastomotic stenosis and obstruction at the gastrojejunostomy in the first few months after surgery occur in less than 5% of patients after gastric bypass and usually can be managed with endoscopic dilation.

LONG-TERM OUTCOMES OF BARIATRIC SURGICAL INTERVENTION

Cohort data have shown bariatric surgical intervention to have a lower all cause mortality than intensive medical management for patients with morbid obesity. This association holds true regardless of the type of surgical intervention. Compared with maximal medical therapy, surgical intervention also improved outcomes for the treatment of type 2 diabetes, hypertension, sleep apnea, and dyslipidemia. There is no difference seen in hospitalization rates and major cardiac events, suggesting that postsurgical complications are not a higher burden than complications seen from existing comorbidities in patients treated medically.

Overall surgical complication rates for sleeve gastrectomy versus bypass are similar. The rates of reoperation are also similar, but the reasons for reoperation differ depending on the index operation. Gastroesophageal reflux may be worsened with sleeve gastrectomy. In the presence of significant reflux, a hiatal hernia, or esophageal metaplasia, sleeve gastrectomy should not be the operation of choice. There exists no consensus as to the role of preoperative esophagogastroduodenoscopy, although we routinely perform endoscopy to rule out metaplasia should the patient admit symptoms of reflux.

Internal hernias are a complication seen only in gastric bypass and duodenal switch because there is no small bowel mesentery or mesenteric window associated with sleeve gastrectomy. Patients should be counseled as to this possibility and a sleeve gastrectomy may be preferred in the absence of reflux disease in patients prone to hernia formation, adhesive disease, or with extensive prior abdominal surgery.

Ultimately, the decision as to which surgical intervention to undertake is complex and should be made in consult of the individual patient and in conjunction with the patient's goals. Regardless of the method chosen, there remains significant variation in response to surgical intervention, an area of active investigation in the field.

Suggested Readings

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MANAGEMENT OF SMALL BOWEL OBSTRUCTION

[illegible]

[illegible]

[illegible] CLINICAL PRESENTATION

[illegible]

Physical Examination

[illegible] allows a clinician to completely differentiate strangulated from nonstrangulated bowel. However, the art of physical examination is still important for clinicians as it is often the only useful thing to help a clinician decide when they should take a patient to the operating room. The examination should begin by evaluating for overall systemic signs of toxicity. [illegible] signs such as tachycardia, decreased

TABLE 1 American Association for the Surgery of Trauma Severity Grading Criteria for SBO

Grade	Descriptive	Radiographic Criteria	Operative Criteria
I	Partial SBO	Minimal intestinal distension	Minimal intestinal distension with no evidence of obstruction
II	Complete SBO; bowel viable and not compromised	Intestinal distension with transition point without bowel compromise	Intestinal distension with transition point; no evidence of bowel compromise
III	Complete SBO with compromised but viable bowel	Intestinal distension with transition point; no distal contrast flow; evidence of complete obstruction or impending bowel compromise	Intestinal distension with impending bowel compromise
IV	Complete SBO with nonviable bowel or perforation with localized spillage	Evidence of localized perforation or free air; bowel distention with free air or fluid	Intestinal distension with localized perforation or free fluid
V	Perforation with diffuse peritoneal contamination	Bowel perforation with free air and fluid	Intestinal distension with perforation, free fluid, and evidence of diffuse peritonitis

BOX 1 Causes of Small Bowel Obstruction

Adhesions
Hernia
- Incisional
- Inguinal/umbilical
- Abdominal wall
- Richter's
- Paraesophageal
- Obturator

Inflammatory/infectious
- Crohn's disease
- Ileitis
- Abscess

Neoplasm
- Primary intestinal mass
- Lymphoma
- Metastatic disease

Other
- Gallstone ileus
- Traumatic intramural hematoma
- Foreign body
- Intussusception

urine output, or orthostasis may be manifestations of the dehydration associated with gastric losses in SBO but may also point to signs of ischemia or perforation. The clinician should be especially suspicious of ischemia when patients present with fever, altered mental status, or other toxic signs. Although bacterial translocation from the intraluminal compartment has been shown to be a possible cause of the systemic inflammatory response, systemic signs should be considered a sign of strangulation or ischemia until proven otherwise. These indications should urge the surgeon in the operating room immediately.

Abdominal inspection should begin by noting any surgical scars and ruling out abdominal wall or groin hernias as causes of mechanical obstruction. The hallmark of the physical examination in a patient with SBO is abdominal distension, especially in the context of old surgical scars. There is a direct relationship between the severity of abdominal distension and the proximal nature of the SBO, with distension being worse in more proximal obstructions (duodenum/jejunum); however, it is important that patients with a closed-loop obstruction may display little to no abdominal distension. Basic characteristic signs of abdominal auscultation note "high pitched tinkling" sounds that may become more muffled as the bowel progressively distends and may become absent when peritonitis ensues in the setting of impending or acute bowel ischemia. Although these auscultative findings are worth noting, they are generally not reliable as independent markers of the grade of obstruction or likelihood of ischemia. Percussion may reveal tympany throughout the abdomen; however, dullness to percussion may be present over fluid-filled bowel loops. Pain to light percussion, local tenderness or guarding, are signs of peritonitis and merit exploration. Rectal examination is mandatory because it can identify fecal impaction, rectal masses, blood, or the rare obturator hernia, all of which would critically alter management.

DIAGNOSIS AND WORKUP

After a thorough history and physical examination, laboratory values and imaging can aid in identifying which patients require urgent operation or have failed conservative therapy. Recent data have shown the accuracy of predictive models that use clinical/radiographic parameters to evaluate the likelihood of postoperative complications or the likelihood that the SBO will require operation for bowel resection. We use the following clinical and radiographic factors in our decision making regarding operation for SBO[6–12]:

Laboratory Studies

No single laboratory finding definitively rules out bowel ischemia or perforation; however, laboratory values can aid in characterizing the severity of the presentation and helping determine which patients should be taken directly to the operating room. Basic laboratory values for serum sodium, potassium, chloride, blood urea nitrogen, and creatinine/glomerular filtration rate can aid in the diagnosis and management of dehydration. Although patients may have a metabolic alkalosis as a result of persistent vomiting, metabolic acidosis can be a sign of bowel ischemia or malperfusion in other organs. Lactic acidosis has a sensitivity of up to 100% in the diagnosis of intestinal ischemia, but is a late finding and clinicians should be careful not to undertriage patients without a lactic acidosis. The lack of a lactic acidosis should not be used as a decision point in avoiding operation because it carries a specificity of approximately 48%. A C-reactive protein level greater than 7 mg/L and leukocytosis level higher than 10×10^9 have been used in predicting ischemia and correlate with the need for bowel resection. Other studies have demonstrated that a high serum procalcitonin levels can be useful in predicting the failure of conservative management; a serum procalcitonin threshold of 0.5 ng/mL or greater was found to have an 83% positive predictive value and 91% negative predictive value for bowel ischemia at operation.

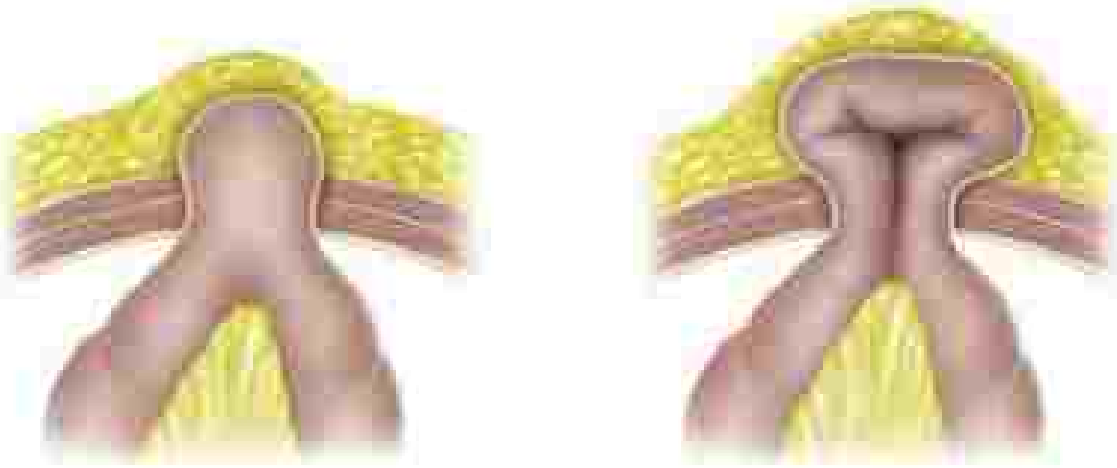

FIG. 1 [illegible]

BOX 2 Clinicoradiologic Parameters Associated with Bowel Ischemia/Need for Bowel Resection

History/physical
- Pain lasting more than 6 days
- Rebound or guarding on abdominal examination

Laboratory
- C-reactive protein >75 mg/L
- Procalcitonin > [illegible] ng/mL
- Leukocytosis >10 × [illegible]
- Lactic acidosis

Computed tomography
- Presence of >50 mL of free fluid
- Free fluid density >[illegible] HU
- Reduced bowel wall enhancement
- Intramural hemorrhage
- Pneumatosis
- Portal venous gas
- Bowel wall thickening >3 mm

Imaging

Plain radiography is generally obtained as a first step in imaging a patient with suspected SBO. Although not as sensitive or specific as computed tomography (CT), it is cheap, easily accessible, expeditious, and may obviate the need for CT in the presence of free intraperitoneal air (Fig. 2). When flat and upright plain films are obtained, radiography carries a 67% sensitivity and 63% specificity for diagnosing SBO. The most specific findings for SBO on plain radiographs are dilated small bowel loops greater than 3 cm along with decompressed distal loops, air-fluid levels, and a paucity of gas in the colon (Fig. 3). A "gasless abdomen" represents filling of bowel loops with sequestered fluid resulting from obstruction and should not mislead a person to underestimate the severity of SBO because of a lack of air-fluid levels (Fig. 4). A "string of pearls" sign can be seen on upright or decubitus radiographs as an obliquely oriented linear row of air bubbles in the abdomen; these represent small pockets of gas along the superior wall of the small bowel that are trapped between the plicae circulares. In the event of an abdominal catastrophe or hemodynamic instability, the surgeon can forgo radiography and proceed directly to the operating room.

In a stable patient, a CT scan with intravenous contrast can help to provide a valuable picture of the patient with SBO. The CT scan can identify the etiology of the SBO (e.g., hernias, tumors, malrotation),

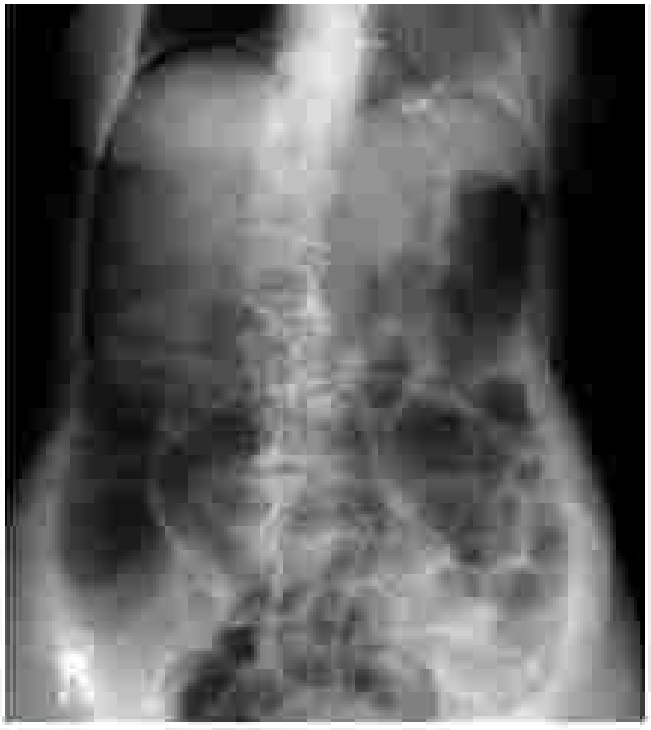

FIG. 2 Plain upright radiograph demonstrates free intraperitoneal air under the right hemidiaphragm in a patient with small bowel obstruction and bowel perforation.

the degree of obstruction being if partial or complete, the potential location of the obstruction by identifying transition points, and can identify markers of ischemia, perforation, or necrosis. The sensitivity and specificity of CT scans in identifying SBO are greater than 90%. Although the use of oral in conjunction with intravenous contrast is useful in differentiating partial versus complete obstruction by evaluating the passage of oral contrast into decompressed bowel segments, omission of oral contrast facilitates the identification of areas of where the bowel wall demonstrates decreased or delayed enhancement, an important marker of bowel ischemia. The low attenuation gas and fluid within the obstructed lumen generally provide adequate contrast relative to the normally enhancing bowel wall which can be obscured by high attenuation oral contrast material.

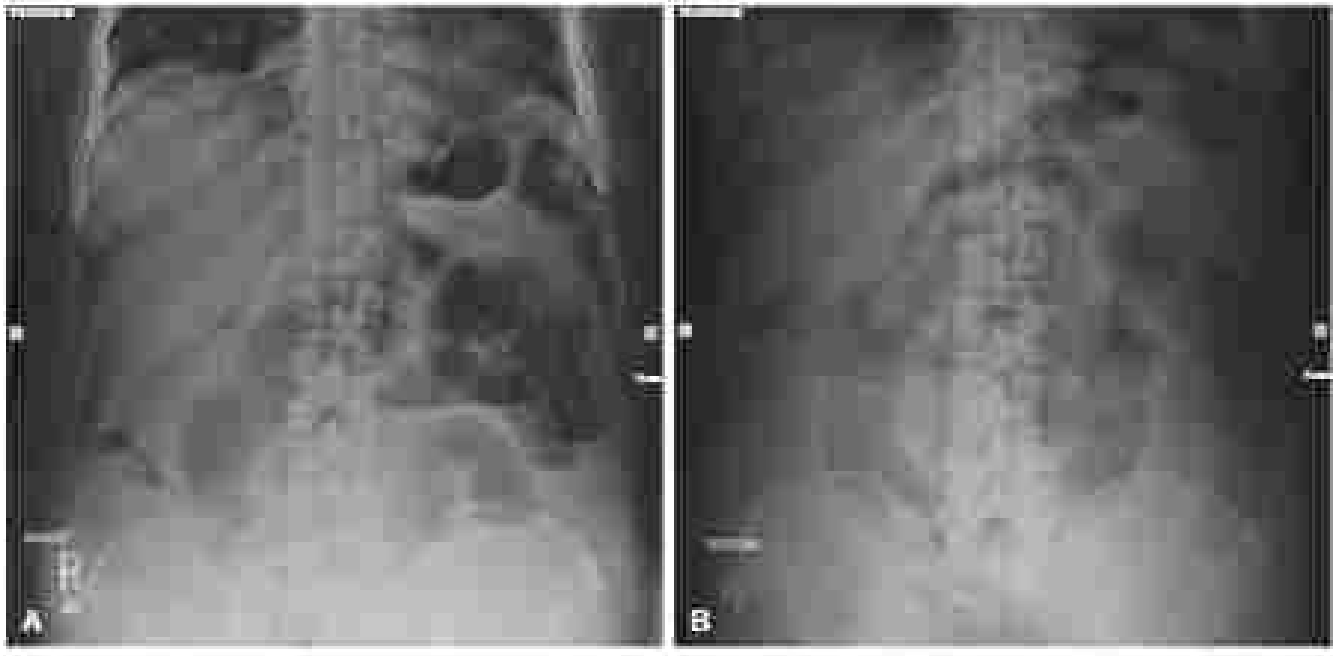

FIG. 3 Plain abdominal upright radiographs of a patient with a complete small bowel obstruction. (A) Differential air fluid levels and upright films. (B) Dilated loops of small bowel with no evidence of colonic gas.

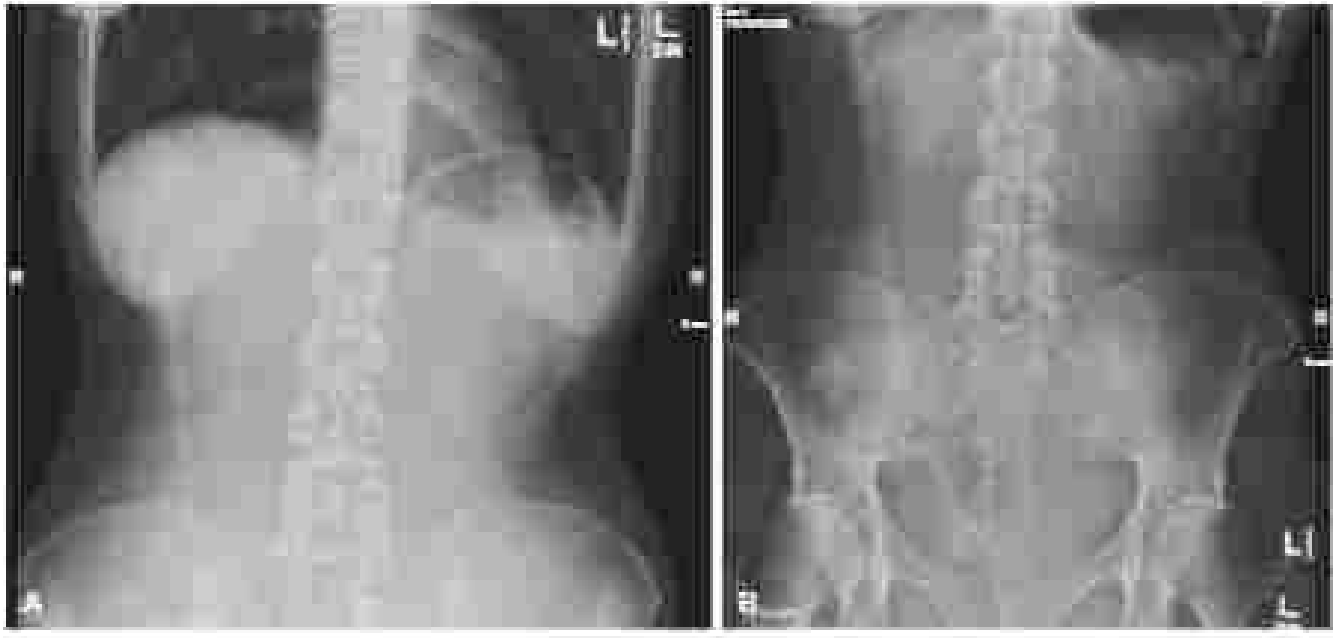

FIG. 4 Abdominal radiograph demonstrates a "gallus abdomen" in the upper (A) and lower (B) abdomen of a patient with small bowel obstruction.

As with radiography, the hallmark of SBO on CT is dilated (>3 cm) proximal small bowel with decompressed distal small bowel and colon. One advantage of CT is the increased ability to identify the transition point or zone where the dilated bowel transitions to decompressed bowel, highlighting the site of obstruction (Fig. 5). The location of obstruction on CT correlates with the location at the time of surgery approximately 70% of the time, making this a potentially useful guide to surgical approach. It is noteworthy, however, that the presence of a transition point on CT does not accurately identify patients in need of surgery nor does it identify patients who will fail operative management and should not be used as a major criterion in influencing operative versus nonoperative management.

Because physical examination and laboratory evaluation alone are not sufficient to rule out ischemia, CT is widely relied on for this role. In patients with proven bowel obstruction, the sensitivity for detecting ischemia ranges from 75% and 100%, and the specificity ranges from 67% to 98%. A high index of suspicion when interpreting CT scans is key. A number of studies have identified radiologic parameters that recognize patients at high risk for ischemia or in need for bowel resection. High density intraperitoneal free fluid (>10 HU) in one retrospective series was predictive of the need for surgical intervention in patients with SBO (sensitivity 53%, specificity 82.5%). Interperitoneal free fluid of more than 500 mL or volume expansion of fluid density, and a reduction in small bowel wall contrast

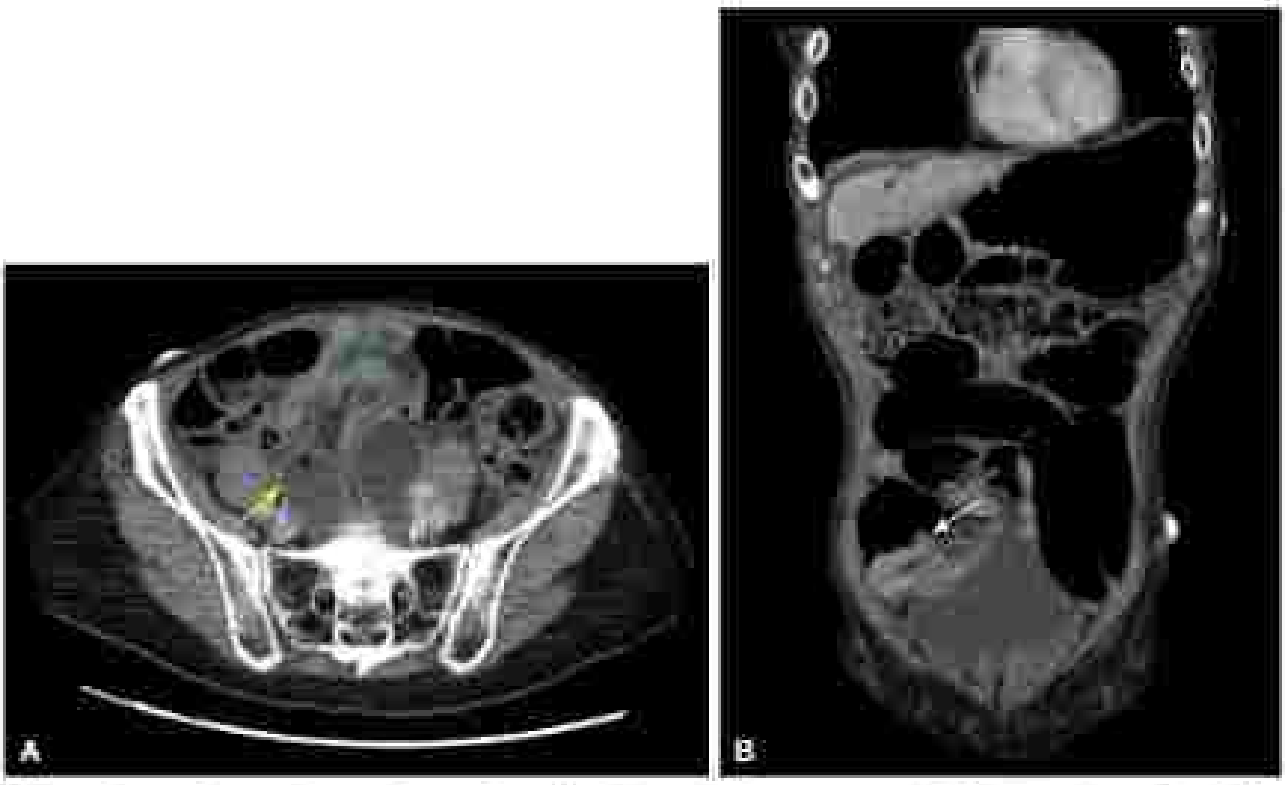

FIG. 5 Computed tomography scan demonstrating a complete small bowel obstruction with a transition point. (A) Axial image shows dilated small bowel loops (*, *) with adjacent decompressed small bowel loops (arrow, arrowhead) in the anterior abdomen. (B) Coronal image demonstrates the transition point (arrow).

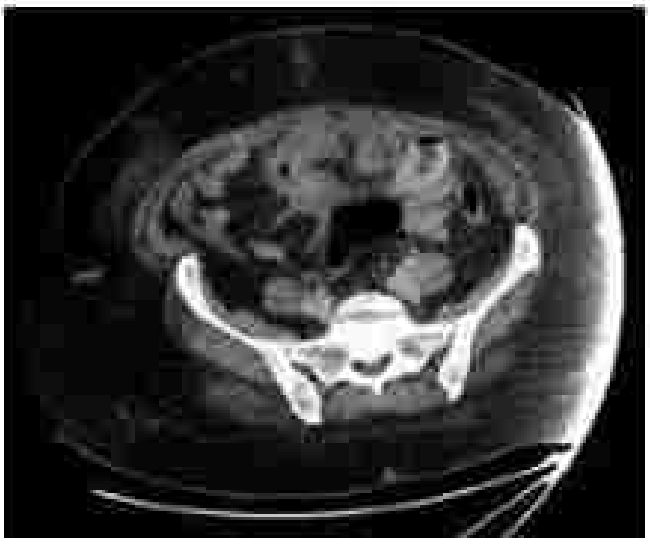

FIG. 6 Computed tomography scan demonstrates bowel wall thickening in a patient with a complete small bowel obstruction.

enhancement are strongly associated with bowel manipulation in SBO. Other important CT findings that are associated with ischemia include bowel wall thickening greater than 3 mm (Fig. 6), mesenteric edema or fluid, decreased bowel wall enhancement, "target sign" (hyperenhancement of the mucosa relative to the remainder of the bowel wall), pneumatosis, or portal venous gas.

An important type of obstruction that may be difficult to identify on CT but is a surgical emergency is the closed loop obstruction. Closed loop obstructions are a type of complete obstruction in which an intestinal loop is obstructed at two adjacent points, generally by adhesion or volvulus, creating a segment with no proximal or distal outlet that is at high risk for impending strangulation (Figs. 7 and 8). This requires prompt identification and surgical intervention. Classically, on CT, the incarcerated small bowel can be seen as fluid filled distended loops with a U shape configuration, a corresponding radial distribution, with stretched and thickened mesenteric vessels converging toward the point of obstruction; there may also be a swirling of the mesentery. Other signs include the "beak sign" or two collapsed adjacent loops.

NONOPERATIVE MANAGEMENT

Absent signs of ischemia or intra-abdominal catastrophe, a trial of conservative management is typically preferred in most patients. The mainstays of nonoperative management are bowel rest, nasogastric decompression, and fluid therapy, with serial abdominal examinations. Nasogastric decompression is achieved with a Salem sump tube that is flushed regularly to ensure patency. Prospective studies failed to show the superiority of long nasointestinal tubes over nasogastric tubes. Fluid management should be dictated by electrolyte correction, replacement of missed oral intake leading to presentation, replacement of nasogastric tube losses, as well as urine output as guided by a Foley catheter for patients in whom urine output cannot be accurately measured. Patients with SBO warrant prompt surgical consultation and admission to a surgical service. A review of more than 100,000 admissions for SBO demonstrated that 73% are managed by a medical attending and 27% are managed by a surgical attending, and that being on a medical service was independently associated with a longer length of stay, greater inpatient costs, a higher rate of 30-day readmission, and a delay in time to surgical intervention.

In the setting of adhesive SBO, the success of nonoperative management ranges from 65% to 80% in retrospective series. During a trial of nonoperative therapy, a change in the status of a patient to

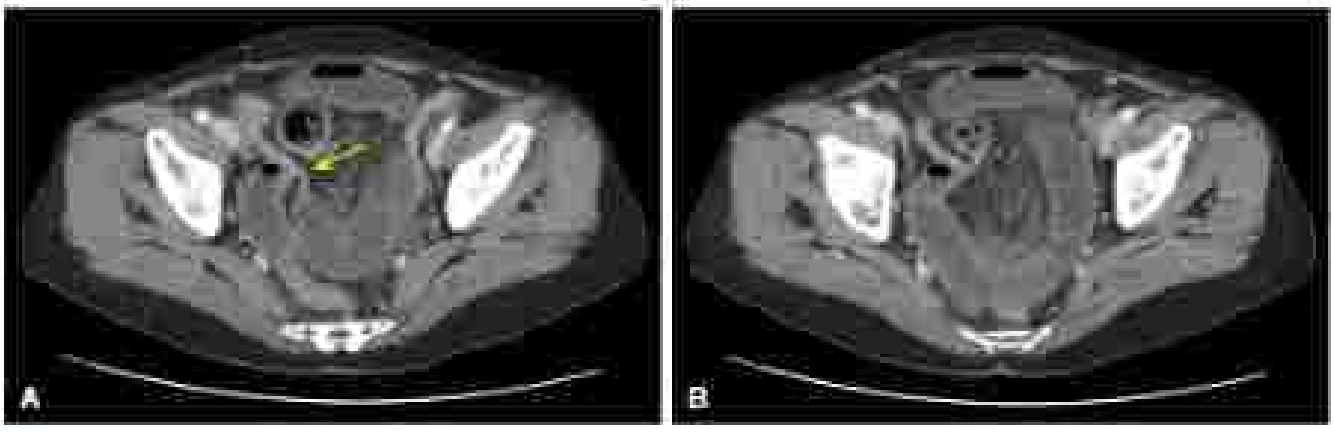

FIG. 7 Computed tomography images of a patient demonstrating findings consistent with a closed-loop obstruction. (A) One clear transition point is visible adjacent to (B) a second transition point can also readily be discerned. The intervening bowel loop is distended.

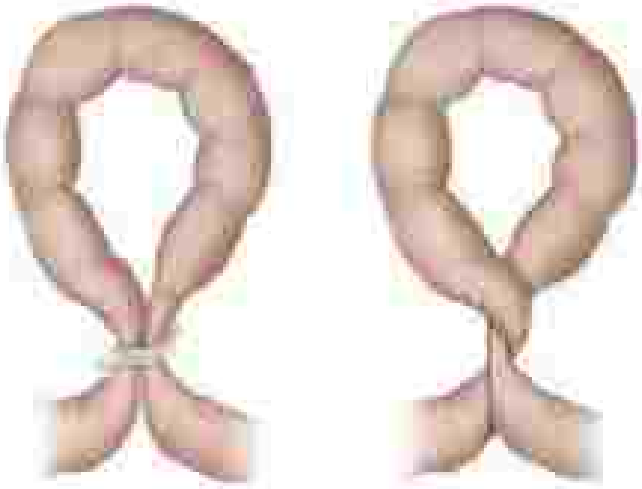

FIG. 8 Illustration of a closed-loop obstruction. Adhesive bands can cause an obstruction at two adjacent segments of bowel (left). A volvulus caused by twisting of a segment of bowel (right) is also a common cause of closed-loop obstruction.

indicate a complete obstruction should prompt surgical intervention. The use of serial abdominal radiography is of little use in guiding management, and we find that following the abdominal examination and nasogastric tube output are more informative to treatment decisions. That being said, an abdominal radiograph 24 hours after an initial CT with water soluble contrast that shows contrast reaching the colon demonstrates the likely resolution of the SBO. Failure of contrast to reach the colon in 24 hours should be noted because it is predictive of failure but should not stand alone to dictate operative decision making.

Although the decision to proceed with surgical therapy is dictated by the overall clinical status of the patient, a delay in operation is associated with a substantial increase in morbidity and mortality. The appropriate duration of nonoperative therapy varies widely in the literature. The World Society of Emergency Surgery recommends a period of 72 hours and the Eastern Association for the Surgery of the Trauma guidelines recommend a period of 3 to 5 days of conservative management. Failure to resolve after 72 hours of conservative therapy is highly predictive of nonoperative failure. In our practice, we generally observe patients for a period of 72 hours, but the decision to operate is individualized based the etiology of the SBO and the patient's clinical status. For example, patients with obstructions secondary to Crohn's disease may require a longer period of medical optimization and parenteral nutrition.

OPERATIVE MANAGEMENT

Once the need for surgery has been determined, the remaining challenge consists of choosing the appropriate approach.

Open laparotomy has been and continues to be the dominant surgical strategy for SBO when compared to laparoscopy, with approximately 70% to 80% of SBOs being treated via laparotomy. In the case of an open approach, a midline laparotomy provides adequate access for entry into the abdominal cavity. Care must be taken to avoid bowel injury during abdominal entry by being cognizant of bowel that may be adherent to abdominal wall, especially if in the setting an area of previous scar. Preferentially entering the abdomen in virgin areas far from previous incisions and going from "known" to "unknown" can help mitigate the risk of bowel injury during entry. If a clear transition point is visible and consistent with CT imaging, it is not necessary to perform a complete lysis of adhesions; however, it is important to confirm the bowel can be run distally to the ileocecal valve to ensure that there is no downstream obstruction. If an abdominal wall or inguinal hernia is the cause of the obstruction and is in need of mesh repair, absent any spillage or contamination, a synthetic mesh is appropriate. In the case of spillage, contamination, or iatrogenic injury, if a mesh is required, biologic mesh should be used. After lysis of adhesions, the bowel should be thoroughly inspected for injuries. Perforations or iatrogenic injuries that are larger than 50% of the bowel lumen necessitate resection. Smaller injuries can be repaired primary. We prefer a two layered repair with a full thickness, braided, absorbable suture followed by a seromuscular Lembert suture; however, a one layer repair is also appropriate. Importantly, when primarily repairing the bowel, bites should be taken transversely so as not to narrow the bowel lumen.

Perforated or clearly ischemic bowel should be resected. If the viability of an intestinal segment is uncertain, the surgeon may choose to temporarily close the abdomen and re-explore in 24 to 48 hours to definitively determine bowel viability. A Doppler scan can also be used to determine blood flow. The technique of leaving the patient with an open abdomen is also useful in cases of hemodynamic instability or abdominal catastrophe. In this case, the surgeon can resect the necrotic bowel and leave the patient to discontinuity, returning for a definitive assessment when the patient can tolerate the procedure. If a small bowel mass is encountered as the reason for an SBO, an oncologic resection should be performed. This should include a 5- to 10 cm margin as well as resection of the associated lymph nodes. In this case, rather than cutting the mesentery to the small intestine close to the bowel wall, the mesenteric resection should follow a triangular shape, with the apex of the triangle pointing to the base of the mesentery. At the conclusion of the operation, ensure the patient has a functioning nasogastric tube and manually confirm its position prior to fascial closure.

More recently, there has been a substantial increase in the volume and proportion of SBOs that are treated with the laparoscopic approach. In multiple retrospective case-matched series, laparoscopy is associated with shorter procedure times, shorter hospitalization, and less postoperative complications when compared with open surgery. Small studies have suggested that the use of laparoscopy may result in the lower incidence, extent, and severity of adhesions to parietal surfaces, but no trial evidence has shown that this translates to a decrease in the recurrence of SBO. Some retrospective studies have suggested that the laparoscopic approach may be associated with a higher incidence of bowel interventions (resection/repair), which may be a surrogate for iatrogenic injury; however, the data on this topic remain sparse and divided. In our experience, we will start an operation for SBO laparoscopically if there is a suspicion that there is a single adhesive band as the cause of obstruction, which can be easily lysed, or if the bowel appears sufficiently decompressed on imaging to allow enough visibility and maneuverability for laparoscopy.

We prefer an open Hasson approach away from any previous surgical scars to minimize the risk of bowel injury during entry into the abdomen. When running the bowel laparoscopically to identify the transition point, beginning distally at the ileocecal valve where the bowel is decompressed and working proximally toward the ligament of Treitz, mitigates the risk of grasping potentially delicate dilated bowel that is more prone to injury with light manipulation. When it is necessary to handle dilated segments, care must be taken to avoid iatrogenic injuries from the laparoscopic graspers. In the case that a small bowel resection is necessary, we prefer performing an extracorporeal anastomosis because dilated and fluid-filled bowel loops will cause some level of intra-abdominal spillage during anastomosis creation, whether it be stapled or hand sewn, that will be difficult to control even in the most experienced hands. Although the enthusiasm for laparoscopic SBO management is growing, the ultimate goal of the procedure is to complete the necessary operation safely and efficiently with minimal morbidity to the patient. The safety of the patient and the ability to complete the necessary surgical tasks always supersede maintaining a minimally invasive approach.

CONCLUSION

SBO represents a spectrum of disease that ranges from the mild, self-limiting symptoms of a partial obstruction to bowel necrosis that necessitates urgent surgical intervention. Although a large proportion of obstructions can be managed nonoperatively, surgeons will continue to face the difficult challenge of deciding on whom to operate, when to operate, and which approach to use. A high index of suspicion in those at risk for bowel ischemia with the aid of clinical, laboratory, and imaging findings helps surgeons identify patients with subtle or atypical presentations. Although open surgical intervention is the dominant surgical strategy for SBO, laparoscopy has demonstrated safety and efficacy and should be considered.

SUGGESTED READINGS

[illegible]

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[illegible]

[illegible]

[illegible] standard of care. Evaluating trends and outcomes in laparoscopic management of small bowel obstruction using the American College of Surgeons National Surgical Quality Improvement Program database. [illegible]

[illegible] adhesive small bowel obstruction: a study of the nationwide inpatient sample. [illegible]

[illegible] pathological score for predicting the risk of strangulated small bowel obstruction. [illegible]

[illegible] is associated with a survival benefit for patients with adhesive bowel obstruction. Ann Surg. [illegible]

Management of Crohn's Disease of the Small Bowel

Heather L. Yeo, MD, MHS, MBA, MS, and
Fabrizio Michelassi, MD

The incidence of Crohn's disease is increasing worldwide. Currently, the US Centers for Disease Control and Prevention estimate its incidence at 201 in 100,000 adults, the highest in industrialized countries. Within 10 years of diagnosis, nearly one-half of all patients require surgical management; however, surgery is not curative and many patients require multiple surgical procedures and complex surgical care throughout their lifetimes.

Crohn's disease is a chronic inflammatory disease that can occur anywhere along the gastrointestinal tract, with the terminal ileum being the most commonly affected site. The inflammation affects the full thickness of the gastrointestinal tract and can lead to development of strictures, perforations, hemorrhages, fistulas, or malignant transformations. The pathophysiology is unknown, although research points to dysregulated gut mucosal immune responses to environmental triggers in genetically predisposed individuals. The clinical course is characterized by unpredictable cycles of disease activity and quiescence, making it difficult to manage.

The presentation of Crohn's is varied and follows three main disease phenotypes: fibrosing, fistulizing, and inflammatory. The fibrosing phenotype is characterized by intestinal strictures and manifests itself with abdominal pain, possibly diarrhea, and partial or complete intestinal obstructions. The fistulizing phenotype presents with fever, abscess, or fistulas, whereas the inflammatory phenotype manifests itself with a painful, tender mass. The broader spectrum of signs and symptoms may include hematochezia, anemia and weight loss, fatigue, nausea and vomiting, malnutrition, vitamin deficiency, and growth failure in the young. Many of the symptoms are nonspecific; other gastrointestinal diseases such as infectious gastroenteritis, appendicitis, and diverticulitis must be ruled out.

The diagnosis depends on a detailed history, including family history, and a complete physical examination. Imaging, both radiologic and endoscopic, is critical to confirm the diagnosis, map its extent, and eventually follow the course of the disease. Computed

More recently, there has been a substantial increase in the volume and proportion of SBOs that are treated with the laparoscopic approach. In multiple retrospective case-matched series, laparoscopy is associated with shorter procedure times, shorter hospitalization, and less postoperative complications when compared with open surgery. Small studies have suggested that the use of laparoscopy may result in the lower incidence, extent, and severity of adhesions to parietal surfaces, but no real evidence has shown that this translates to a decrease in the recurrence of SBO. Some retrospective studies have suggested that the laparoscopic approach may be associated with a higher incidence of bowel interventions (resection/repair), which may be a surrogate for iatrogenic injury, however, the data on this topic remain sparse and divided. In our experience, we will start an operation for SBO laparoscopically if there is a suspicion that there is a single adhesive band as the cause of obstruction, which can be easily lysed, or if the bowel appears sufficiently decompressed on imaging to allow enough visibility and maneuverability for laparoscopy.

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tomography enterography or magnetic resonance enterography are the radiologic tests of choice. Upper and lower endoscopy provides direct observation and tissue for histopathologic diagnosis. Capsule endoscopy can be used for examination of the small bowel in the absence of strictures but is rarely necessary with modern radiologic examinations. At initial presentation, around 40% of patients manifest terminal ileal disease, 30% have colonic disease, 10% have duodenal and jejunal disease, 10% have perianal disease, and 20% have disease in more than one anatomic location.

MULTIDISCIPLINARY MANAGEMENT

Optimal management of Crohn's disease occurs within the expertise of a multidisciplinary team that comprises gastroenterologists, surgeons, radiologists, pathologists, nutritionists, specialty nurse clinicians of stoma nurses, social workers, and associated specialties as needed. Complex cases should be reviewed within this context and treatment plans should be formulated after consideration of multidisciplinary team input. Although not curative, surgery is critical in the management of the disease for many patients. Where applicable, patients should be considered for clinical trials.

MEDICAL MANAGEMENT

The majority of patients present with mild to moderate disease or spend long periods with their disease in clinical remission. For this early disease, treatment with 5-aminosalicylates or budesonide, depending on disease location, is a standard of management. Patients with severe disease are usually treated more aggressively with early introduction of immune modulators or biologic therapies. Acute flares are treated with corticosteroids and then, once in remission, patients are advised to start maintenance therapies.

The medical treatment of Crohn's disease has advanced significantly in the last decade with the introduction of anti–tumor necrosis factor biologic agents. Some early data suggest that biologics reduce mucosal healing. This observation has led many to change management with biologics used upfront rather than after more conventional treatments have failed.

Several longitudinal cohort studies suggest that biologics therapies may alter the course of disease and lessen the need for surgical treatment. It is likely that the reduction of local inflammation and possible mucosal healing induced by biologics may be effective in eliminating the need for surgical treatment in milder forms of the disease. Yet, there is no evidence that they are as effective in the more aggressive forms.

INDICATIONS FOR SURGERY

Overall, the goals of surgical treatment are alleviating symptoms and improving quality of life, while preserving bowel length. Obstructive and septic complications are the most common indications for surgery in small bowel Crohn's disease. Intestinal obstructions are usually partial or high grade and, in the absence of findings consistent with an acute abdomen, they can usually be resolved with bowel rest, time and supporting measures. The most common septic complication necessitating surgery is a perforation with an inflammatory abscess after appropriate percutaneous drainage of the abscess and a course of intravenous antibiotics, the diseased segment requires resection in most cases. Inflammatory masses with failure of medical management require surgical treatment as well. Most fistulae are not an indication for surgery unless they cause repeated urinary tract infections (enterovesical fistulae), sexual embarrassment (enterovaginal fistulae), or challenges with personal hygiene (enterocutaneous fistulae). Rare indications for surgery include free perforation, hemorrhage, and cancer. Cancer may manifest indirectly as a complete intestinal obstruction that does not resolve spontaneously with bowel rest and supportive measures as described previously.

The presence of disease at multiple sites along the gastrointestinal tract may make operative decisions more complex but does not alter the basic recommendations for treatment.

PREOPERATIVE PLANNING

Preoperative Medications

It is well established that the chronic, long-term use of steroids (a common practice of the past, which should not be performed nowadays) has a deleterious effect on wound healing and increases the risk of postoperative infectious complications. Whether the preoperative use of short-term steroids or antimetabolites increases the risk of postoperative complications is controversial. Nevertheless, it makes sense to try to reduce the dosage of these medications to the extent possible, but this is not feasible in the majority of patients because symptoms quickly recur. If a patient comes to surgery on steroids, perioperative steroids supplementation may be necessary to avoid acute adrenal insufficiency.

The recent widespread use of biologics has raised similar questions on their influence on postoperative outcomes. The literature is mixed, with some studies showing no effect and others showing a modest increase in postoperative infectious complications, especially if surgery occurs within 2 months from the last dose. In view of these reports, it is advisable to schedule the surgery, if at all possible, 2–3 or 8 weeks from the last dose.

In patients with long-term steroid treatment or biologics, consideration should be given to an intestinal diversion at the time of surgery especially if the patient has experienced weight loss, shows malnutrition, or has hypoalbuminemia. In these cases, the preoperative discussion with the patient should include also mentioning the formation of a temporary stoma.

Timing

Although not curative, surgery is critical in addressing complications of the disease and improving the patient's quality of life. Yet, determining the optimal timing of surgery may prove to be difficult in a chronic disease that alternates flares to periods of relative quiescence and in a lifelong disease in which surgical interventions should be minimized for patient convenience and to avoid the dreaded consequence of a shorter bowel. Emergency procedures are fortunately seldom necessary because free perforation, generalized sepsis, and acute gastrointestinal hemorrhage are rare. Every effort should be made to transform urgent conditions to elective situations. A complete bowel obstruction can usually be resolved with bowel rest, time, and supporting measures; an abscess should undergo percutaneous drainage and a course of intravenous antibiotics. In the presence of a large phlegmonous mass, bowel rest and total parenteral nutrition may be required to reduce the local inflammation, make a challenging procedure less so and avoid placing undiseased bowel at risk.

The most difficult situation is represented by a patient who is not doing well yet has not developed a clear complication of the disease. This situation, commonly called failure of medical treatment, refers to recognizing that medical treatment has failed to restore the patient's quality of life and surgery is necessary. Unfortunately, the desire to avoid surgery, the temptation of continuing or changing medical treatment in the hope of a miraculous response, and the chronicity of the condition that masks the overall worsening of the patient's general condition from day to day all conspire against a decision in favor of surgery. Waiting too long can lead to operating on a sicker patient who is more malnourished. As discussed earlier, the decision should be made carefully with a multidisciplinary team of surgeons and gastroenterologists.

Nutritional Status and Preoperative Preparation

Once a decision regarding elective surgery has been made, the patient's current health status must be evaluated to initiate preoperative planning. The patient's general medical condition must be considered and maximized. If nutritional deficits exist, and time allows, nutritional improvement should be pursued. This can be done in consultation with a nutritionist as enteral nutrition supplementation is preferred to parenteral when possible.

An enhanced recovery after surgery protocol should be initiated. Standard oral mechanical and antibiotic bowel preparation should be performed preoperatively unless the patient has a long-term, high-grade obstruction. In these cases, a prolonged period of clear liquid diet only, in combination with oral antibiotics just before surgery, is recommended. All patients should be given standard prophylactic intravenous antibiotics just before surgery. Fluid and electrolyte imbalances and any existing profound anemia also should be corrected before surgery. If a diversion is possible, a stoma site should be selected in the least inconvenient location on the anterior abdominal wall and marked preoperatively.

TECHNICAL CONSIDERATIONS OR SURGICAL INTERVENTION

Key to management of these patients is accurate preoperative planning, but often selecting the appropriate procedure cannot be decided until a thorough intraoperative examination is performed. The entire small bowel from the ligament of Treitz to the ileocecal valve should be carefully assessed. This can be done via laparotomy or laparoscopy. Special attention should be paid to all Crohn's related processes: strictures, phlegmonous masses, abscesses, and fistulae should all be documented. We recommend creating a "roadmap" and using that to plan the operation. The ultimate goal in addressing complications of the disease, alleviating symptoms, and improving quality of life while preserving bowel length through a safe procedure. Surgical techniques that can be used include: strictureplasty, intestinal resection, intestinal bypass, abscess drainage, fistula repair, diversion, or a combination of all these techniques.

A thorough preoperative discussion with the patient is critical, particularly in cases with extensive disease or cases that will require intervention in multiple intestinal segments. The possible nutritional effects of intestinal loss, as well as the possible role of a stoma should be discussed. The more information the patient and family understand regarding the plan, the better.

COMMON PROCEDURES FOR SMALL BOWEL CROHN'S

Bowel-Sparing Procedures

Bowel sparing procedures are covered in depth in another chapter. A brief mention is made here to put them in perspective with other surgical procedures for Crohn's.

From 20% to 30% of small bowel Crohn's disease can be managed with a strictureplasty as the only surgical procedure or in association with additional strictureplasties or bowel resection(s). Short isolated segments of stricture are appropriate for a Heineke-Mikulicz (3–7 cm) or a Finney (7–15 cm) strictureplasty. Longer segments or chain of like formations should be considered for a side to side isoperistaltic Michelassi strictureplasty. Multiple different strictureplasty techniques can be used in conjunction with simultaneous bowel resections in a patient with multifocal disease in an attempt to preserve intestinal length.

After opening the diseased segment in preparation for a strictureplasty, it is important to inspect the mucosa to rule out underlying pathology. If there are any suspicious abnormalities, a biopsy should be obtained for frozen section to rule out cancer or dysplasia because this will also rule out the use of strictureplasty in favor of a bowel resection.

Heineke-Mikulicz Strictureplasty

The most commonly used and simplest strictureplasty is the Heineke-Mikulicz strictureplasty. After isolating the diseased segment, two stay sutures are placed on either side of the structured area. A longitudinal enterotomy is then made along the antimesenteric border of the small bowel across the stricture and extended for 2 cm into the normal bowel on either side. The enterotomy is then closed in a transverse fashion in one or two layers.

Finney Strictureplasty

The Finney strictureplasty is used for medium length strictures up to 10 to 15 cm. The diseased bowel is folded on itself at the half point. A row of interrupted sutures is placed between the two loops of the folded bowel and a longitudinal U shaped enterotomy is made. The back wall of the enterotomy is closed in a continuous fashion and then continued anteriorly. A second layer of seromuscular sutures is then placed anteriorly.

Side-to-Side Isoperistaltic Strictureplasty (Michelassi Strictureplasty)

The Michelassi strictureplasty is used to preserve bowel in long segment disease or in areas with multiple strictures close to each other. The bowel is transected at the midpoint of the diseased segment. The proximal loop is then moved over the distal loop so they are lying in an isoperistaltic side to side manner. A back row of 3-0 sutures is used to approximate the two loops all the way to the end. A longitudinal enterotomy is performed on both loops and the intestinal ends are spatulated. The inner suture lines are performed in a continuous fashion with absorbable sutures and the anterior layer is inverted with an outer layer of nonabsorbable 3-0 sutures.

Bowel Resection

A bowel resection is the most common surgical procedure in Crohn's disease. Division of the intervening mesentery may be challenging because of its thickness and friability. In this situation, it is advisable to obtain proximal control with a vascular clamp across the vascular pedicle providing blood supply to the diseased loop. A vessel sealing energy source can then be used to seal and transect the mesentery with care. Partial and slow release of the vascular clamp allows vessels may need to be ligated with figure of eight 2-0 braided sutures. The use of the vascular clamp transforms a challenging situation to a manageable one. Attempting to blindly clamp the thickened mesentery while bleeding without previously obtaining proximal control can make things much worse. Surgeons should be cautious of thickened and inflamed Crohn's mesentery, particularly if it extends all the way into the retroperitoneum. Bleeding in this situation can be treacherous and can put the patient at risk of substantial blood loss and injuries to adjacent bowel and retroperitoneal structures.

Stoma

Occasionally a large inflammatory mass does not respond to treatment with fasting and total parenteral nutrition. In these cases, surgery may be necessary, but the surgeon may be confronted with a very challenging situation in which multiple internal loops of small bowel are found densely adherent to the inflammatory mass. A resection is not advisable because it would sacrifice a large amount of normal intestine; instead, a carefully constructed proximal stoma may provide the patient the appropriate time to let the inflammatory mass regress for an easier procedure at a later time when the normal loops of bowel can be safely dissected off the mass and preserved.

ANATOMIC CONSIDERATIONS

Duodenum

Duodenal disease manifests itself with delayed gastric emptying, nausea, and epigastric fullness resulting from one or multiple strictures along its course. Balloon dilation can be attempted especially in the presence of a single, short stricture. When surgery becomes necessary, strictureplasty techniques are preferred to bypass. Isolated strictures in the first, second, and third portions of the duodenum are usually amenable to a Heineke-Mikulicz strictureplasty, whereas strictures in the fourth portion of the duodenum may require a Finney strictureplasty with the first loop of the jejunum.

Bypass is used when strictureplasty is not feasible either because the length of a stricture or because of multiple strictures. Most

commonly this is accomplished with a gastrojejunostomy. Before the procedure, it is advisable to perform a gastric pH study. In the presence of an acid milieu, a vagotomy is added to the bypass to minimize the risk of postoperative marginal ulceration. In the presence of a neutral or near-neutral milieu, the vagotomy is omitted for fear that it may contribute to dumping and diarrhea. If the structures to be bypassed are distal in the inferior genu of the duodenum, a duodenojejunal bypass should be considered between the second portion of the duodenum and the jejunum. This configuration avoids the risk of a marginal ulcer and the need for a vagotomy.

The gastrojejunostomy can be performed in either an antecolic or retrocolic fashion and the anastomosis can be hand sewn or stapled. The anastomosis is typically performed using the most dependent part of the stomach on the greater curve. The most proximal loop of jejunum that can be brought up to the greater curve is used. A posterior row of interrupted sutures is placed to approximate the stomach and the small bowel. A 5-cm gastrojejunostomy is then constructed with a continuous inner layer of 3-0 absorbable suture and is reinforced with a front row of interrupted nonabsorbable sutures.

Small Bowel

Small bowel disease should be cared for with bowel-preserving procedures if at all possible or with bowel resection or stoma followed by bowel resection (see the previous section). Occasionally, small bowel disease develops into other hollow viscera. In the presence of an enteroenteric fistula located in the loop of bowel to be removed, the intestinal resection will remove the fistula en bloc. If the fistula connects with a normal loop of small or large bowel, the fistula can be divided and the defect in the small bowel can be debrided and closed primarily, ensuring the lumen of the bowel is not be compromised. In this case, a limited resection of the target loop of bowel needs to be performed as well. The diseased bowel is then, of course, resected. If the fistulized organ is the bladder, the opening should be debrided and closed in multiple layers if at all possible. Sometimes an intervening wall abscess makes closure difficult or impossible, even after debridement from chronic inflammation. Whether a closure is feasible or not, a urinary catheter is left in place for decompression for 7 days, after which a cystogram should be performed to check on the integrity of the bladder wall before removing the urinary catheter. If the fistulized organ is the vaginal cuff in a patient after a hysterectomy or the abdominal wall, all is necessary is the drainage of any intervening abscesses and debridement.

The most challenging operative situation is diffuse and complex jejunoileitis. In this situation, the surgeon is faced with many epienteral sites separated by inches of normal and possibly dilated bowel for a considerable length of small bowel. Deciding what needs resection, what can be managed with strictureplasty, and what can be left alone requires careful consideration, judgment, and a precise knowledge of the symptoms and complications that brought the patient to surgery. The most important consideration to remember in these cases is that surgery is not curative in Crohn's disease but merely palliative; hence, the surgeon needs to know what symptoms/complications need to be palliated/addressed. In addition, the most important directive at surgery is to carefully examine the entire bowel from ligament of Treitz to ileocecal valve, documenting the findings in a roadmap, which then becomes the basis of a comprehensive, individualized plan of action.

The extent of the disease does not necessarily mandate an open procedure. The diseased segments can be eviscerated progressively segment by segment, however, if there is any concern or struggle with stability, an open procedure may be preferable.

Terminal Ileum

Isolated disease of the terminal ileum is the most common site requiring surgery and accounts for nearly one half of all patients referred for surgical intervention. Most commonly, these patients present with obstructive symptoms or septic complications with or without fistula. Management is usually based on an ileocolic resection, although stricturoplasty can be used on limited anastomotic strictures of the anterior ileum after a previous ileocolectomy.

When the ileocolectomy is performed laparoscopically, the pneumoperitoneum is created through a trocar placed in a periumbilical or umbilical position. Once the pneumoperitoneum is established, a 30-degree laparoscope is placed through the umbilical port and two additional 5-mm ports are inserted in the left upper and left lower quadrants, respectively. The terminal ileum and cecum can then be mobilized in a medial to lateral or lateral to medial approach. The vascular pedicle is then sealed and transected with an energy device. If the pedicle is thickened and friable all the way to the base, it is advisable to take it under direct vision through an extension of the umbilical trocar incision. An ileocolic anastomosis can then be performed in a number of ways, hand sewn or stapled, and in a number of configurations, end to end, side to side, or end to side. The senior author prefers a hand sewn end to end anastomosis. A new anastomosis, the antimesenteric side to side hand sewn anastomosis or a Kono S anastomosis, is being studied to validate claims that it is associated with milder endoscopic recurrence at 3 and 12 months postoperatively and much lower incidence of recurrence in need of resection in the first 5 years postoperatively.

POSTOPERATIVE CARE

The enhanced recovery after surgery protocol should be continued postoperatively with narcotic-sparing analgesia. A nasogastric tube is typically not necessary. Patients are discharged once there is clear evidence of sufficient bowel function to maintain hydration independent of intravenous fluids and adequate pain control on oral medications. If a patient has a stoma, discharge can only occur after the patient has learned how to take care of the appliance and the stoma output is under control (usually <1000 mL/24 hours). At discharge, patients are given information regarding warning signs of complications and given a quick and clear pathway back to the team should any concerns arise.

POSTSURGICAL MEDICAL MANAGEMENT

It is well known, and even assumed, that Crohn's disease will recur, and that at a microscopic level it will do so early at the anastomotic site. Recently, the American Gastroenterological Association has published guidelines on the management of Crohn's disease after resection suggesting early postoperative medical therapy in high-risk groups and observation for low-risk patients. In those patients suffering from reduced bowel length affecting nutrition, the recent Food and Drug Administration approval of teduglutide (Gattex) for short bowel syndrome offers great promise.

Suggested Readings

De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385:1406–1417.

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Use of Strictureplasty in Crohn's Disease

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Crohn's disease (CD) is an inflammatory disease that establishes full thickness inflammation in the gastrointestinal tract that is chronic with acute exacerbations. It can afflict any site along the gastrointestinal tract, but most commonly initiates in the terminal ileum. Surgery for CD does not cure, but rather treats difficult symptoms as an adjunct to effective medical therapy. However, surgery takes center stage in managing the most troubling complications of CD. The transmural inflammation of the bowel wall in CD will lead to abscess formation, enteroenteral fistula, enterocutaneous fistula, perforation, and stricture in many patients. Stricture formation most commonly becomes symptomatic when it occurs in the small bowel.

The baseline surgical treatment of symptomatic CD has been resection of the involved bowel with either restoration of intestinal continuity or a stoma. Resection removes the Crohn's diseased tissue, which is believed to have specific advantages for the patient. Strictureplasty has been considered a less preferred, or backup, option, inferior to resection, used only when bowel preservation for the patient predominates as a consideration. That thinking is changing. Based on circumstances, strictureplasty should be considered an equal first treatment option, rather than the reserve option for many patients.

OVERVIEW

Strictureplasty carries the significant advantage of avoiding the loss of gastrointestinal length. Some speculate that relieving the obstruction via strictureplasty (Box 1), thereby resulting bowel content stasis, can by itself contribute to resolution of inflammation in the involved bowel. Strictureplasty requires some fundamental differences in approach and technique. The suturing is to abnormal bowel, and the anastomotic surfaces that are joined frequently involve diseased inflamed tissue. In CD resection, the margins are typically grossly unresolved, as suturing is to normal bowel. The minimally invasive evolution in surgery has moved a great deal of inflammatory bowel surgery to a laparoscopic approach. A complicated strictureplasty procedure involves suturing of difficult tissue with thick, less mobile mesentery, making a laparoscopic technique more difficult and less attractive. Nevertheless, the advantage of bowel preservation in a disease in which many patients will undergo multiple operations is important and attractive.

INDICATIONS AND CONTRAINDICATIONS

The etiology of bowel stricture formation is most likely related to repeated episodes of inflammation, resolution, and remodeling of the bowel wall, leading to replacement of the normally pliable tissue with a thickened, unpliable bowel wall segment that, over time, narrows the lumen. This leads to obstructive symptoms. The time course of this process varies from patient to patient and may be modified by medications such as steroids, immunomodulators, or biologics, including tumor necrosis factor-α antagonists and integrin blockers. Over time, the involved segment of bowel may become less responsive to increasingly aggressive medical management, and surgical intervention will become necessary for obstructive symptoms.

Strictureplasty can be undertaken throughout the small bowel but has been less frequently used in the colon, because the concern for neoplasm is increased (Box 2). Strictureplasty should not be used in the presence of active sepsis or significant acute inflammation, such as phlegmon or abscess, or in the face of generalized peritonitis. Fistula of the involved bowel is also a relative contraindication (Box 3). Under these circumstances, the increased risk of suturing and joining infected badly inflamed tissue does not appear warranted. However, strictureplasty might still play a role in another diseased segment in conjunction with a fistula at another site. Obviously, if there is concern regarding tumor, the segment must be resected using oncologic principles. Severe malnutrition mitigates against strictureplasty because of the increased demand for effective tissue healing.

PREOPERATIVE PREPARATION

The importance of team management of patients with CD cannot be overemphasized, with the surgeon and the gastroenterologist as the critical (but not the only) team members. Today, because of the effective armamentarium of medical therapy, the overwhelming balance of surgery is elective and not emergent. Therefore the balance between the patient's symptoms, their "readiness" for surgery, and their medical therapy profile all play heavily into decisions regarding surgery. Any septic focus should be controlled with antibiotics, percutaneous drainage, or both. Nutritional status should be evaluated, and patients who are nutritionally compromised should undergo nutritional repletion by a liquid enteral diet, if needed, to reverse their catabolic state before surgery with an aim to reduce postoperative complications.

Optimal surgical outcome requires careful preoperative evaluation and planning. The scope and nature of the patient's past and current disease activity should be evaluated and documented. Obtaining a thorough history of prior operations and operative reports to help full to understand the patient's current anatomy. Colonoscopy should be performed to determine whether there is any colonic disease that might require surgical treatment. Any colonic stricture must undergo biopsy to rule out the possibility of malignancy. Although colonic strictureplasty may be considered if there is a real need to preserve colonic length, the risk of an occult malignancy in a colonic stricture is relatively high, and resection should be the preferred procedure. The extent of small bowel disease should be defined before surgery. Magnetic resonance enterography (MRE) is the gold standard today to assess structural anatomy and inflammatory state. MRE provides key information regarding the state of inflammatory versus mechanical stricturing; primarily inflamed strictures are more likely to respond to medical therapy. Computed tomography enterography, often with water as the contrast agent, is also useful. Together these provide an effective map of the distribution of disease activity, as well as any unsuspected enteroenteral fistulae, contained perforations, and an overall estimate of small bowel length. Preoperative stoma site marking should be considered as well, particularly in patients likely to possess surgical challenge based on preoperative assessment.

INTRAOPERATIVE EVALUATION

The first step in any CD abdominal procedure is to exhaustively assess the state of disease. The bowel should be examined laparoscopically or via laparotomy, with the preoperative imaging in mind, matching the imaging findings to the visual appearance of the bowel. The prime question being considered during this evaluation is whether affected strictured segments are candidates for strictureplasty, will require resection, or can be left alone in the case of just fat creeping with no bowel wall effects. The small bowel usually betrays the presence of any CD by the presence of creeping fat, wall thickening, and mesenteric thickening. Additionally, any abscesses or fistulae must also be addressed in the surgical plan. The colon is more subtle; mucosal disease can be present with the external wall looking normal.

BOX 1 Surgical Objectives in CD Surgery

Preoperative Objectives

- Maximize or exhaust nonsurgical treatment options before surgery
- Surgical intervention should be limited to the treatment of symptomatic complications of CD
- Evaluate nutritional status before surgery
- Consider supplemental nutrition to improve nutritional status before surgery when nutritional status is poor

Intraoperative Objectives

- Spare bowel length
- Utilize alternative strategies to resection when appropriate to preserve sufficient length of the remaining bowel and minimize the propensity for short bowel syndrome
- Spare the ileocecal valve when possible
- Biopsy any suspicious ulcers or mucosa for malignancy

BOX 2 Indications for Strictureplasty

- Diffuse involvement of the small bowel with strictures
- Prior small bowel resection greater than 100 cm
- Rapid recurrence of CD with obstruction
- An obstructing, chronic small bowel stricture without associated sepsis

BOX 3 Contraindications to Strictureplasty

- Albumin level <2 g/dL
- Free or contained perforation of the bowel associated with the stricture
- Phlegmonous inflammation, internal fistula, external fistula involving affected site
- Stricture close in proximity to a resection site
- Multiple strictures within a short segment in a patient who has not had prior small bowel resections or in a patient with sufficient small bowel length
- Any stricture with pathologic evidence of dysplasia or malignancy

STRICTUREPLASTY TECHNIQUES

Strictureplasty techniques can be categorized as short, intermediate, and long (Table 1 and 2). Short strictureplasty technique applies to strictured segments 7 cm or less, usually using a Heineke-Mikulicz type technique. Intermediate strictureplasty is used for segments between 7 and 15 cm, using a Finney type strictureplasty. Longer strictureplasty is usually indicated in situations where a length of bowel has close multiple tight strictures over a longer length of bowel. In these instances, the Michelassi side-to-side strictureplasty is indicated.

SHORT STRICTUREPLASTY

Short strictures (<7 cm) are best dealt with using a strictureplasty technique derived from the Heineke-Mikulicz pyloroplasty performed for pyloric stenosis. A Heineke-Mikulicz type strictureplasty (Fig. 1) is performed by first placing two 3-0 sutures, either unabsorbable or absorbable, on the side of the bowel at the midportion of the stricture to act as stay sutures. The surgeon then creates an antimesenteric longitudinal incision with electrocautery. This incision divides the stricture and should be carried out at an equal distance of 2 cm proximally and distally into normal, thin-walled, nonthickened bowel (Box 4). For ease of closure, it is essential that the longitudinal incision stays truly on the antimesenteric border. The mucosal surface of the affected and neighboring bowel are then evaluated. Mucosal biopsies of the stricture for frozen section analysis are obtained to rule out the presence of dysplasia or malignancy. This is especially important if an ulcer is noted. With a first segment open, neighboring segments can also be evaluated. One method is to thread a well-lubricated Foley catheter in the lumen of the bowel to another affected segment. The balloon is then inflated and gently pulled through affected bowel to gauge the

TABLE 1 Stricture Length and Recommended Strictureplasty Technique

Stricture	Recommended Technique
Short (<7 cm)	Heineke-Mikulicz
Intermediate (7 to 20 cm)	Finney
Long (>20 cm)	Side-to-side isoperistaltic

TABLE 2 Technique Used in Meta-analysis, Including 4538 Strictureplasties

Type of Strictureplasty	%	N
Heineke-Mikulicz	79	3566
Finney	16	857
Side-to-side isoperistaltic	3	154
Other	2	111
Totals	100	4538

From Campbell L, Attilo R, Warner I, et al. Comparison of conventional and unconventional strictureplasties in Crohn's disease: a systematic review and meta-analysis. Dig Caloe Dysfunct. 2011;2(5):714-726.

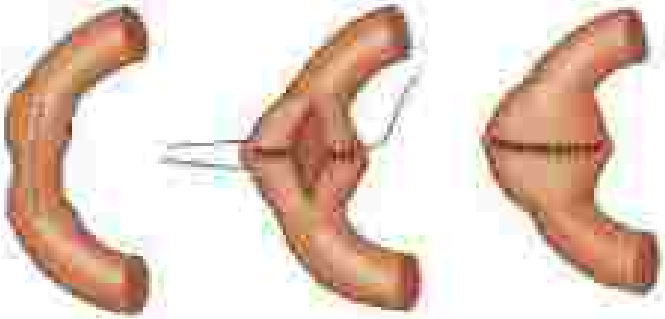

FIG. 1 Heineke-Mikulicz strictureplasty on an isolated stricture. A single-layer suturing technique is performed to close the longitudinal enterotomy transversely, maximizing an anastomotic lumen.

BOX 4 Strictureplasty Operative Strategy

- Extend incision 1 to 2 cm beyond the diseased segment
- Biopsy any suspicious ulcers and mucosa to exclude carcinoma
- Obtain excellent hemostasis
- Closure with an absorbable or nonabsorbable suture in a one- or two-layer fashion
- Label resection at strictureplasty site with metallic clip

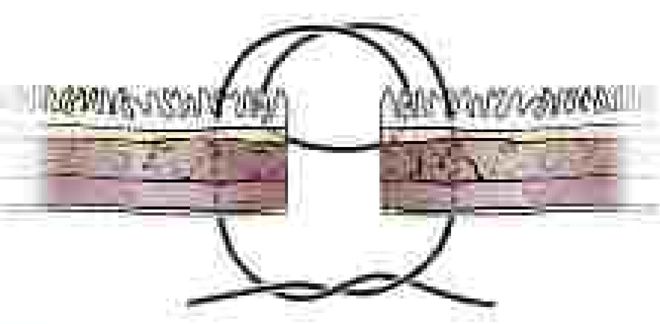

FIG. 2 Modified Gambee stitch. [illegible] Modified Gambee stitch [illegible] *Am J Surg* [illegible]

size and tightness of the closure. For closure, the stay sutures are pulled perpendicular to the long axis of the bowel (as in Fig. 1). Then the enterotomy is closed in one or two layers. A single suture technique particularly suited to strictureplasty is the modified Gambee stitch (Fig. 2). This single layer technique ensures appropriate approximation of the mucosa and serosa, while leaving the blood supply intact between sutures. In the instance of a two-layer closure, a running absorbable inner layer and an interrupted Lembert nonabsorbable suture outer layer is used. This transverse closure strictureplasty technique is ideal for short strictures, but not for longer segments.

It is important to obtain excellent hemostasis. Bleeding from a strictureplasty site is one of the most common and troubling potential postoperative complications. Labeling the mesentery at each strictureplasty site with radiopaque metal clips may assist with discriminating between multiple sites in the event of postoperative hemorrhage. Selective mesenteric angiography with intraarterial vasopressin infusion will control most episodes of bleeding. If bleeding continues despite conservative medical therapy, the metallic clips may help localize the bleeding strictureplasty site and prevent the need to open all of the strictureplasty sites to localize the bleeding at the time of surgery. Alternatively, India ink blue dye can be injected at the time of selective mesenteric angiography for intraoperative localization.

The Heineke-Mikulicz strictureplasty can be performed laparoscopically. With effective suturing skills, the surgeon can simply perform the procedure with intracorporeal suturing technique. However, Crohn's tissue is notoriously unforgiving, making the technical aspects critical. If the mesentery allows, the affected segment can be delivered through a small laparotomy and the sutures placed under direct vision.

INTERMEDIATE STRICTUREPLASTY

The Finney strictureplasty (named after the Finney pyloroplasty) resembles a side-to-side anastomosis (Fig. 3). This strictureplasty may be useful in a patient with a medium-length stricture (7 to 20 cm) or for a segment with multiple short strictures closely grouped together with intervening dilated short segments of bowel. The bowel is folded at the stricture, with the normal proximal and distal bowel brought alongside one another. If a hand-sewn technique is used, there are two options. First, if the strictured area is mildly stenotic and the bowel is of reasonable quality, the entire stricture may be opened along the antimesenteric border, and a hand-sewn, essentially side-to-side anastomosis may be performed along the length of the enterotomy (Finney strictureplasty, Fig. 3). Second, if the stricture is too tight or the bowel is not suitable for suturing, then a true side-to-side anastomosis between the proximal and distal normal bowel can be performed, leaving the strictured segment in place as a short bypassed segment (Jaboulay strictureplasty, Fig. 4). Similarly, if a stapling device is used, a side-to-side anastomosis can be fashioned between the normal proximal and distal bowel, leaving the strictured segment in continuity. There is some concern with the Jaboulay

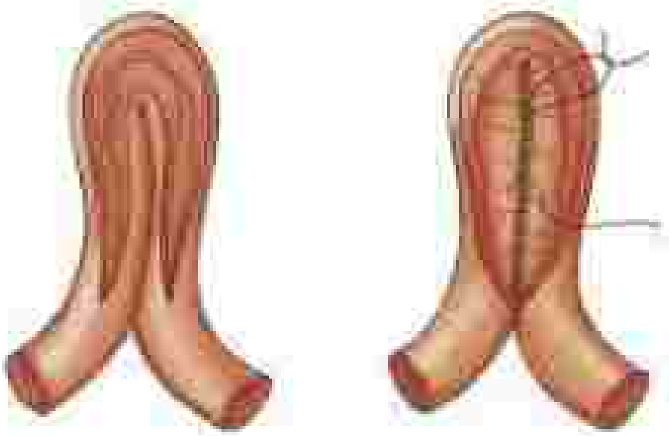

FIG. 3 A Finney strictureplasty can be used for the treatment of a long stricture. [illegible]

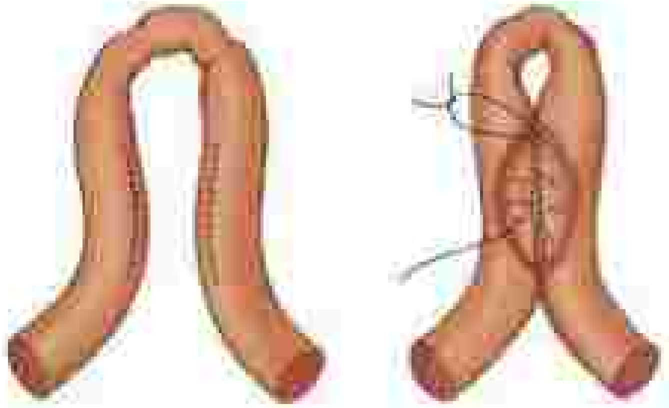

FIG. 4 Jaboulay strictureplasty can be used to bypass a stricture that is too narrow or a stricture in which the bowel is not suitable for suturing.

strictureplasty technique in that it results in a bypassed segment. Although the segment is short, there are potential long-term ramifications, including bacterial overgrowth and malignant degeneration.

In patients with two strictures in close proximity, a modification of the Heineke-Mikulicz strictureplasty technique has been created. The bowel is entered on the antimesenteric border, and both strictures are divided, as is the normal intervening segment. The resulting long enterotomy is closed transversely (Fig. 5).

When the bowel is markedly dilated proximal to a short stricture, the size discrepancy between the proximal and distal normal bowel often precludes a Heineke-Mikulicz-type strictureplasty. In these cases, a Moskel-Walske-Neumayer strictureplasty can be performed (Fig. 6). This strictureplasty technique is essentially a Y-to-V advancement flap closure of the stricture. The stricture is opened along the antimesenteric border in a Y-shaped enterotomy, with the Y portion in the dilated bowel just proximal to the stricture. The strictured segment is then pulled apart, and the antimesenteric segment of the proximal dilated bowel is advanced into the strictured area and closed in a transverse fashion, with one side of the closure being normal bowel along the entire length and the other being the two strictured bowel edges.

Although it is possible to perform the necessary intracorporeal suturing to perform these more challenging procedures laparoscopically, most surgeons will accomplish these procedures

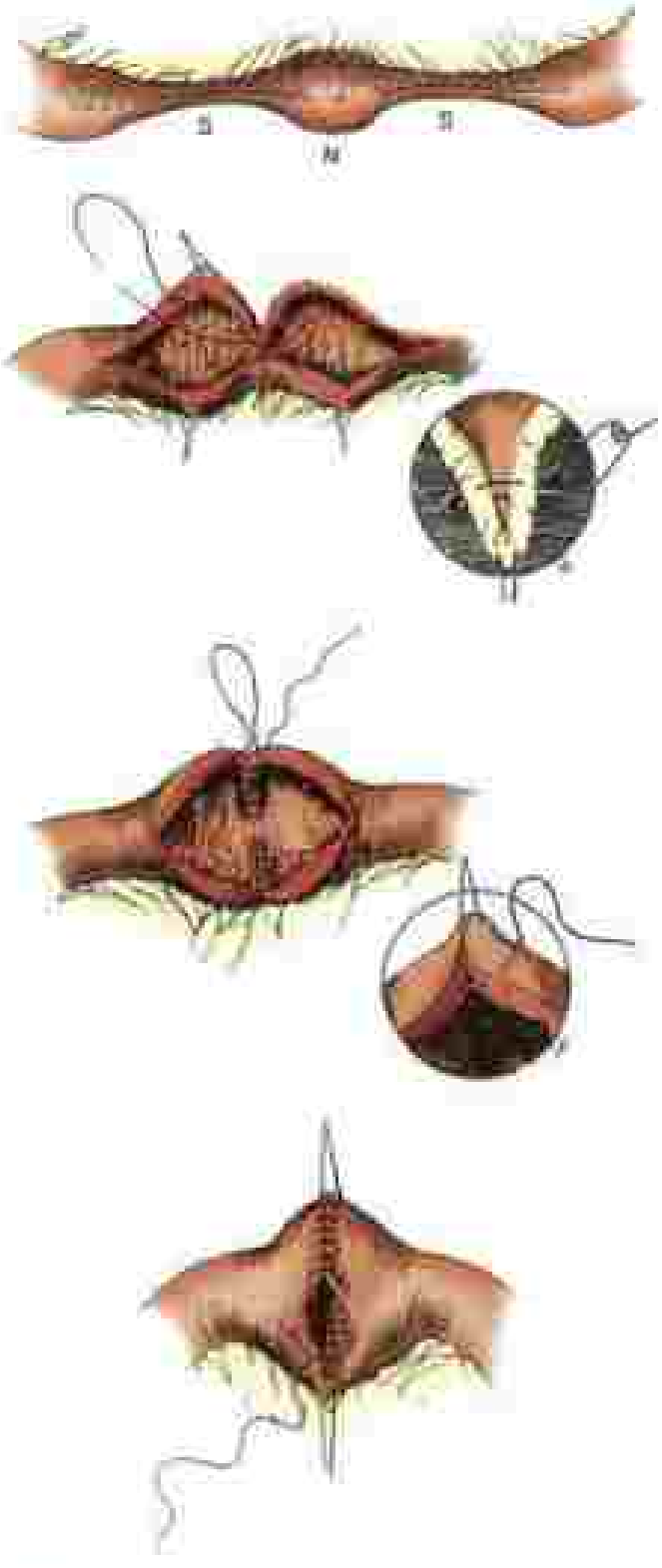

FIG. 3 Modified Heineke-Mikulicz strictureplasty can be used for two short segment strictures that are close to one another with a normal or dilated segment of bowel between them.

FIG. 4 Modified Heineke-Mikulicz strictureplasty is used when there is a significant or a difference between the proximal and distal bowel segments adjacent to a short stricture. Instead of a longitudinal incision, a U-shaped enterotomy is performed and then closed in a transverse fashion.

LONG STRICTUREPLASTY

The side-to-side strictureplasty as described by Michelassi et al. and is applicable for long, multiple strictures in a segment of small bowel. This is a unique, versatile procedure. A long segment of bowel that would result in a proximal, extensive resection can be retained as a side-to-side isoperistaltic strictureplasty. In this technique, the segment is completely divided transversely at the midpoint of the strictured segment. Unlike other strictureplasty techniques, the proximal and distal limbs are then transected perpendicular to the long axis of the bowel to produce the two segments of bowel to be overlapped and positioned side-to-side along the entire length of the divided segments. If possible, the dilated segments of one of the bowel segments ends is lined up with strictures in the other segment. Both strictured segments are opened along the anti-mesenteric border and the anti-mesenteric faces of bowel are sewn one to the other in an isoperistaltic fashion. The lowered suturing technique is an outer layer of interrupted sutures with an inner layer of running absorbable suture. Once the divided loops are approximated with limbers interrupted sutures, the bowel is opened longitudinally at the antimesenteric location. The inner layer is then constructed with a two-layer continuous suturing technique. The stricture is completed with interrupted nonabsorbable suture connecting the inner layer. This technique does not result in bypassed segments of bowel.

Colonic strictureplasty has limited utility because the colon is not essential for nutrient absorption and an isolated colonic stricture has a low incidence of harboring an occult malignancy. However, in some patients in whom preservation of colonic mucosal surface area is of utmost importance, such as a patient with short bowel syndrome, a colonic strictureplasty may be performed.

RESULTS

Increasingly large studies and meta-analyses support the view that strictureplasty is at least equivalent to resection for the treatment of Crohn disease. A University of Toronto group reported a large series of 901 strictureplasty procedures over 5 years from 1982 to 2002. Most patients underwent 1 to 2 operations, including the strictureplasty

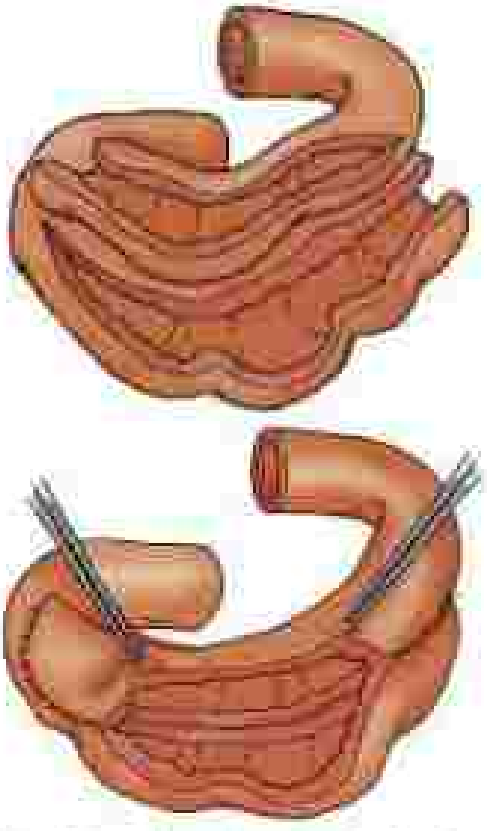

FIG. 7 Side-to-side isoperistaltic strictureplasty is used for a long segment of involved bowel that would require resection because of multiple non-stricture structures. The involved bowel is divided in the middle of the segment, and in a mirrored pattern of orientation to allow the two segments to lie side by side one another and laid side to side in an isoperistaltic fashion. An enterotomy is performed with the two cut edges closest to one another closed in a back wall and the others closed in the front wall. (From Kennedy GT, Zaghiyan K, Fleshner PR, et al. Strictureplasty for Crohn's disease made simple. J Am Coll Surg. 2016;223(1):197.)

procedures over 25 years. Outcomes measures reported were short-term complications, surgery free survival, need for further surgery, and quality of life. Median follow-up was 94 months. On multivariate analysis, only one factor was related to the need for further surgery: the patient's age at the time of the first strictureplasty. Quality of life measures were also impressive. The authors conclude that strictureplasty is safe with acceptable long-term outcomes.

One of the largest systematic reviews and meta-analyses of the safety and efficacy of strictureplasty for CD was published by Yamamoto et al. in 2007 (Table 3). A total of 3250 strictureplasties were performed, with a mean number of three at one operation (range, 1–21). A bowel resection for long strictures, perforation, fistula, or abscess was performed in 61% of these patients (668 of 1086). The overall complication rate was 12% (132 of 1127) for jejunoileal stricturoplasty or both. The most common complications were septic complications in 4% (leak, fistula, or abscess in 39 of 1057 patients), of which 60% required reoperation for sepsis. Other complications included hemorrhage 3% (36 of 1057), ileus 3% (34 of 1057), wound infection 2% (19 of 1057), and bowel obstruction 1% (11 of 1057). Risk factors for complications included hypoalbuminemia, preoperative weight loss, emergency operations, and presence of an intra-abdominal abscess with peritoneal contamination, anemia, and older age. The recurrence rate for jejunoileal or ileum strictureplasty or both was 9% (), recurrence requiring reoperation occurred in 30% of patients (312 of 1078). The median

TABLE 3 Stricture Location in 3081 Strictureplasties in 1112 Patients

Location	%	#
Jejunum and/or ileum	94	2242
Anastomotic strictureplasty	4	99
Duodenal	1	35
Colon	1	27
Not specified	22	678

Data from Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. Dis Colon Rectum. 2007;50(12):1968–1986.

follow-up duration was 107 months. Risk factors for recurrence included younger age, short duration of disease, and short interval since previous resection.

Michelassi and colleagues recently reported 25-year follow-up on side-to-side isoperistaltic strictureplasty in CD in 40 patients with extensive fibrostenosing CD with very impressive results. The authors state, "The majority of patients maintain the original side-to-side isoperistaltic strictureplasty after a median follow-up of 11 years." This was a rarely used option (more than 2000 patients underwent surgery over these 25 years for CD), but it is an important option for patients with difficult extensive disease and the need to preserve bowel length.

A key study may provide insight into new thinking regarding strictureplasty as opposed to resection for CD. In this study, a series of 29 patients with terminal ileal disease abutting the cecum underwent modified side-to-side isoperistaltic strictureplasty to include the ileocecal valve. The median stricture length was 10 cm. Median postoperative follow-up was 21 months and consisted of magnetic resonance imaging, radiologic scoring, and endoscopy. The authors report marked improvement in mucosal and bowel wall thickness in many of the studied patients in the absence of tissue resection. The authors state that, "We speculate that the alteration of fecal stasis may play a key role in postoperative mucosal healing, modifying the microbial-mucosal interaction." This suggests that resolving the stasis of bowel contents may play a role as important as or more important than tissue resection. Although this is speculative, it may be that future surgical interventions may focus more on bowel content flow and less on tissue resection.

SUMMARY

Strictureplasty is an integral part of the surgical management of patients with obstructive jejunoileal CD and ileocolonic recurrence. The primary role of strictureplasty is to preserve small bowel length in a patient population prone to recurrence and multiple surgical interventions over a lifetime. The most commonly performed strictureplasty is the Heineke-Mikulicz technique. The length of the stricture and location dictate the specific technique of strictureplasty to be used. Although preoperative evaluation of patients with CD and consultation with a gastroenterologist experienced in inflammatory bowel disease should be performed in all patients with complications of CD requiring surgery.

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MANAGEMENT OF SMALL BOWEL TUMORS

Sandra R. DiBrito, MD, PhD, and Mark D. Duncan, MD, FACS

Small bowel malignancies are rare, difficult to diagnose, and have low treatment guidelines. Because small bowel tumors present with vague and common symptoms, it is imperative that the surgeon keep them on the differential for abdominal pain, obstruction, and gastrointestinal blood. However, the majority of patients referred to surgeons for small bowel tumors have a suspicious mass on imaging. Evidence-based guidelines on management of small bowel malignancy are difficult to find, and given the rarity of these lesions, there is little information in the literature to provide reference for clinical decision making.

PRESENTATION

The typical presenting symptoms of small bowel tumors are vague and highly variable. Many patients present to surgeons as a referral from a primary care provider or a gastroenterologist with a known mass, discovered following workup for gastrointestinal (GI) bleeding or encountered incidentally on imaging. Others will present with colicky pain from obstruction, either partial or complete, and will be found to have a small bowel tumor during surgery. The mass itself can be intraluminal or circumferential, directly responsible for obstruction, or can have surrounding fibrosis that results in stricture and adhesions to the mesentery or retroperitoneum. Small bowel tumors (SBTs) are frequently asymptomatic but can present with bleeding or obstruction.

Nonspecific symptoms such as weight loss and vague abdominal pain are concerning for malignant neoplasms such as adenocarcinoma and lymphoma, particularly in the context of a known small bowel mass; however, these nonspecific symptoms should prompt broad investigations because small bowel tumors are one of the rarer malignancies. Neuroendocrine tumors that are productive of vasoactive amines can present with a wide range of symptoms, from epigastric pain and ulcerations to flushing, sweating, and diarrhea. Most are asymptomatic, however, and are found incidentally on imaging workup for other conditions.

Predisposing Conditions

Familial adenomatous polyposis, hereditary nonpolyposis colon cancer, and Peutz-Jeghers syndrome are genetic cancer syndromes that predispose to small bowel malignancy. Crohn's disease, celiac sprue, and chronic inflammatory conditions involving the small bowel also predispose to small bowel malignancy, and risk increases with increased severity and longer duration of disease. Patients with cystic fibrosis have 19 times higher incidence than the general population, and with an additional two- to five-fold higher risk following lung transplantation. Obesity, tobacco use, and high dietary intake of red meat, smoked foods, alcohol, and refined sugar have all been shown to have an association with small bowel tumors, but the links between these risk factors and tumorigenesis are not clear. In fact, the etiology of small bowel tumors that are not associated with either chronic inflammatory diseases or genetic cancer syndromes is poorly understood.

Examination and Diagnostics for Patients With Small Bowel Tumors

On physical examination, it is only rarely possible to palpate an abdominal mass. Laboratory workup should include the standard complete blood count to look for anemia or elevated white blood cell count in the acute setting if signs of perforation are present. Elevated liver enzymes or amylase suggest possible duodenal mass or obstruction. Carcinoembryonic antigen is often elevated in small bowel adenocarcinoma but is not sensitive or specific. Serum 5-HIAA and chromogranin A should be routinely tested if there is a strong clinical suspicion of neuroendocrine tumor based on symptoms or imaging features.

Imaging

On presentation with obstructive symptoms, a computed tomography (CT) scan with intravenous (IV) contrast allows clinicians to visualize the location of obstruction and possibly even the mass itself (Fig. 1). Masses can be constricting, occasionally demonstrating an "apple core" appearance with a circumferential constriction of the lumen. Some masses are polypoid, projecting intraluminally, and are better visualized with oral contrast. Close evaluation of the contour of the bowel is necessary to find submucosal lesions, and the keen surgeon should also thoroughly evaluate the mesentery for associated enlarged nodes or a mesenteric based mass. Occasionally, enlarged nodes are the only sign of a nearby small tumor. Negative CT scans should not rule out small bowel tumor because they are not particularly sensitive in this condition. However, CT does detect abnormalities in up to 80% of patients who do have a small bowel tumor. CTs are also valuable for staging nodes and metastatic lesions (Table 1). Additional specialized imaging modalities such as octreotide or positron emission tomography/computed tomography scans are helpful in localization of neuroendocrine tumors, but these more costly studies should be reserved for patients in whom a high clinical suspicion is present (Fig. 2).

Endoscopy

Esophagogastroduodenoscopy can detect tumors into the third portion of the duodenum and is an excellent tool to begin the workup for GI blood or other symptoms that are suspicious for GI tumors. Endoscopic ultrasound is a useful adjunct to standard esophagogastroduodenoscopy but, in the discussion of small bowel tumors, is limited to evaluation of duodenal lesions. For more distal evaluations, balloon-assisted deep enteroscopy or push endoscopy techniques can be performed by expert gastroenterologists and allow for visualization of most or even all of the small bowel lumen. This, however, is only rarely used and only available in specialized centers. Video capsule endoscopy also affords the ability to evaluate the

de Buck van Overstraeten A, Wolthuis A, Vermeire S, Verbeeck J, Fieuws S, Hoentjen F, Buisson A, Bommelaer G, et al. Modified side-to-side isoperistaltic anastomosis over the ileocaecal valve: an alternative to ileocaecal resection in extensive terminal ileal Crohn's disease. J Crohns Colitis. 2016;10:437–442.

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mucosal surface of the entire small bowel, with an average of 30,000 images captured in the small bowel alone during an examination. With the assistance of neural networks and machine learning, the interpretation of these studies is becoming more sensitive and specific, making it an increasingly helpful tool for the investigation of small bowel tumors. Video capsule endoscopy does not allow for tissue diagnosis and is contraindicated in patients with obstructive symptoms.

MANAGEMENT

Benign

Several types of benign small bowel neoplasms exist, and all are quite rare. Adenomas can be categorized as either villous, tubular, or Brunner's gland associated. As in colorectal cancer, some adenomas have malignant potential. There are no firm guidelines regarding management of these masses, but conventionally, the colorectal cancer pathway is followed with endoscopic resection if possible. Adenomas have increased malignant potential when associated with familial adenomatous polyposis. The number, size, histology, and dysplastic characteristics of the polyps should guide management using the Spigelman classification.

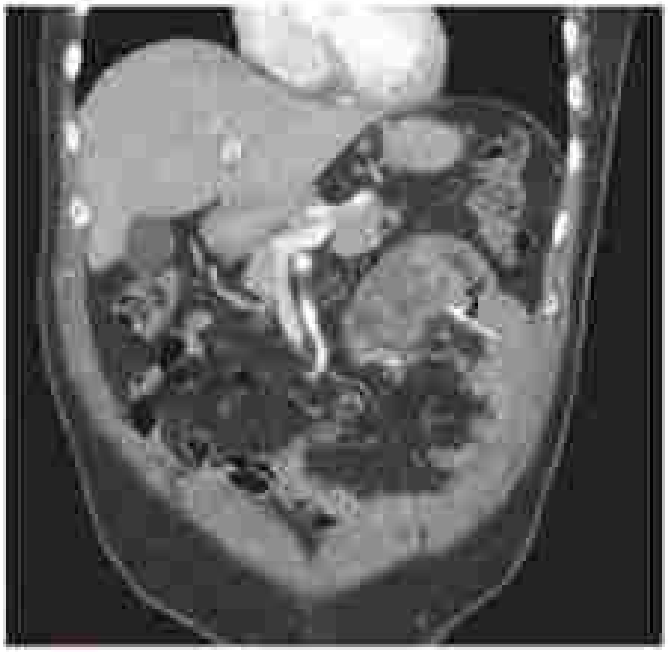

FIG. 1 Adenocarcinoma in the fourth portion of duodenum (arrow).

surgical resection is warranted for large adenomas that are not amenable to endoscopic resection, particularly if biopsy reveals villous features. In addition, patients should be screened for synchronous colorectal lesions with colonoscopy.

Leiomyomas are small tumors that are present in the submucosa of the small bowel. They are routinely small, firm, and well circumscribed. Although they may cause obstruction and require resection for this reason, their presence alone is not an indication for surgery. Differentiating between leiomyosarcoma and leiomyoma can be difficult, and often these lesions are surgically resected to rule out malignant disease.

Lipomas are diagnosed relatively easily on CT because of their characteristic fatty density. Hamartomas associated with Peutz-Jeghers syndrome should be resected only if causing bleeding or obstructive symptoms. In addition to lipomas and hamartomas, fibromyomas and ganglioneuromas do not require resection although biopsy may be necessary for diagnosis confirmation. Hemangiomas can be present along the length of the small bowel. Fortunately, these are easily differentiated on CT with IV contrast or magnetic resonance enterography obviating the need for biopsy.

Malignant

Malignant tumors of the small bowel are rare, with estimates of 10,420 cases in the United States and only 1450 mortalities for 2018. Small bowel cancer comprises 1% to 2% of GI malignancies only. Because of the rarity of these cases and available retrospective data, very few guidelines are available even worldwide for treatment of small bowel malignancy, and those are routinely derived from expert opinion based on multiple management of colon cancer. For this reason, each case should be evaluated on an individual basis and overseen by a multidisciplinary oncology team led by the surgical oncologist.

Neuroendocrine Tumors

Derived from neuroendocrine cells, known as Kulchitsky cells, neuroendocrine tumors are found throughout the crypts of Lieberkühn and are the most common small bowel tumor. As secretory tumors, their presentation can be defined by the hormone or amine output; however, most are found incidentally. Carcinoid tumors that secrete serotonin are the most common neuroendocrine tumor in the small bowel, comprising more than 20% of the malignant lesions in the small bowel. Although carcinoid tumors can occur anywhere in the GI tract, 45% of them occur in the small intestine, and most are found within 60 cm of the ileocecal valve. Between 40% and 80% of GI carcinoids spread to the mesentery with nodal metastasis present on presentation. On CT scan, carcinoid lesions are hypervascular, in contrast to adenocarcinomas, which are only moderately enhancing (Fig. 2). They tend to extend through the serosa and can cause fibrobastosis of the mesentery secondary to a desmoplastic reaction. Frequently, the primary small bowel lesion is not visualized on imaging, and the presenting finding is bulky mesenteric adenopathy

TABLE 1 TNM Staging Small Bowel Adenocarcinoma

Stage	Tumor	Nodes	Metastases	5-Year Survival (%)
I	T1: Lamina propria or submucosa T2: Through submucosa into muscularis propria	None	None	77
IIA	T3: Through muscularis propria into subserosa	None	None	55
IIB	T4: Through serosa, visceral peritoneum	None	None	
IIIA	Any T	N1: 1-2 regional nodes	None	36
IIIB	Any T	N2: 3+ regional nodes	None	
IV	Any T	Any N	Distant nodes, other organs, peritoneum	5-10

Data from Amin MB, Edge SB, Greene FL, et al, eds. Small intestine. In: *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017:221-234.

FIG. 2. Gallium positron emission tomography/computed tomography scan demonstrating focal uptake of somatostatin receptor tracer in primary neuroendocrine tumor.

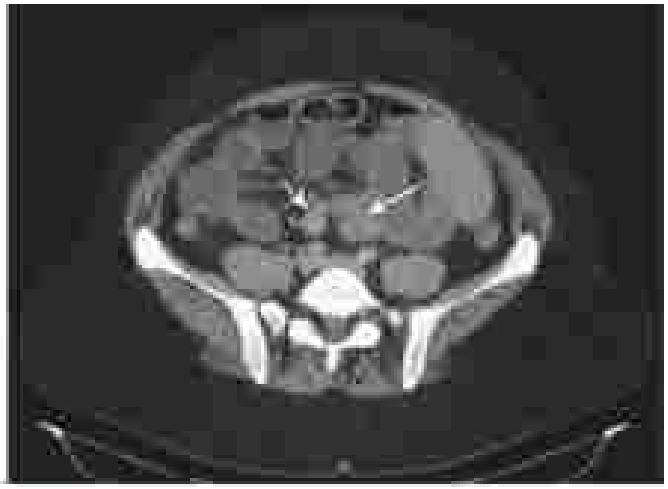

FIG. 3. Small bowel neuroendocrine tumor specifically carcinoid (large *arrow*) and associated lymphadenopathy (*small arrow*).

The regional spread of carcinoid tumors necessitates en bloc resection of the mass and mesentery, including an extensive lymphadenectomy, which is often more amenable to an open exploration (Fig. 4). During the operation, it is important to inspect for multicentric disease and liver metastases. Even if these are present, however, it is still recommended to resect the primary lesion both for local control and longevity. Evidence indicates that 60% of the disease burden should be removed to yield the most durable symptomatic improvement, so any disease that seems resectable should be targeted at the time of surgery. For duodenal carcinoid, endoscopic resection may be possible for small lesions. Anterior wall duodenal lesions may be directly excised with laparoscopic or open surgery. For select posterior lesions, local excision through an anterior duodenotomy to expose the posterior wall is an excellent approach. When both an anterior and posterior duodenotomies are performed, a gastrojejunostomy is recommended to avoid obstruction from narrowing of the duodenum. A Fogarty balloon, introduced through the gallbladder or cystic duct, and passed proximally through the ampulla can provide guidance during resection of tumors in the second portion of the duodenum. A cholecystectomy is then performed. This avoids opening the common bile duct. If the tumor is too close to the ampulla to be safely resected, a pancreaticoduodenectomy may be the only recourse.

Typical small bowel carcinoid resection removes 1 to 2 feet of small bowel, with wide lymphatic mesenteric clearance. The mesenteric involvement of this disease is often underestimated and can be misleading, necessitating more bowel resection than originally anticipated in some cases. It is important that patients are counseled about the risks of extensive resection preoperatively. Cases with extensive involvement of small bowel mesentery require careful deliberation. In some cases, leaving mesenteric disease behind in a disconcerting but necessary consideration to avoid short gut syndrome. . . .e emphasize that although extensive resection should be considered for debulking symptomatic, multifocal, or metastatic disease, the consequences of a near complete enterectomy, if less than 100 cm of small bowel remain, certainly outweigh the benefits of resection for these cases. Similarly, if the disease is extensive but relatively asymptomatic, with heavy mesenteric involvement to the root, the operative suite may best be left out of the treatment plan and systemic medical treatment with octreotide is warranted.

FIG. 4. Carcinoid tumor marked by adjacent tattoo dye and nodal metastases.

Both multiple endocrine neoplasia type 1 and neurofibromatosis predispose patients to small bowel neuroendocrine tumors; however, these occur primarily in the foregut, presenting as gastrinomas or somatostatinomas.

Adenocarcinoma

More than one third of small bowel cancers are adenocarcinoma and occur primarily in the duodenum. Unfortunately, because they are relatively asymptomatic until they are large enough to be obstructive or cause clinically evident bleeding, more than half of these tumors present at advanced stages, one third with nodal spread, and one quarter with distant metastases. Because of this, the 5-year survival following diagnosis is nearly 40% in most cases. Surgical resection is the mainstay of therapy, with a segmental resection and accompanying wide local excision of the mesentery to collect the nodal basin (Fig. 5). For those at the terminal ileum, an ileocolectomy should be performed. For duodenal lesions at the ampulla, a pancreaticoduodenectomy is necessary.

For unresectable primary disease, it is reasonable to perform a palliative surgical bypass of the obstructive lesion. Palliative radiation for unresectable disease is usually not beneficial. Clinical trials are ongoing to improve local and systemic control of unresectable disease, and surgeons are encouraged to help patients seek out these resources if possible.

GIST

Mesenchymal tumors such as GIST are most often found in the stomach (~50%) but also develop in the small bowel, with 25% in the jejunum. Derived from the interstitial cells of Cajal, they comprise approximately 10% of small bowel tumors. About 20% to 30% of GISTs are malignant at presentation, more often malignant when involving the small bowel. On CT scan, they appear as smooth, well-defined masses arising from the small bowel wall, demonstrating exophytic growth patterns and internal heterogeneity. They may have areas of central hemorrhage or necrosis (Fig. 5). GISTs rarely metastasize to nodes or spread outside of the abdominal cavity, but can be aggressive. Metastases to the liver can present with multiple normal bowel nodules. The primary lesions are known for causing ulceration through the mucosa, presenting with bleeding. GIST can be differentiated from other sarcomas of smooth muscle by immunostaining for c-KIT. Activating mutations of the KIT oncogene can be seen in more than 80% of GISTs. CT guided biopsy is usually not necessary as radiographic appearance is distinctive and resection is indicated.

A laparoscopic approach for resection of GIST is often ideal. These tumors are exophytic, making them easier to locate than other small bowel tumors during laparoscopic exploration, and because they do not spread via lymphatics, lymphadenectomy is not required. A short segmental enterectomy with only 2 cm margins is recommended. If the tumor is bulky or if adjacent organ involvement is suspected, preoperative imatinib can aid in shrinking the mass to facilitate resection. Unfortunately, more than 50% of these tumors recur within 5 years. To prolong disease free survival, high risk patients should be treated postoperatively with a minimum of 12 to 24 months of imatinib, and studies are ongoing regarding longer or even indefinite

FIG. 5 Small bowel adenocarcinoma.

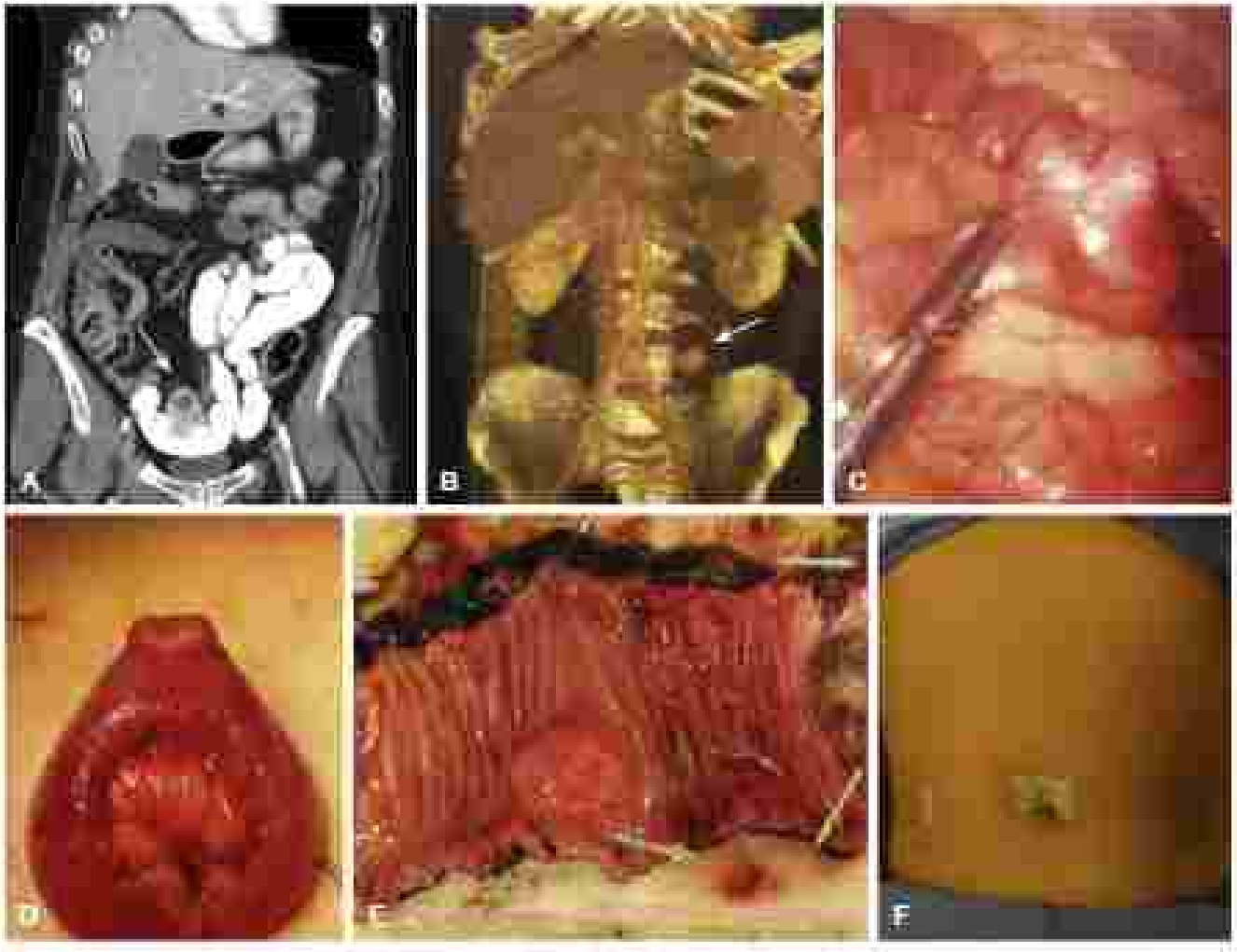

FIG. 6 (A) Small bowel gastrointestinal stromal tumor (GIST) on computed tomography (CT) scan with intravenous contrast. (B) CT on three-dimensional vascular reconstruction of C, … appearance. (D) Small bowel anastomosis after laparoscopic installation. (E) … enlarged appearance of mesenteric portion of GIST. (F) Appearance of post-operative abdomen following minimally invasive GIST resection.

TABLE 2 Disease Progression in Small Intestine GIST

Stage	Tumor	Nodes	Metastases	Mitotic Rate	Observed Patients with Disease Progression After Resection (%)
I	T1: <2 cm T2: 2 to <5 cm	None	None	Low	6–8% 0–3
II	T3: >5 to <10 cm	None	None	Low	24
IIIA	T4: >10 cm	None	None	Low	52
	T1: <2 cm	None	None	High	50
IIIB	T2: >2 to <5 cm	None	None	High	73
	T3: >5 to <10 cm	None	None	High	85
	T4: >10 cm	None	None	High	90
IV	Any	Regional	None	Any	
	Any	Any	Distant spread	Any	

*Most staging criteria are the same for GIST of esophagus, colon, rectum, and peritoneum. Staging of gastric or omental GIST is different. Progression rates of small bowel GIST are significantly worse than gastric GIST.

GIST, gastrointestinal stromal tumor.

Data from AJCC Cancer Staging Manual, 8th ed. New York: Springer; 2017:221–234.

treatment to prevent recurrence. High-risk features include tumor size >2 cm, high mitotic index, poorly differentiated cell type, presence of metastasis, and positive margin (Table 1).

Sarcoma

Sarcoma, typically leiomyosarcoma, is rare, occurring most often in the ileum. Five-year survival is approximately 50%. Radical surgical excision is recommended if the primary disease is resectable. Similar to adenocarcinoma, if the disease is deemed unresectable, surgical bypass should be considered. Palliative radiation has a greater role in sarcoma management compared with other small bowel tumors.

Lymphoma

The small bowel is the most frequently encountered extranodal site for lymphoma. This tumor is usually non-Hodgkin's type lymphoma and involves the small bowel mesentery more commonly than the luminal surface. It is most common in the ileum, the most lymphoid-rich region of the small bowel. Clinicians should maintain a high suspicion for other sites of involvement because a solitary small intestinal lesion is a rare presentation for lymphoma. Patients with celiac disease have a 20-fold higher risk of GI lymphoma, and patients with chronic immunosuppression including transplant recipients and those with human immunodeficiency virus are also at an increased risk. On CT with IV contrast, the mass often appears well circumscribed and homogeneous (Fig. 7).

A tissue diagnosis is required for lymphoma, and because there are a variety of non-Hodgkin's subtypes, it is imperative that enough tissue is harvested to perform the full battery of cytopathology and flow cytometry. The subtype dictates the tumor behavior, treatment, and prognosis. Most small bowel lymphomas do not require resection, but rather are best treated with multidrug chemotherapy. The 5-year survival is 50%, with poorer prognosis in males and the elderly. Surgery may be necessary for obstruction, or the diagnosis of lymphoma may be made postoperatively after surgical intervention for small bowel obstruction has already taken place. In patients without signs and symptoms of small bowel obstruction, CT-guided or endoscopic biopsy is appropriate to guide therapy. Indeed, the main role of biopsy in small bowel tumors is to distinguish lymphoma because most all other small bowel masses require resection as the primary management.

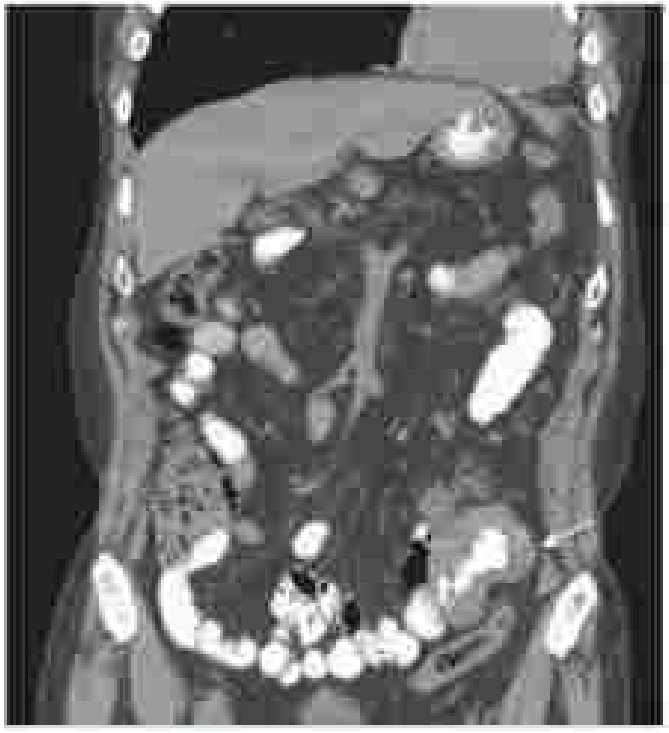

FIG. 7 Small bowel lymphoma (arrow).

Metastatic Disease

Secondary involvement of the small bowel from other metastatic lesions presents as multifocal advanced cancer and not as an isolated small bowel lesion. Lung, melanoma, breast, colon, and cervical cancer can all spread to the small bowel. Sarcomas and adenocarcinomas can also affect the small bowel, either through direct erosion or carcinomatosis of overlying peritoneum. As an innocent bystander, the small bowel may need to be resected or bypassed, depending on the type and stage of primary tumor.

SUMMARY

Small bowel tumors are rare and present with a constellation of common symptoms. Late diagnosis makes the prognosis of small bowel malignancy particularly poor, and a thorough workup to rule out small bowel tumors should be undertaken in anyone with vague abdominal pain and gastrointestinal symptoms with no other apparent source. Aside from small bowel lymphoma, most other suspicious small bowel masses do not require biopsy and should be resected. Neoadjuvant management of these malignant lesions has room for investigation, and surgeons should feel compelled to lead efforts to discover optimal treatment paradigms and create guidelines.

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MANAGEMENT OF DIVERTICULOSIS OF THE SMALL BOWEL

Ryan R. Francescon, MSc, and John V. Fanfair III, MD, FACS

Although diverticulosis of the small bowel remains relatively uncommon, appropriate management is clinically important. The reported prevalence from multiple autopsy series ranges from 0.3% to 1.5%. Diverticulosis of the small bowel has been observed in approximately 2% to 6% of small bowel contrast studies and in 7% of patients undergoing endoscopic retrograde cholangiopancreatography. Most small bowel diverticula are asymptomatic, and it is estimated that less than 4% become overtly symptomatic, with an estimated 10% of patients reporting of chronic nausea, bloating, flatulence and diarrhea.

Small bowel diverticula can be congenital or acquired and can be classified as true diverticula (containing all layers of the intestinal wall) or false diverticula (containing only mucosa, submucosa, and serosa). They can occur in the duodenum, jejunum, and ileum but are most commonly found in the duodenum. Most asymptomatic small bowel diverticula are identified incidentally at colonoscopy or on radiographic study and are usually managed nonoperatively. Advances in endoscopy have also increased the recognition and diagnosis.

A fair amount of literature exists addressing the management of complications from diverticulosis of the small bowel. There have been hundreds of publications, most of which are case reports including review of the literature. Since larger series have attempted to extrapolate the findings to the general population however, their utility remains limited.

DETECTION AND MANAGEMENT OF ASYMPTOMATIC (INCIDENTALLY DISCOVERED) SMALL BOWEL DIVERTICULOSIS

In the current era of radiologic imaging combined with advances in endoscopy, diverticulosis of the small bowel is being diagnosed more frequently. Despite the seeming increase in detection, there has not been a notable increase in symptomatic diverticula. Most truly are discovered incidentally and while still asymptomatic.

Duodenal and periampullary Diverticula

Duodenal diverticula are the most common diverticula of the small bowel, accounting for approximately 82% to 78% of cases. They are usually solitary and asymptomatic. Although they are found in 1% to 6% of all upper gastrointestinal radiologic series, they are discovered even more commonly at autopsy. Fortunately, less than 10% become symptomatic because surgical intervention can carry significant morbidity and mortality.

Duodenal diverticula can develop congenitally or as an acquired entity. In addition to those classically described, pseudodiverticula or windsock diverticula also can occur congenitally in the duodenum as prolapse of mucosa or incompletely divided congenital septa. They typically arise from the second portion of the duodenum and can extend as far as the fourth portion. Frequently, pseudodiverticula are associated with other congenital anomalies: malrotation, omphalocele, annular pancreas, congenital biliary cysts, and various cardiac and urinary congenital abnormalities. Symptoms vary depending on the size and location, especially regarding proximity to the ampulla of Vater.

Asymptomatic diverticula, by definition, are discovered incidentally on radiographic or endoscopic examination and at autopsy for another reason. Because most are asymptomatic, it has become the standard recommendation to not operate or resect any asymptomatic small bowel diverticula, especially because an asymptomatic patient cannot be made better.

There is statistical justification for operating only on symptomatic diverticula of the small bowel, which is infrequent because less than 10% are symptomatic and less than that ever come to operation. Conversely, there is also statistical justification for not operating on asymptomatic diverticula. Zani and colleagues calculated that 250 patients with incidental Meckel's diverticulum would need to undergo intestinal resection to prevent 1 death.

Jejunoileal Diverticula

Diverticula arising in the jejunum and ileum account for 10% to 25% of all small bowel diverticulum; however, about 10% of these are likely to become symptomatic. They are commonly multiple 80% occur in the jejunum, 15% occur in the ileum, and 5% occur in both.

These jejunoileal (false) diverticula are thought to develop as a result of myoneural abnormalities, often dysmotility in the migrating motor complexes, leading to spastic contractions that result in prolonged, increased intraluminal pressures. Over the course of many years, this is thought to lead to the formation of the false diverticula. Enteroclysis is the best radiographic study to evaluate jejunoileal diverticula, often to confirm the diagnosis. CT/magnetic resonance enterography likewise has been used increasingly in diagnosis. The use of capsule endoscopy also has a role in the diagnosis and evaluation of jejunoileal diverticula, especially asymptomatic but not infected.

As with most other diverticula of the small bowel, surgical resection is not warranted in an asymptomatic patient with jejunoileal diverticula or those discovered incidentally. There has been no proven role for prophylactic resection.

Meckel's Diverticula

Meckel's diverticulum is the most common congenital small bowel abnormality and accounts for the remaining 25% of small bowel

SUMMARY

Small bowel tumors are rare and present with a constellation of common symptoms. Late diagnosis makes the prognosis of small bowel malignancy particularly poor, and a thorough workup to rule out small bowel tumors should be undertaken in anyone with vague abdominal pain and gastrointestinal symptoms with no other apparent source. Aside from small bowel lymphoma, most other suspicious small bowel masses do not require biopsy and should be resected. Neoadjuvant management of these malignant lesions has room for investigation, and surgeons should feel compelled to lead efforts to discover optimal treatment paradigms and create guidelines.

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MANAGEMENT OF DIVERTICULOSIS OF THE SMALL BOWEL

Ryan R. Francescutti, MSc, MD, and John W. Harmston, MD, FACS

Although diverticulosis of the small bowel remains relatively uncommon, appropriate management is clinically important. The reported prevalence from multiple autopsy series ranges from 0.3% to 1.5%. Diverticulosis of the small bowel has been observed in approximately 2% to 6% of small bowel contrast studies and in 7% of patients undergoing endoscopic retrograde cholangiopancreatography. Most small bowel diverticula are asymptomatic, and it is estimated that less than 6% become overtly symptomatic, with an estimated 10% of patients reporting of chronic nausea, bloating, flatulence and diarrhea.

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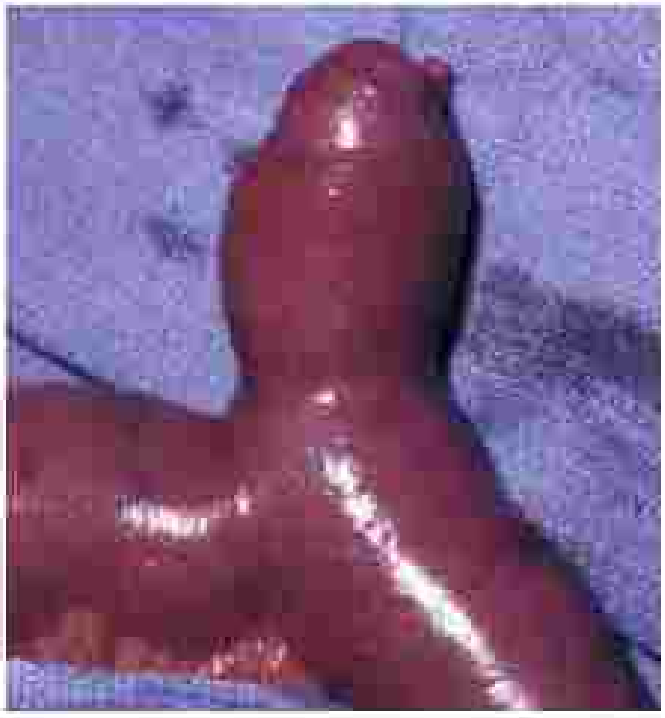

FIG. 1. Common presentation of a Meckel's diverticulum projecting from the antimesenteric border of the ileum. [From Feldman, Sleisenger, and Scharschmidt's Gastrointestinal and Liver Disease, 7th ed. Philadelphia: Saunders, 2002.]

diverticulosis. A Meckel's diverticulum is the remnant of a persistent portion (from failure of obliteration) of the proximal vitelline (omphalomesenteric) duct, which connects the embryonic midgut to the yolk sac. It only occurs on the antimesenteric border of the ileum as a true diverticulum, which contains all layers of the intestinal wall.

Meckel's diverticula are located approximately 2 feet from the ileocecal valve often containing one of two types of heterotopic tissue, most commonly gastric (75%) or pancreatic (15%) (Fig. 1). The "rule of two" follows that Meckel's diverticula occur twice as commonly in males in 2% of the population and become symptomatic in 2% of cases usually within the first 2 years of life, they can extend over 2 inches in length and predominantly cause two types of symptoms: bleeding and obstruction.

The lifetime risk of an asymptomatic Meckel's diverticulum becoming symptomatic is very low. Most Meckel's diverticula become symptomatic within the first 2 years of life and certainly by the age of 10. Based on 19 autopsy studies, in which seven reported postnatal autopsies, Meckel's diverticulum has a prevalence of 1.23%. Mortality from Meckel's diverticulum is low (<0.001%) and is most common in the pediatric population. Incidentally discovered Meckel's diverticula should be left in situ because the risk of postoperative complication from resection outweighs the risk of late complications.

A comprehensive systematic review done by Yaxt and colleagues concluded that there is no compelling evidence in the literature to support prophylactic resection of an incidentally discovered Meckel's diverticulum at operation for an unrelated condition, even in young children. Nonetheless, palpable evidence of ectopic tissue intraoperatively, a prior history of diverticulitis, hemorrhage, or intussusception, or the presence of a nondiverticular band serves as a relative indication. Most experts concur that a symptomatic or incidentally discovered Meckel's diverticulum in a young child should be resected.

MANAGEMENT OF SYMPTOMATIC SMALL BOWEL DIVERTICULA

Duodenal Diverticula

The investigational modalities of choice for duodenal diverticula include esophagogastroduodenoscopy and endoscopic retrograde cholangiopancreatography. These two modalities have become the cornerstone of visualizing duodenal diverticula, especially to clarify the relationship with and proximity to the ampulla of Vater and any contiguous biliary or pancreatic ductal structures. Increasingly, CT and magnetic resonance cholangiography are being used for imaging, often ordered as a follow up study to better characterize findings from standard contrast radiography.

Symptomatic duodenal diverticula are often the most difficult to manage because they usually include or are adjacent to the ampulla of Vater, specifically biliary and pancreatic ductal structures. Endoscopic therapy, including sphincterotomy as well as temporary stent placement, typically is attempted first. Operative management is reserved until after the inability to undergo endoscopic therapy or failure of endoscopic therapy.

Operative treatment of duodenal diverticula can be difficult and can be associated with significant morbidity and mortality, especially in inexperienced hands. Keys to the operative approach include a wide Kocher maneuver, clarification of the anatomy, relationship of the diverticulum to biliary and pancreatic ductal structures, identification of all biliary and pancreatic ductal structures, liberal use of intraoperative ductal stents, transverse or oblique closure of the duodenum, and sometimes a T-tube patch, including cholecystectomy with any operation for duodenal diverticula. The diverticulum usually is resected, often with a stapler after extensive mobilization, or it can just be inverted.

Jejunoileal Diverticula

Symptomatic jejunoileal diverticulitis is diagnosed most often using CT/magnetic resonance enterography. After enterography, unrelated, symptomatic jejunoileal diverticula also may be evaluated by push enteroscopy, double balloon endoscopy, and capsule endoscopy. Jejunoileal diverticula can present as diverticulitis, refractory inflammation, obstruction, perforation, and hemorrhage. Complicated jejunoileal diverticula often require surgical management, although jejunoileal diverticulitis usually can be managed nonoperatively, at least initially.

Most recommendations support segmental resection of jejunoileal diverticula, when necessary, especially to prevent narrowing of the small bowel. The real possibility of postoperative complications (reason to not operate when asymptomatic) is the usual reason offered for including incidental appendectomy at the time of operation.

Meckel's Diverticulum

Meckel's diverticula can become symptomatic in many ways. Most commonly, acid produced by ectopic gastric mucosa causes ulceration along the mesenteric border of the ileum, of those with hemorrhage, 90% contain gastric mucosa. Meckel's diverticulum can be a cause of chronic and acute gastrointestinal hemorrhage in the broader pediatric population but also occurs in adults.

Diagnostic modalities usually include a form of angiography or radioisotope scintigraphy (Fig. 2). Angiography can be useful during active hemorrhage, where it shows bleeding into the diverticulum or distal small bowel. Angiography is even more useful when it demonstrates a persistent right vitelline artery arising from the superior mesenteric artery or an enlarged, long, nonbranching, embryonic ileal artery leading to the diverticulum. The most useful arteriographic finding is a nonbranching end artery in the right lower abdomen containing a cluster of small, irregular arteries at its distal distribution. These often contain irregular arteries in the wall of the diverticulum and vitelline artery remnants as well as increased parenchymal blush from the ectopic gastric mucosa lining the diverticulum.

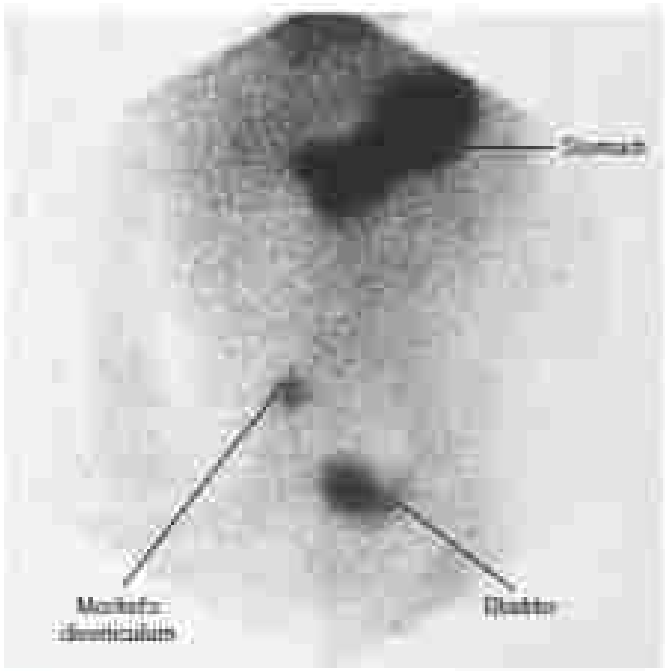

FIG. 2. Technetium 99m pertechnetate scintigram from a child with a Meckel's diverticulum clearly differentiated from the stomach and bladder. (From McKenzie S.J. In: JM, Wolf BG, et al., eds. Textbook of Surgery. 15th ed. Philadelphia: Elsevier; 2001.)

Meckel's scintigraphy uses technetium 99m pertechnetate, which is concentrated and then secreted by mucous-producing cells (gastric mucosa). It is important to remember that a Meckel's scan identifies ectopic gastric mucosa, not the hemorrhage. To obtain a quality study, it is often necessary to obtain oblique, lateral, or posterior films to distinguish a diverticulum from other activity. The activity in a Meckel's diverticulum should occur at about the same time as activity in the stomach. Depending on the center and radiologist, the sensitivity of a Meckel's scan is reportedly as high as 75% to 85% and supposedly can be increased by pretreatment with pentagastrin or glucagon.

In adults, Meckel's diverticula commonly are seen as small bowel obstruction (42%). After adequate resuscitation, obstruction is managed operatively as quickly as possible usually by wedge excision and primary closure or amputation with a surgical stapler.

Diverticulitis (25%) within a Meckel's diverticulum is often indistinguishable from acute appendicitis and is managed by segmental resection and primary anastomosis. Hemorrhage (20%) and ulceration are managed by segmental resection and primary anastomosis. At operation for hemorrhage, segmental resection is recommended because the ulcer is typically on the mesenteric border of the ileum opposite the antimesenteric border location of the Meckel's diverticulum and occasionally distal to it. Despite improved diagnostic modalities, most bleeding Meckel's diverticula are diagnosed at celiotomy.

Appendectomy should be considered at any operation for a symptomatic Meckel's diverticulum to prevent any future diagnostic dilemmas. Some texts also describe the need to search for an asymptomatic Meckel's diverticulum during appendectomy and or any acute abdomen exploratory laparotomy and if identified diverticulectomy should be considered.

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Management of Motility Disorders of the Stomach and Small Bowel

Robert Sitrin, MD, PhD, and Pankaj Jay Pasricha, MBBS, MD

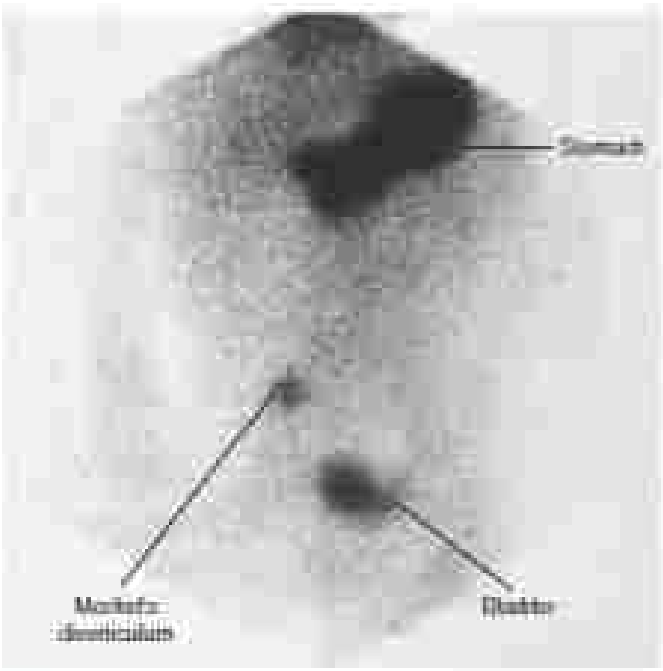
Entry of solids and liquids into the stomach normally results in gastrointestinal relaxation to allow the initial storage of food for proteins and fat digestion. Receptive relaxation, thought to be vagally mediated, will occur within the first 20 seconds, followed by adaptive relaxation within the first 15 minutes. Fundal tone then increases because of hormone response to intraluminal amino acids, which facilitates emptying of chyme into the distal stomach. Antral contraction occurs against a partially closed pylorus at a rate of 3 cycles/min, grinding contents to allow for expulsion. It has long been thought that damage or dysfunction of the vagus nerve mediates gastric dysmotility, whether from surgical intervention (upended or inadvertent) or chronic illness. Evidence has accumulated that damage to the interstitial cells of Cajal (pacemaker cells) in the gastric wall may also be important in diabetic and idiopathic gastroparesis, related to or independent of vagal dysfunction. The complex interplay between dimensualities in antral contractility, pyloric relaxation (which modulate emptying), and fundic accommodation, which mediate symptoms in these patients, likely explains the difficulties in improving symptoms in patients with gastroparesis, whether a pharmacologic or surgical approach is used.

Disorders of gastric motility are typically divided into disorders of delayed emptying (gastroparesis) and rapid emptying (dumping); however, in reality this distinction is not that clear cut in the clinic as there may be considerable overlap in symptomatology. This review will discuss postsurgical effects on gastric motility.

■ DELAYED GASTRIC EMPTYING (GASTROPARESIS)

Gastroparesis is a disorder characterized by symptoms of nausea, vomiting, early satiety, postprandial fullness, and abdominal pain. Gastroparesis is most often idiopathic; in one third of the patients, the etiology is suspected to be secondary to diabetes (either type 1 or type 2). Other causes (such as scleroderma, Parkinson's, or surgical injury) are important to recognize but relatively uncommon.

Regardless of the etiology, the pathogenesis of gastroparesis has not been established. In diabetics and postsurgical cases, vagal neuropathy or injury may lead to disruption of processes that are at least partially dependent on a healthy vagus such as gastric accommodation, antral motility, and pyloric relaxation. Impairment of all three



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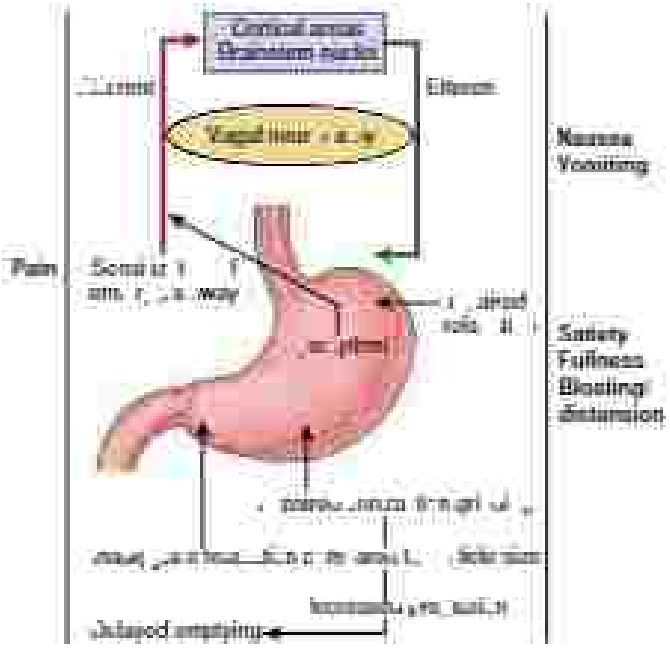

FIG. 1 Proposed pathophysiologic basis of symptoms experienced by patients with gastroparesis. *(From Soffer EE, Parkman HP. Investigational drug therapies for the treatment of gastroparesis. Expert Opin Investig Drugs. 2013;22:1111–1122.)*

of these processes has been reported to a lesser or greater extent in patients. In both idiopathic and diabetic gastroparesis there is a loss of gastric interstitial cells of Cajal associated with evidence of alternative macrophage activation. Interstitial cells of Cajal loss in turn correlates inversely with gastric emptying time in these patients, implying a possible etiologic link.

Although gastroparesis implies a delay in gastric emptying by definition, it has become clear that there is poor correlation between the severity of delay and symptoms in these patients. A significant number of patients have normal emptying although their symptoms are indistinguishable from those in patients with overt delay; this syndrome is likely part of the spectrum of gastroparesis and has been termed chronic unexplained nausea and vomiting or gastroparesis-like syndrome. In these patients, other mechanisms (e.g., impaired gastric accommodation, sensitization of vagal afferent pathways) may account for the symptomatology (Fig. 1).

Most patients who present with symptoms of delayed gastric emptying postoperatively will complain of early satiety and frequently with nausea exacerbated after meals. They may vomit undigested food many hours after eating, often the next day. There may be accompanying abdominal pain. Liquids are typically better tolerated than solid foods, but not always. Inpatient oral intake may lead to dehydration, weight loss and nutritional compromise. Some patients have frequent emergency room visits for these symptoms.

History taking should include prior GI tract surgery (especially foregut), presence of diabetes or thyroid disease (especially if poorly controlled), presence of connective tissue disorders such as scleroderma, and history of chronic constipation. Medication history should include use of anticholinergics or opiates. Symptoms of intense nausea and vomiting occurring in a periodic fashion that lasts a few days at a time with the patient being well in the interval is suggestive of cyclic vomiting syndrome. In such patients, a history of relief with hot showers or baths is highly suggestive for cannabinoid induced hyperemesis, which is associated with chronic marijuana use. On the other hand, the absence of nausea in a patient along with "vomiting" that occurs within a few minutes should raise suspicion for rumination disorder. On physical examination, most patients either have a normal weight or, somewhat counterintuitively, are overweight. Patients with poorly controlled type 1 diabetes are the most likely to be underweight and overtly malnourished. Abdominal examination often reveals tenderness in the epigastric region on deep palpation. More superficial tenderness should elicit consideration of chronic abdominal wall pain that can occur secondarily, especially around laparoscopic scars (a history of cholecystectomy for "gallbladder dyskinesia" is common in these patients). In our opinion, looking for a succussion splash, as has been advocated historically, is not only seldom fruitful, but often results in worsening of nausea and pain. We do not recommend it. If it has not already at the time of presentation, mechanical obstruction of the stomach (and occasionally more distally) must be ruled out principally by endoscopy. We often use computed tomography or magnetic resonance enterography to obtain both cross-sectional imaging and evaluate bowel patency. Occasionally, these tests will lead to a radiologic suggestion of superior mesenteric artery syndrome, particularly in patients who report recent loss of significant amounts of weight. This can lead to a clinical dilemma, in our experience, although decompression surgery is often attempted in these patients, it seldom leads to reversal of their symptomatology and should be approached with caution. The current gold standard for the diagnosis of gastroparesis is the 4 hour gastric emptying scintigraphic using a solid egg based meal study, now carried out by most nuclear medicine departments in the United States. Patients should be instructed to abstain from opioids for several days before the study. In addition, diabetic patients should have a finger stick glucose level at acute hyperglycemia (>250 to 300 mg/dL) by itself can delay gastric emptying (in addition to causing nausea).

MEDICAL APPROACHES

Patients are started on a low fat, low fiber diet, and encouraged to eat more frequent small meals (up to six) daily instead of a single daily meal. A small controlled trial of a "microparticle" diet has been shown to improve symptoms in patients. Patients with more severe gastroparesis may be recommended a "step" approach, starting with liquids, and graduating to more solid meals. Common deficiencies (iron, B12, vitamin D) should be looked for and corrected.

In people with diabetes, tight glucose control is the key for both long-term improvement as well as symptomatic amelioration resulting from frequent hyperglycemic excursions. In the past, physicians have shied away from aggressive measures to control diabetes in this population from concerns about the unpredictable timing of meal-related glucose surges because of the delay in gastric emptying. A recent study from the Gastroparesis Clinical Research Consortium suggests, however, that the use of insulin pumps in patients with type 1 diabetes leads to fewer hypoglycemic (as well as hyperglycemic) events, reduction in HbA$_{1c}$, and significant improvement in symptoms related to gastroparesis.

The traditional approach for treating gastroparesis is to improve gastric emptying by so-called prokinetic agents (Table 1), but it is no longer clear that delayed gastric emptying is solely responsible for the pathogenesis of symptoms and there is poor correlation between improvement in emptying and clinical relief, leading to the search for alternative approaches. In this country, metoclopramide is the only prokinetic approved for gastroparesis. It is a dopamine 2 (D_2) receptor antagonist that provides a potent central antinausea effect that probably contributes more to its efficacy than the peripheral prokinetic effect on gastric emptying. As to be expected with any D_2 receptor antagonist that penetrates the brain, its use is associated with higher risk of extrapyramidal effects, both acute (spasmodic dystonia) and chronic (tardive dyskinesia), especially in the elderly. The latter risk has led to the US Food and Drug Administration (FDA) issuing a black box warning and led to a decline in its use. Domperidone is a closely related D_2 receptor antagonist but does not cross the blood-brain barrier and is widely used in the rest of the world. Although never formally approved in this country, it was recommended frequently by US physicians (with patients either filling their prescriptions at

TABLE 1 Medication for GI Motility Disorders

Drug	Indication	Mechanism	Dose	Side Effects
Metoclopramide	Gastroparesis (FDA approved for this indication)	Central/peripheral dopamine receptor antagonist, 5HT3 receptor antagonist, 5HT4 receptor agonist (prokinetic and antiemetic)	5–10 mg 3 times daily	Up to 30% CNS parkinsonism, tardive dyskinesia (FDA black box warning)
Domperidone	Gastroparesis (not available in the United States except under FDA IND)	Peripheral dopamine receptor antagonist (prokinetic and antiemetic)	10–20 mg 4 times daily	Can cause QTc prolongation, with risk of arrhythmia, hyperprolactinemia
Erythromycin	Gastroparesis (off-label)	Motilin receptor agonist (prokinetic)	50–250 mg up to 4 times daily	May worsen nausea, vomiting, abdominal pain; tachyphylaxis with long-term use requires drug holidays; can cause QTc prolongation with risk of arrhythmia
Mirtazapine	Gastroparesis (off-label)	Alpha adrenergic, 5HT2, 5HT3, and H1 receptor antagonist (prokinetic, antiemetic)	15–30 mg every day at bedtime	Somnolence, increased appetite, and weight gain
Prucalopride	Constipation, gastroparesis, POI, CIPO (off-label)	Highly selective 5HT4 receptor agonist (prokinetic, serotonergic)	1–2 mg daily	Headache, nausea, abdominal pain, diarrhea
Aprepitant	Chemotherapy-induced and postoperative nausea and vomiting (FDA approved), gastroparesis (off-label)	NK-1 receptor antagonist (antiemetic)	125 mg/day	Lightheadedness, nausea
Ibuprofen	Nausea (off-label)	5HT3 receptor agonist, dopamine receptor antagonist (improves gastric fundal compliance)	10–20 mg 2 or 3 times daily (maximum, 40 mg/day)	Dizziness, nausea, headache
Pyridostigmine	Constipation, CIPO, POI (off-label)	AChE inhibitor	30 mg/day to 60 mg 3 times daily	Nausea, vomiting, diarrhea
Octreotide	Symptomatic rapid gastric emptying (off-label)	Somatostatin agonist (inhibits GI motility and secretion)	50–100 μg subcutaneously before meals (up to 3 times daily); can convert to depot intramuscular once dose stability is achieved	Diarrhea
Olanzapine	Nausea (off-label)	5HT2A and dopamine receptor antagonist	5–20 mg daily	Weight gain, somnolence, hyperprolactinemia
Alvimopan	Prevention of POI	Peripheral mu-opioid receptor antagonist	6–12 mg 0.5–5 hours before surgery, then 6–12 mg by mouth every 12 hours from 1 to 7 days postoperatively (not >15 doses)	Nausea, vomiting, abdominal distension

AChE, acetylcholinesterase; CIPO, chronic idiopathic intestinal pseudo-obstruction; CNS, central nervous system; FDA, US Food and Drug Administration; GI, gastrointestinal; IND, investigational new drug; PO, postoperative ileus.

compounding dispensaries or in other countries). Recently, however, substantial concerns have been raised about the cardiovascular proarrhythmic risk from domperidone leading to warnings in Europe. This has led to stricter regulation of domperidone dispensation by the HPA in this country.

Other classes of prokinetic agents include motilin agonists (erythromycin) and 5HT4 receptor agonists (prucalopride). Erythromycin is useful for improving gastric emptying in the short term (e.g., in hospitalized patients) but has never been rigorously evaluated for symptomatic relief with long-term use, which is limited by tachyphylaxis, advocating some practitioners to prescribe "drug holidays" to allow for recovery from the same. Its prokinetic effect is limited to the upper gastrointestinal (GI) tract. Prucalopride, a 5HT4R agonist is in the same class as tegaserod and is a more general prokinetic effect. There is little to no published evidence on its utility in gastroparesis, however; many patients also have slow transit constipation and may benefit from relief of colonic distention with perhaps secondary effects on symptoms such as nausea, bloating, and fullness.

Other pharmacologic treatment is clearly directed at ameliorating symptoms, particularly nausea. Classical antinauseants such as the 5-HT3 receptor antagonists are generally considered first line therapy in this regard, typically beginning with ondansetron (which is also available in an orally disintegrating tablet form). Alternatives include granisetron, which is available as a subcutaneous delivery patch. The patient response is variable, ranging from significant improvement to no relief; with higher doses, constipation can be a problem. Other nonspecific antinauseants such as promethazine or prochlorperazine should be recommended as rescue medications but many patients may have to use these on a daily basis. Vestibular antinauseants such as dimenhydrinate or scopolamine (in transdermal patch form) may be beneficial in the occasional patient. A more general approach to nausea has been in the form of neuromodulators (e.g., tricyclic antidepressants such as nortriptyline). Although most of them have prominent anticholinergic activity, these drugs generally do not affect motility when used in low doses (e.g., less than 50 mg nortriptyline). Anecdotal reports have suggested significant relief, however, a relatively large randomized controlled study showed no improvement in nausea. A more promising agent in this regard is mirtazapine, which is increasingly being used to treat nausea (it has potent 5HT3 receptor antagonism), improve appetite, and to a lesser extent modulate pain. Buspirone is an anxiolytic that is an agonist of the 5HT1A receptor, which may also be responsible for its ability to improve gastric accommodation. It can therefore be particularly useful in patients with prominent early satiety.

SURGICAL APPROACHES

Nutritional interventions are often delayed unnecessarily in patients who are unable to maintain weight. At the first visit, therefore, it is important to devote time to both a nutritional assessment and a plan to deliver adequate calories and other nutrients. In patients who are stable in weight, diet can also be used judiciously to minimize symptoms (see the previous sections). In patients on a trajectory that is leading to more than 10% weight loss, early intervention should be planned in the form of intestinal feeding tubes inserted either directly via surgical or radiologic jejunostomy or indirectly via a gastric port (gastrojejunostomy). Gastric ports are used by some patients to vent the stomach between meals; this may provide some symptomatic relief, although the utility of this approach has not been tested rigorously. In general, these feeds are well tolerated although in some patients with significant small bowel dysmotility there may be a limiting rate of infusion. If successful, jejunostomy tube placement can maintain nutrition without the substantial risks of line sepsis seen in long-term home total parenteral nutrition (TPN). These tubes may be uncomfortable and localized infection may occur.

Despite these measures, TPN may be required in some patients who have severe weight loss and intractable vomiting. This should be seen as a temporizing measure to provide gut rest for 2 to 3 months while replenishing nutritional needs and avoiding further exacerbation of symptoms. Longer term TPN is fraught with risk for infections and thromboembolism and has been associated with increased risk of death in these patients.

Gastric electrical stimulation is a technique in which electrodes are implanted onto the gastric antral serosa using open or laparoscopic techniques. The Enteria device is FDA approved under a Humanitarian Device Exemption for use in gastroparesis, which means that its efficacy is unproven. Randomized crossover trials have shown modest or no symptom benefit with the device when on versus off, although prospective open label trials have suggested benefit, particularly in diabetic patients. The putative mechanism of action is thought to be modulation of vagal signaling as in its current form the device does not improve gastric emptying. The role of this treatment in gastroparesis therefore remains unclear.

Other approaches have targeted the pyloric sphincter, based on the rationale that its dysfunction could result in gastric outlet obstruction. Although the prevalence and contribution of this pathophysiologic mechanism has never been established with any confidence, there have nevertheless been many therapies directed at it. Early studies of intrapyloric botulinum toxin injection showed symptom improvement in gastroparesis but were not confirmed in randomized controlled trials. Laparoscopic pyloroplasty and more recently, endoscopic pyloromyotomy (gastric per oral endoscopic myotomy) have been evaluated in treatment of drug refractory gastroparesis of surgical and nonsurgical origin. Retrospective studies suggest symptom and gastric emptying improvement up to 3 to 6 months of follow up, as have some prospective studies. However, lack of prospective randomized sham controlled data with validated outcomes, and short follow up would not support its general use at this time.

Near total or completion gastrectomy has been proposed as possible treatment for refractory patients. Retrospective data spanning 20 years from the Mayo Clinic on patients with prior partial gastrectomy and truncal vagotomy indicates that only one half of patients could sustain themselves with oral nutrition, and another study of patients with post Nissen gastroparesis showed no benefit in symptom control or nutritional status with near total gastrectomy.

RAPID GASTRIC EMPTYING (DUMPING SYNDROME)

Disorders of rapid gastric emptying (dumping syndrome) are characterized by fast passage of liquid or hyperosmolar chyme into the duodenum. Dumping has been most often seen after surgery and is increasingly recognized due to the popularity of bariatric procedures although it can also be seen after a variety of others such as classical vagotomy and pyloroplasty. Neuroendocrinologic and esophagectomy. Currently the most common cause of this syndrome are Roux-en-Y gastric bypass or sleeve gastrectomy, which are associated with nearly a 40% incidence of symptoms putatively ascribed to dumping as a result of impaired gastric storage and/or rapid and uncontrolled entry of nutrients into the small intestine. In some patients, these symptoms resolve over time, but may persist for years in a significant minority. Idiopathic dumping syndrome also probably exists but may not be suspected in the absence of a culpable surgical cause without performing more sophisticated tests.

Theories on the genesis of symptoms resulting from rapid gastric emptying are generally in keeping with our knowledge of the postprandial physiologic response. Hyperosmolar chyme or liquid rapidly enters the duodenum. This leads to rapid shifting of fluid into the lumen, and release of gut peptide hormones with vasoactive and gut motor effects. These are thought to mediate the symptoms of early dumping, which typically begin 30 minutes after ingestion. Symptoms are proportional to the osmolarity of the bolus. These symptoms include early satiety, nausea, abdominal pain, and vasomotor

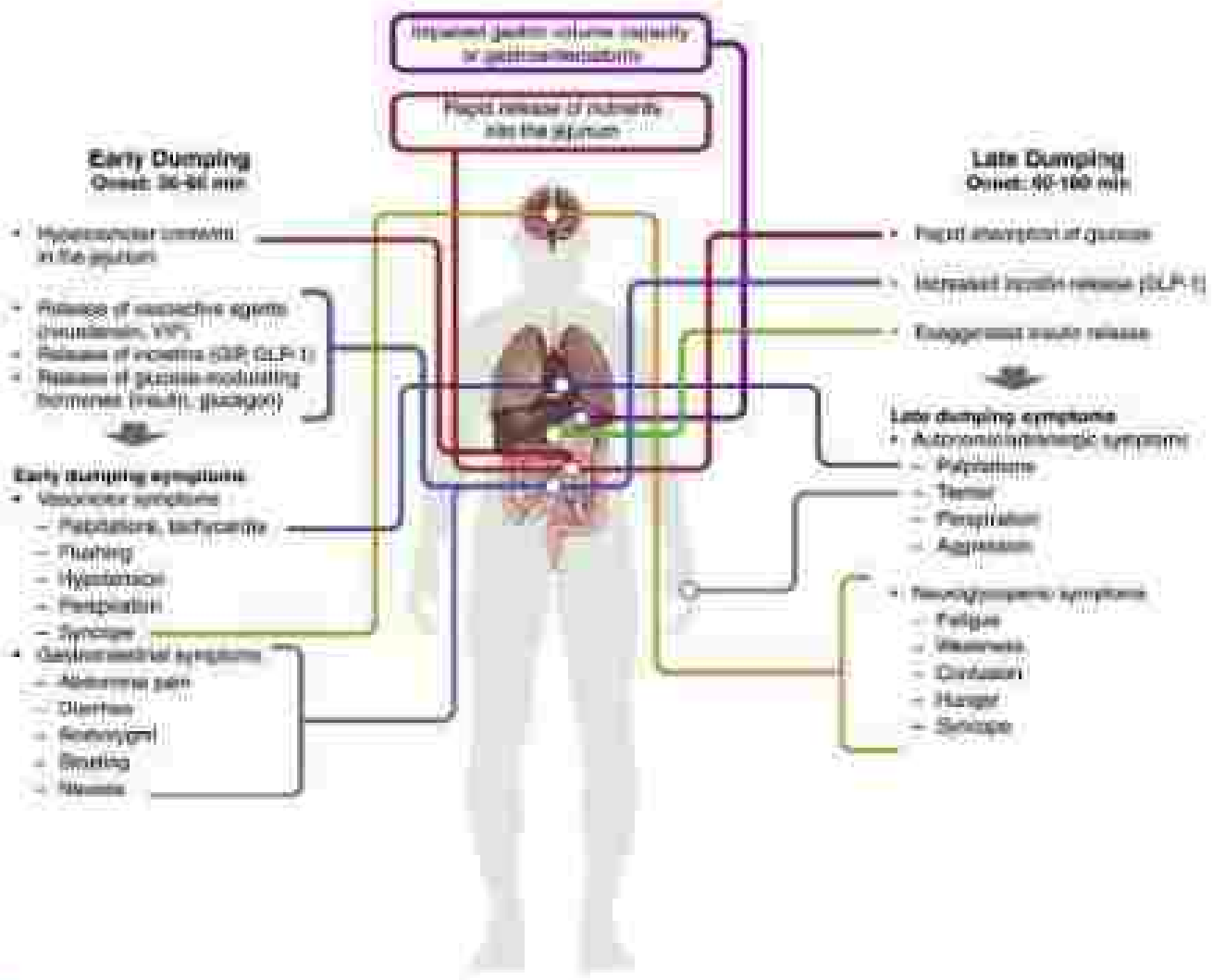

FIG. 2 Pathophysiology of dumping syndrome. *GIP*, gastric inhibitory polypeptide; *GLP-1*, glucagon-like peptide-1; *VIP*, vasoactive intestinal peptide. (From Kim M, Kim H, Kwon H, et al. Dumping syndrome after esophagogastric surgery: pathophysiology, diagnosis, and management. *Korean J Intern Med*. 2017;32(4):609–617.)

symptoms (tachycardia/palpitations, lightheadedness, diaphoresis, and tremor). Paradoxically, many of these symptoms can be seen in patients with gastroparesis, indicating their nonspecific nature. Symptoms may last for an hour and be incapacitating. Early dumping symptoms are often but are always accompanied by late symptoms as well, typically 2 hours or more after a meal. In about one-quarter of patients, late dumping manifests itself in isolation and can make the diagnosis more difficult to make. Late dumping is thought to be from hypoglycemia in response to the excessive rate of carbohydrate absorption leading in turn to exaggerated release of incretin peptides (GLP1 and GIP) and an "overswing" insulin response. This leads to hypoglycemia and associated autonomic responses. These concepts are illustrated in Fig. 2.

DIAGNOSIS

The diagnosis of dumping syndrome begins with maintaining a high index of suspicion in the right clinical setting, typically with a history of upper GI surgery. Various clinical scoring systems have been suggested as aids to this regard, but their utility in the clinical setting is not clear and lack rigorous validation. Simple measures such as asking the patient to monitor their blood sugar levels at the time of symptoms are complicated by the fact that finger stick capillary blood methods are not considered accurate in the hypoglycemic range. Nevertheless, if obtained, a plasma glucose level of less than 72 to 40 mg/dL is considered consistent with post-gastric bypass hypoglycemia. The role of continuous ambulatory glucose monitoring in this setting is unclear, even if it were practical.

For these reasons, a provocative test for hypoglycemia in a monitored setting is considered the gold standard, even though not endorsed by most endocrine societies because of problems with specificity. This is either a classical oral glucose tolerance test or a mixed meal test, done in a carefully monitored setting. A positive oral glucose tolerance test for early dumping in this setting consists of increase in hematocrit of more than 3% or increase in heart rate greater than 10 per minute after 30 minutes. Late dumping is diagnosed if hypoglycemia develops between 1 and 3 hours after ingestion.

Finally, others have advocated studying gastric emptying by scintigraphy, with 1 hour emptying of more than 60% of the meal indicating rapid emptying. If this criterion is met, it is supportive of the diagnosis in the right clinical context. On the other hand, many symptoms of early dumping occur within minutes of ingestion and standard nuclear medicine tests do not provide information during this time period, so a negative test does not necessarily rule out the diagnosis.

TREATMENT

The first step in treatment is diet modification. Simple sugars and dairy products are avoided, as are large carbohydrate loads. Complex carbohydrates, proteins, fat, and fiber are encouraged as they

will slow gut transit time. Water intake should be plentiful to avoid dehydration but should not be taken one half hour before or after meals. Patients have also been advised to not eat while upright, but an alternative is to be supine for 30 minutes after meals, which is thought to slow gastric emptying and increase venous return.

Next line therapy usually consists of over the counter measures to reduce gastric emptying. This can be achieved by substances such as guar gum, pectin, and glucomannan, several studies attest to the efficacy of these agents in this setting when administered at doses of at least 15 g with meals. Patients may not always tolerate these supplements because of gas and bloating or find them unpalatable. Further, the concomitant restriction on fluid intake with a meal may theoretically increase the risk of obstruction from these highly viscous compounds.

When these measures are not sufficient, drug therapy may be prescribed. Acarbose is an alpha glycosidase hydrolase inhibitor that impairs the breakdown of luminal carbohydrates, thus limiting the glucose surge that triggers late dumping syndrome. Although several studies suggest its utility in this setting, unabsorbed carbohydrate loads in the colon may exacerbate other symptoms such as flatulence and diarrhea. Pharmacologic therapy for early (and late, if present) dumping consists of somatostatin analogs such as octreotide (available in short- and long-acting forms), and the long-acting drugs lanreotide and pasireotide. These drugs work by slowing gastric emptying, inhibiting CCK-1 and other hormones and preventing postprandial vasodilation. Symptom control in up to 80% of patients has been demonstrated in controlled studies. If a trial of subcutaneous dosing 30 minutes before or after meals is successful, a longer acting depot preparation can be substituted with equivalent efficacy. Steatorrhea is the most significant side effect, although usually mild. Other side effects include an increased risk for gallstone formation, diarrhea, nausea, and local pain (at injection sites).

Other drugs that have been tried on an anecdotal basis or in small numbers include diazoxide or nifedipine (both of which are thought to act by decreasing calcium-activated insulin release from pancreatic beta cells). Continuous enteral feeding by a gastric or jejunal route has been used in some patients as an alternative to pharmacologic therapy with the rationale that avoiding fluctuations in glycemic levels after a steady state has been achieved will prevent the endocrine and autonomic reflexes that contribute to the pathogenesis of symptoms. Finally, refractory patients have been offered surgery usually in the form of reversal of the bypass or other interventions; in some cases, pancreatectomy has been performed when persistent beta cell hyperplasia or nesidioblastosis is suspected. Although uncontrolled reports suggest that this may be effective, given the drastic nature of the surgery, it should only be considered after a thorough diagnostic evaluation and exhaustive trial of other measures.

SMALL BOWEL MOTILITY DISORDERS

Small bowel motility disorders are not commonly seen but can be divided into reversible disorders such as adynamic ileus, and very progressive disorders such as familial chronic intestinal pseudo-obstruction and acquired scleroderma. Less common disorders such as bypass enteropathy after bariatric surgery, small bowel intussusception, and dysmotility in intestinal ataxia will not be discussed.

ADYNAMIC ILEUS

Adynamic ileus is actually a generalized gut motility disorder involving the entire GI tract including the small bowel. It is most commonly seen in the presence of a systemic inflammatory disorder (i.e., sepsis), retroperitoneal hematoma or other trauma, or after abdominal surgery (postoperative ileus [POI]). The pathophysiologic basis of intestinal dysfunction in POI is complex with many factors (intestinal inflammation, autonomic imbalance, perioperative opioid use, electrolyte and fluid imbalance, and perhaps activation of defensive intrinsic enteric nervous system programs). Further, the contribution of colonic, small intestinal and gastric dysfunction may vary in individual patients.

Patients with adynamic ileus will present with vomiting, abdominal distension, and obstipation, with physical examination findings of ringing bowel sounds. Abdominal radiographs will usually reveal distension of the small bowel and/or colon. Prevention of ileus in the postoperative setting is a major emphasis for patients undergoing abdominal or related surgery. The risk is higher for open rather than laparoscopic approaches and can be further attenuated by judicious intraoperative use of opioids, limiting intestinal trauma and using epidural rather than general anesthesia. Electrolyte and electrolyte homeostasis are important to maintain. Early feeding and ambulation are encouraged, and many programs suggest coffee and chewing gum as adjuncts to promote early recovery. Pain control with nonsteroidal anti-inflammatory drugs (and selective COX2 inhibitors such as celecoxib) may not only provide effective opioid sparing analgesia but may also improve motility probably by reducing neural inflammation. However, the use of classical nonselective anti-inflammatory drugs must be balanced against the risk for mucosal injury and kidney dysfunction in this setting. Systemic lidocaine infusions after surgery may also help prevent the development of POI while reducing pain. Alvimopan (a peripheral mu opioid receptor antagonist) has been shown to shorten recovery time after gut surgery and has been approved for the prevention of POI in patients who have been treated with narcotic analgesics; however, its use is heavily restricted because of the risk for cardiovascular ischemia. Methylnaltrexone, the other peripherally acting mu opioid receptor antagonist, has not been shown to be of benefit for POI.

If ileus has set in, treatment is usually conservative, with continuing attention to the factors just outlined. Although the use of routine nasogastric or nasoduodenal tubes is discouraged for prophylaxis, decompression with these tubes becomes important in established cases for relieving discomfort and vomiting. The role of pharmacological agents remains unclear. Although erythromycin may help improve gastric motility in patients in whom this is a predominant factor, metoclopramide is not considered helpful in this setting. Other prokinetics such as prucalopride have the potential to improve POI but have not been rigorously tested for this indication. Further, the lack of intravenous formulations may further limit their efficacy in these patients. Acetylcholinesterase inhibitors such as neostigmine or pyridostigmine may be tried in refractory cases, particularly if colonic ileus dominates. Gastroparesis control studies have also been reported to be helpful in some patients.

CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION AND ASSOCIATED SMALL INTESTINAL BACTERIAL OVERGROWTH

This relatively rare disorder is often first suspected in a patient who has presented with recurrent small intestinal obstruction and typically undergone one or more exploratory surgeries with no mechanical etiology found. In some cases, there is a strong family or genetic history. Familial visceral myopathy is primarily a smooth muscle dysfunction in which gut contraction amplitude and coordination of contraction are reduced. Eventually it affects all gut and genitourinary smooth muscle but may start in the esophagus, duodenum, colon, or urinary tract. Familial visceral neuropathies are also described with both autonomic and enteric neural dysfunction contributing to abnormal gut contractility and transit. Other genetic causes include mitochondrial neurogastrointestinal encephalopathy disease, a multisystem disorder with prominent GI dysfunction and associated neurologic phenotype (ptosis/ophthalmoplegia, peripheral neuropathy, leukoencephalopathy) affects teens and young adults and is caused by a mutation in the gene encoding for thymidine phosphorylase. Non-hereditary causes of chronic idiopathic intestinal pseudoobstruction (CIIPO) include scleroderma, paraneoplastic syndromes (e.g., small cell lung cancer associated with circulating antibodies against the

neuronal (hu antigen). In some patients, no obvious cause is apparent and "neuromuscular dysmotility" is ascribed as a nonspecific descriptor. The lack of specialized centers for interpretation of subtle changes in the enteric nervous system/visceral muscle remains a problem in these cases, even if bowel segments are available for review.

Patients may present with symptoms in late childhood/teenage years with vague chronic GI symptoms, or in early adulthood after years of more specific intermittent symptoms including dysphagia, bloating, abdominal pain, or constipation. In severe, usually genetic cases, megaesophagus or megaduodenum may be seen on contrast studies. Abdominal radiographs can indicate significant dilation in the entire small bowel down to the colon, sometimes with gastric dilation as well. Computed tomography or magnetic resonance enterography may be useful radiologic techniques to document the extent and severity of the bowel dysfunction. While gut scintigraphy and wireless motility capsules are useful to measure small bowel transit, but the former is not generally available and the latter is contraindicated if there is suspicion of mechanical obstruction (risk of impassage of capsule). Antroduodenal manometry has been used to identify classic low amplitude contractions described in visceral myopathy as well as abnormalities of the migrating myoelectric complex thought to be from neuropathy, but these findings correlate poorly with histology. The most sensitive diagnostic method is diagnostic laparoscopy (rather than laparotomy) to rule out mechanical obstruction and to obtain full thickness small bowel biopsies, which should be examined by an expert GI pathologist to rule out visceral neuropathy. Often such expertise is not available on site and slides need to be sent to specialized centers. It is important to ask for an opinion on the presence of intramural inflammation (eosinophils, lymphocytes, and other immune cells) as these patients may respond to a trial of immunomodulator therapy.

Treatment is supportive. There are some data supporting the use of prokinetic agents, a placebo controlled randomized controlled trial indicates that pyridostigmine reduces symptoms and the need for rescue analgesics in adults with CIPO. These patients often have small intestinal bacterial overgrowth and empirical treatment with drugs such as rifaximin or other antibiotics may be useful. In some practices, lactulose based breath testing is recommended before initiation of these drugs, but the sensitivity and specificity of this test is poor and a negative result does not rule out small intestinal bacterial overgrowth. Because of the chronic nature of the disorder, patients with CIPO who respond to antibiotics may have to be treated multiple times per year. This can be either done based on symptom exacerbation or occasionally prophylactically (e.g., metronidazole for 2 to 3 weeks every month). Octreotide injections are often used in these patients because this drug can reduce small bowel contractions and may improve symptoms and the frequency of small intestinal bacterial overgrowth recurrence. This drug is expensive, however, and not always covered by medical insurance carriers. Pyridostigmine has also been used in CIPO in children and adults with reported benefit but may not be as effective as octreotide. Tunneling or gastrostomy can help decompress patients in later stages of the disorder, but fistulas form through these tubes must be replaced intermittently. Many patients with severe disease will eventually require chronic TPN support. The role of small bowel transplantation continues to evolve and there are few centers which offer this. Nevertheless, outcomes continue to improve and it is important to offer this as a potential option in this unfortunate group of patients.

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Management of Intestinal Failure

Jason S. Hawkinworth, MD, and Thomas M. Fish ian, MD

The field of intestinal failure (IF) has witnessed transformative advancements since the advent of parenteral nutrition (PN) more than 40 years ago. Once a uniformly lethal condition, IF now has an excellent prognosis, with a 90% long term survival rate. In the last decade alone, medical and surgical advances, including implementation of multidisciplinary care teams, standardization and rejuvenation of intestinal lengthening procedures, improved central line care, utilization of novel glucagon like peptide 2 (GLP-2) analogs, and lipid sparing PN formulations have revolutionized the care of the patient with IF. For patients with IF and complications of PN, intestine transplant offers an excellent option, with continually improving outcomes. In this chapter, the etiology and epidemiology, medical and surgical management, and transplantation for IF are reviewed.

Definitions and Etiology

Intestinal Failure

The function of the intestine includes digestion and absorption of nutrients and the maintenance of a barrier against the external environment. IF is defined as a critical reduction of functional gut mass below the minimum amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements. A practical approach to define the degree of IF includes the amount of PN required for maintenance of nutritional status in adults and of growth in children. This also provides a way to track progress following any medical or surgical intervention in a patient with IF.

neuronal dysfunction). In some patients, no obvious cause is apparent and "neuromuscular dysmotility" is ascribed as a nonspecific descriptor. The lack of specialized centers for interpretation of subtle changes in the enteric nervous system/visceral muscle remains a problem in these cases, even if bowel segments are available for review.

Patients may present with symptoms in late childhood/teenage years with vague chronic GI symptoms, or in early adulthood after years of more specific intermittent symptoms including dysphagia, bloating, abdominal pain, or constipation. In severe, usually genetic cases, megaesophagus or megaduodenum may be seen on contrast studies. Abdominal radiographs can indicate significant dilation in the entire small bowel down to the colon, sometimes with gastric dilation as well. Computed tomography or magnetic resonance enterography may be useful radiologic techniques to document the extent and severity of the bowel dysfunction. While gut scintigraphy and wireless motility capsules are useful to measure small bowel transit, but the former is not generally available and the latter is contraindicated if there is suspicion of mechanical obstruction (risk of impaction of capsule). Antroduodenal manometry has been used to identify classic low amplitude contractions described in visceral myopathy as well as abnormalities of the migrating myoelectric complex thought to be from neuropathy, but these findings correlate poorly with histology. The most sensitive diagnostic method is diagnostic laparoscopy (rather than laparotomy) to rule out mechanical obstruction and to obtain full thickness small bowel biopsies, which should be examined by an expert GI pathologist to rule out visceral neuropathy. Often such expertise is not available on site and slides need to be sent to specialized centers. It is important to ask for an opinion on the presence of intramural inflammation (eosinophils, lymphocytes, and other immune cells) as these patients may respond to a trial of immunomodulator therapy.

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Management of Intestinal Failure

Jason S. Hawkesworth, MD, and Thomas M. Fishbein, MD

The field of intestinal failure (IF) has witnessed transformative advancements since the advent of parenteral nutrition (PN) more than 40 years ago. Once a uniformly lethal condition, IF now has an excellent prognosis, with a 90% long-term survival rate. In the last decade alone, medical and surgical advances, including implementation of multidisciplinary care teams, standardization and rationalization of intestinal lengthening procedures, improved central line care, utilization of novel glucagon-like peptide 2 (GLP-2) analogs, and lipid-sparing PN formulations have revolutionized the care of the patient with IF. For patients with IF and complications of PN, intestinal transplant offers an excellent option, with continually improving outcomes. In this chapter, the etiology and epidemiology, medical and surgical management, and transplantation for IF are reviewed.

■ DEFINITIONS AND ETIOLOGY

Intestinal Failure

The function of the intestine includes digestion and absorption of nutrients and the maintenance of a barrier against the external environment. IF is defined as a critical reduction of functional gut mass below the minimum amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements. A practical approach to define the degree of IF includes the amount of PN required for maintenance of nutritional status in adults and of growth in children. This also provides a way to track progress following any medical or surgical intervention in a patient with IF.

TABLE 1 Pediatric and Adult Intestinal Failure Etiologies

Adult	Pediatric
Mesenteric ischemia	Congenital short bowel
Crohn's disease	Congenital enteral disease
Radiation enteritis	Chronic intestinal pseudo-obstruction
Chronic intestinal pseudo-obstruction	Volvulus
Surgical complications	Necrotizing enterocolitis
Familial polyposis	Hirschsprung's disease
Cancer	Crohn's disease

Etiology

The etiology of IF can be anatomic or functional and varies by pediatric or adult demographics. The most common anatomical etiology of IF is short gut syndrome (SGS), which is generally characterized by a state of malabsorption following extensive loss of small intestine. The clinical consequences of SGS depend on the length and site of the resected small intestine, the state of the intestinal remnant, and the age of the patient. These factors influence the capacity of the remnant intestine to function as well as the potential for adaptation. Functional etiologies of IF involve conditions that impair the normal absorption of nutrition.

In children, the etiology of IF is commonly congenital and, whether related to SGS or functional disorders, often requires protracted or indefinite PN support. SGS is the cause of permanent IF in 50% of pediatric cases and is often secondary to congenital anomalies of the digestive tract, such as intestinal atresia and gastroschisis. In patients born with a normal gastrointestinal tract, the most frequent cause of SGS is necrotizing enterocolitis, especially in premature infants. Midgut volvulus from malrotation is another cause of SGS when it results in ischemia and necrosis with subsequent extensive intestinal resection.

Functional disorders of the intestine include neuromuscular motility disorders and a variety of enteropathic diseases. Hirschsprung's disease is a common cause of functional IF and is due to congenital intestinal aganglionosis. Hirschsprung's disease commonly affects the rectum and sigmoid, but when the aganglionosis involves a significant portion of the small intestine it can result in IF. Chronic intestinal pseudo-obstruction is a heterogeneous group of enteric nerve and muscle diseases characterized by intestinal obstruction in the absence of a lumen occluding lesion. Severe variants of chronic intestinal pseudo-obstruction often result in IF and require lifelong medical care. Congenital diseases of enterocyte development such as microvillus atrophy, autoimmune enteropathy, and intestinal epithelial dysplasia or "tufting enteropathy" cause IF.

In adults, SGS represents more than 80% of IF cases, and includes ischemia, Crohn's disease, desmoid tumors, Gardner's syndrome, and familial polyposis, trauma, volvulus, and rare causes such as radiation enteritis and postbariatric surgery. IF secondary to Crohn's disease is a unique entity because it may be related to extensive primary disease and/or multiple resections. Notably, the use of available immunosuppressive and biological antiinflammatory therapies as well as use of less invasive surgeries such as strictureplasty has reduced the incidence of IF in Crohn's disease. SGS related to mesenteric thrombosis is commonly associated with hypercoagulable states, which may have implications for anticoagulation management, particularly in the setting of intestinal transplant (Table 1).

INTESTINAL ADAPTATION

Small intestine that remains following a massive gut loss demonstrates enhanced absorptive function through numerous mechanisms collectively described as adaptation. Adaptation may be sufficient to permit restoration of nutritional autonomy even in cases in which the magnitude of intestine loss is extensive. In the absence of complete adaptation, patients remain committed to varying amounts of supplemental PN indefinitely. The probability of weaning patients off PN becomes less than 10% if weaning is not obtained during the first 4 years of PN in children and 2 years in adults.

The small intestine epithelium is perpetually proliferating and differentiating and is largely responsible for adaptation. The intestinal epithelium can morphologically and functionally adapt to the loss of functional surface area through crypt cell hyperplasia, villus lengthening, and increased absorptive function. Although adaptation has been demonstrated in numerous animal models, evidence for adaptation in humans includes improved fluid and electrolyte absorption over time following massive intestinal resection.

Several factors predict long-term PN, including a remnant jejunoileal length less than 50 to 100 cm in older children and adults and less than 20 to 40 cm in small children. Enterocolonic continuity and the ileocecal valve are also important determinants of successful adaptation. Site of resection is predictive of IF prognosis because jejunal resection is better tolerated than ileal resection; the ileum has an increased capacity to adapt and is also the site of bile acid and vitamin B12 absorption and synthesis of gastrointestinal hormones such as enteroglucagon. In the setting of SGS, the colon becomes important by absorbing sodium, water, some amino acids, and short-chain fatty acids.

CLINICAL ASSESSMENT

The clinical assessment of a patient with IF includes history and physical examination, imaging and endoscopy studies to determine the anatomy and length of intestine, assessment for liver dysfunction, and nutritional assessment. Critical components of the initial history include the etiology of IF, the anatomy and length of intestine, number of central lines and any central line complications including infections and thrombosis, and a detailed nutritional assessment. Physical examination should emphasize hydration and nutritional status, type and site of central line, and any signs of vascular thrombosis, chronic liver disease, or cardiovascular disease.

In some cases, it can be difficult to determine the anatomy and length of intestine. It is critical to review all prior surgical documentation, which should annotate the specific anatomic findings, including small and large intestine length and appearance. Intestinal length and quality should be verified by a combination of imaging with upper gastrointestinal series, barium enema, and upper and lower endoscopy. Endoscopy can also be used to obtain tissue biopsies and intestinal effluent sampling.

Nutritional assessment begins with patient weight, percentage of parenteral and enteral intake, and bowel function questions including diarrhea, nausea, vomiting, and bloating. A dietician evaluation is critical in this process. Physical examination should include accurate height and weight with calculation of body mass index. Signs of inadequate nutrition on PN include poor dentition, loss of subcutaneous fat, and temporal muscle wasting. Laboratory evaluation includes serum electrolytes, albumin level, prothrombin time, vitamin B12, and fat-soluble vitamins.

Evaluation of the small bowel absorptive capacity can be performed with functional assays such as the D-Xylose test. Citrulline has been identified as a biological marker of good functional mass and can be correlated to remnant small bowel length and absorptive capacity. Citrulline is a nonessential amino acid that is primarily produced by enterocytes and is not incorporated into peptides or proteins. A postabsorptive plasma level of citrulline lower than 20 μmol/L is associated with permanent IF when measured beyond a 2-year period of adaptation following extensive small bowel resection.

MEDICAL MANAGEMENT

Enteral Nutrition

Despite the loss of significant intestinal length or function, it is possible to maintain nutrition by enteral route in patients with IF. Enteral

TABLE 2 Parenteral Nutrition–Related Organ Dysfunction

Organ System	Complications
Liver	Steatosis, cholestasis, fibrosis, cirrhosis, portal hypertension
Gallbladder	Sludge, cholelithiasis, acalculous disease
Kidney	Chronic dehydration, renal insufficiency, hypernatremia, nephrolithiasis
Intestine	Bacterial overgrowth, increased permeability, bacterial translocation
Bone	Osteomalacia, osteopenia, osteoporosis
Immune	Immunosuppression
Neurologic	Memory disturbance

nutrition (EN) is vital for normal intestinal growth and function and adaptation is optimized with the provision of EN. EN promotes adaptation through intestinal epithelial contact with nutrients, promotion of mucosal hyperplasia, pancreaticobiliary secretion, and trophic hormone stimulation. Observational studies have correlated early EN with PN weaning in pediatric patients. The recommended formulations of EN vary depending on the length and site of remaining intestine.

Parenteral Nutrition

PN is the cornerstone of medical management of IF. Parenteral solutions have improved with increased understanding of energy, fluid, and micronutrient requirements. Careful prescribing and monitoring of PN patients can reduce complications. Although PN is an effective therapy, it is associated with significant morbidity. PN complications include central venous catheter–related, metabolic, and organ dysfunction.

Central venous complications include infection, occlusion, mechanical problems, and central vein thrombosis. Up to 15% of patients will experience a central venous catheter complication and PN is a risk factor. Improvements in catheter design and aseptic placement techniques have reduced septic complications.

Metabolic complications include derangements in hydration, electrolytes, and macro- and micronutrients. Fluid and electrolyte disturbances may be exacerbated in the setting of a high output ileal, jejunostomy, enterocutaneous fistula, or a patient with compensatory hyperphagia. An acute setting initiation of PN in a severely malnourished patient may result in rapid, intracellular shifts of magnesium, potassium, and phosphate leading to severe hypophosphatemia and hypokalemia, known as *refeeding syndrome*. Commercially available lipid, multivitamin, and trace element preparations provide the 35 essential nutrients (electrolytes, minerals, vitamins, and trace elements) and have reduced the potential for micronutrient deficiencies.

PN can result in the dysfunction of a variety of organs (Table 2). Liver disease represents one of the most important and lethal PN complications and is known as intestine failure–associated liver disease (IFALD). The pathophysiology of IFALD is poorly understood but appears to be multifactorial and related to a systemic inflammatory response associated with an influx of cytokines and bacterial toxins to the liver, inducing inflammation and collagen synthesis. Progression of IFALD to chronic and advanced disease, including fibrosis, cirrhosis, portal hypertension, and ultimately hepatocellular failure, occurs more commonly in young children than adults. The only proven treatment for IFALD is PN reduction with increased enteral feeding that is made possible by adaptation of the remnant bowel or by intestine replacement with a transplant.

Small Intestine Bacterial Overgrowth

Healthy enteric flora is critical to the normal function of the intestinal mucosal barrier and immunity. Anatomic and functional abnormalities intrinsic to patients with IF can predispose to small intestine bacterial overgrowth (SIBO). SIBO increases the risk of intestinal bacterial translocation, compromises the absorptive capacity in IF and may prevent PN weaning, and can exacerbate the hepatotoxicity related to PN. Treatment of SIBO includes reversing any predisposing anatomic conditions, and pharmacologic promotility treatment of functional disorders. Cyclical antibiotic therapy can be used but may increase the risk of multidrug resistant bacteria.

Recent Medical Advances in IF

Recent medical advances, including implementation of multidisciplinary care teams, utilization of novel GLP-2 analogs, and lipid-sparing PN formulations have transformed care of the patient with IF. Recent single-center reports have all confirmed a decrease in mortality with IF survival rates as high as 90% in some series. Successful liver sparing PN practices combined with the adoption of comprehensive, multidisciplinary approaches to IF management may be decreasing the incidence of end-stage liver disease in IF. These data represent a cumulative effect of multiple improvements in the management of IF and is a paradigm shift in the field.

Multidisciplinary coordination and individualization of care for the IF patient has been shown to decrease mortality from IFALD and sepsis, as well as improve enteral autonomy and even transplant outcomes. The comprehensive team should include a physician leader with expertise in gastrointestinal disease, a surgeon with gastrointestinal and transplant expertise, nurse coordinator, nutritionist, and social worker to optimize the patient outcome.

One of the most important recent advancements in the management of IFALD is the development of liver sparing lipid emulsions. Specifically, increasing evidence supports the substitution of soy oil–based intravenous lipid emulsion high in omega-6 polyunsaturated fatty acids with preparations derived from fish oil rich in omega-3 fatty acids. The underlying mechanisms of omega-6 fatty acid–induced liver injury are related to oxidative stress and inflammatory mediators and is an area of intense investigation. Multiple studies using various formulations of fish oil lipid emulsions have consistently demonstrated resolution of cholestasis in patients with IFALD.

GLP-2 is an amino acid intestinotrophic factor that has been shown to increase crypt villous length and epithelia proliferation in animal studies. Recent clinical trials have demonstrated improvements in intestinal absorption and nutritional status following treatment with GLP-2 analogs, thus is an extremely promising area of medical advancement in the treatment of IF.

SURGICAL MANAGEMENT

The role of surgical management in IF is to optimize use of the gastrointestinal tract. Because EN has been demonstrated to enhance intestinal adaptation, surgical interventions to facilitate EN are paramount to the successful management of IF. In PN dependent patients, surgical recruitment of any bypassed or unused remnant intestine can be performed by closing enterocutaneous fistulas or surgical enterotomy.

Some patients develop bowel dilation and dysmotility during the adaptation process, which can lead to decreased absorptive capacity and risk of bacterial overgrowth. In these cases, surgical lengthening and tailoring procedures can taper the dilated intestine and increase the total small intestinal length.

Bianchi was the first to describe an intestinal lengthening procedure by creating a tunnel in the vascular plane between the mesenteric vessels and then longitudinally stapling the intestine. The Bianchi lengthening procedure was demonstrated to be superior over

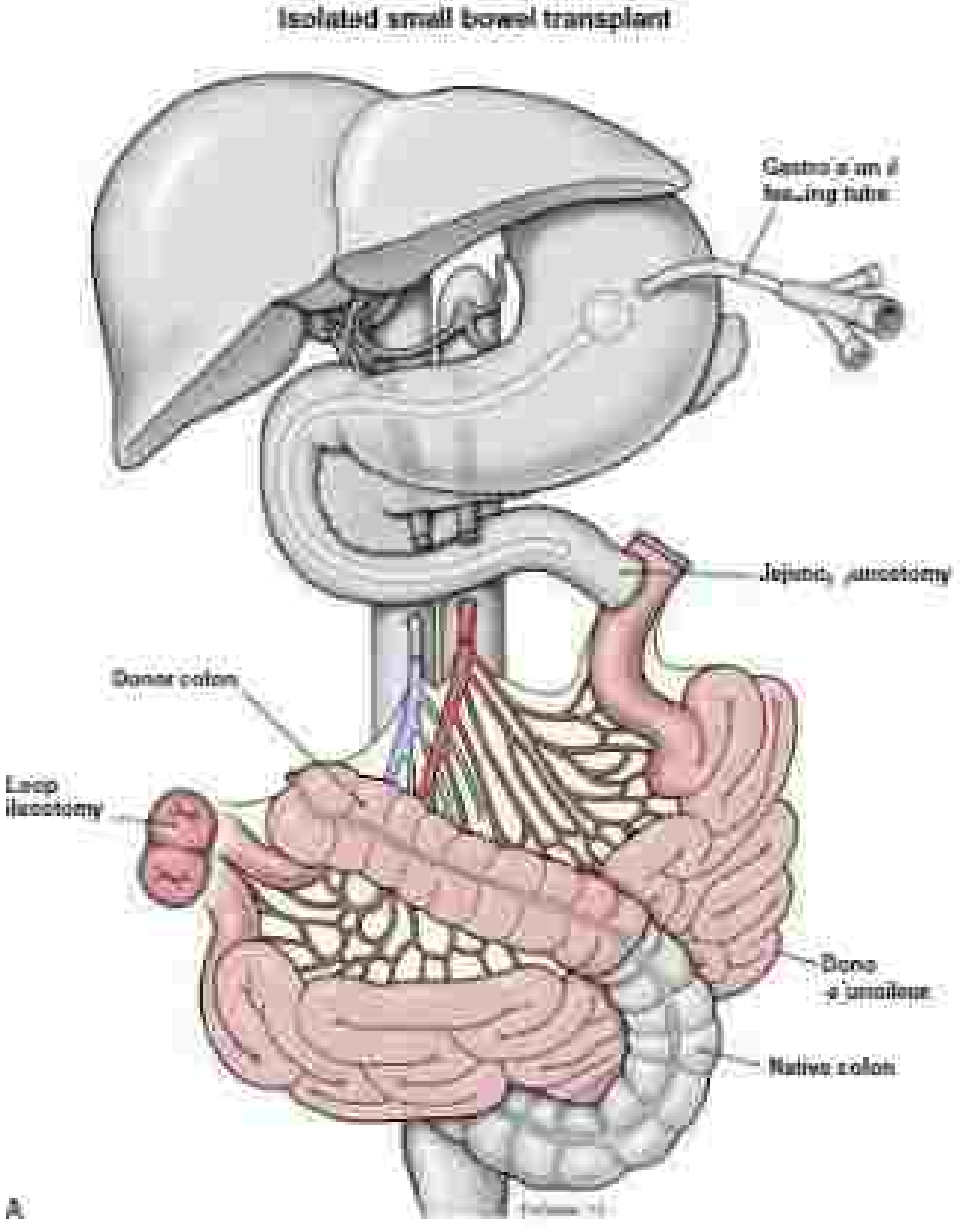

FIG. 1 Visceral transplantation for IFALD graft variations with graft to native ileum in gray (A) Isolated intestine graft (jejuno-ileum with native colon) variation.

simple adaptation in an experimental model. Clinical experience, mostly in children, demonstrated clinical improvement in the majority of patients, with 84% of survivors achieving independence from PN. The complexity of this procedure and associated complications has prevented its widespread application.

The predominant lengthening surgery currently is the serial transverse enteroplasty (STEP) procedure. STEP lengthening is performed by firing linear staplers alternately from the mesenteric and antimesenteric edge of the dilated small intestine. The clinical experience with the STEP procedure is growing and current data suggest that weaning from total PN is achieved in at least 50% of patients. The STEP procedure appears to be safer than the Bianchi lengthening procedure, with fewer reported complications.

Patient selection is critical to ensuring a successful surgical intervention in the setting of IF. Particular attention must be made to the patient's liver function because cirrhosis may be a contraindication and has considered for transplantation.

INTESTINE TRANSPLANTATION

As intestinal transplantation continues to improve, this therapy offers the hope of enteral independence and improved survival for patients with advanced IF. When patients with IF experience complications on PN that threaten survival, intestine transplantation is indicated. These complications include recurrent life-threatening central line associated sepsis, extensive central vein thrombosis that precludes confident preservation of PN catheter access, progressive IFALD, and repeated episodes of severe dehydration and associated electrolyte disorders that are refractory to standard management.

The term intestinal transplant comprises not only isolated intestinal transplant, but also combined liver-intestinal and multivisceral transplants (Fig. 1). The defining component of these variations is the small intestine (i.e., jejunum-ileum). When only the jejunum and ileum are transplanted, this is conventionally known as an isolated

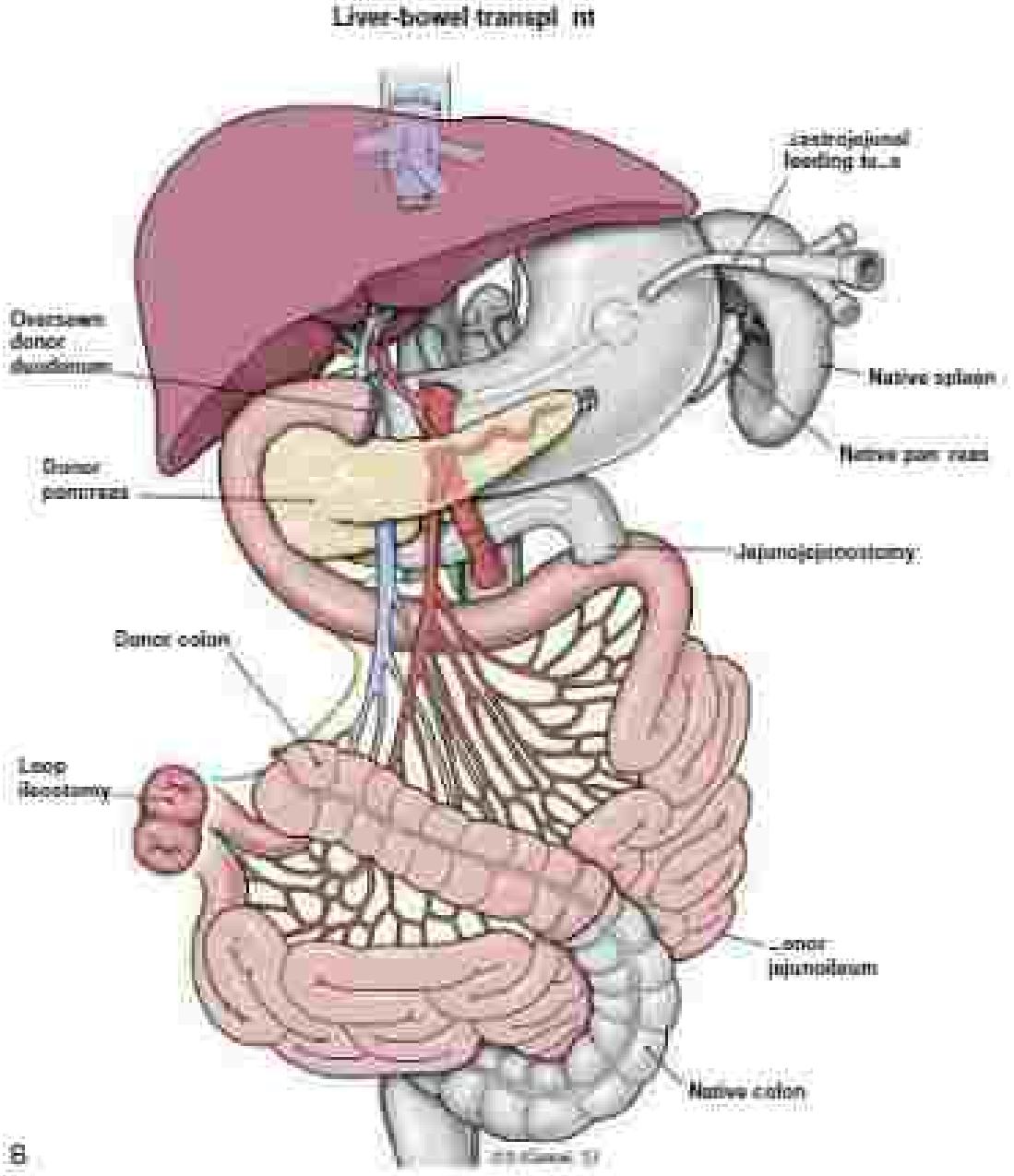

FIG. I, cont'd (B) Composite liver-intestine graft (en bloc liver, duodenum, pancreas, jejunum with colon) with native hepatic preservation, including native pancreaticoduodenectomy.

intestinal transplant. In the setting of advanced liver disease, combined liver and intestine are generally transplanted en bloc with the pancreas. The native hepatic is preserved in children whenever possible, and venous drainage with a portocaval shunt is required. Multivisceral transplantation that incorporates the stomach and entire duodenum may be appropriate in patients with extensive foregut tumor, trauma, and pseudo-obstruction. A segment of colon including ileocecal valve may be included with any of these variants, particularly in patients with little or no native colon remaining after resection or in patients with Hirschsprung's disease. The type of operation selected for an individual patient thus depends on the etiology of IF, state of existing abdominal and vascular anatomy, and severity of IFALD.

Short-term outcomes after intestinal transplant are excellent because of progressive surgical advances, improved detection and control of acute cellular rejection, and a decrease in lethal infections. According to the International Intestinal Transplant Registry, favorable prognostic variables include patients who have been admitted directly from home to undergo transplantation, younger patients, a first transplant, and those who receive antibody induction therapy or maintenance steroids. In contrast, long-term survival rates after intestine transplant remain modest, equaling only about 50% after 5 years for all types of intestinal transplants. For recipients of a liver-inclusive graft, graft survival beyond the first post-transplant year closely exceeds that of the isolated intestinal transplant because of relative immunologic tolerance provided by the liver. Immunologic risk factors for graft loss include not only transplantation without liver, but also defective innate immunity in the recipient because of nucleotide binding oligomerization domain containing protein 2 mutations similar to those in patients with severe forms of Crohn's disease. Recently, the role of donor specific antibody (DSA) has emerged as an important risk factor for rejection and malabsorption

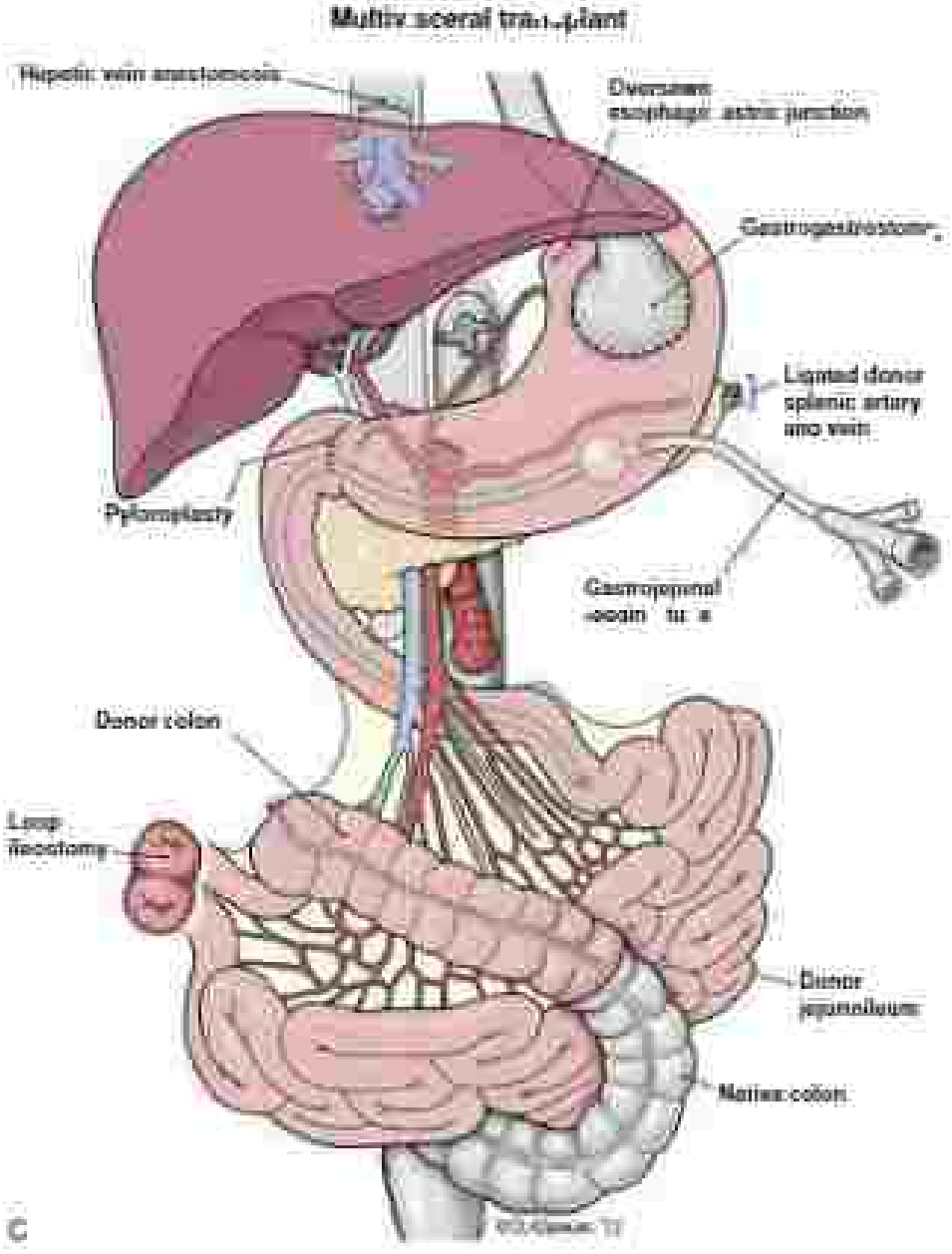

FIG. 1, (cont'd) (C) Multivisceral graft (stomach, duodenum, pancreas, jejuno-ileum with colon). (From Hoekstra H, Monkhorst TS, Fidelman Kempen-Voogd N, et al. Intestinal function as monitor in concert with other organs. In: Stein AP, Wiesner L, eds. Solid Organ Transplantation in Infants and Children. Springer; 2011.)

of preformed DSA with a virtual cross-match strategy with long-term management of de novo DSA may improve outcomes following intestine transplantation, particularly in the sensitized liver exclusive recipient.

CONCLUSIONS

IF is a rare, although devastating, condition that has profound implications for the quality of life and mortality for those affected. However, in the modern era, no patient with massive intestinal loss should be approached with the historically fatalistic approach. Cumulative improvements in the medical and surgical management of IF have resulted in long-term survival in more than 90% of patients. As transplant outcomes continue to improve, intestine transplantation may become the definitive treatment option for the IF patient.

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Management of Enterocutaneous Fistulas

Josef E. Fischer, MD

Gastrointestinal cutaneous fistulas are among the most catastrophic outcomes of gastrointestinal surgery. Complications of gastrointestinal surgery include anastomotic leaks, abscesses after drainage, leaving residual purulence, and abscesses after operation.

Although I do not have much data on the point to follow, I believe that the training of gastrointestinal surgeons has become less rigorous, less indispensable, and associated with fewer difficult cases. With the emphasis on work hours, there are fewer cases with less independence and greater faculty supervision. The emphasis on laparoscopy may result in a greater leak rate than following open cases by the comparatively inexperienced surgeon. As new gastrointestinal surgeons sign contracts, they often have comparatively rigid and attractive work hours, which should not be denigrated because these hours allow the surgeons more time to spend with their families. There is more emphasis on overnight and having a senior surgeon in the operating room, especially in difficult cases.

In a complicated situation such as a patient with a gastrointestinal cutaneous fistula, it is probably easier to divide the history into current periods and the attempts to have the patient recover. The phases of treatment outlined in Box 1 are somewhat different and more detailed than the five steps that I have written about in the past (stabilization, investigation, decision, definitive therapy, and healing). To a certain extent, this updated schedule is the result of good and bad experiences. What I have learned is that there is little room for error. Meticulous care and meticulous operation will result in lower mortality. A review of the past 50 gastrointestinal cutaneous fistulas I have performed shows that there has been no patient mortality. I believe that this is largely the result of waiting 5–6 months after the discovery of the fistula for reoperation. At this point, the adhesions have softened and are often filmy, resulting in fewer enterotomies and an easier operation.

STABILIZATION AND RECOGNITION

The most important aspect of initial treatment for the patient suspected of a gastrointestinal cutaneous fistula is the restoration of blood volume. In the past 20 years, there has been some movement away from colloid and blood; however, in the case of the gastrointestinal cutaneous fistula, crystalloid alone is inadequate. Albumin, occasionally plasma, or occasionally fresh frozen plasma for clotting factors, and blood, especially fresh whole blood when the surgeon suspects that the patient has a clotting abnormality, are the best option. I am aware that the blood banks typically dispense the oldest blood to the patient. Although small numbers of blood banks say that old blood is just as good to administer as fresh blood, there is evidence to the contrary, especially in patients who are critically ill. The surgeon in charge should insist on the freshest blood available and, when necessary, components such as platelets, fresh frozen plasma, and other components of blood, which will be essential.

DRAINAGE OF OBVIOUS ABSCESSES

Unfortunately, patients discovered to have a gastrointestinal cutaneous fistula often have an accompanying abscess. This often is associated with a high fever. The fever is associated with catabolism and an increase in the loss of protein. If the abscess is recognized, it should be delineated as best as possible. This can be done with various radiologic procedures. If the patient is sick and cannot be separated, it is essential to take the patient to the operating room. Drainage of an abscess is not something to be undertaken lightly or at the end of the schedule. If one is in a small facility, the patient must be transferred to an appropriate tertiary facility. The surgeon should have ample help, including another surgeon of known skill and, if possible, experience with drainage of abscesses. Whenever possible, the surgeon should convince the operating room staff that this procedure must be scheduled in the morning so that an ample number of surgeons is available to assist if necessary.

INVESTIGATION AND DEFINITION OF THE ANATOMIC SITUATION

The definition of the anatomic situation is not an emergency. It is much more important to get the patient's fluid situation and his or her infection under control and stabilize nutrition so that anabolism proceeds. If not, catabolism will proceed. These patients can lose up to 500 g of protein daily, so it is absolutely essential that peritonitis be drained and the patient's temperature return to normal so that catabolism decreases. A computed tomography scan may not be necessary, unless an abscess is suspected, and drainage is urgent. If there is an obvious abscess, this should be drained with a catheter if possible. If the surgeon cannot drain it, once the patient is stabilized, drainage should proceed in the operating room with adequate help, adequate culture, crystalloid, and blood, and the sepsis is eradicated as best as possible.

NUTRITIONAL ASSESSMENT AND BEGINNING NUTRITIONAL REPLENISHMENT

Nutritional support cannot be delayed because patients lose protein daily. It is highly unlikely that the patient can begin enteral nutrition quickly when major nutritional support is required. Thus, one starts the patient with total parenteral nutrition. An experienced surgeon should place a subclavian line under good conditions with adequate help and under strict aspsis. Nutritional support should begin immediately and the blood sugar should be checked so that life-threatening hyperglycemia does not occur. After the anatomic situation is stabilized and abscesses are drained so that sepsis is eliminated, decision making can begin. Supplying the patient with enteral nutrition as meeting the entire needs of the patient may not be possible, but there is reasonable evidence that the combination of enteral and parenteral nutrition may result in better anabolism. In some patients, enteral nutrition may not be possible.

SPONTANEOUS CLOSURE

Spontaneous closure occurs in approximately 30% to 35% of patients. In a few patients with specific types of fistulas, the percentage may be higher. The anatomy will usually predict which fistulas will close. Sepsis prevents closure. The fistula may open and close depending on the anatomy, sepsis, and cleaning up the abdominal wall. A cleaner, healthier abdominal wall around the fistula may aid spontaneous closure.

Aids to Closure

Keep the edges of the fistula clean, especially from gastrointestinal contents. Stenge (Fig. 1) may help in using a soft latex tube, usually of urologic design and various sizes. An extra hole with a No. 14 whistle tip catheter in gentle suction within a 22 or 24 yellow latex stump will help aspirate gastrointestinal contents from around the

BOX 1 Phases of Care of Patients With Gastrointestinal Fistulas

I. Resuscitation: first 24 hours
  A. Stabilization
    1. Restoration of blood volume
      a. Minimize crystalloid
      b. Albumin
        Plasma: especially fresh frozen, for clotting factors
      c. Fresh blood: avoid the "old blood"
        A practice of many blood banks
      d. Platelets when necessary
II. Recognition and drainage of obvious abscesses 24–48 hours
  A. High fever
  B. An accelerated rate of catabolism: up to 500 g of protein daily
  C. Radiologic investigation
    1. The most experienced surgeon and collaborating radiologist
    2. Transfer when necessary to a tertiary facility
    3. Drainage in the operating room: cases should be done in the morning with adequate assistance
    4. When possible use a soft latex catheter (see Fig. 1)
III. Nutritional assessment and beginning nutritional supply: resuscitation 24–48 hours
  A. Minimize delays
    1. Patients may lose 500 g of protein daily
    2. Enteral nutrition cannot make up all needs quickly
  B. Start parenteral nutrition
    1. A central line should be placed by an experienced surgeon
  C. Repeated measuring of blood sugar to avoid significant hyperglycemia
  D. After stabilization
    1. A combination of central and parenteral nutrition is probably best 48–72 hours
  E. How much nutrition
    1. 80–120 g of protein daily @ 5% hours
    2. Calories: 2200–3600 (depending on fever, sepsis)
    3. 30% fat
    4. Adequate
      a. Trace metals
      b. Vitamins
      c. Essential fatty acids
IV. Spontaneous closure up to 28 days
  A. Occurs in 30%–35% of patients
    1. The anatomy usually predicts which fistulas will close
    2. Sepsis prevents closure
    3. Some fistulas may open and close
    4. Healthier nonseptic abdominal wall more likely to close
  B. Aids to closure
    1. Keep edges protected and clean
    2. Sumps with gentle suction
      a. Keep moist and pat away from edges
V. Operation
  A. If no closure has occurred by 28 days, operation
    1. 60 days for infected hernia
    2. 120–150 days for clean hernia
  B. The incision
    1. The incision must be closed: if not, fistula will reopen
    2. Go to areas that are easier
    3. The operation should begin early
    4. Keep skin edges clean with antiseptic soaked blue towels or plastic drapes
VI. Lysis of adhesions
  A. Scissor dissection is safer
  B. Free everything up before attacking the fistula
  C. You will probably have to resect 18 inches of small bowel in removing the fistula
VII. The anastomosis
  A. Two layers of interrupted permanent suture
VIII. Postoperative care 150–270 days
  A. Do not be in a rush to feed the patient
  B. When feeding, maintain calories and protein until bowel function is normal
  C. Make certain calorie and protein intakes are adequate before stopping total parenteral nutrition
IX. Maintain nutrition and start rehabilitation 6 months
  A. Patients have lost protein, muscle, and neurologic function
  B. Patients may take up to 1.5 years before regaining total neural function
  C. Warn patients, tell them the length of time it will take
  D. Tell patients not to quit their jobs

fistula. The protection may be with powders such as karaya powder or more recently with some of the better plastic material, which is adherent to the edge of the fistula and protects the skin (Fig. 2).

Suction is broken by urologic type soft sumps, keeping the irritating material away from the edges of the sump (see Fig. 2). Notice that the area is large and sumps themselves may be multiple, making certain that bowel or other noxious material does not irritate the skin and prevent healing.

OPERATION

Operation will be required in between 50% and 65% of patients. This should only be attempted after an adequate trial of soft sumps, antibiotics, nutrition, and keeping the patient's abdomen clean. My rule is to allow the patient to be treated with sumps and wound protection that keeps the wound clean for 60 days without sepsis. When the absence of sepsis, suction, and other protection of the wound have been successful for 60 days and show no sign of closing, the surgeon prepares for operating.

The incision is an extremely important part of the operative procedure (Fig. 3). If you cannot close the incision after a resection, it is likely that an open-ended closure of the fistula will fail. The incision should be made in a clean area so that it is likely to allow the lysis of adhesions away from the fistula and, if possible, to avoid making further enterotomies. The surgeon should start in clean soft abdomen. My practice is to allow 5.5 to 6 months to elapse so that the adhesions within the abdomen become firm, and entering the abdomen and freeing up the bowel avoids enterotomies. The surgeon must start far away from the fistula and must not force the lysis of adhesions. If you are not making progress in one area, put some soft laparotomy packs soaked in antibiotic solution (Kantrex is my favorite) and go elsewhere. Start early in the morning and do not put any other procedures on the operative schedule. The worst thing you can do is hurry the procedure because you undoubtedly will make unintended enterotomies. These procedures will take between 6 and 8 hours, so be prepared, you may want some nourishment and hydration in the middle of the case.

After you have made the incision and sterilized the skin and the fascia and have some freedom, my practice is to take blue towels, soaking the edges in Kantrex and sew them in place; that way, you will not contaminate the edges with stool or septic material, and the case will remain clean until you get to the fistula (Fig. 4).

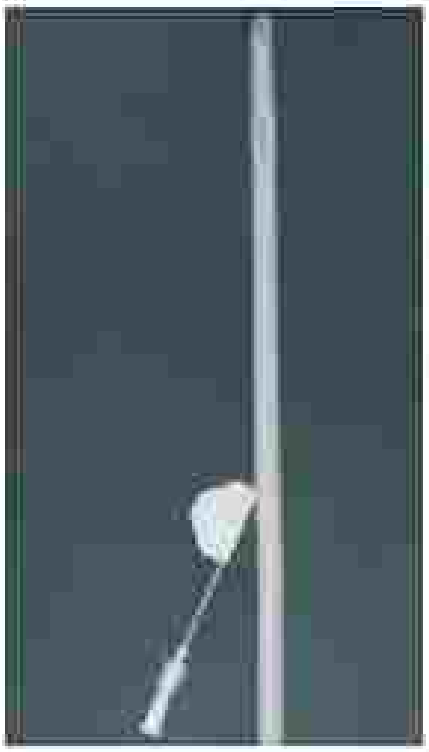

FIG. 1 Sump system for management of fistulae. (From Hocker JR, et al. In: Yeo CJ, ed. Yeo's Atlas of Surgical Anatomy. Philadelphia: Elsevier, Mosby, 2017.)

LYSIS OF ADHESIONS

You should go from where the incision was made to freeing up everything else. Achieve dissection is safer. Once everything else is free, you must attack the fistula. It is usually not possible to free up the skin around the fistula and mobilize the fistula without enterotomies. As much as 10 inches of small bowel, which is dissected in and around the fistula, will likely be sacrificed. If you begin making enterotomies, take a break and sit down; you will have to resect shorter lengths of bowel with enterotomies and will have less chance of short bowel syndrome (Figs. 5 and 6).

The anastomosis should be a two layer interrupted anastomosis carried out with permanent suture. Do not use an absorbable suture. Do not test the anastomosis for a period by giving oral intake. If you give oral intake too early, the anastomosis may disrupt and there may be a leak.

POSTOPERATIVE CARE

The patient should be ambulated, and the wound should be managed with healthy dressings.

Do not be in a rush to feed the patient, especially solid food. You may continue with enteral nutritional support but certainly do not let total parenteral nutrition decrease to a point at which the patient is not getting adequate protein and calories. Wait until the patient is having regulated bowel movements (preferably soft).

If the area in which you will be working and the anastomosis had infected contents, do not rush to stop the antibiotics.

If the area in which you were working had drainage, maintain the suction until the drainage dries for a time.

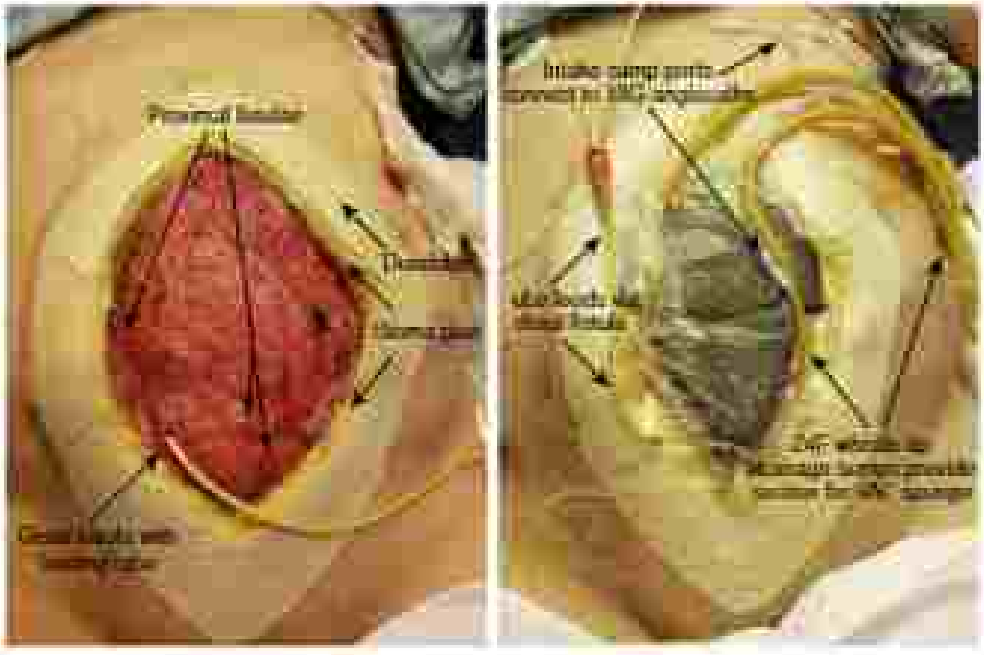

FIG. 2 Vacuum-assisted closure dressing in situ. (From Hocker JR, et al. In: Yeo CJ, ed. Yeo's Atlas of Surgical Anatomy. Philadelphia: Elsevier, Mosby, 2017.)

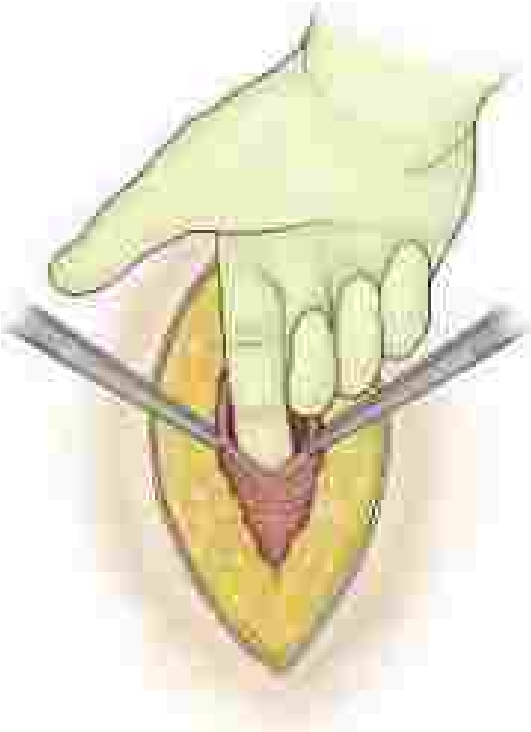

FIG. 3 Once the surgeon has made the skin incision and clears the subcutaneous tissue from the fascia, he or she lifts the fascia with a pair of Allis clamps so that one can see and then uses either a finger to separate the bowel from the underside of the fascia, without making an enterotomy. (From Mulholland MW, Lillemoe KD, Doherty GM, et al, eds. Greenfield's Surgery: Scientific Principles & Practice. Philadelphia: Lippincott Williams & Wilkins; 2017.)

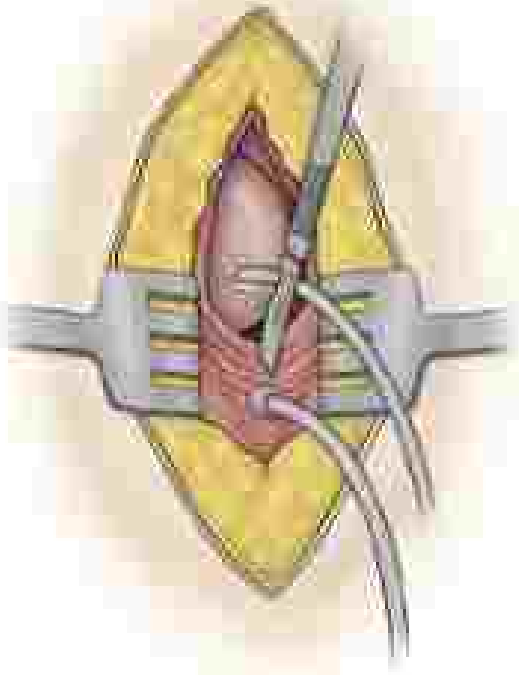

FIG. 5 Further dissection of the abdomen: the bowel and fistula are cleared down to the bottom of the wound. The fistula can be excised without fear of enterotomy. The goal is to resect the area with the fistula and the only adherent area is rarely larger than 12 inches of bowel. Entero-enteric anastomoses are made only to 12 inches of bowel or less. (From Mulholland MW, Lillemoe KD, Doherty GM, et al, eds. Greenfield's Surgery: Scientific Principles & Practice. Philadelphia: Lippincott Williams & Wilkins; 2017.)

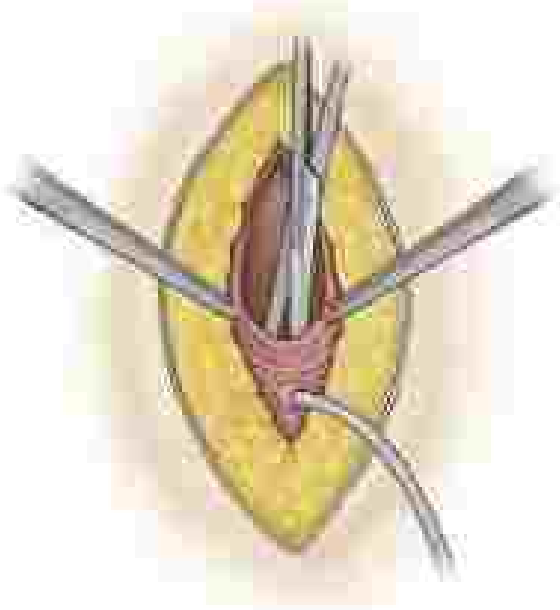

FIG. 4 Both the skin incision and the fascia incision are lengthened carefully as the undersides of the fascia is separated from the bowel and one can see clearly. The fascia may be divided with Metzenbaum scissors or a No. 15 blade scalpel.

MAINTAIN NUTRITION AND START REHABILITATION

Remember that most of these patients have lost body mass. Allow nutrition to proceed before putting them through a vigorous aspect of rehabilitation. Make certain that bowel movements are regular and above all do not use a cathartic in the presence of a fistula anastomosis.

Allow 4 to 6 months of rehabilitation before patients should think about returning to work. They have lost much protein, they will have also lost some of their neurologic function, and they will complain that they cannot think clearly. Resumption of function is important but if done too early, the patient will get depressed.

RESUMPTION OF FUNCTION

Most of these patients have lost body mass and neurologic function. If they return to work too early, particularly if they have a position of responsibility, they will find that they cannot think clearly and make mistakes. They will then retire prematurely. My experience is it will take up to 18 months for the nervous system to recover. I insist that patients wait 18 months before going back to work and make certain that they do not attempt to run their business early but only as a loyal work associate. Once they return slowly to the job, they will find that they can think as clearly as in the past. That will avoid depression that will occur by returning to work too early.

A fistula is a devastating event for a patient. Muscle protein and neurologic function are likely to deteriorate. Do not let patients return to work too soon. They should return slowly over months. That will keep them, their families, and their jobs intact.

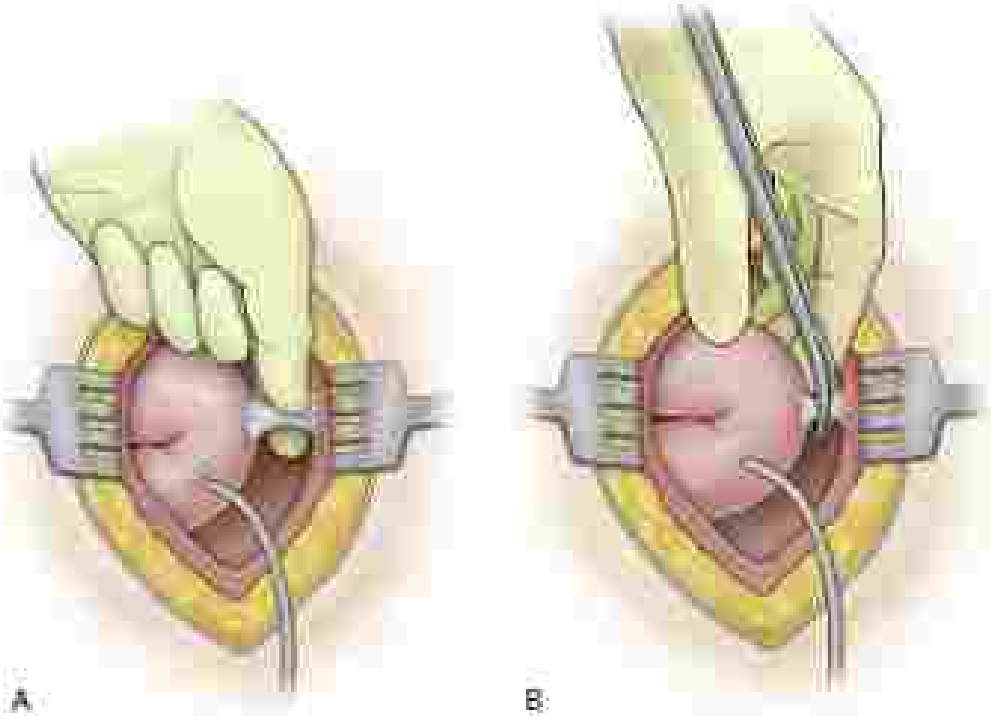

FIG. 6 Adhesions can sometimes be dealt with by compressing the adhesions from a broad base to a narrow base. When the adhesion is narrowing and is easily visible, the narrowed adhesion can be sharply divided. (From Fischer JE, et al. eds. Fischer's Mastery of Surgery. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.)

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Preoperative Bowel Preparation: Is It Necessary?

Travis P. Webb, DO, MHPE

Elective colorectal resection is usually performed with mechanical bowel preparation (MBP) and antibiotic prophylaxis. Surgical site infection rates for patients undergoing colorectal surgery range from 5% to 30%, depending on the patient population and the definition of infection used. Although the use of MBP and antibiotics has become standard practice, there is controversy regarding the benefit of MBP. Some surgeons believe that MBP is necessary to decrease the risk of anastomotic leak and surgical site infection, whereas others believe that MBP is unnecessary and may actually increase the risk of complications. Recent studies have shown that MBP is not associated with a decrease in anastomotic leak or surgical site infection. Furthermore, MBP may be associated with dehydration, electrolyte abnormalities, and increased length of stay. Despite this evidence, MBP is still commonly used in practice. Surgeons who perform colorectal surgery should be aware of the evidence regarding MBP and should be able to counsel patients on the risks and benefits of MBP.

Historical Background

Surgical site infection is a common complication after colorectal surgery. Historically, the rate of surgical site infection was 50% to 80%. Surgeons began to recognize that the presence of bowel contents was associated with an increased risk of infection. Early attempts to reduce the risk of infection included diverting stool proximal to the anastomosis and performing a staged procedure. Over time, surgeons began to perform primary anastomoses with MBP and antibiotics, thereby reducing the risk of infectious complications. During the 1970s and 1980s, when mortality after colon resection was 10% and SSI was as high as 80% to 90%, studies began to describe multiple strategies of mechanical and antibiotic preparation that led to improved outcomes. By the 1990s, the oft-cited Condon nonrandomized mechanical bowel preparation strategy was widely adopted. It was believed that mechanical cleaning facilitated the action of nonabsorbable oral antibiotics. As bowel preparation moved to the outpatient setting in recent decades, however, the oral antibiotic component was often omitted because it was considered unnecessary if intravenous antibiotics were administered at the time of incision. Recent data now argue that this omission was ill advised.

Mechanical Bowel Preparation

Oral mechanical bowel preparation comes in several forms. Polyethylene glycol (PEG) solutions typically are given in large (4 L) or reduced volumes (2 L) when bisacodyl is added. PEG solutions are osmotically balanced and provide colonic cleansing through washout, whereas the addition of bisacodyl stimulates colonic peristalsis. Hyperosmotic preparations with insoluble salts containing phosphates or magnesium achieve cleansing by drawing water into the bowel lumen. The risk of electrolyte imbalances is therefore higher with hyperosmotic preparations and should be used with caution in at-risk patients. Multiday regimens using nasogastric tubes for whole gut irrigation are largely of historic interest and no longer widely used. See Table 1 for additional details on available mechanical preparations and their use.

Data for Mechanical Preparation

Between the 1970s and 2011, many observational and randomized studies failed to show a difference in key outcomes between MBP and no preparation. Surgeons have been questioning the value of MBP almost since its inception. Indeed, there is substantial, level 1 evidence from large randomized trials clearly indicating that MBP alone offers no advantage over no bowel preparation in elective colorectal surgery. The Cochrane *The Value of Stoma in Reversal* first addressed this topic in 2003 and has since published three updates (2006, 2009, and 2011). The most recent update includes data from 26 published articles, encompassing 7,665 patients. Examining a series of outcomes, including wound infection, anastomotic leak, peritonitis, reoperation and mortality, the authors conclude that mechanical bowel preparation (and rectal enema) may be omitted safely without any statistically significant difference in postoperative complications.

One often cited weakness of prior studies (and their subsequent meta-analyses) is the heterogeneity of mechanical preps and, fundamentally, the inclusion of a range of different operations. In 2014 the Agency for Healthcare Research and Quality conducted a clinical effectiveness review to expand upon the Cochrane reviews. The authors aimed to examine additional factors such as anatomic location of surgery, operative approach, and even a range of mechanical preparations

TABLE 1 Mechanical Bowel Preparations

Preparation Type	Product Example	Volume	Administration	Notes on Use
PEG (electrolyte lavage)	CoLyte[a] GoLYTELY	3.8 L 4000 mL	…on solid food for at least 2 hours before ingestion of the solution; 240 mL (8 oz) every 10 minutes until rectal output is clear or 4 L are consumed	…Divided dose regimens (1 L the night before procedure, 1 L morning of procedure) may improve patient tolerance. PEG is considered safer than osmotic laxatives/NaP for patients with electrolyte/fluid imbalances, renal or liver insufficiency, CHF, or renal or liver failure.
Sulfate-free PEG (improved smaller tasty, more palatable for patients)	NuLYTELY …ntLyte[a]	4000 mL 4000 mL	No solid food for at least 2 hours before taking the solution; 240 mL (8 oz) every 10 minutes until rectal output is clear or 4 L are consumed	Similar efficacy to PEG
Low-volume PEG and bisacodyl tablets (decrease volume related discomfort [e.g., bloating, cramping])	…ulyte and bisacodyl tablet bowel prep MiraLAX	2000 mL 255 g in 2000 mL	Only clear liquids on the day of the preparation. Two sets of bisacodyl delayed-release tablets (5 mg) at noon. Wait for bowel movement or maximum of 4 hours; 240 mL (8 oz) low-volume PEG (i.e., HalfLytely) or 240 mL (8 oz) of clear liquid containing one capful of MiraLAX or other PEG; 8 oz every 10 minutes until 2 L are consumed.	Equally effective as 4 L solutions; additional studies needed to guide safety
Aqueous NaP with…tions	Fleet	90 mL with 48 oz additional liquid	Only clear liquids can be consumed on the day of preparation. Two doses of 30–45 mL (2–3 tbsp) of oral solution are given at least 10–12 hours apart. Each dose is taken with at least 8 oz of liquid followed by an additional minimum of at least 16 oz of liquid. The second dose must be taken at least 3 hours before the procedure.	May cause significant…ical shifts. Not for use in pediatric or elderly patients or those with bowel obstruction, gut dysmotility, other structural intestinal disorders, renal or liver failure, or congestive heart failure. NaP may cause ulceration or mucosal abnormalities; do not use in patients with inflammatory bowel disease. Patients with compromised renal function or those taking…CE inhibitors or ARBs are at risk for phosphate nephropathy. In 2006, the FDA issued an alert regarding the risk for acute phosphate nephropathy, a type of acute renal failure, with use of oral sodium phosphate solutions or tablets.
Oral sodium phosphate (tablet)	…trasol (discontinued)	32–40 tablets with 64 oz clear liquid	Dosage is 32–40 tablets: 20 tablets on the evening before the procedure and 12–20 tablets the day of the procedure (3–5 hours before). The 20 tablets are taken as 4 tablets every 15 minutes with 8 oz of clear liquid. Bisacodyl is prescribed by some physicians as an adjunct.	Early tablet components included higher concentration of microcrystalline cellulose per tablet, which left residue obscuring the mucosal surface. Later tablet composition decreased microcrystalline cellulose concentration. Overall, tablet NaP is not associated with significantly improved patient tolerance when compared with aqueous NaP.
Adjuncts to mechanical preparation	Agent	…Tablets/Dose	Mechanism	…se

TABLE 1 Mechanical Bowel Preparations—cont'd

Preparation Type	Product Example	Volume	Administration	Notes on Use
Enemas	Tap water Soap suds Fleet enema Fleet bisacodyl enema Fleet mineral oil	500–1000 mL 500–1000 mL 4.5 mL 10 mg (1.25 oz; 37 mL) 60 mL	Distention and lavage of rectum and distal colon	Routine addition of enemas to oral preparations does not improve the quality of bowel cleansing, but does increase patient discomfort. Use enemas in patients presenting for endoscopy with poor distal colon preparation and in patients with distal functional distal colon (e.g., Hirschsprung).
Bisacodyl	Bisacodyl	5-mg tablet	Poorly absorbed diphenylmethane that stimulates colonic peristalsis; used as adjunct for NaP or PEG preparations	Can been found to decrease the volume of PEG preparation required
Saline laxatives	Magnesium citrate (liquid) Picolax (sodium picosulfate/ magnesium citrate)	7.9–300 mL	Hyperosmotic saline laxatives that increase motility by increased intraluminal volume	Addition of magnesium citrate to PEG allows for lower volume preparations. Use with extreme caution in patients with renal insufficiency or renal failure because of exclusive renal excretion of magnesium.
Senna	Senna Senokot Senna Syrup (8 mg/5 mL)		Anthraquinone derivatives (glycosides and sennosides) are activated by colonic bacteria and directly increase the rate of colonic motility with a subsequent increase in colonic transit and reduced water and electrolyte secretion.	Senna with PEG may improve the quality of preparation and reduce volume required.
Simethicone	Gas-X Mylicon Mylanta Generic formula (some 180 mg)		Antifoaming agent used to prevent foam formation after PEG preparation. Mechanism of action is unclear.	May improve lumen visualization and patient tolerance of bowel prep.
Metoclopramide	Reglan Generic formula (some also available)	5 mg	Dopamine antagonist gastric prokinetic, increasing the amplitude of gastric contraction, with increased peristalsis in duodenum and jejunum but without change in colonic motility	May reduce nausea. Slowing does not improve colonic cleansing
Carbohydrate electrolyte solutions	Cleprado ClearPEG Generic formula (some	20 oz.	Used with PEG and/or NaP solutions to improve flavor and prevent NaP/ related fluid and electrolyte shifts	Carbohydrate based solutions more palatable for patients; however, associated with a theoretical risk of colonic gas-induced explosion if these carbohydrates are metabolized by colonic bacteria into explosive gases.

[illegible]

[illegible]

[illegible]

used, despite a broad array of sixty studies (including 44 randomized controlled trials, 10 nonrandomized comparative studies, and 6 single group cohorts), the authors concluded that the evidence base is weak. They could not identify evidence of any benefit of mechanical bowel preparation, however, they could not exclude modest effects (30%–50%) in either direction for overall mortality, anastomotic leak, wound infection, or peritonitis. In the end, it was concluded that the heterogeneity of study methods, small sample sizes, and inadequate reporting prohibited meaningful comparisons of MBP strategies. In examining anatomic location of surgery, only one outcome, anastomotic leak, had sufficient data for analysis, and the results showed no difference between MBP and no MBP in either colon or rectal location. More recent meta analyses, including one in 2018, have further verified that MBP alone has no significant effect on patient outcomes.

Because of the lack of benefit, patient complaints of prep-related discomfort, and physician concerns regarding electrolyte imbalances, dehydration, mucosal injury, and other adverse events, MBP has been abandoned in many areas of the world. Certainly, complications do arise for the routine use of MBP, but adverse events from bowel preparations are poorly reported in the literature. Based on the current available evidence, MBP alone generally is not recommended for routine elective colon operations.

DATA ON ORAL ANTIBIOTIC PREPARATION

Few data exist regarding OA given without MBP, but, a recent 2017 study using data from the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) attempted to determine whether OA alone is beneficial. This study matched 14,61 (OA) with 9800 (MBP) and 8819 (MBP+OA) patients to determine whether OA alone reduced patient morbidity. They concluded that OA alone compared with MBP significantly reduced SSI, anastomotic leakage, postoperative ileus, and major morbidity after colorectal surgery. They suggest that the addition of MBP may not be necessary. Because this is a retrospective study of a national database, randomized controlled trials are warranted to further clarify this issue.

Several oral antibiotic regimens have been described over the past century. Refer to Table 2 for common examples of oral antibiotic prophylaxis.

MECHANICAL AND ORAL ANTIBIOTIC PREPARATION

Evidence is now strong that, when compared with no bowel preparation, MBP+OA is beneficial in patient outcomes. A 2014 Cochrane Review on antimicrobial prophylaxis for colorectal surgery showed that combined oral and intravenous prophylaxis reduced the risk of SSI by 44% when compared with intravenous antibiotic administration alone (relative risk, 0.56; 95% confidence interval, 0.43 to 0.74). The data, derived from 14 studies including 2465 participants, were deemed high quality, such that further research is very unlikely to change our confidence in the estimate of effect.

Recent publications from statewide and nationwide data registries support this conclusion; combined preoperative oral antibiotic and mechanical bowel preparation is associated with reductions in SSIs, anastomotic leakage, ileus, and health services utilization outcomes such as length of stay and readmission. This includes several studies using data from NSQIP, which have identified decreased infectious complications associated with combined oral antibiotic and mechanical bowel prep. The most recent analysis using data from 2012 and 2015 includes 27,864 patients and revealed lower rates of SSI, organ space infection, wound dehiscence, and anastomotic leakage without increased risk of *Clostridioides difficile* infection. An analysis of Veterans Affairs data came to similar conclusions, with lower readmission rates for infectious complication and shorter length of stay seen among the patients receiving oral antibiotic bowel preparation when compared with mechanical only or no preparation groups. Studies from the Michigan Surgical Quality Collaborative also have identified a decreased rate of abdominal abscess (1.4% vs 2.1%) or SSI (5.0% vs 6.2%) between propensity matched pairs receiving mechanical bowel preparation and oral antibiotics compared with those with neither mechanical nor oral antibiotic preparation. The Michigan data also have been used to evaluate preoperative *C. difficile* colitis, revealing lower rates (0.2% vs 1.9%) among the oral antibiotic group.

Given the evidence from current literature, guidelines for the surgical management of elective colorectal illnesses have been updated by many societies. In 2016, and 2017, the American Society of Colon and Rectal Surgeons, Society of American Gastrointestinal and Endoscopic Surgeons, Surgical Infection Society, and American College of Surgeons recommended that all patients undergoing elective colorectal surgery should receive an MBP+OA.

TABLE 2 Oral Antibiotic Regimens

Oral Antibiotic Prophylactic Regimen*	Use in Prior Literature
Neomycin + erythromycin	Coppa, 1988; Kaiser, 1985; Khubchandani, 1980; Lau, 1988; Nichols, 1973; Stellato, 1989
Metronidazole + neomycin	Gastinne, 2005; Hamel, 1986; Lewis, 2003; Nelis, 1990 (includ. oral bacitracin); Reynolds, 1980
Metronidazole + kanamycin	Lazorthes, 1982; Matthiessen, 1983; Takesue, 2006
Tinidazole + neomycin	Persson, 1987
Kanamycin + erythromycin	Ishida, 2001; Kobayashi, 2007

*Modified from Pollock CE, Mills KT, Kelly JH, Caplinger C. Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infection after colorectal surgery: a meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2011;26(6):705–718. †Each of these oral antibiotics was combined with a range of intravenous antibiotics in the studies listed.

CONCLUSIONS

Recent literature indicates that MBP+OA reduces complications for patients undergoing colorectal procedures. Although mechanical bowel preparation alone does not appear to provide a benefit, oral antibiotics without mechanical bowel preparation is rarely used and has not been adequately studied. The effects of oral antibiotic prophylaxis without first cleaning the colon are not conclusive and should be a focus for future research. Additional areas for further research include the use of bowel preparation in laparoscopic or minimally invasive approaches and in rectal surgery.

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Management of Diverticular Disease of the Colon

Ira L. Leeds, MD, MBA, S.M, and Sandy N. Fa g, M

Colonic diverticula are common among the general population, and pathologic states associated with diverticula may be increasing. These protrusions of colonic mucosa between fibers of the muscularis propria, more appropriately termed pseudodiverticulum, are thought to be a precondition for diverticulitis and diverticular bleeding. Diverticular disease routinely ranks in the top 10 listed diagnoses for ambulatory care in the United States and is the most commonly reported gastrointestinal diagnosis for inpatient hospitalization.

The natural history of colonic diverticula and their resulting disease states is poorly understood. The quantity of diverticula is positively correlated with age: diverticula are present in 65% of the Western population by 85 years and less than 5% of the population younger than age 40 years. Their occurrence is thought to be associated with degradative changes to the integrity of the colon. Age-related collagen structural changes and increased intraluminal pressure often associated with constipation are thought to aggravate existing colonic wall vulnerabilities at the site of the penetrating branches of the vasa recta through the muscularis propria. The effect of increased intraluminal pressure as a contributing factor is supported by studies demonstrating a role of the environment in pathogenesis. Western populations eating similar diets have a much more substantial burden of diverticula in the sigmoid colon, whereas Asian countries demonstrate diverticula predominantly in the right colon. Evidence also exists for an important genetic risk contribution with sibling cohorts and twin studies demonstrating relative risks ratios three times greater than the general population.

The presence of colonic diverticula, or diverticulosis, is necessary but not sufficient to cause diverticular disease. The most recent evidence suggests that only 4% of patients with diverticulosis ever develop symptoms of diverticulitis. This is markedly lower than previously thought, and diverticular bleeding is thought to be similarly rare. For this reason, the only recommendation we give patients with asymptomatic diverticulosis is to increase fiber and fluid intake.

Ongoing debate exists as to why and how otherwise benign diverticula occasionally progress to disease. Manifestations of diverticular disease appear to be specific to their anatomic configuration. Diverticulitis is more commonly associated with sigmoid colon diverticula. Although diverticulitis has typically been conceptualized as an infectious process caused by bacterial overgrowth with or without obstruction akin to appendicitis, similarities between diverticulitis and inflammatory bowel disease have led some to suggest an autoimmune etiology.

Diverticular bleeding typically occurs from right colon diverticula. Right sided diverticula tend to be larger and may be due to the thinner colonic wall at this location. The penetrating arterial branches of the vasa recta end up draped over the herniating colonic mucosa. Recurrent inflammation of the vessels leads to eccentric intimal thickening that may increase the propensity for spontaneous hemorrhage.

This chapter describes the approach to management of diverticulitis and diverticular bleeding.

DIVERTICULITIS

Presentation and Diagnosis

Acute diverticulitis classically presents as left lower quadrant pain, fever, and leukocytosis. Symptoms of more complicated disease such as feculoma, pneumaturia, stool passed via the vagina, and progressively worsening constipation are suggestive of fistula (see The Management of Rectovaginal Fistula) or stricture formation. Numerous other diagnoses can mimic symptoms of diverticulitis, and the initial workup of suspected diverticulitis focuses on ruling out similarly presenting conditions, including appendicitis, inflammatory bowel disease, ischemic bowel, neoplasia, and gynecologic conditions. A urinalysis is helpful to evaluate for a urinary tract infection or nephrolithiasis. Although with some specificity limitations and contraindications in select patients, computed tomography (CT) of the abdomen and pelvis with intravenous and oral contrast is the best initial modality for diagnosing and staging suspected diverticulitis, addressing alternative diagnoses, and identifying diverticulitis associated complications. Magnetic resonance imaging is an alternative diagnostic imaging modality. CT magnetic resonance colonography is used infrequently and primarily in chronic diverticulitis to further evaluate stricture complications.

Staging is a critical component of the diagnostic workup because it is highly predictive of the success of the different management strategies described in this chapter. Staging definitions are myriad, and different systems often have categories of disease severity that overlap. We exclusively use the modified Hinchey classification system based on the original 1978 staging and updated to reflect diagnostic sophistication afforded by modern CT imaging (Table 1; Fig. 1). To accommodate other common classification schemes, we use modified Hinchey stage 0/Ia and "symptomatic, uncomplicated diverticulitis" interchangeably. Importantly, physical examination should be correlated with CT imaging findings as only patients, by definition, at least Hinchey III, may have limited findings on imaging. Our initial approach to management of acute diverticulitis is shown in Fig. 2.

Management of Symptomatic, Uncomplicated Diverticulitis (Modified Hinchey Stage 0 or Ia)

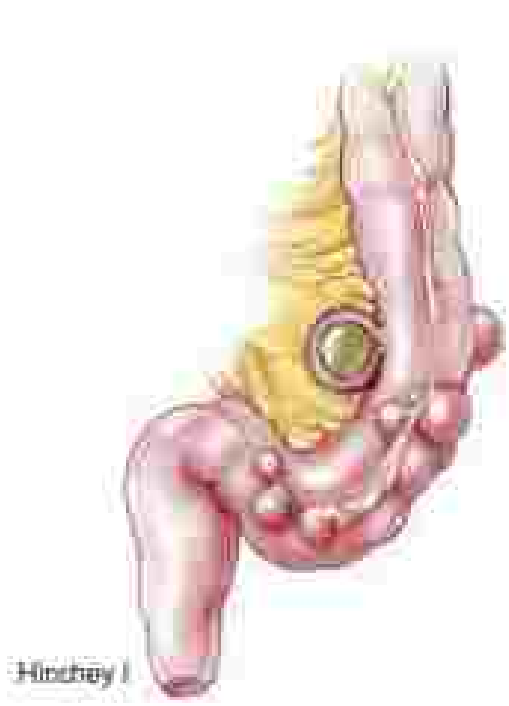
Treating patients with symptomatic, uncomplicated diverticulitis is one of the most rapidly evolving areas of colorectal surgery, with limited consensus among current evidence, expert consensus, and surgical practice. Supported for many years by professional guidelines and as demonstrated in the multicenter Spanish Hospitalization or Ambulatory Treatment of Acute Diverticulitis trial in 2014, most patients with uncomplicated disease have been treated with a single intravenous dose of antibiotics, 10 days of outpatient antibiotics, and close follow up if clinically appropriate.

The Swedish Antibiotic Therapy or Acute Uncomplicated Colonic Diverticulitis trial has challenged this paradigm by demonstrating that inpatient admission for intravenous fluid resuscitation with or without antibiotics was not associated with any difference in future diverticulitis complications, faster hospital discharge, or recurrence. Adoption of an antibiotic-free treatment strategy more broadly is not yet recommended because of the inpatient monitoring of antibiotic-free patients performed in these studies versus the outpatient follow up typically used with antibiotics in most other settings.

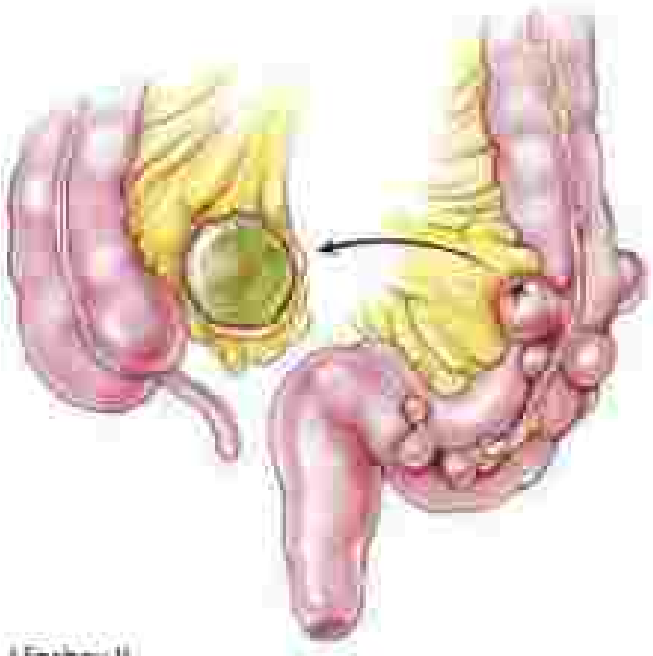
In our practice, patients with uncomplicated diverticulitis who are hemodynamically stable, medically uncomplicated, and are able to hydrate well are treated with oral antibiotics and outpatient follow up. If any of the criteria are not met, we recommend hospital admission for at least 2 days to start antibiotics, fluid resuscitate, and maintain a diet under supervision. Oral antibiotics should have excellent gram negative and anaerobic coverage with favorable positioning with reference to an institution's local antibiogram. Resolution of symptoms guides diet advancement. Current evidence suggests nonoperative management success in more than 90% of appropriately selected individuals. If still symptomatic 5 to 7 days after initiating treatment or if the patient's clinical status worsens, a CT scan of the

TABLE 1 Modified Hinchey Classification for Acute [illegible] ertic litis

Stage	Definition	Associated CT findings
0	Mild clinical diverticulitis (uncomplicated diverticulitis*)	Diverticula, with or without associated colonic wall thickening
Ia	Confined pericolic inflammation, phlegmon	Colonic wall thickening with pericolic soft tissue changes
Ib	Pericolic or mesenteric abscess	Stage Ia findings plus local abscess
II	Pelvic, distant intraabdominal, or retroperitoneal abscess	Stage Ia findings plus anatomically distinct, distant abscess
III	Generalized purulent peritonitis	Ileus; with fluid not confined to an abscess cavity; peritoneal wall thickening
IV	Generalized fecal peritonitis	Impossible to distinguish from stage III findings



Hinchey I



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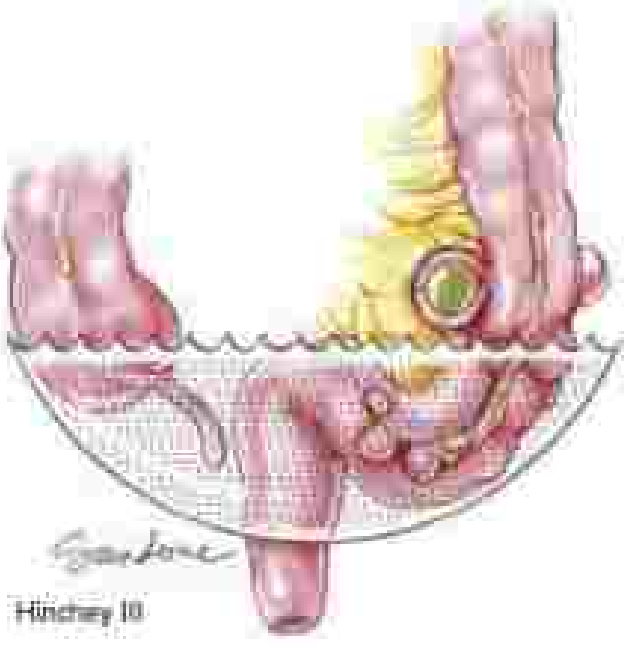
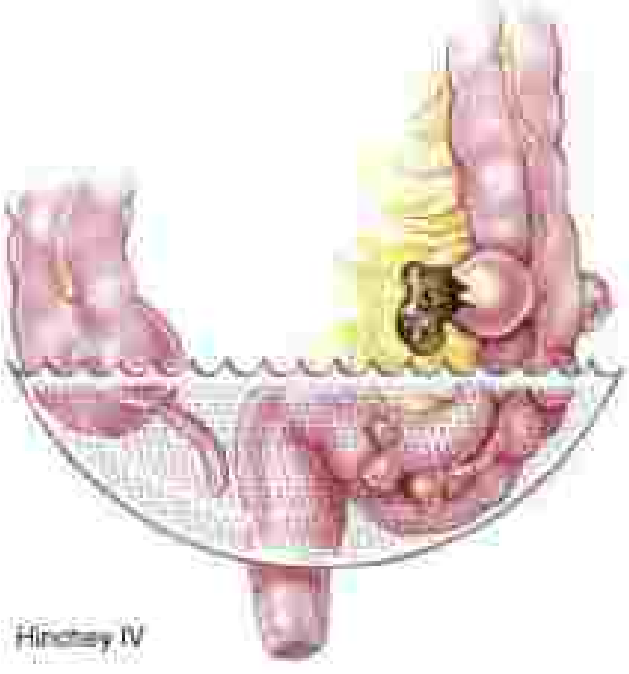


Hinchey III



Hinchey IV

FI [illegible] Hinchey [illegible] [illegible]

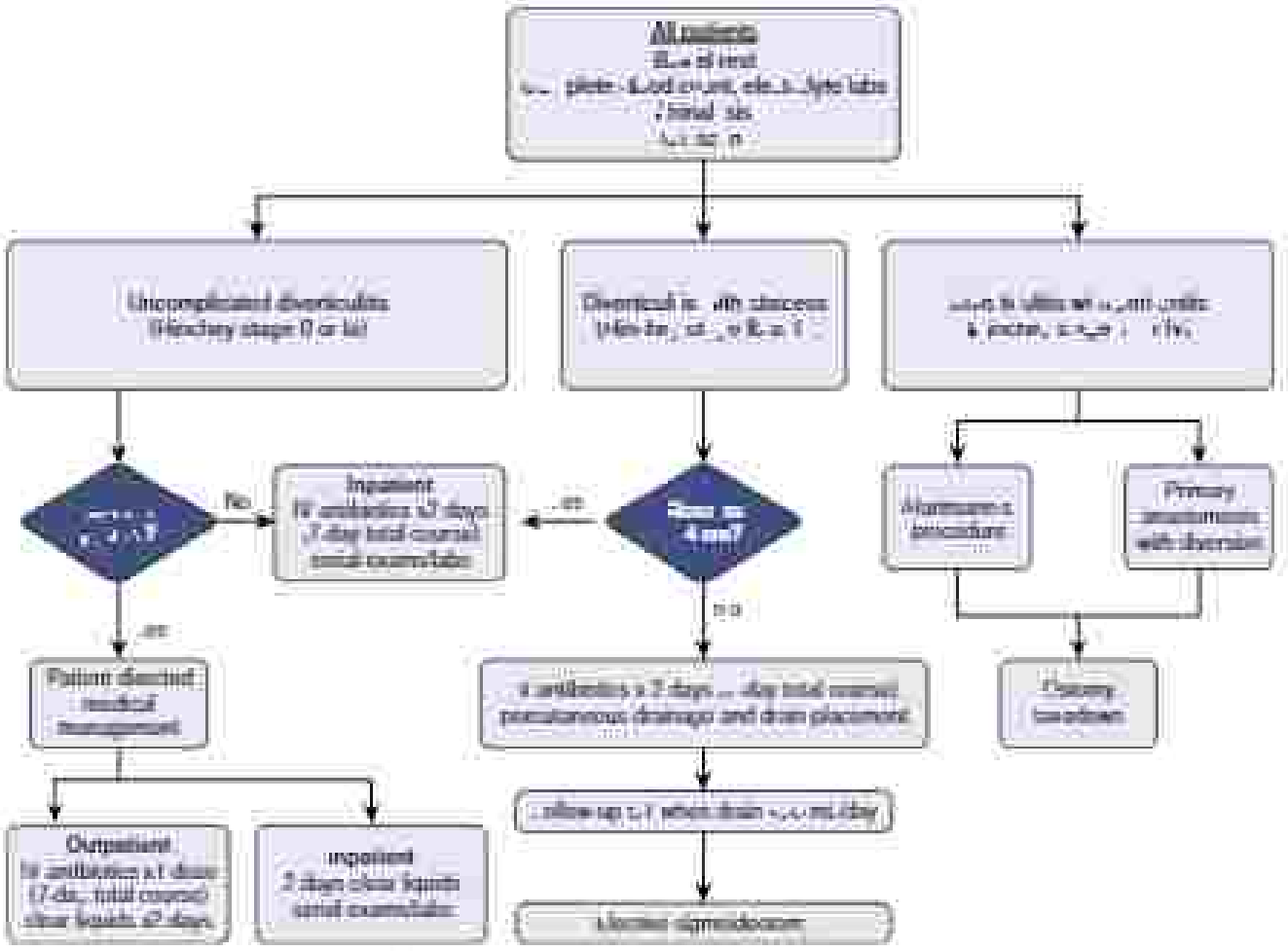


FIG. 2.

abscesses and pelvis is repeated to assess for new complications of diverticulitis with the present expectation that a subclinical complication, such as an abscess, has now declared itself.

Management of Diverticulitis Complicated by Diverticular Abscess (Hinchey Stage Ia or Ib)

Abscesses occur in approximately 1 of 5 cases of acute diverticulitis. For small abscesses (<4 cm in largest dimension), a step-up approach to management that has been supported in a number of small studies. In general, small abscesses are not amenable to percutaneous drainage and are treated with intravenous antibiotics. The published literature consistently finds that more than 75% of patients with a small abscess can be managed successfully with this approach and avoid an emergent operation. If patients with small abscesses do not improve on intravenous antibiotics, repeat imaging to obtained 5 days after antibiotic therapy to evaluate for progression to a larger abscess that may then be amenable to percutaneous drainage. Patients with larger abscesses are managed with percutaneous drainage.

Once the patient clinically improves with intravenous antibiotic therapy and/or drain placement, fits or low diet is advanced. If clinical examination improves, leukocytosis resolves, drain output is less than 30 mL/day, then a repeat CT scan is obtained to determine resolution of the abscess and subsequent drain removal.

If the patient progressively worsens on conservative management with intravenous antibiotics and/or percutaneous drainage, then surgical management with abscess drainage, colectomy, and/or diversion may be required.

Management of Free Perforation (Hinchey Stage III or IV)

Diffuse peritonitis or systemic inflammatory response syndrome in the context of diverticulitis on imaging is consistent with perforation. Patients with evidence of freely perforated diverticulitis require emergent surgery without delay. Reasonable adjuncts that should be included if they do not delay surgical intervention are fluid resuscitation and antibiotic administration. These patients are extremely sick, mortality rates for fecal peritonitis even with appropriate surgery can be as high as 30%.

The management of perforated diverticulitis should be driven by clinical examination, laboratory results, and imaging findings. Although select cases of pericolic/mesenteric can be managed non-operatively, multiquadrant peritonitis or hemodynamic instability are hard indications for surgical intervention.

Three common strategies exist for emergent surgery in perforated diverticulitis: two stage colectomy, one stage colectomy, and laparoscopic lavage without resection. The historical standard of care has been two stage colectomy with an emergent Hartmann's procedure (sigmoidectomy, closure of the rectal stump, proximal end colostomy) followed by elective colostomy takedown 3 to 6 months later. A promising modification of this traditional approach has been the use of primary anastomosis and diverting ileostomy. Two multicenter, randomized controlled trials in Switzerland and France (Primary vs. Secondary Anastomosis for Hinchey Stage III–IV Diverticulitis: a Prospective Randomized Trial) have compared a traditional Hartmann's procedure to primary anastomosis with diverting ileostomy. Overall morbidity and mortality between the two approaches was similar, but

the primary anastomosis groups had markedly better rates of stoma reversal (80% vs. 57%, $p<0.001$). When a patient is hemodynamically stable enough to support a longer operation and local inflammation allows it, we prefer to perform a primary anastomosis with diverting ileostomy.

One-stage colectomy or primary anastomosis without diversion, has been proposed and used as a management strategy for acute diverticulitis that does not require any additional operations. This approach is attractive because it avoids the need for stoma reversal and the resulting morbidity associated with a second operation. Importantly, more than half of patients undergoing Hartmann's procedure never return to the operating room for colostomy reversal. No randomized trials have addressed this approach, and the existing evidence cannot rule out a selection bias demonstrating that patients receiving a primary anastomosis without diversion are not less sick at the time of decision making. Thus, the one-stage colectomy is reserved for a select group of patients who are hemodynamically stable, nutritionally replete, and undergo colectomy under optimal conditions of minimal stool spillage.

Laparoscopic lavage, laparoscopic irrigation and drain placement without resection, has been an alternative approach widely used since the 1990s. This approach was predicated on concerns that emergent surgery itself was equally as injurious to the patient as the underlying life-threatening perforation. Laparoscopic lavage was proposed as an option to obtain source control while limiting tissue manipulation of a hostile abdomen. In the past few years, several multicenter, randomized controlled trials have reported results that have seriously questioned the role of laparoscopic lavage as a reasonable management option. A meta-analysis recently reexamined the question pending results of a number of studies including three major trials (Swedish-Norwegian Scandinavian Diverticulitis Trial, the Swedish-Danish Treatment of Acute Diverticulitis Laparoscopic Lavage vs. Resection trial, and the Belgian Italian Dutch Ladies (LOLA trial). Results of these trials consistently demonstrated no composite benefit to laparoscopic lavage over immediate resection and a 3-times increased risk of further need for an invasive procedure. Given these results, we do not advocate for the routine inclusion of laparoscopic lavage as a therapy consideration. Two rare exceptions to this rule are (1) patients with equivocal imaging for free perforation who are found to have no diffuse peritonitis and a contained abscess on diagnostic laparoscopy and (2) patients who are laparoscopically explored and have extraluminal inflammation so severe as to prohibit a safe Hartmann's procedure.

Postdiverticulitis Colonoscopy Evaluation

Historically, a colonoscopy 6 weeks after nonoperative management for acute diverticulitis has been recommended because of an episode's association with colorectal cancer and premalignant advanced adenomas (3 cases per 1000 follow-up patients in observational studies). This practice is currently supported by limited prospective evidence of benefit for colorectal cancer. Our current practice is to obtain a colonoscopy 6 weeks after the first episode of acute diverticulitis or in patients for whom a recent colonoscopy has not been performed. Although CT colonography is an acceptable alternative, CT imaging obtained as part of the original episode of diverticulitis has been shown to be inadequate to rule out a neoplastic etiology.

Postdiverticulitis Elective Surgery

The management of diverticulosis following an episode of diverticulitis has changed markedly over the decades. An important distinction in current practice is that uncomplicated diverticulitis (Hinchey stage I or II) should be managed differently from higher stage disease.

Historically, initially uncomplicated diverticulitis was thought to be progressive relapsing, with each additional episode being worse than the one before. The concern was that patients would eventually develop a complication from diverticulitis, such as a free perforation. This premise has been disproven, with current evidence supporting that there is no difference in mortality or colostomy incidence whether a patient with uncomplicated diverticulitis has elective resection of the diseased colon segment after the first versus after the fourth episode. Thus, patients are counseled that if they were likely to have complicated disease, they are statistically most likely to have the complication with their first episode. Current recommendations leave the choice of resection versus expectant management up to inpatient patient considerations, including the patient's existing lifestyle, tolerance for the unpredictability of a future flare, comorbidities (e.g., an immunosuppressed transplant patient) that may increase the risk of even an elective surgical intervention, and risk of occult neoplasia. Age is not an independent risk factor for future disease; it has been shown that younger individuals have similar severity to older patients but carry a longer cumulative risk of recurrence because of longer life expectancy.

Management following nonoperative uncomplicated diverticulitis is less ambiguous. Although high-quality evidence is not available, retrospective series report recurrence rates following a complicated episode of up to 40%. A resection will likely reduce this recurrence risk, but the benefit of elective resection versus "watch and wait" with urgent resection has not been proven. For those with abscesses requiring percutaneous drainage, fistula, or symptomatic stricture, we recommend elective resection. For those with small abscesses that resolve with antibiotics alone, we encourage a shared decision-making approach with the patient. Furthermore, intramural extraluminal gas seen on initial CT imaging or associated phlegmon is not considered complicated disease and these findings are managed conservatively with antibiotics as uncomplicated diverticulitis.

Certain late complications of diverticulitis warrant further diagnostic assessment, if suspected. Fecaliths or pneumaturia warrant a CT cystogram (± cystoscopy) to evaluate for a colovesical fistula. A patient endorsing stool or air coming from her vagina should have a comprehensive gynecologic pelvic examination and CT with rectal contrast to assess the location of a likely rectovaginal fistula. Obstructive symptoms and imaging consistent with a colonic stricture should be further evaluated with colonoscopy because the operative approach should adapt to a limited resection for a benign stricture versus a wider oncologic resection for neoplasia.

Special Populations in Diverticulitis Management

The surgeon should recognize that diverticulitis in immunocompromised patients manifests as a unique disease process. Immunosuppressed transplant recipients, those on chronic steroids, and HIV-positive patients may present with delayed diagnosis and an impaired immune system to address the eventual infectious source that promulgates complicated diverticulitis. Mortality rates in these populations can be as high as 40%. These patients should be treated more aggressively and may do better with early surgical intervention for source control. A number of other patient populations are also at higher risk of recurrence and complications from diverticulitis. In addition to the immunocompromised, patients with late-stage kidney disease and collagen vascular disease are more susceptible to complications such as perforation and may benefit from more aggressive early intervention.

Surgical Technique and Considerations

There surgical approaches exist for colorectal surgery: robotic, laparoscopic, and open surgery (Fig. 3). Data from the prospective, multicenter, randomized control Sigma trial showed that laparoscopic sigmoid resection and electively for diverticular disease offered advantages over open sigmoid resection. The laparoscopic approach was associated with short-term benefits of a 31.4% reduction in major complications, less pain, and shorter length of hospital stay. Total postoperative long-term morbidity showed a 27% reduction in major morbidity for patients undergoing laparoscopic surgery for diverticular disease. Longer operative times were seen with laparoscopy. Given these benefits, we prefer a laparoscopic approach if a patient's abdominal surgical history and comorbidities are suited to it.

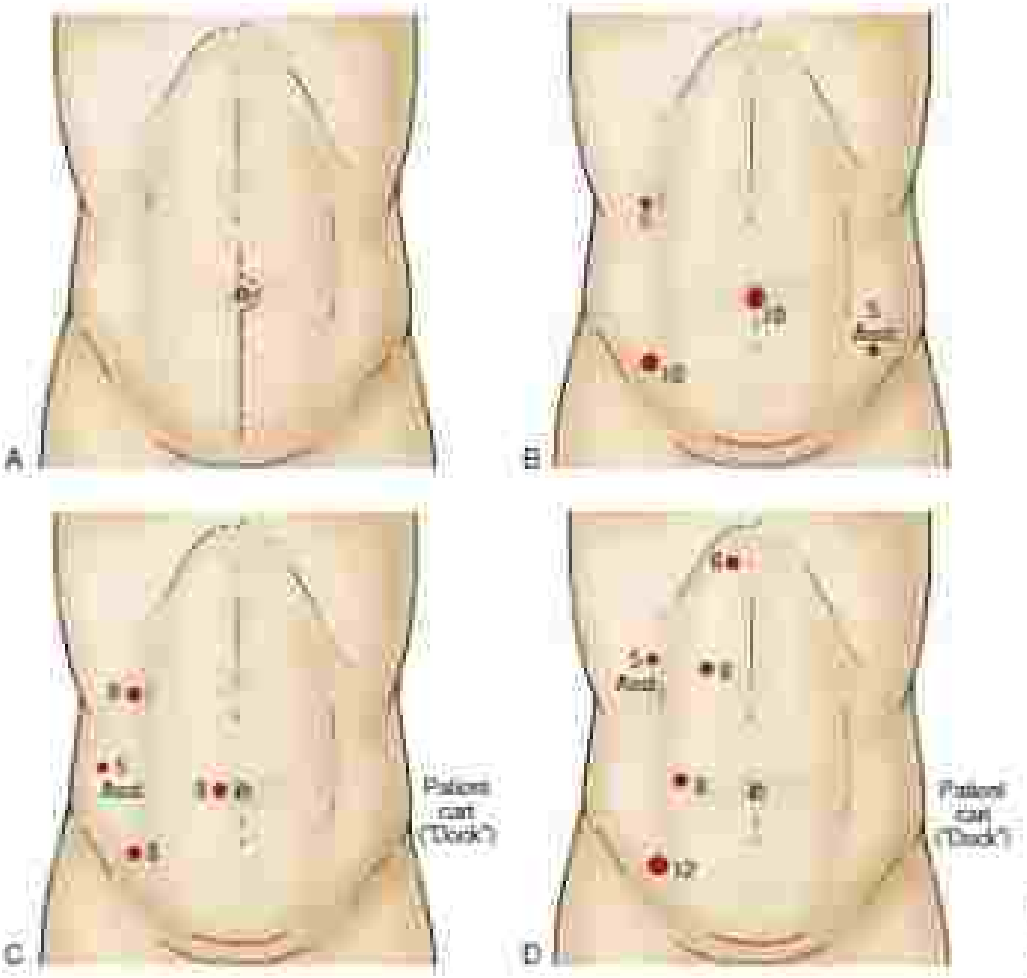


FIG. 3 (A) Open incision. (B) Laparoscopic or robotic. (C) Si Robotic incision. (D) Xi Robotic incision.

Laparoscopic access to the abdomen includes a periumbilical camera port while triangulating the right upper and right lower quadrant ports. The right lower quadrant port is usually a larger sized port to accommodate an endoscopic gastrointestinal stapler. A left, lower quadrant, 5-mm port may be placed to help retract the sigmoid colon during resection.

Currently, two robotic platforms exist and both are manufactured by Intuitive Surgical da Vinci Surgical Systems. Port placement for the Si robot is similar to that described previously for laparoscopy, however, the robotic camera port is placed just to the right of the umbilicus. For the multiquadrant da Vinci Xi, four 8-mm robotic ports are placed in a diagonal line, each a handbreadth apart, spanning from the right side of subxiphoid to two fingerbreadths medial to the right anterior superior iliac spine.

Regardless of surgical approach, the key steps of the operation remain the same. Because of surrounding inflammation, there is a high likelihood of the left ureter being adherent to surrounding structures. It is strongly recommended that the patient undergo cystoscopy and placement of ureteral stents to facilitate identification of the ureter. Although studies show that ureteral stent placement does not decrease the rate of ureteral injury during surgery, the stents may help identify a ureteral injury and facilitate concurrent repair as needed during the initial operation.

The next step is ligation of the inferior mesenteric artery (IMA). From a minimally invasive approach, the most optimal way to isolate the IMA is via a medial to lateral approach. The peritoneum overlying the sacral promontory is incised going up to the base of the inferior mesenteric artery. A medial to lateral dissection aids in identifying the left ureter retroperitoneal and allows it to be isolated from harm. The inferior mesenteric artery is then taken at a high ligation if there is suspicion for malignancy, but may be taken distally if there is no evidence of malignancy. The sigmoid colon is then fully mobilized by incising the white line of Toldt after IMA ligation. If the operation is performed in open fashion, then often a lateral to medial approach is used to identify the left ureter by mobilizing the sigmoid colon via incising the white line of Toldt. The IMA is identified by palpation of the mesentery.

Once the resection target is fully mobilized, the splenic flexure is then mobilized by continuing mobilization of the descending colon as well as taking down the omentum and gastrocolic ligament. The proximal margin of resection is located at the rectosigmoid junction, which helps reduce the risk of recurrence by leaving behind high-risk diverticula located on the sigmoid colon. Landmarks to identify the transition from sigmoid to rectum include the sacral promontory, the peritoneal reflection, confluence of the taenia coli, and distance from the anal verge (12–15 cm). The best indicator is to follow the taenia coli, which are three linear muscles running longitudinally along the colon until they splay or coalesce at the proximal rectum. A stapler is fired to transect the bowel at the proximal rectum after clearing the posterior mesentery to ensure that the entire sigmoid colon is removed.

If an anastomosis is indicated, an end-to-end anastomosis stapler is used. If local diversion is indicated, a colostomy is created when there is no anastomosis or a diverting loop ileostomy is created to protect a colorectal primary anastomosis.

In the case that there is a difficult dissection, such as a phlegmon or colovesical fistula, an open approach may be required to delineate the colon from the ureter or to perform finger fracture to delineate the ureter or colovesical fistula. In general, no pelvic drain is required if the distal dissection remains above the anterior peritoneal reflection. In the case of a colovesical fistula, a drain is placed at the bladder repair to evaluate for a urine leak postoperatively.

DIVERTICULAR BLEEDING

Although diverticular bleeding is traditionally considered self-limiting, the risk of near-term recurrent bleeding without a hemostatic intervention is more than 50%. Risk factors independently associated with diverticular bleeding in those with colonic diverticula include long-term use of nonsteroidal antiinflammatory drugs, antiplatelet agents, and anticoagulants.

The most critical feature of managing a consult for diverticular bleeding is discriminating other etiologies of bleeding per rectum. Colonic diverticula are common, and gastrointestinal bleeding can arise from numerous other etiologies. Approximately 15% of patients with hematochezia ultimately have an upper gastrointestinal source. Among patients who ultimately have a lower gastrointestinal source of bleeding, diverticula are the cause in only one-third of lower gastrointestinal bleeding cases. See Lower Gastrointestinal Bleeding in this text for a comprehensive review of the diagnostic workup.

Initial Management Approach

Our abbreviated approach to the nonsurgical management of diverticular bleeding includes the following. On initial presentation, intravenous access is established, serial hemoglobins are obtained, patients are placed on bowel rest, and the transfusion threshold is set to a hemoglobin goal of 7 to 8 g/dL. There is institutional variation in the bleeding localization study of choice. Initial diagnostic studies used to localize gastrointestinal bleeding include colonoscopy, CT angiography, and nuclear medicine–tagged red blood cell scan (scintigraphy). A colonoscopy is performed to visualize the source of bleeding and perform therapeutic hemostatic measures, such as epinephrine injection, bipolar cautery, endoclipping, and band ligation. Although we prefer this approach for its ability to directly evaluate bleeding and any potential therapy applied, the visualization associated with an emergent colonoscopy in an unprepped colon can be prohibitively difficult, resulting in an endoscopic procedure that may be nondiagnostic and nontherapeutic.

There are number of other modalities that should be used as needed. A technetium-labeled red blood cell scan has the advantage of detecting bleeding rates as low as 0.1 mL/min; however, a tagged red blood cell scan's sensitivity is undermined by its inaccuracy to localize lesions. False localization rates up to 25% with this diagnostic modality have been previously reported. CT angiography of the abdomen and pelvis has localization sensitivity down to bleeding rates of 0.5 mL/min and can provide immediate evidence of whether a formal angiographic procedure is likely to be successful. When bleeding is localized by CT angiography or nuclear medicine–tagged red blood cell scan, catheter-directed angiography may be used for selective angioembolization versus vasopressin infusion. The greatest limitation of angiography is that it is limited to identifying active bleeding only with a rate of at least 0.5 mL/min. In addition, localizing bleeding with another method before conventional angiography may better limit the contrast load administered with more selective arterial branch angiography.

Surgical Considerations for Diverticular Bleeding

The algorithm (Fig. 4) typically addresses more than 80% of diverticular bleeds. For patients who acutely fail this approach and continue to bleed, emergent surgical resection is warranted. Indications

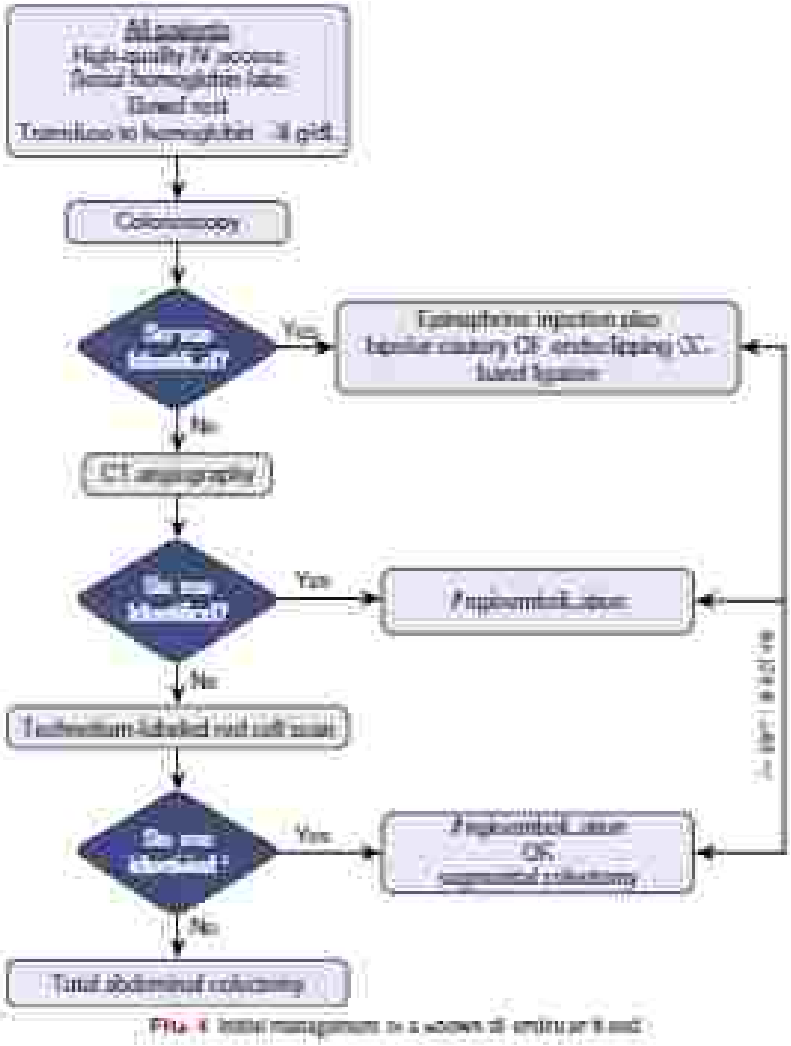


FIG. 4 Initial management in a patient with acute lower GI bleed.

for emergency surgery include requiring more than 4 to 6 units of blood within 24 hours, continuous bleeding for more than 72 hours, or rebleeding on the same admission. For patients operated on specifically for ongoing high-volume transfusion needs, local diversion to the form of an ileostomy is recommended because of the increased risk of anastomotic leak associated with the increasing number of blood transfusions.

The more difficult decision is how to best manage patients who have a life-threatening bleed that is fully addressed through endoscopic therapy or angioembolization alone. Although surgical resection of the offending lesion remains the definitive option for management and prevention of recurrent bleeding, specific indications for transitioning from a "watch and re-treat" paradigm to a surgical approach continue to be debated.

Patients who will ultimately require a life-saving surgical resection for recurrent diverticular bleeding would likely do better with an elective colectomy following a prior episode because mortality rates for emergent colectomy for bleeding are more than 25%. In contrast, rates of lifetime rebleeding for all diverticular bleeding presentations are 17% to 25%, suggesting that most patients do not ever require reintervention. Prophylactic surgical resection between bleeding episodes may be appropriate for the carefully selected patients that may be at high risk for rebleeding (i.e., long-term need for anticoagulation or antiplatelet therapy, social/rebleeding events) and benefit the most from undergoing surgery electively rather than emergently. If an operation is appropriate, careful consideration must be taken before performing a segmental resection given the high risk of rebleeding compared with those undergoing total abdominal colectomy (18% vs 4%). For those patients requiring surgical therapy without confident localization, we do not recommend a segmental resection.

Surgical Technique

If the patient is hemodynamically stable, we prefer to perform the operation via a minimally invasive approach. For patients actively being transfused and who are hemodynamically unstable, an open approach is recommended because of the additional time associated with minimally invasive operations. For those patients in whom the sigmoid colon is localized as the source of bleeding, please refer to the previous discussion of a sigmoid resection for diverticulitis.

In the case of total abdominal colectomy, the surgical technique for diverticular bleeding proceeds from the discussion above for distal colon resection for diverticulitis. After mobilization of the splenic flexure, the omentum and gastrocolic ligament are taken down further to the hepatic flexure. The hepatic flexure is mobilized and the right colon is mobilized by incising the white line of Toldt. The small bowel is mobilized from the right lateral abdominal wall. The proximal point of transection is beyond the ligament of Treves at the terminal ileum. The mesentery for the entire colon is then taken down with suture or a vessel sealing device. An ileorectal anastomosis is considered in the elective setting; however, if the patient has required multiple blood transfusions and/or is hemodynamically unstable, then he or she requires an ileostomy.

Conclusion

The most common disease manifestations of diverticulosis are diverticulitis and diverticular bleeding. Uncomplicated acute diverticulitis can be managed with antibiotics and outpatient follow-up alone or with patients or inpatient supervision with or without antibiotics. Complicated diverticulitis is best managed with a step-up approach under inpatient supervision with clinical condition of the patient determining when more invasive measures are appropriate. Emergency surgery for diverticulitis is required in cases of peritonitis. Elective surgery is indicated for complicated diverticulitis, but should be considered on an individualized basis for cases of uncomplicated disease.

Diverticular bleeding can almost always be managed with endoscopic and angioembolic techniques. In rare cases of ongoing bleeding, emergency resection is warranted. Elective resection should be approached on an individualized basis because of the moderate risk of rebleeding. If pursued, diverticular bleeding must be definitively localized for segment resection, or a total abdominal colectomy is warranted.

Suggested Readings

Angenete E, Thornell A, Burcharth J, et al. Laparoscopic lavage is feasible and safe for the treatment of perforated diverticulitis with purulent peritonitis—the first results from the randomized controlled trial (RCT) of LADIES. Annals of Surgery. 2016;263(1):117–122.

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Management of Chronic Ulcerative Colitis

Yasmin Rojas-Khalil, MD, and S-ran Galandiuk, MD

The management of chronic ulcerative colitis has changed significantly over the last 15 to 20 years. It has become a disease treated less commonly by surgeons because of the advent of stronger antiinflammatory medications. Beginning with the use of infliximab (Remicade), which was approved for use in ulcerative colitis in 2005, followed by adalimumab (Humira, 2012) and golimumab (Simponi, 2013), fewer patients with this disorder are requiring surgical management.

Ulcerative colitis patients seen in consultation for surgery largely fall into three main groups: (1) those who have severe disease and are not responding to medications, whether it be in the hospital or as an outpatient; (2) those who have significant side effects of medications used to treat their colitis; and (3) patients who require surgery due to the presence of colonic neoplasia (dysplasia or colorectal cancer). Most patients with chronic ulcerative colitis have a disease course characterized by exacerbations and remissions. Exacerbations can be caused by viral or bacterial infections (for example, "*Clostridium difficile* colitis") or by environmental factors, such as smoking cessation,

for emergency surgery include requiring more than 4 to 6 units of blood within 24 hours, continuous bleeding for more than 72 hours, or rebleeding on the same admission. For patients operated on specifically for ongoing high-volume transfusion needs, local diversion to the form of an ileostomy is recommended because of the increased risk of anastomotic leak associated with the increasing number of blood transfusions.

The more difficult decision is how to best manage patients who have a life-threatening bleed that is fully addressed through endoscopic therapy or angioembolization alone. Although surgical resection of the offending lesion remains the definitive option for management and prevention of recurrent bleeding, specific indications for transitioning from a "watch and re-treat" paradigm to a surgical approach continue to be debated.

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Management of Chronic Ulcerative Colitis

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The management of chronic ulcerative colitis has changed significantly over the last 15 to 20 years. It has become a disease treated less commonly by surgeons because of the advent of stronger antiinflammatory medications. Beginning with the use of infliximab (Remicade), which was approved for use in ulcerative colitis in 2005, followed by adalimumab (Humira, 2012) and golimumab (Simponi, 2013), fewer patients with this disorder are requiring surgical management.

Ulcerative colitis patients seen in consultation for surgery largely fall into three main groups: (1) those who have severe disease and are not responding to medications, whether it be in the hospital or as an outpatient; (2) those who have significant side effects of medications used to treat their colitis; and (3) patients who require surgery due to the presence of colonic neoplasia (dysplasia or colorectal cancer). Most patients with chronic ulcerative colitis have a disease course characterized by exacerbations and remissions. Exacerbations can be caused by viral or bacterial infections (for example, *Clostridium difficile* colitis) or by environmental factors, such as smoking cessation,

TABLE 1 Montreal Classification for Ulcerative Colitis (UC)

Extent		Location
E1	Ulcerative proctitis	Rectum
E2	Left-sided UC (distal UC)	Distal to splenic flexure
E3	Extensive UC (pancolitis)	Extends proximal to splenic flexure
Severity		**Definition**
S0	Clinical remission	Asymptomatic
S1	Mild UC	<4 stools/day (with or without blood), absence of systemic illness, normal inflammatory markers (ESR)
S2	Moderate UC	>4 stools per day, minimal signs of toxicity
S3	Severe UC	>6 bloody stools daily, pulse rate >90 beats/min, temperature >37.8°C, hemoglobin <10.5 g/100 mL, and ESR >30 mm/h

Modified from Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55:749–753.
ESR, erythrocyte sedimentation rate; UC, ulcerative colitis.

Smoking has opposite effects on the different types of inflammatory bowel disease. Cigarette smoking has a protective effect on ulcerative colitis, whereas it is known to exacerbate symptoms of Crohn's disease. In some patients, the use of nonsteroidal anti-inflammatory medications can also exacerbate colitis, as can severe emotional, work related, or other types of stress. There is usually concordance within families, meaning that if one member of a family has ulcerative colitis, another affected family member will usually have the same disease. In other words, having family members with mixed disease, for example, one member having ulcerative colitis and another having Crohn's disease, is unusual and often implies a misdiagnosis.

PRESENTING SYMPTOMS AND DIAGNOSIS

Diarrhea is the most common symptom of ulcerative colitis. This is often bloody diarrhea, accompanied by significant urgency. Patients often need to rush to get to the bathroom to avoid having episodes of incontinence. In addition, there is a great amount of tenesmus, where patients have a sensation of constantly needing to go to the bathroom as a result of significant mucosal irritation in the lower rectum. It is important to obtain stool cultures for ova and parasites, culture, and sensitivity as well as *C. difficile* toxin to exclude an infectious cause. Once this is done, endoscopy should be performed to obtain a visual inspection of the colon, to assess the extent of disease, and to obtain biopsy specimens for histologic diagnosis. Extent and severity of disease is graded using the Montreal Classification (Table 1). According to this system, the extent of ulcerative colitis can have one of three classifications, depending on the degree or extent of colonic involvement: E1 refers to ulcerative proctitis, with involvement limited to the rectum, E2 refers to ulcerative colitis limited to the left colon, and E3 refers to ulcerative colitis extending proximal to the splenic flexure including patients with pancolitis. The Montreal Classification also has a stratification for symptom severity, with S0 referring to asymptomatic disease, S1 referring to mild disease with 4 or fewer bowel movements a day without blood, and normal inflammatory markers; S2 referring to moderate disease with more than 4 bowel movements a day, but no signs of systemic toxicity, and S3 referring to severe disease with at least 6 bloody bowel movements a day, a pulse rate 90 beats/min or greater, temperature 37.8°C or higher, hemoglobin less than 10.5 g/dL, and an erythrocyte sedimentation rate (ESR) greater than 30 mm/hr. The Mayo scoring system is one of the most common endoscopic scoring systems used to grade the severity of ulcerative colitis (Table 2). In cases where the delineation between ulcerative colitis and Crohn's disease is not clear based on endoscopic, biopsies or endoscopic appearance, the term *inflammatory bowel disease, unclassified* is used. This is in contrast to the term *indeterminate colitis*, a term that is based solely on histologic diagnosis of colectomy specimens. Typical histologic signs of ulcerative colitis include crypt abscess formation, polymorphonuclear cells in the lamina propria, and mucosal ulceration. In severe forms, widespread inflammation can even proceed to frank tissue necrosis.

TABLE 2 Mayo Endoscopic Subscore for Ulcerative Colitis

Score	Disease Activity	Endoscopic Finding
0	Inactive	Normal
1	Mild	Erythema, decreased vascular pattern, mild friability
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

Modified from Lémann T, Bommelaer T, Ollivier G, et al. The modified Mayo endoscopic score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. J Crohns Colitis. 2011;5:466–862.

MEDICAL THERAPY

Once the diagnosis is established, treatment is usually begun with aminosalicylate preparations, as shown in Table 3. If the disease becomes more severe or is not responsive to aminosalicylates, patients may be treated with oral or intravenous steroids. At this point, however, patients are frequently escalated to biologic therapy. Several biologics are approved for treatment of ulcerative colitis. For longer term maintenance, another option is antimetabolite therapy, also shown in Table 3. Many of these treatments are associated with an increased risk of non-Hodgkin's lymphoma with prolonged use. The use of biologics in combination therapy with antimetabolites can be associated with much higher complication rates. Because colectomy can be curative in ulcerative colitis patients, many believe that such aggressive medical therapy should not be pursued.

INDICATIONS FOR SURGERY AND CHOICE OF OPERATION

The frequency with which patients with ulcerative colitis present for surgery has been decreasing with the advent of newer treatments for ulcerative colitis, as outlined in the preceding section. However, many patients still present for surgery for ulcerative colitis. The most common indication for surgery is failure of medications to control symptoms of the disease. Less common reasons for surgery are the presence of severe extraintestinal manifestations, growth failure in children, or the presence of cancer or dysplasia. It is thought that,

TABLE 3. Medical Treatment of Ulcerative Colitis

Category	Example	Application Form	Expense
Probiotics	Lactobacillus, Bifidobacterium	Food, capsules, pills, powders	---+
Antibiotics	Metronidazole, ciprofloxacin, rifaximin	PO, IV	--
Aminosalicylates	Sulfasalazine	PO	-
	5-ASA products	PO, suppositories, enemas	--
Immunosuppressives	Conventional steroids	PO, IV	-
	Budesonide	PO	
	Azathioprine	PO	++
	Tofacitinib	PO	-$$
Biologics	Infliximab	IV	+++$
	Adalimumab	SC	$
	Golimumab	IV	+++$
	Vedolizumab	IV	+++$

5-ASA, 5-aminosalicylic acid; IV, intravenous; PO, by mouth; SC, subcutaneous.
(From Galandiuk S, Crohn disease: In: Ashley DW, editor. Surgery. Hamilton, ON: Decker Medicine; May 2014.)

with the increasing use of biologic medications that prevent ongoing mucosal inflammation, in the future the frequency of surgery for cancer or dysplasia will greatly be decreased. This is due to the fact that the pathogenesis of cancer development in inflammatory bowel disease is cancer arising in a field of chronic inflammation. If the chronic inflammation is stopped early on, there will perhaps be a reduction in cancer incidence in this population. This is an outcome that is very much to be hoped for.

FAILURE OF MEDICAL THERAPY

Patients in this category fall into two groups, those who present for elective surgery having failed multiple treatments, and those presenting with fulminant disease requiring urgent or emergency surgery. We will deal first with the emergency cases.

Fulminant Colitis

In hospitalized patients in whom one is consulted for evaluation, one must be on the watch for the development of toxic megacolon. Toxic megacolon can occur with any type of acute colitis in which the mucosa sloughs, and the patient becomes septic due to loss of the barrier function of their colonic mucosa. These patients will exhibit tachycardia, fever, leukocytosis, and, if their colitis is severe enough, development of a colonic ileus with distention of their transverse colon. This is readily apparent on a plain abdominal film. By definition, this distention should be 5 cm or more on a plain abdominal film (Fig. 1). It should, however, be stressed that this colonic distention does not have to be present for a patient to have a toxic megacolon. The most important part of this term is "toxic," meaning that they are septic from their colitis. These patients also frequently have hypoalbuminemia because they are extremely malnourished from diarrhea; that is, they have a protein losing enteropathy from the severity of their colitis. In many cases, patients in this category may already have a colon that is almost autolytic and need urgent colectomy, or their colon will perforate. In these cases, subtotal colectomy and end ileostomy is the treatment of choice.

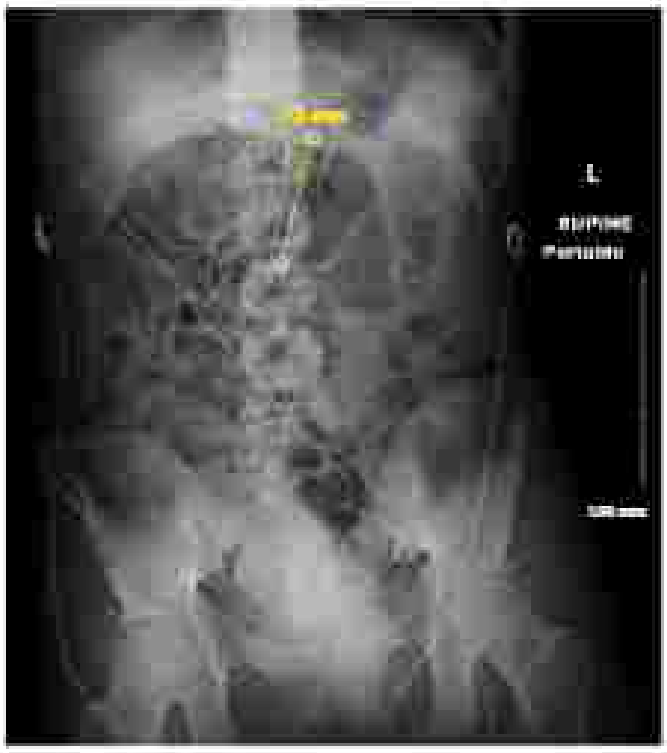

FIG. 1. Toxic megacolon. Abdominal film shows significant distention of the transverse colon in a 20-year-old man with acute ulcerative colitis.

Severe Disease

For the patient coming for an assessment for an elective operation, the two operations that are typically performed for ulcerative colitis not responding to medical therapy include the total proctocolectomy (TPC) with ileal J pouch–anal anastomosis (IPAA) and TPC with end ileostomy. The choice of which operation to perform is determined by the patient's mobility and their sphincter function. For patients with an intact sphincter function who are mobile, ileal J pouch–anal anastomosis provides for a good quality of life with good function. Patients with poor sphincter function and poor mobility will, however, be better served with an end ileostomy. Other factors, such as a patient's employment and body habitus, should also be taken into consideration. If a patient's employment does not permit them ready use of bathroom facilities, permanent ileostomy may be a better choice. Before offering an operation, the surgeon must be aware that the "perfect" results after ileal pouch–anal anastomosis for ulcerative colitis typically consist of five or six bowel movements during the day and one at night. Although this is not associated with urgency, imagine what a fireman or a miner or someone working on machinery where they are unable to take a break for 12 hours would do with this type of operation. In such individuals ileal J pouch–anal anastomosis may not be the wisest choice but because you can do an operation, does not mean you should do it. In patients who are on biologic therapy, overall, increased infectious complications have been described after surgery. Generally speaking, the trend has been to go toward three stage operations in many patients. For example, first doing a subtotal colectomy and ileostomy, then proceeding with the proctectomy and ileal pouch–anal anastomosis and temporary ileostomy, and then a third operation to close the ileostomy.

DYSPLASIA/CANCER

The majority of data regarding frequency of malignancy in ulcerative colitis are based on older studies predating our current knowledge of

the increased risk of colon cancer in these patients. It is difficult to pinpoint accurate statistics regarding the frequency of dysplasia and cancer in ulcerative colitis. It is generally accepted that the risk of cancer in these patients is approximately 4 times the risk in the general population, beginning 8 years after disease onset. It is recommended that, beginning at 8 years of disease duration, these patients undergo an annual colonoscopy with surveillance biopsies. It formerly was believed that one would have to do at least 33 colonic biopsies to have a fairly good representative sample to detect dysplasia. However, today, the technique of chromoendoscopy is increasingly being used to perform targeted endoscopic biopsies. This involves spraying the colon as one withdraws the colonoscope with dyes such as indigo carmine to highlight suspicious areas for targeted biopsy. There have been long-term studies that have shown that polypoid areas of dysplasia can be safely resected, and these patients were followed up over time without undergoing colectomy and, more importantly, without developing colon cancer. Although this is still a controversial field, it appears that a select group of patients can be safely managed in this conservative manner without colectomy provided that they are willing to undergo close endoscopic surveillance. Patients with multifocal dysplasia, those with flat-elevating dysplasia, and patients with colorectal cancer obviously will require colectomy.

C. DIFFICILE INFECTIONS

An acute *C. difficile* infection can cause a significant exacerbation of inflammatory bowel disease and can lead to toxic megacolon. In a patient with an acute flare, stool cultures should always be obtained to exclude coexisting *C. difficile* infection.

BLEEDING

The presence of severe lower gastrointestinal bleeding is a relatively uncommon indication for emergency surgery in patients with ulcerative colitis.

GROWTH FAILURE IN CHILDREN

In children, 22% will present with growth failure, anemia, or other extraintestinal manifestations as their predominant initial feature. Although it is more common in children with Crohn's disease, growth failure occurs in approximately 10% of children with ulcerative colitis. The cause of this is multifactorial and can be due to issues such as malabsorption, decreased caloric intake, cytokine-induced growth hormone resistance, and use of corticosteroids among others. Inappropriate treatment and monitoring may result in failure of achieving optimal adult bone mass, placing them at risk of fractures and growth retardation. Obtaining bone densitometry to determine bone mineral density may be useful in monitoring pediatric patients. Failure to perform surgery in a timely manner may result in delayed onset of puberty, or short stature.

EXTRAINTESTINAL MANIFESTATIONS

In some cases, severe extraintestinal manifestations may be an indication for surgery. There are certain extraintestinal manifestations such as ankylosing spondylitis and primary sclerosing cholangitis that are not affected by surgery. Others, such as some types of mono-articular arthritis, may improve with surgery.

SURGERY

In the emergency setting, total abdominal colectomy with end ileostomy and Hartmann's pouch is the procedure of choice. In the semi-emergency setting, the most common choices include colectomy with ileal pouch–anal anastomosis, total proctocolectomy with end ileostomy, and, less commonly, total proctocolectomy with continent ileostomy. We will discuss each of these.

SUBTOTAL COLECTOMY WITH END ILEOSTOMY AND HARTMANN'S POUCH

In patients who present with toxic megacolon and need urgent surgery, a subtotal colectomy with end ileostomy and Hartmann's pouch is the preferred operation. If these patients have a significant amount of bowel distention and ileus, an open colectomy is often best, because there is less of danger in the abdomen, and laparoscopy is not safe. These colons can be extremely fragile. For this reason, it is not uncommon for the staple line in the Hartmann's stump to dehisce several days after surgery. It is often wise to keep a longer Hartmann's stump and incorporate this between the leaves of the fascia, as shown in Fig. 2, closing the subcutaneous tissue over this. In this manner, if the Hartmann's stump dehisces, one merely has a minor wound infection, which when opened, leaves one with controlled mucous fistula, rather than a pelvic abscess. In cases where the patient is less ill, this procedure can be performed laparoscopically, making the second surgery easier because fewer adhesions are present. Leaving a longer rectal stump also makes the performance of the next stage of the procedure, such as a J-pouch, easier, because the rectal dissection has not yet been started and all planes are virgin.

TPC AND IPAA

Route of Access and Type of Anastomosis

Ileal pouch–anal anastomosis, shown schematically in Fig. 3, can be done via several different routes of access: open, laparoscopically, or robotically. No matter the route of access, we refer readers to the chapter in the *7th Edition of Mastery of Surgery* in the Suggested Reading list. There are several technical components common to all types of access. The colectomy is performed with careful preservation of the ileocolic vessels. The ileal pouch–anal anastomosis can be performed either with a stapled or a hand-sewn approach. Conventionally, a stapled approach will be used because of its technical ease and rapidity. This depends on whether there is concern for dysplasia, cancer, or adenomatous polyp disease in the rectum and its location. If there is concern for dysplasia or cancer in the lower rectum, or polyposis extending to the dentate line, a hand-sewn approach with

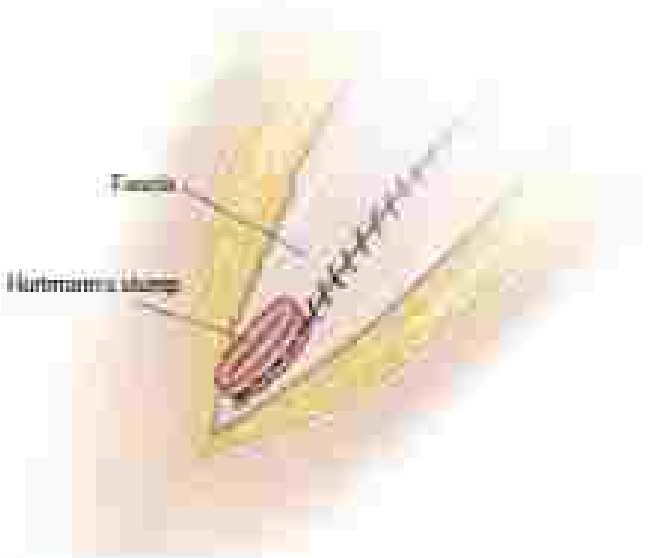

FIG. 2 Hartmann's stump between fascia. The rectal stump is interposed between the fascia during closure of a subtotal colectomy for toxic megacolon.

can moderate to often used. A hand-sewn approach is more technically challenging and much less commonly done than previously.

J-Pouch and Rectal Transection

A J pouch is typically constructed using two firings of a 100-mm linear stapler. The ideal length of the J pouch is 15 cm. I prefer to close the enterotomy in the apex of the J pouch through which the staplers have been fired, that is, common enterotomy, with another firing of a 75-mm linear stapler after the anvil of a 29-mm circular endoluminal stapler has been inserted into the pouch. Then, pierce the apex of the J pouch with the shaft of this anvil, which avoids having to place a purse-string suture. I use a curved stapler to divide the rectum. In cases that are performed laparoscopically or robotically, an Echelon or similar type of linear stapler can be used to divide the lower rectum. The plane of transection should always be verified by digital rectal examination. One would optimally like to have less than 1 cm of remaining rectum left. It must be that this remains, after surgery, patients can incur "cuffitis," which is inflammation due to residual inflammatory bowel disease in the remnant rectum distal to the ileal pouch rectal anastomosis. Ideally, one would like this to achieve an ileal pouch *anal* anastomosis, rather than an ileal pouch rectal anastomosis.

Mesenteric Lengthening Maneuvers

Many patients with ulcerative colitis may have gained weight due to steroid use or, just based on body habitus, may have a thick mesentery. For this reason, it may be difficult to get the small bowel to reach down to the pelvis. One easy tip is that if the apex of the J pouch can easily reach down to the symphysis pubis, there should be little tension on the anastomosis. It is important to mobilize the small bowel mesentery away from the retroperitoneum up to the level of the duodenum to allow it to stretch easily down to the pelvis. If there is tension, there are a number of techniques that can be used to provide additional mesenteric length. One of these is "peritoneal windowing." This can be achieved by tacking the peritoneum on the anterior and posterior aspects of the small bowel mesentery in a stepladder fashion (Fig. 4). This maneuver will provide significant additional mesenteric length. If these maneuvers alone do not provide adequate length, another maneuver that will frequently provide additional length is division of either the ileocolic or superior mesenteric arteries as shown schematically in Fig. 5. If tension is applied at the apex of the J pouch, one can feel which of these vessels is more taut. This vessel can then be divided. This typically will provide an extra 2 to 3 cm of additional mesenteric length. If none of these maneuvers are sufficient, configuration of a different type of pouch, for example, an S pouch, may be necessary, because this sometimes will reach, when a J pouch will not. S pouches are, however, associated with other emptying problems, such as efferent limb syndromes, and should generally be avoided, if possible.

Fecal Diversion

A loop ileostomy is generally constructed approximately 40 cm proximal to the J pouch or as distal as can be performed without undue tension. Because the superior mesenteric artery is fairly tethered along the spine, creating a loop ileostomy, especially in individuals with a short mesentery or those who are significantly above ideal body weight, can sometimes be a challenge. In patients in whom there is significant tension, use of an ileostomy rod is sometimes necessary. Because of the tension involved here, these ileostomies are often less than ideal, meaning that they sometimes are more recessed than end ileostomies and may require use of a convex ileostomy appliance to have significant eversion so that patients do not have postoperative skin irritation. The use of an ileostomy belt is necessary with these appliances as well. In creating a loop ileostomy, it is helpful to wrap the bowel with a sheet of hyaluronic film to reduce the amount of postoperative adhesions. This facilitates closure of the ileostomy at 8 weeks after surgery. The more proximal the ileostomy is located, the greater the likelihood that a higher amount of antidiarrheal medication will be required in the postoperative period. It is important not to discharge the patient from the hospital unless the stoma output is less than 1 L/24 h for most. The patient should also be instructed that, in general, he or she should not be emptying the ileostomy appliance more than 5 times a day if they let the ileostomy appliance get half full before emptying it. More than this will lead to dehydration. Dehydration is one of the most common reasons for readmission to the hospital, and, in this era where readmission is considered a parameter of bad care, this is particularly important. Technical postoperative complications include infectious complications, such as leaks, pelvic abscess, pouch vaginal fistulas, or "cuffitis" from leaving a too long rectal segment of residual inflammatory bowel disease in situ.

After surgery, in assessing these patients, digital examination will ensure that these patients are not developing an ileal pouch anal anastomotic stricture. Examination in the office is focused on signs of dehydration. Typically, a gastrografin enema is performed on these patients anywhere from 4 to 6 weeks after surgery. If this shows intact healing of the ileal pouch–anal anastomosis, closure of the loop ileostomy can be done anywhere after 8 weeks after the initial surgery. The most important view to obtain on gastrografin enema is a lateral view, because ileal pouch–anal anastomotic leaks typically occur posteriorly, and these may not be seen on studies that only show anterior projection views (Fig. 6).

Ileal pouch–anal anastomosis can be done in a one-stage approach, and this is largely an issue of surgeon judgment. These patients should not be on a dose of prednisone more than 20 mg and should not be on medications that significantly impair wound healing or increase the rate of infection, and, during surgery, there should be no tension on the ileal pouch–anal anastomosis. In patients with a loop ileostomy at the time of loop ileostomy reversal, closure can often be done without a resection by simply unwrapping the stoma and simply closing the enterotomy. The wounds can be closed primarily, left open, or closed in a purse-string manner.

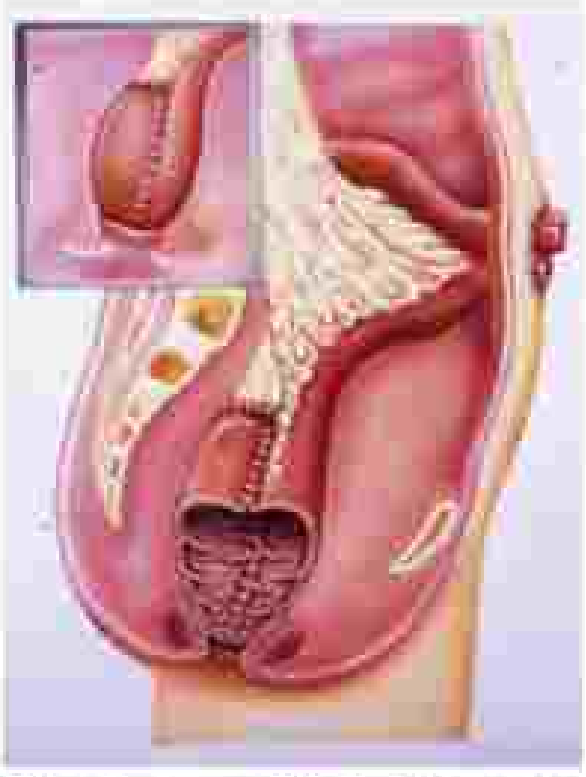

FIG. 3 Schematic representation of an ileal pouch–anal anastomosis with temporary diverting loop ileostomy.

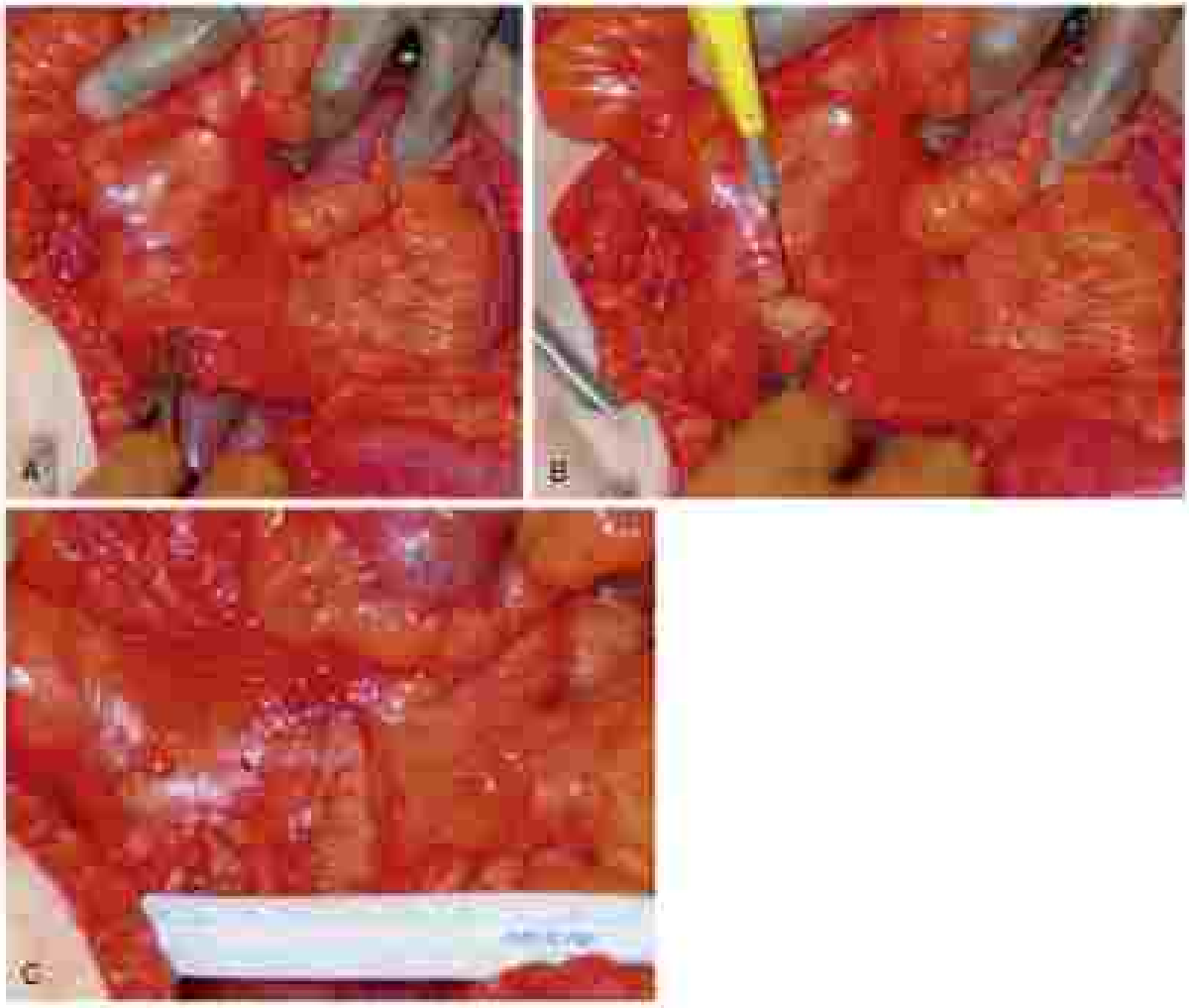

FIG. 4 Mesocolic lengthening maneuver. (A) The mesentery of the small bowel is elevated away from the underlying vessels using a hemostat. (B) Electrocautery is used for division of the mesenteric peritoneum on "peritoneal windowing." (C) Once the peritoneum has been divided, each of the areas of peritoneal windowing is shown to have resulted in more than 1 cm added length.

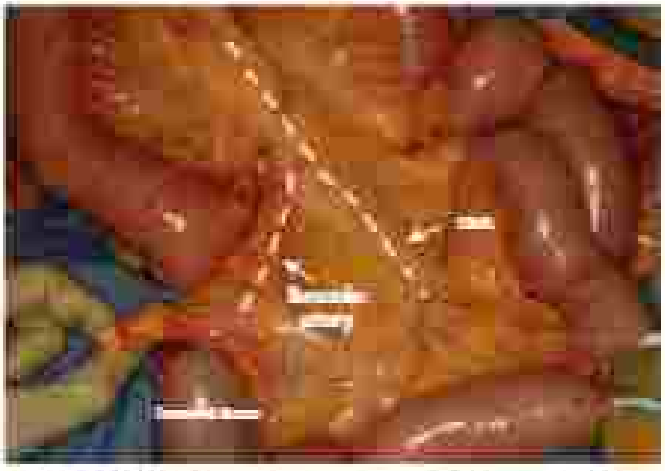

FIG. 5 Ileocolic and superior hemorrhoidal vessels. If tension is placed on the apex of the ileal pouch, the surgeon can assess width of these vessels to assess greater tension. (From Gonzalez S, Pemberton JH, Kelly KA, Dozois EJ, Ready JB, Sarr MG. Ileal pouch-anal anastomosis and ileoanal reservoir using the double-stapled technique: current status after 1,005 consecutive cases. J Am Coll Surg. 2005;201:735–740.)

Postoperative Course

In the postoperative period, the normal functional results of an ileal pouch anastomosis would be like to its bowel movements a day, with one nocturnal bowel movement. A majority of patients need to take antidiarrheal medications in the early postoperative period, because the ileal pouch only begins significant functional improvement in the first 6 months after surgery. The most common complication after surgery is pouchitis, characterized by episodes of frequent watery bowel movements and cramp abdominal pain, sometimes accompanied by low-grade fever. These symptoms are quickly ameliorated by antibiotics such as metronidazole or ciprofloxacin. Some patients may experience chronic pouchitis or repeated or continuing flares of pouchitis. Interestingly, patients undergoing ileal pouch anal anastomosis for familial polyposis rarely have these complications. Conversely, patients who have ulcerative colitis have a very high frequency of chronic pouchitis and, for that reason, are generally considered poor candidates for ileal pouch anal anastomosis. When undergoing this procedure, they must be counseled at length regarding the relatively poor expected functional results.

In patients who undergo this procedure for inflammatory disease or in whom indeterminate colitis is diagnosed on the colectomy specimen, there is a significant risk of being eventually diagnosed with Crohn's disease. Many of these patients can still retain their ileal pouch; however, a significant number of these patients do have to be maintained on immunosuppressive medication to do so.

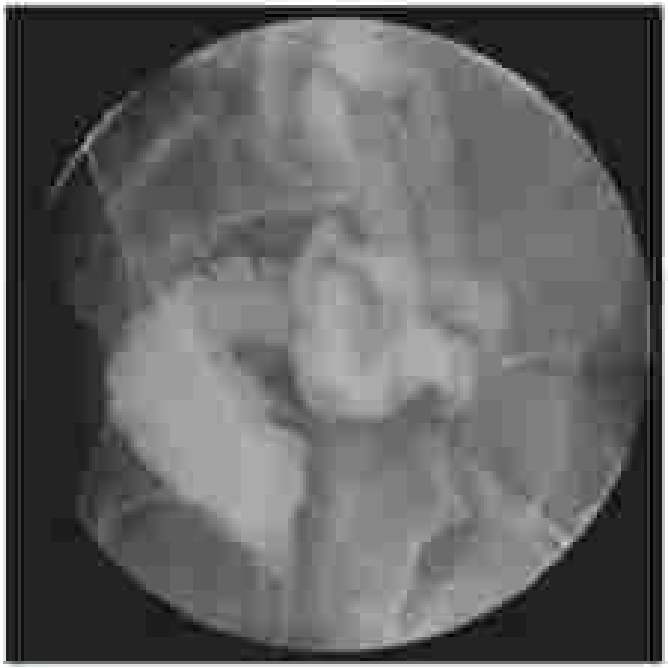

FIG. 6 Pouchogram. A lateral view during gastrografin enema is obtained to assist in locating a posterior leak. The contrast is shown at the tip, the contrast-filled ileal pouch is in the middle.

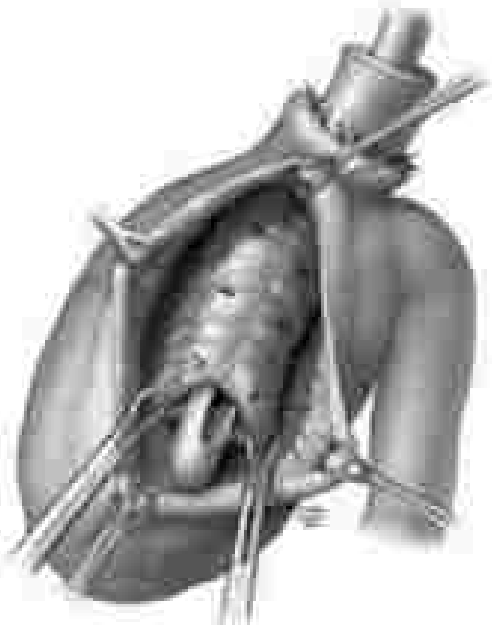

FIG. 7 Kock pouch, a continent pouch that allows patients to self-catheterize. The intussuscepted segment of ileum distal to the ileostomy provides for continence. A catheter is passed through the ileostomy during contraction of the pouch as shown. *(From Dukes C. J. Colon, Rectum and Anus. London: Butterworth's Medical Publications, 1957.)*

Impaired Fertility

One of the relatively recently discovered complications associated with ileal pouch–anal anastomosis is fertility impairment. Women undergoing this procedure should be counseled that undergoing this procedure may significantly impair their ability to become pregnant by natural means. Although women who undergo this procedure can become pregnant easily with in vitro fertilization, altered tubal anatomy due to adhesions may significantly reduce fertility. They should be made aware of this before surgery. In addition, because patients with an ileal pouch–anal anastomosis usually have bowel movements that are the consistency of pudding or oatmeal, intact sphincter function is imperative. Obstetric anal sphincter injury is always a risk with pregnancy. If there is any increased risk of sphincter damage, that is, with a prima gravida, a very large child, or breech delivery, women should be counseled regarding this, and this should be discussed with the patient's obstetrician. A cesarean section is preferable to a sphincter injury.

TPC AND END ILEOSTOMY

End ileostomy, although not popular among patients, can lead to an extremely good quality of life. It is associated with the need to wear a stoma appliance or drainage bag. Although there is a great amount of fear on the part of the patient before surgery, this can lead to a great improvement in quality of life. Stoma appliances are air and water tight. They typically need to be emptied four or five times a day. Patients can go swimming and participate in sports activities with a stoma appliance. For the patient who has had a sphincter injury, for those who are elderly with decreased mobility, or those who have jobs that do not allow them to have access to bathroom facilities, this operation is still the preferred option, and it has the advantage of being a one-stage operation. When this is performed for benign disease, it is performed with an intraphincteric proctectomy. Unlike an abdominal perineal resection, where the entire external anal sphincter is excised for cancer, here, dissection is performed between the internal and external anal sphincter, without excising the levator muscle, to create a smaller wound that will heal more rapidly and provide for stronger pelvic floor.

TPC WITH CONTINENT ILEOSTOMY (KOCK POUCH)

This operation was very popular in the early 1970s, before the development of the ileal pouch–anal anastomosis. It was originally developed by Nils Kock, from Sweden, in 1969. Many modifications, such as that by Barnett, exist, and it is sometimes performed for patients who have failed ileal pouch–anal anastomosis. In this operation an ileostomy is created with an intussuscepted segment of small bowel positioned between the ileostomy and the abdominal wall. This intussuscepted piece of bowel serves as a continence valve (Fig. 7). Patients "catheterize" the stoma using a special catheter multiple times a day to empty their ileostomy and avoid the need to wear a stoma appliance. These stomas are continent for air, gas, and liquid stool but have a high rate of requiring revisional surgery, and this surgery works best in thin individuals. This operation has fallen out of favor and is performed much less frequently today, because this continence inferring intussuscepted segment of bowel frequently tends to dysmotility, requiring operative revision. Furthermore, when this operation fails, a large amount of bowel is lost because of the amount of bowel needed to create the continent "nipple valve" and the stoma reservoir is typically 50 centimeters.

CONCLUSION

In conclusion, surgeons will likely be seeing fewer patients in consultation for surgery for ulcerative colitis in coming years because of more effective medical therapy. It is, however, expected that, when they do see these patients, many of these will be seen due to failed medical management. These patients will be significantly immunosuppressed. Performing staged procedures should be considered. There is a significant risk of these patients also having coexisting *C. difficile* infections, and this should always be checked for to ensure that therapy for coexisting *C. difficile* infection does not need to be instituted. Indications for surgery for cancer or dysplasia will likely be seen less often in the coming years. When selecting an operation, good patient selection is key. For ileal pouch–anal anastomosis, good sphincter function and good patient mobility are required.

Suggested Readings

Gabbiadini S, Iorizzo M, Fanner RW, Fischer R. Ileorectal pouch procedure for ulcerative colitis and familial adenomatous polyposis. In: Fischer J, ed. Fischer's Mastery of Surgery. 7th ed. Philadelphia, Wilkins (Lippincott Williams & Wilkins, 2019:1732–1741.

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Rosen M, Dhawan A, Saeed S. Sacral inflammatory bowel disease in children and adolescents. JAMA Pediatr. 2015;169:1053–1060.

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Shen J, Ullrich J, Shafer S, et al. Clinical, pathologic, and outcome study of hyperplastic and sessile serrated polyps in inflammatory bowel disease. Mod Pathol. 2015;28:1648–1656.

Management of Toxic Megacolon

Madhavi V. Nishtala, MD, Gautam Bandoo, MD, and Scott A. Steele, MD, MBA, FACS, FASCRS

Toxic megacolon is a rare, life-threatening complication of colitis. It is defined by the total or segmental nonobstructive dilatation of the colon in the presence of sepsis. It is often a complication of Crohn's disease, ulcerative colitis, or various infectious colitis, most commonly *Clostridium difficile*–associated disease. Less common causes include ischemic colitis, volvulus, diverticulitis, and obstructive colon cancer. This chapter reviews the evaluation and management of patients with toxic megacolon.

The overall incidence of toxic megacolon (TM) is unknown, with different etiologies having varying rates of occurrence. Lifetime incidence of TM developing from ulcerative colitis (UC) ranges from 1% to 2.5%, with a slightly higher incidence in patients admitted to the hospital for UC, ranging from 4% to 17%. The incidence in patients with antibiotic-associated pseudomembranous colitis (*i.e.*, *Clostridium difficile*) is up to 3% and is expected to increase proportionately with increasing prevalence and potency of this disease.

It is important to understand that any inflammatory condition of the colon can lead to colonic dilation and TM. This occurs most commonly from the inflammatory bowel diseases (IBDs) of Crohn's colitis and UC, infectious causes including *C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Escherichia coli* O157, and ischemic colitis. Less frequent causes of TM include parasitic infection with *Entamoeba histolytica* and cryptosporidium and cytomegalovirus colitis in patients with HIV or AIDS, pseudomembranous colitis secondary to methotrexate therapy, and Kaposi's sarcoma (Box 1). Additional risk factors are hypokalemia, hypomagnesemia, discontinuation of 5-aminosalicylate agents or steroids, barium enemas, and drugs that slow colonic motility, including narcotics and antiadrenergic and anticholinergic medications. Interestingly, colonoscopy has also previously been identified as an exacerbating factor to colitis, subsequently leading to TM, although it is unclear whether it is the bowel preparation or the actual scope that renders the colon susceptible.

Although the pathogenesis of TM is not fully understood, several mechanisms have been described that contribute to the disease process. In patients with IBD, it is thought that mucosal inflammation leads to the release of inflammatory mediators and bacterial products, increasing the amounts of inducible nitric oxide synthase in the muscularis propria, ultimately shifting excitatory nitric oxide–nitric oxide inhibitory smooth muscle tone, causing paralysis and dilatation of the colonic wall. Transmural extension of this inflammatory response beyond the mucosa into the smooth muscle layer with replacement by granulation tissue is characteristic of TM. Further, in TM, the muscle layer is invaded by neutrophils, which produce more nitric oxide, cytokines, proteolytic enzymes, and leukotriene B4. These inflammatory factors further damage the muscular layer, leading to bacterial translocation and bacteremia. While taken up systemically, these cytokines, in conjunction with bacteremia, lead to signs of toxicity, including tachycardia, hypotension, fever, altered mental status, lower abdominal tenderness and distention with or without peritonitis. Similar mechanisms are also at play with other inflammatory and infectious processes, although again, the definitive and universal pathogenesis is yet to be fully elucidated.

DIAGNOSIS

The diagnosis of TM relies on both clinical and radiologic findings. A thorough history and physical examination must first be obtained, including history of IBD diagnosis with extent of colonic involvement and medical therapy, recent hospitalizations and antibiotic use, and use of medications including corticosteroids or antimotility or chemotherapeutic agents. The majority of patients present with the signs and symptoms of colitis, including diarrhea (frequently bloody), fevers, chills, and abdominal cramping. As the onset of TM, constitutional signs such as fever, tachycardia, or hypotension develop. Altered mental status, abdominal distention and tenderness, constipation, obstipation, and reduced bowel sounds may also occur. Peritonitis is highly suspicious for perforation. A markedly decreased level of consciousness, analgesics, or high doses of corticosteroids may mask abdominal tenderness and other signs or symptoms of TM.

Jalan criteria is currently the best accepted criteria used to make a clinical diagnosis of TM. A clinical diagnosis of TM is made by fulfilling any three of Jalan's criteria: fever higher than 101.3°F (>38.5°C), heart rate greater than 120 beats/min, white blood cell count higher than 10.5 × 10⁹/L, or anemia. Additionally, patients must have one of these signs: dehydration, altered sensorium, electrolyte disturbances, or hypotension (Box 2).

Plain abdominal radiographs are highly useful in diagnosing and monitoring the progression of TM. On supine films, typical features include dilation of the transverse or right colon, usually between 6 and 15 cm (Fig. 1). The descending colon, sigmoid colon, and rectum rarely appear distended. On upright films, multiple air fluid levels in the colon and thickening of the colon wall are often present, with absence of normal haustral patterns. Air filled crevices between large pseudopolypoid projections in the colonic lumen may indicate deep mucosal ulcerations. Repeat radiographs are indicated for changing clinical status. Although the colonic absolute width on the radiograph aids with diagnosis of TM, the overall clinical picture of the patient is more important because systemic toxicity with colonic dilatation is seen in patients with acute obstruction from volvulus, polyps, tumors, and intraluminal obstructing tumors. For patients with obstructing disease, there is no air in the colon below the point of obstruction. Further investigation with barium enema or colonoscopy may be required to characterize the location and type of obstruction.

Ultrasonography and computed tomography (CT) may be used in addition to plain films to confirm diagnosis and identify the underlying cause of the colitis. Typical signs of severe colitis include diffuse colon wall thickening, thickened haustra with alternating bands of high and low density (accordion sign), multilayered appearance resulting from varied densities of edematous mucosa, hyperemic mucosa (target sign), and pericolic fat stranding (Fig. 2). CT imaging can also determine the extent and severity of disease, including

Suggested Readings

Gabbiadini S, Iorizzo M, Fanner RW, Fischer R. Ileoanal pouch procedure for ulcerative colitis and limited adenomatous polyposis. In: Fischer J, ed. Fischer's Mastery of Surgery. 7th ed. Philadelphia, Wilkins (Lippincott Williams & Wilkins, 2019:1732–1741.

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Madhuri V. Nishtala, MD, Cigdem Bastaci, MD, and Scott R. Steele, MD, MBA, FACS, FASCRS

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BOX 1 Etiologies of Toxic Megacolon

Inflammatory
- Crohn's disease
- Ulcerative colitis

Infectious
- *Clostridium difficile*
- *Salmonella, Shigella, Yersinia, Campylobacter*
- *Cryptosporidium*
- *Entamoeba*
- *Cytomegalovirus*

Ischemia

Malignancy: Kaposi's sarcoma

Medications
- Discontinuation of steroids
- Opioids
- Anticholinergics
- Chemotherapy

Other
- Hypokalemia, hypomagnesemia
- Barium enema
- Colonoscopy

Modified from Cast JE, Stark PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. *Am J Gastroenterol* 2003;98(11):2320–31.

BOX 2 Diagnosis of Toxic Megacolon

Clinical Presentation

Diarrhea, bloody diarrhea
Constipation, obstipation
Abdominal pain and tenderness
Abdominal cramping, distension
Decreased bowel sounds

Radiographic Findings

Dilation of transverse or ascending colon >6 cm
Small bowel and gastric distension
Computed tomography: colonic dilation, diffuse colonic wall thickening, submucosal edema, pericolic stranding, ascites, perforations, abscesses, ascending peritonitis

Jalan's Criteria (≥3 of the Following Signs)

Fever >100.2°F (>38.5°C)
Heart rate >120 beats/min
White blood cell count >10.5 ×10⁹/L
Anemia

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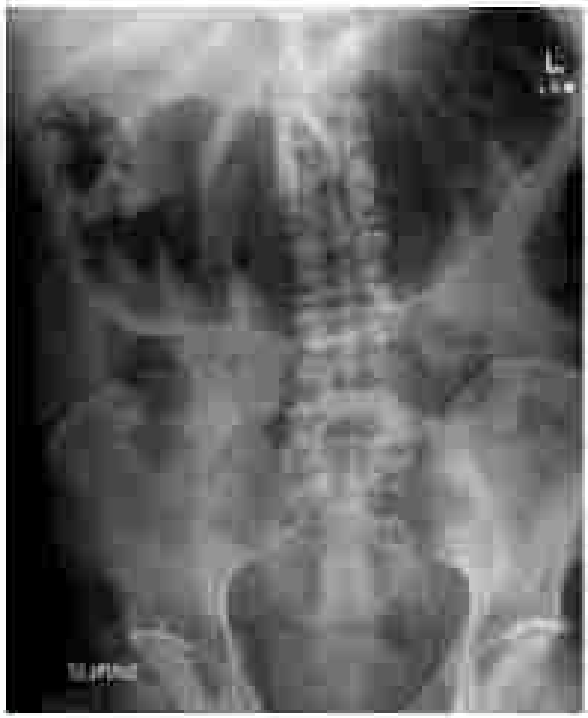

FIG. 1 Plain film radiograph demonstrating the classic dilation of the transverse colon associated with toxic megacolon.

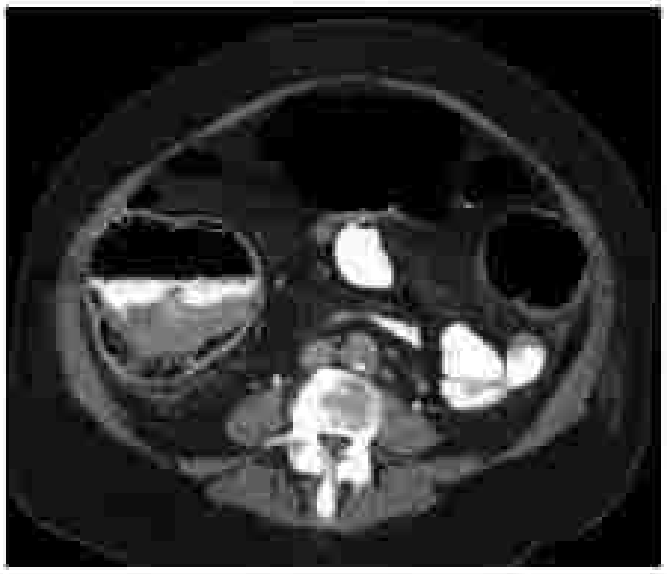

FIG. 2 Computed tomography scan demonstrating axial view of colonic dilation, diffuse colon wall thickening, mucosal edema, and pericolic fat stranding characteristic of toxic megacolon.

complications such as colonic perforation and vascular compromise. This imaging is particularly helpful in patients with AIDS who may have multiple simultaneous abdominal disease processes.

Laboratory studies may have nonspecific abnormalities that reveal the extent of the systemic toxicity in TM. Leukocytosis with a left shift is commonly found, particularly for patients with *C. difficile*–associated diarrhea, in which the white blood cells may commonly exceed 30,000. Steroid use may cause or exaggerate this shift. Immunocompromised patients will instead exhibit neutropenia. Anemia may occur because of occult blood loss. Electrolyte abnormalities are common, with metabolic alkalosis occurring from volume depletion, hypokalemia, and hypoalbuminemia (<3 g/dL), all of which indicate a poor prognosis. Metabolic acidosis suggests ischemic colitis. Elevations in the erythrocyte sedimentation rate and serum C-reactive protein are common. Stool samples must be sent for culture, ova and parasites, and *C. difficile* toxin detection. Although the most sensitive assay for *C. difficile* is stool culture, results are slow and can cause a delay in diagnosis. Real-time polymerase chain reaction (PCR) assay is a more expedient gold standard test used to detect *C. difficile* toxin. PCR is highly sensitive and can also identify incidental carriers of *C. difficile*, but does not distinguish between colonization and clinical infection. Enzyme immunoassays for *C. difficile* glutamate dehydrogenase are

rapid screening tests for infection, but cannot distinguish between toxigenic and nontoxigenic strains and must be followed by PCR testing in a two-step process. Enzyme immunoassays for *C. difficile* toxins A and B also yield results within hours; although this assay is inexpensive and commonly used, it has poor sensitivity. Because bacteremia occurs in 25% of patients with TM, blood cultures and antimicrobial must also be obtained.

Although endoscopy may be of value to determine the underlying diagnosis, it is highly risky and may perforate the colon. Limited sigmoidoscopy without bowel preparation is considered safe and can be used to differentiate between inflammatory or infectious disease in the rectum or sigmoid colon. It is recommended to only advance the endoscope to obtain histologic diagnosis; however, lower endoscopy is limited and may still miss disease processes that spare the rectum and sigmoid such as cytomegalovirus inclusion bodies in ascending colon ulcers and rectum-sparing pseudomembranous *C. difficile* colitis. Endoscopy must use minimal to no insufflation to prevent perforation or worsening ileus. Colonoscopy should never be used except for managerial patients who require endoscopic decompression. Colonoscopic decompression is a technically difficult procedure and contraindicated in patients with colonic perforation or peritonitis. A decompression tube should be placed at the time of colonoscopy to reduce the necessity for repeated colonoscopy in the future. Air is suctioned from the colon with the decompression tube in place as the colonoscope is gently removed. To minimize air infusion, the entire colon should not be examined and the decompression tube should not be delivered into the cecum. The decompression tube should be placed to gravity drainage and flushed every 4 to 6 hours.

Depending on the underlying disorder, gross endoscopic appearance may vary as well. *C. difficile* colitis can present with erythema, friability, and characteristic pseudomembranes. Crohn's disease appears as rectum-sparing discontinuous longitudinal ulcerations, small aphthous ulcers, and cobblestoning of the mucosa. The characteristics of UC include proximally spreading rectal ulcers, edematous mucosa, erythema, mucosal friability, and loss of vascular markings. Other underlying etiologies may simply demonstrate gross dilation with diffuse inflammatory changes and a lack of typical folds.

Medical Therapy

Close monitoring of the patient's weight and hemodynamic status, performing serial abdominal examinations, and obtaining plain abdominal radiographs every 12 to 24 hours are critical to determine the necessity and timing of surgical intervention. Fluid replacement should be aggressive, using crystalloids such as isotonic saline unless shock or severe hypoalbuminemia are present necessitating administration of colloids. In addition, electrolytes must be replaced, especially with avoidance of hypokalemia. The number and consistency of bowel movements are also critical indicators of the patient's status. Reduction in the number of bowel movements often means deterioration in patient status with further colonic dilation and ileus. Conversely, increasing diarrhea may indicate a positive response to therapy. Surgery is indicated for patients who show no improvement in the first 48 to 72 hours after developing TM.

Patients should be placed on complete bowel rest and should receive adequate supplementation with intravenous (IV) fluids. Bowel rest is started with the patient receiving nothing by mouth and a nasogastric or longer tube inserted into the small intestine for bowel decompression. Long intestinal tubes are reported to be more effective than nasogastric tubes in colonic decompression, but also must be placed into the ileum under fluoroscopic guidance; therefore, their practical use is often limited. Although there is no firm evidence that decompression changes prognosis and outcome, it does have theoretical benefit and may facilitate surgery, if required. Because of risk of perforation, use of rectal tube for decompression is controversial. All narcotics, antidiarrheal, and anticholinergic agents (including, for example, antidepressants) that may slow gastric motility should be discontinued.

Total parenteral nutrition is controversial and has shown no proven benefit in preventing surgery or decreasing length of hospital stay. It may be administered in patients who are malnourished or have taken no nourishment for an extended period.

Antibiotics are recommended, not as primary therapy for IBD or for toxic dilation, but rather to reduce mortality should the perforation occur. Furthermore, bacteremia can be present even in the absence of perforation and carries with it a high mortality. Patients are typically placed on broad-spectrum antibiotics; however, there is no evidence to support this. Conversely, antibiotics should be discontinued in pseudomembranous colitis and oral/IV metronidazole and oral vancomycin should be initiated if *C. difficile* is positive.

Medical Management of Patients with IBD

IV corticosteroids are the mainstay of conventional medical therapy and their usage should not be delayed while awaiting microbiologic tests. In patients who have been on prior steroid therapy, hydrocortisone is administered in a standard dose of 100 mg every 6 to 8 hours (or methylprednisone is to 15 mg every 6 hours), which is usually given for 3 days. Higher doses of steroids or extension of therapy have no effect on outcomes or colectomy rates. Sulfasalazine or 5-aminosalicylate play no role in the treatment of TM caused by IBD. Neither 6-mercaptopurine nor azathioprine are indicated in patients with IBD and TM due to their slow onset of action. Due to the inherent risk of colonic perforation, it is recommended to start antibiotics in TM even without evidence for infectious etiology.

Medical Management of Patients With Clostridium difficile–Associated Disease

Medical therapy for TM related to non-IBD related colitis is directed specifically to the disease process. In particular, pseudomembranous colitis should be aggressively treated with withdrawal of offending antibiotics and oral or IV metronidazole or oral vancomycin should be initiated. Surgery should not be delayed if clinical parameters continue to worsen. Vancomycin enemas have been recommended recently for inadequate intraileum concentrations resulting from poor intestinal motility; however, enemas may fail to treat right-sided colonic disease. For this particular case, in addition to the previously mentioned bowel decompression techniques for TM, colonoscopic decompression with intraileostomic perfusion of vancomycin can be used (though as stated previously—endoscopy use in TM needs to be performed on an individual base and with extreme caution). This technique is contraindicated for the other causes of TM.

Surgical intervention may be necessary in up to 40% of patients with TM from *C. difficile* colitis. Indications for surgery include peritonitis, progressive dilation of the colon, lack of clinical improvement over the first 48 to 72 hours, and uncontrolled bleeding.

Surgical Therapy

Timing of surgery to patients with TM remains controversial. Because mortality continues to be high, several investigators have proposed that surgery should be performed as soon as possible, especially in case of rapid clinical deterioration and the presence of signs of end-organ failure. Absolute indications for surgery include perforation, uncontrollable rectal bleeding, and clinical deterioration with progressive dilation.

Diverting ileostomy was the most commonly used surgery for fulminant colitis with TM before the 1960s, which was complicated by high rates of perforation resulting from dilated colon despite proximal diversion. Soon after, surgical therapy for TM shifted to total abdominal colectomy and ileostomy; this approach reduced the mortality rate to 14.3% from 67% associated with ileostomy alone. For selected patients at risk for iatrogenic perforation because of friable and edematous colon during colectomy, Turnbull advocated colonic decompression and proximal diversion using a skin level colostomy and loop ileostomy with definitive surgery planned 6 months later (Fig. 3). The blow-hole procedure is now rarely performed except

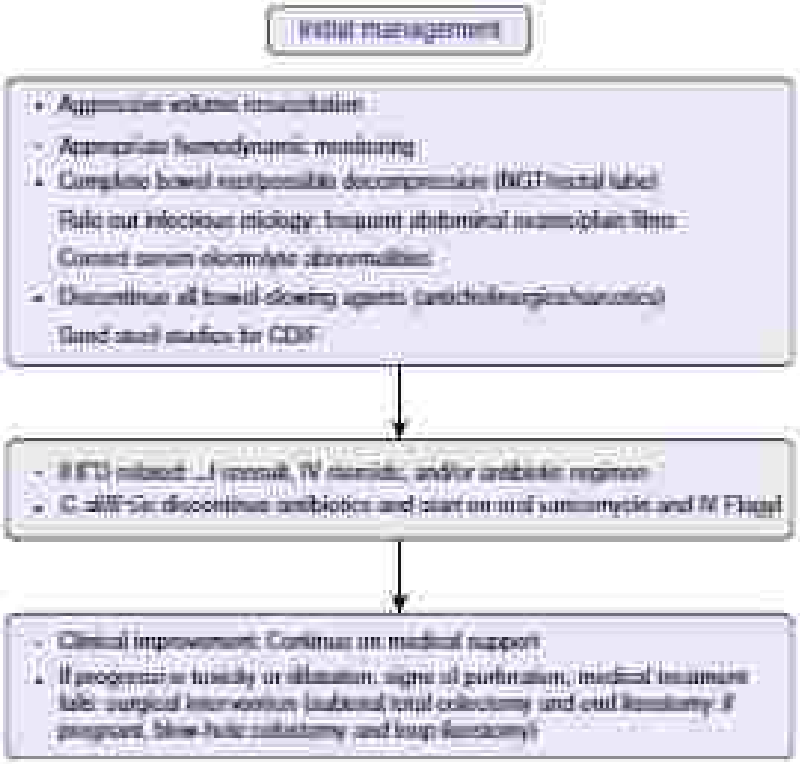

FIG. 3. Management algorithm for toxic megacolon. *CDF*, Clostridium difficile; *GI*, gastrointestinal; *IBD*, inflammatory bowel disease; *IV*, intravenous; *NGT*, nasogastric tube.

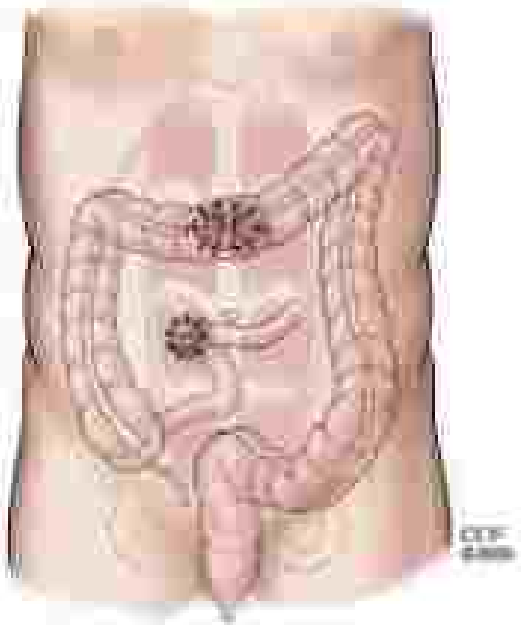

FIG. 4 Blow-hole colostomy and loop ileostomy. (Courtesy Cleveland Clinic Center for Medical Art & Photography. Copyright 2002-2010.)

to a few high-risk situations, including pregnant women, patients with colonic microperforations, high lying splenic flexure and dense adhesions, or prohibitive comorbidity. The operation is contraindicated in cases of abscess, hemorrhage, or free perforation.

Currently, the most commonly used surgical procedure for TM is the subtotal/total colectomy, mucous fistula, and end ileostomy, as this approach is associated with a lower morbidity and mortality than other techniques (Figs. 5 and 6). There are several options for the management of the rectal stump. If the stump is left intraperitoneally, a rectal tube may be placed for decompression to prevent blowout. If the stump left for an extended period, mucous fistula can be created or the stump can be placed subcutaneously (Fig. 6).

The open approach is the standard of care in the most severely ill patients (Fig. 7). Careful mobilization of the colon and vascular hypotenuse to the colonic wall minimizes injuries during difficult dissection. This technique removes the focus of bacterial translocation and preserves the rectum and local continence. This is especially true in cases for which the differential diagnosis of UC or Crohn's disease is not obvious before surgery. Patients with a pathophysiologic diagnosis of Crohn's disease should be required to undergo reconstruction with an ileoproctostomy or rectectomy if rectal disease is absent or well controlled (Fig. 8). If the diagnosis of UC is established, the remaining rectum should be resected on an elective basis and a restorative proctectomy with an ileal pouch and anastomosis should be the method of choice. The unmatched pelvic floor and perineal region after subtotal colectomy offers ideal anatomic conditions for preservation of the autonomic sacral nerves (bladder, erectile function), thus making it possible to achieve a satisfying postoperative quality of life. In cases of *C. difficile* colitis with TM, end ileostomy with colonic lavage of vancomycin, mitigate enemas have been recently described as an emerging technique.

OUTCOMES

Timing of surgery is still unclear in the literature because of the high mortality of TM when surgery is delayed; therefore, the consensus is that surgical management should be performed as soon as the diagnosis of TM is made. It has been shown that 67% of patients with severe UC had surgery even after initially successful medical management. In patients without perforation, Bjuderow and Winner reported an 8.7% mortality rate while in 51% of emergency patients with perforation. Given this information, signs of progression of the disease must be treated aggressively with surgical intervention, and perforation should be avoided. Contrarily, some reports have shown preservation of the colon with successful

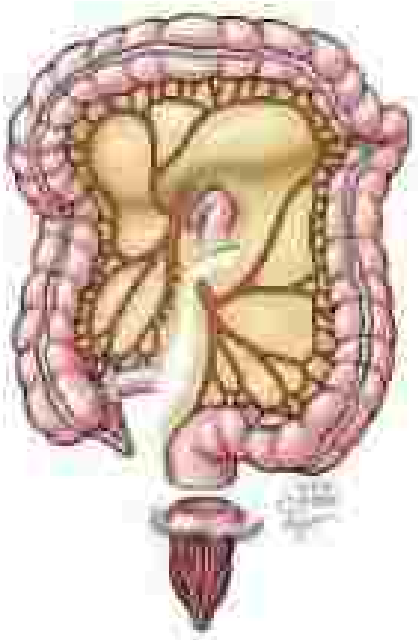

FIG. 5 Subtotal colectomy and end ileostomy. (Courtesy Cleveland Clinic Center for Medical Art & Photography ©2005-2010.)

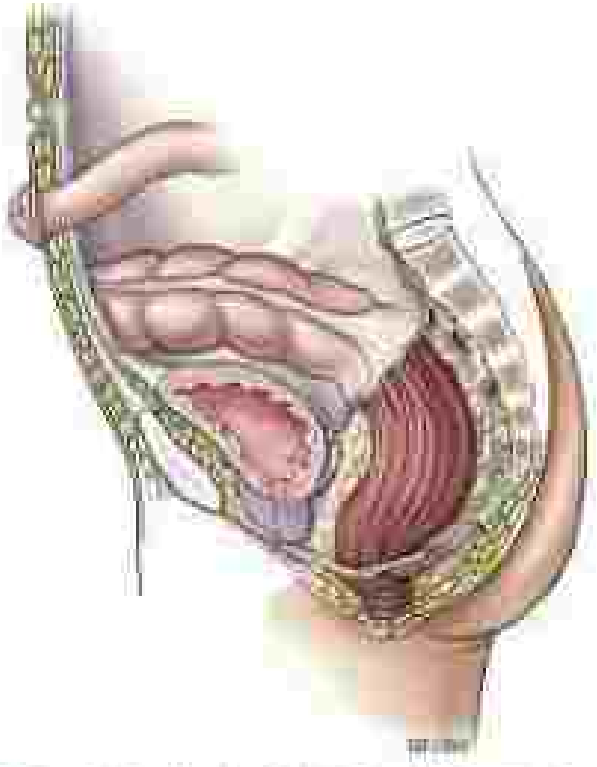

FIG. 6 The distal sigmoid can be divided, closed, and delivered to the anterior portion of the wound to create above the fascia limb. (Courtesy Cleveland Clinic Center for Medical Art & Photography ©2005-2010.)

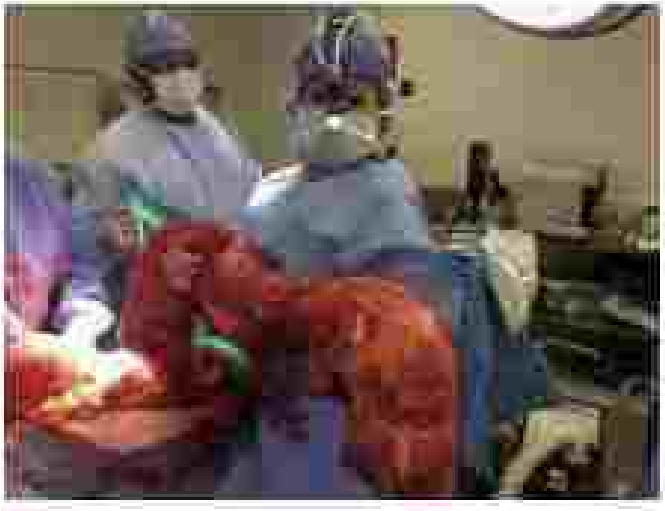

FIG. 7 Total abdominal colectomy for patient with toxic megacolon.

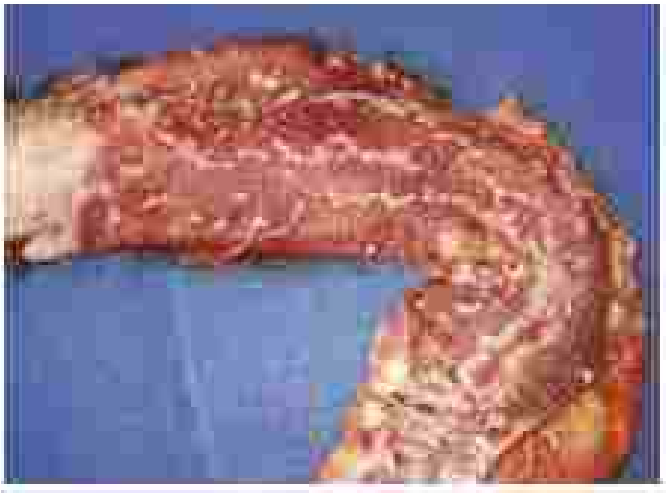

FIG. 8 Gross pathology specimen from patient with Crohn's disease complicated by toxic megacolon.

conservative management at long-term follow-up. These conflicting results in the literature may be related to the definition of TM and different initial presentations of patients, but there is an overall trend toward early surgical intervention. Over the years, different surgical approaches have been developed to manage TM, with subtotal colectomy with end ileostomy being the current operation of choice. Mortality has been improved markedly within the past 30 years.

Advances in intensive care management and early surgical intervention with close follow up have improved the prognosis for patients with TM.

SUMMARY

In summary, surgical intervention remains a mainstay in the management of TM. Medical therapy is directed toward treating the underlying cause, whether inflammatory or infectious. Although short trials of medical therapy are certainly warranted, any sign of complication (either clinically or on CT scan), worsening, or failure to improve is an indication for colectomy. The timing of surgery is crucial, and delay in surgical management can result in perforation and a poor prognosis. Surgeons should be consulted early in the course of the disease, and frequent surgical reevaluation is necessary. The long-term prognosis of medically managed UC related TM is poor, with high rates of eventual colectomy and recurrence, and causes consideration as to the futility of medical therapy.

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MANAGEMENT OF CROHN'S COLITIS

Isabelle C. Le Leannec, MD, MEng, and Elizabeth Wick, MD

Crohn's disease (CD) is a chronic, incurable, transmural inflammatory disorder that has myriad presentations, affecting any segment of the gastrointestinal tract from the mouth to the perianal area as well as extraintestinal sites. Crohn's colitis (CC) is one of its most common presentations. Approximately 50% of patients with Crohn's have ileocolitis, involving both the terminal ileum and colon; 20% have disease limited to the colon. As an important distinction from patients with ulcerative colitis (UC), approximately half of CD patients with CC will have rectal sparing. Perianal disease occurs in approximately one third of patients. CD is seen primarily in the United States and Europe, with an incidence of 6 patients per 100,000, but Asian and South American countries are seeing a higher recent incidence of CC as well.

Crohn's patients have a bimodal age-distribution at the time of presentation (20s to 30s or 50s to 60s) and with a female predominance. CD is a complex disease whose etiology is still not clear. Genetic and environmental factors both play a role. Patients with a family history of Crohn's are 20 times more likely to develop CD. There is a higher incidence of CD in whites, especially Ashkenazi Jews. *NOD2/CARD15* gene mutations are present in a minority of patients with CD, but testing for this gene is not currently recommended as a clinical diagnostic. Cigarette smoking is the environmental factor found to have the strongest association with Crohn's risk and severity. Similar to other long-standing inflammatory conditions of the gastrointestinal tract that are associated with malignancy, patients with CC are at increased risk of carcinomas, especially colorectal cancer (CRC). The median duration from diagnosis of CC to the development of CRC is 15 years. Patients with CC who undergo operations for CRC are more likely to have advanced CRC than patients with UC. The transmural nature and variable anatomic location of CD and CC leads to a variety of clinical presentations that necessitate differing management strategies. The acuity of disease presentation, anatomic distribution, and nature of the disease process (inflammatory, obstructing/stricturing, or fistulizing) all guide medical and surgical management of CC.

CLINICAL FEATURES

Patients with CC have a variety of clinical presentations. Patients commonly report intermittent, vague, crampy abdominal pain accompanied by diarrhea, with symptoms often occurring for several years before diagnosis. They may describe hematochezia or, less frequently, melena. Fatigue, weight loss, and fever can also be features. The process of transmural inflammation in Crohn's causes strictures and sinus tracts. Strictures from fibrotic change of the bowel lumen can cause intermittent obstruction symptoms. Sinus tracts can evolve into enteroenteric fistulas or enteric fistulas to other organs. These diseases also precede the development of phlegmon or abscess, which are sometimes palpable on examination as an inflammatory mass. Diarrhea occurs as a result of many processes, including excessive fluid secretion and impaired fluid absorption by inflamed bowel. We see malabsorption resulting from inflamed terminal ileum, sometimes related to the loss of bile salts, small intestinal bacterial overgrowth, overlapping irritable bowel syndrome, or effective short gut from extensive fistulas or areas of bypassed absorptive capacity. Perianal disease in the form of fissures, skin tags, abscesses, and fistulas occurs in one third of patients with CD. Extraintestinal manifestations tend to be more concurrent with colonic involvement and include venous and arterial thromboembolism from hypercoagulability, arthritis or arthropathy, eye and skin disorders, primary sclerosing cholangitis, renal stones, bone loss and osteoporosis, pulmonary disease, vitamin B12 deficiency, and secondary amyloidosis. Episodic colitis symptoms are often recognized by patients with Crohn's as flares. Advanced colitis may present with major lower gastrointestinal bleeding, colonic perforation, large bowel obstruction, or fulminant colitis. The Working Party of the World Congress of Gastroenterology has determined successive criteria for classification of CD. Schinna for the predominant clinical forms of CD were first codified in Vienna (1998) and then later updated in Montreal (2005) (Table 1).

DIAGNOSIS

A broader differential diagnosis for CC includes infectious diarrhea, lactose intolerance, irritable bowel syndrome, and UC. *Clostridium difficile* infection is common in patients with CD and should be ruled out. Patients with concomitant extracolonic CD (EC) simplify diagnosis. However, patients frequently present with isolated colonic disease, making the underlying differentiation between CD and UC difficult. The term *indeterminate colitis* has been used to describe patients whose clinical and pathologic diagnoses remain indistinguishable even after resection, from having overlapping features of each disease and/or severe active inflammation that obscures diagnosis. The path to diagnosis should be determined by the acuity and type of presentation, with colonoscopy and biopsy being the first step to diagnosis in patients who present with predominant diarrhea and more chronic symptoms. Endoscopic evaluation can classically reveal skip lesions, or

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TABLE 1 Classification Schemes

	Vienna (1998)	Montreal (2005)
Age at diagnosis (y)	A1: <40 A2: >40	A1: ≤16 A2: 17–40 A3: >40
Location	L1: Ileal L2: Colonic L3: Ileocolonic L4: Upper gastrointestinal tract	L1: Ileal L2: Colonic L3: Ileocolonic L4: Isolated upper disease
Behavior	B1: Nonstricturing, nonpenetrating B2: Stricturing B3: Penetrating	B1: Nonstricturing, nonpenetrating B2: Stricturing B3: Penetrating Perianal disease

segments of intestine that appear inflamed and thickened with intervening normal segments. Although rectal sparing is more typical of CC, pancolitis with continuous disease extending from the rectum proximally can mimic the typical findings of UC. Also commonly seen in UC, pseudopolyps (superficial masses of mucosa, granulomas, resembling polyps) are often present in CC as well. On biopsy, up to 30% of CD patients will demonstrate granulomas; these are diagnostic of the disorder if other causes of granulomas, such as Yersinia infection, Behçet syndrome, tuberculosis, and lymphoma, are excluded. Computed tomographic (CT) imaging can help identify extraluminal disease and extraintestinal abscesses but has limited value in evaluating the intestinal wall or mucosal pathology. CT enterography (CTE) and magnetic resonance enterography (MRE) are increasingly used to evaluate the latter purpose. MRE has the advantage of similar accuracy with no ionizing radiation exposure and can be also used serially to follow treatment response. Small bowel follow-through or enteroclysis with barium have also been used to evaluate for active disease in patients with known CD but have been largely been replaced by MRE and CTE.

Sometimes, patients with no known diagnosis of CD present with acute abdominal pain. In this setting, it is safer to start with cross-sectional imaging, such as a CT scan with intravenous contrast. Usually, patients can be stabilized and are able to undergo further evaluation and medical therapy avoiding emergency surgery. If this is not the case, intraoperative gross examination might reveal extraluminal "creeping fat," in which mesenteric fat has begun to encircle the bowel in areas of active disease or fibrotic, thickened stretches of colon. Importantly, it can be difficult to distinguish colorectal cancer from CC in this setting, so surgical planning should take this into consideration. Intraluminally, the colon features classic findings of deep linear ulcers, also called linear claw or cobblestoning, along the mesenteric border (Fig. 1).

Serologic tests with clinical utility in diagnosing CD include perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA). These tests, included on many inflammatory prognostic panels, are most useful as an adjunct to other diagnostic modalities and are not diagnostic on their own. C-reactive protein levels are often higher in CD than UC and can be checked serially to monitor for evidence of active disease or treatment response. An elevation in fecal calprotectin, a marker of neutrophil activity within the bowel, can be used to distinguish CD from functional bowel disease. Clinical testing for CD-associated genetic markers, such as NOD2/CARD15, is not currently recommended.

TREATMENT

The first step in deciding how to approach treatment of the patient with CC is to stratify the patient as low or high risk (Table 2). Low-risk

FIG. 1 (A) Linear ulcer, or long linear ulcers in the colon of a patient undergoing resection for Crohn's colitis. (B) Close-up view of colonic mucosa showing cobblestoning indicative of severe Crohn's with a combination of linear and transverse ulcerations. The raised areas consist of residual mucosa.

TABLE 2 Low- and High-Risk Features of Crohn's Disease

Low-Risk Features	High-Risk Features
• No or mild symptoms • Normal or mild elevation in C-reactive protein and/or fecal calprotectin levels • Dx. made at age >30 years • Limited distribution of bowel inflammation • Superficial or no ulcerations on colonoscopy • Lack of perianal complications • No prior intestinal resections • Absence of penetrating or stricturing disease	• Diagnosis at a younger age (<30 years) • Tobacco use • Elevated C-reactive protein and/or fecal calprotectin levels • Deep ulcers on colonoscopy • Long segments of small and or large bowel involvement • Perianal disease • Extraintestinal manifestations • History of bowel resections

CD patients have no or mild symptoms, normal or mild elevation in C-reactive protein and/or fecal calprotectin levels, diagnosis after 30 years of age, limited distribution of bowel inflammation, superficial or no ulcerations on colonoscopy, lack of perianal complications, no prior intestinal resections, and an absence of penetrating or stricturing disease. High risk patients with moderate to severe CD may have the following features: diagnosis at a younger age (<30 years), tobacco use, elevated C-reactive protein and/or fecal calprotectin levels, deep ulcers on colonoscopy, long segments of bowel involvement, perianal disease, extraintestinal manifestations, and history of bowel resections. Patients initially classified as lower risk may be subsequently reclassified as high risk if they develop complications or show lack of improvement with initial treatment. Frequency and number of flares, need for glucocorticoids, and history of hospitalizations should also be considered in a patient's risk stratification. Of note, patients who present with symptomatic fibrotic disease, particularly with preextensive dilation, are unlikely to have resolution of these end-stage structural changes with anti-inflammatory medications alone and are more likely to require surgery. Surgical intervention or endoscopic dilation is an important first step for patients with anal or lower rectal fibrotic strictures from Crohn's as distal obstruction can limit the efficacy of medical therapies on the proximal gastrointestinal tract.

Medical Management

Choice of medical therapy depends on the severity of disease, anatomic location, and whether the treatment goal is to induce remission or maintain remission. Two approaches for medical management of CD have come to prominence in the recent past: the step-up (or bottom-up) and top-down strategies. In a step-up approach, patients are started on medications with less potency but fewer side effects first. If treatment goals are not met on the lower potency regimen, these patients are then advanced to drugs that are more potent and potentially more toxic. A top-down strategy starts with placing patients on more powerful agents as first line therapy early in the course of disease before patients become glucocorticoid dependent, or possibly before patients even receive glucocorticoids. There are pros and cons to either approach. Advocates of a top-down strategy hope to disrupt the cycle of chronic inflammation and scar formation associated with chronic CD and limit permanent architectural damage to tissue. More potent therapies such as biologics have been associated with more rapid onset of clinical remission and more favorable long-term side effect profiles when compared with glucocorticoids. The downside to biologics is that they are more expensive, and insurers may limit access to these medications unless patients have tried steroid or antimetabolite therapies first, although access is improving. For the patient with severe ulceration, significant penetrating disease, and other high-risk features, biologic therapy should be the first line.

Low-risk patients are often managed with a step-up approach. First-line therapy for inducing remission in patients with mildly active disease limited to the ileum and right colon is budesonide, an enteric-coated corticosteroid that has a high first-pass rate of hepatic metabolism. Budesonide acts primarily in the bowel lumen, with a smaller systemic effect. Typical course length with subsequent taper is 8 to 12 weeks of therapy. Once remission is achieved with pulse therapy, patients move on to maintenance therapy. Systemic side effects, such as hyperglycemia, hypertension, cataracts, aseptic hip necrosis, striae, and cushingoid appearance, are less common with budesonide than with conventional glucocorticoids such as prednisone. However, prednisone is a useful first line therapy for patients with diffuse colitis, left-sided colonic disease, or for patients with extraintestinal CD who do not respond to budesonide. Typically, patients are started on 40 to 60 mg per day and tapered by 5 to 10 mg per week with a goal to complete the course by 4 to 8 months. For patients who are unable to taper off oral corticosteroids, their disease burden is reclassified as high risk and treatment is often escalated to a biologic medication.

Sulfasalazine, a general anti-inflammatory medication that is cleaved to its active form by colonic bacteria, has been shown to be effective mainly in patients with mild disease limited to the colon. It is less effective than steroids for induction therapy and may be poorly tolerated because of side effects including fever, leukopenia, and agranulocytosis. It is therefore increasingly used for initial treatment mainly in low-risk patients who wish to avoid glucocorticoids and those with extraintestinal manifestation of arthralgias and arthritis. The 5-aminosalicylate (5-ASA) drugs are modifications of sulfasalazine without the sulfapyridine ring. These drugs have been modified into various forms to deliver their therapeutic effects to different sites in the gastrointestinal tract. For colonic drug release in patients with limited ileitis and mild symptoms, this includes slow- or delayed-release oral formulations of mesalamine (e.g., Asacol, Pentasa, Apriso, Lialda, Canasa). There are also topical drugs in the form of a suppository (Canasa) or small volume enema (Rowasa) for delivery to the rectosigmoid. For patients with CC, some data suggest that long-term use of 5-ASA agents may decrease the risk of colon cancer. At this time, the US Food and Drug Administration has not approved 5-ASA agents for the treatment of CD because of lack of efficacy. In the patient with anything other than mild CC, it should not be used.

Once low-risk patients have successfully completed a steroid pulse, they are surveilled for clinical and endoscopic relapse with ileocolonoscopy in 6 to 12 months. Antimetabolite immunomodulator drugs such as azathioprine and 6-mercaptopurine (i.e., thiopurines) or methotrexate may also have a role in maintenance therapy for patients with CC, especially in those who become glucocorticoid dependent. These agents take up to 4 months to have a treatment effect, and as such, they are not useful for treating flares. Dietary interventions such as avoiding lactose and eliminating certain pro-inflammatory foods may also help patients maintain remission, though data are very limited.

A top-down approach is best suited for high-risk patients. Patients who have moderate to severe symptoms of CC should initially be started on a biologic medication with or without a concomitant immunomodulator. There are three anti-tumor necrosis factor (TNF) monoclonal antibody drugs approved for use in CD in the United States, including infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia). Anti-TNF medications are initiated in combination with antimetabolites for improved pharmacokinetics and to reduce immunogenicity against the biologic drugs. They are typically initiated with a loading dose and then given in a series of subsequent maintenance doses. Side effects of anti-TNF agents include reactivation of tuberculosis or histoplasmosis, as well as a twofold increased risk of Hodgkin's lymphoma (less than 1 in 1000). However, the introduction of biologics has generally decreased the incidence of CD patients requiring surgery. Next line biologics include ustekinumab (Stelara), an anti-interleukin (IL)23 antibody, and vedolizumab (Entyvio), an anti-alpha 4 beta 7 integrin antibody. These drugs can also be used first line in CD. Once patients have achieved remission with a biologic agent, they are generally maintained on therapy indefinitely with regular monitoring for adverse events and disease remission (Fig. 2). Thiopurines should not be used long term, especially in young men, who have an increased risk of developing hepatosplenic T-cell lymphoma. Patients older than age 40 also have increased risk of infection and malignancy with combination anti-TNF and thiopurine therapy and may be better suited to initial monotherapy with vedolizumab. High-risk patients who present acutely ill and require hospitalization are typically treated with intravenous steroids, fluid and electrolyte replacement, broad-spectrum antibiotics if indicated, nutritional assessment, and biologic therapy. If this fails or if an obstruction is noted, surgical consultation is warranted.

SURGICAL MANAGEMENT BY INDICATION

Surgical management is necessary when complications of CD arise that cannot be mitigated by medical therapy alone. Given that there is no surgical cure for CD, there must be clearly defined short- and long-term goals for any surgical intervention in these patients. Goals

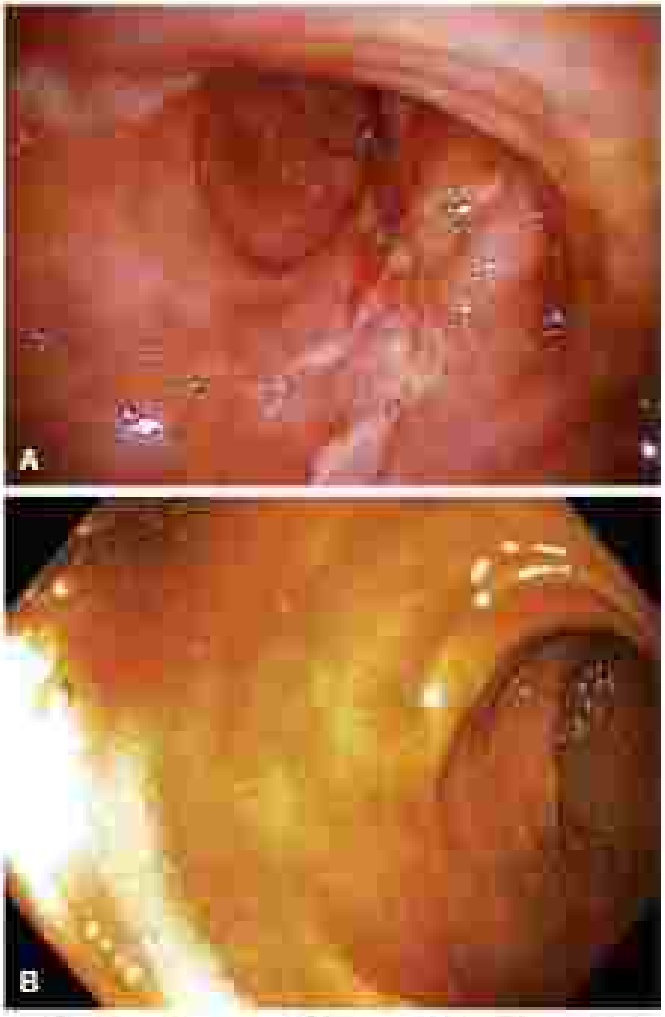

FIG. 1. (A) Colonoscopic view of a patient with severe Crohn colitis before and (B) 1 year after beginning infliximab therapy.

and techniques are driven by the indication for surgery, which is wide ranging in CC. There are many factors that should be considered when selecting the most appropriate operation for a given patient. This includes the condition of the anal sphincter, coexistence of perianal disease, presence or absence of a lower rectal or anal canal stricture, history of fecal incontinence, whether the patient has small bowel disease, patient age and body habitus, and the patient's lifestyle and goals. In addition, before surgical planning, the patient should have a full colonoscopy, if possible, to evaluate for dysplasia, malignancy, and to determine the burden of inflamed and uninflamed mucosa.

Stricture or Obstruction

A significant majority of CC patients will present with stricture as the initial sign of disease. Standard of care is nasogastric decompression, correction of electrolyte and fluid imbalance, and nutritional support. In many cases, this can help to shift surgery from emergent to urgent or semielective. Interventional endoscopists may be able to dilate or stent a colonic stricture to allow for preoperative bowel decongestion and preparation, but this carries a risk of perforation. Malignancy in the structured segment is also of real concern; if the affected area is not resected, biopsies should be taken to exclude cancer. In the end, most strictures that lead to bowel obstruction will need surgery, but decompression and even temporary relief of the stricture can mean that the patient is a candidate for a segmental colectomy as opposed to total abdominal colectomy. Given the complexity of these patients' status (malnutrition, medications, obstruction), frequently the pathology is resected and a stoma is created at the time of surgery as opposed to a primary anastomosis with reversal of possibly at a later operation.

Perforation, Fistulae, and Abscess

Colonic perforations and their sequelae are also common manifestations of CC requiring surgical intervention. Patients will frequently present with chronic perforation that has resulted in abscess, phlegmon, or fistula formation. These are best diagnosed with CT scan, especially in the setting of chronic steroid use, which masks associated inflammation and chronic leukocytosis. Fatty inflammation is often seen in the area of ongoing fistula or perforation. The preferred management of pericolonic abscess in this setting is bowel rest, nutritional support, parenteral antibiotics, and image-guided percutaneous drainage. Urgent operation is required if there is free fecal or purulent peritonitis, if the abscess is not amenable to percutaneous drainage, or if percutaneous drainage fails to adequately resolve the process. Approximately 30% of pericolonic Crohn's abscesses are managed with percutaneous drainage. If there is involvement of the abdominal wall, however, most patients will eventually require a surgical drainage procedure. Following resolution of an intraabdominal abscess, the involved bowel segment is typically resected in up to 30% of patients will have recurrent sepsis. Patients with long segment disease, however, may be managed medically to avoid postsurgical complications such as diarrhea or short gut syndrome.

Massive Lower Gastrointestinal Bleeding

Although massive lower gastrointestinal bleeding is a rare presentation of CC, patients may present with melena or hematochezia severe enough to require surgical intervention. Hemodynamically stable patients may be managed endoscopically or with angiography. Unstable patients require surgical resection, the extent of which is determined by whether the bleeding can be localized to a specific bowel segment.

Severe Colitis, Fulminant Colitis/Toxic Megacolon

In severe colitis, patients may develop ileus from inflammation leading to significant dilation of the colon (i.e., a toxic megacolon) and subsequent worsening perfusion of the bowel wall. These patients may develop fever, tachycardia, leukocytosis, and hypoalbuminemia, which are frequently accompanied by hemodynamic instability. Initial care of these patients is supportive, with the potential addition of steroids, antibiotics, and volume resuscitation to avoid the use of vasopressors. Urgent colectomy may be indicated if the patient does not improve with conservative management to avoid progression to perforation and intraabdominal catastrophe.

Extracolonic Manifestations of CD

Patients with small bowel disease are best treated with resections designed to preserve absorptive capacity and small intestinal length such as strictureplasty. Multiple resections for recurrent small bowel obstructions place patients at risk for short gut syndrome. Perianal Crohn's and cutaneous pyoderma gangrenosum are manifestations of CD that can improve with surgical intervention. Crohn's uveitis, ankylosing spondylitis, and primary sclerosing cholangitis do not improve with intestinal surgery and tend to be progressive. Growth retardation from malabsorption and chronic inflammation is of specific concern in children and an indication for earlier surgical intervention.

Surgical Management by Technique

The extent of surgical resection for CC is defined by the anatomic distribution of disease as well as the nature of the inflammation. Preoperative preparation should include correction of fluid and electrolyte imbalances, anemia, and malnutrition before surgery if possible. It is controversial whether patients requiring surgery who are being treated long term with steroids or biologics should be continued on

these medications to avoid worsening inflammation in the perioperative setting or discontinued to avoid surgical complications. Steroids should be continued through surgery and tapered off gradually after. Evidence suggests there is no increase in adverse outcomes for patients undergoing colectomy for CD in the presence of biologics; however, there have been no studies of how these drugs influence intraoperative decision making.

Patients should be prepared for the possibility of diversion and appropriately marked for a stoma. Extra care is warranted in stoma planning because many CD patients will have these stomas permanently. Mechanical bowel preparation with oral antibiotic preparation should be given in advance of colectomy to reduce the chance of infectious complications (superficial, deep, and organ space infections). Patients with CD are at increased risk for venous thromboembolism and should be given perioperative primary prophylaxis with heparin or low molecular weight heparin.

Emergent Operation

Emergent operation for CC is rare. Indications include perforation, abdominal or pelvic sepsis, obstruction, or major bleeding. The operation of choice is a subtotal colectomy with a long rectal stump and mucous fistula. A mucous fistula brought up in the abdominal wall will not prevent wound complications if the rectal staple line dehisces but will hopefully avoid the complications of a pelvic abscess. The surgeon could also elect to place a rectal drainage tube secured across the anus to prevent rectal stump blow out. Intraoperatively, the safe technique is to work from normal to abnormal tissue. The mesentery tends to be very friable and less amenable to dissection with energy devices and should instead be divided between clamps and ligated.

Segmental Colectomy

Segmental colectomy is an option for patients with CC when there is an area of limited, localized disease. The surgeon should identify proximal and distal areas of healthy bowel and mesentery suitable for anastomosis. Preoperative endoscopic tattooing of the margins can be helpful. Recurrent colitis is higher in patients who have had segmental colectomy so the use of postoperative adjunctive biologic medications is essential. Colonic strictures resulting from CD should generally be resected except in the rare circumstance of a contiguous proximal colonic and short segment terminal ileum stricture, which may be amenable to stricturoplasty.

Ileorectal Anastomosis

Primary ileorectal anastomosis (IRA) following a subtotal colectomy is an option for patients with no evidence of rectal disease who prefer to not have an ileostomy. Patients should be interviewed about their preoperative continence and educated that ileorectal anastomoses are associated with an increase in stool volume and frequency. If a patient already has poor resting rectal tone or a compliant rectum, postoperative bowel function may be intolerable. In patients who are candidates for IRA, digital rectal examination should demonstrate adequate sphincter tone and the rectum should appear distensible on proctoscopy or flexible sigmoidoscopy. Additionally, they should not have perianal CD. Patients with IRA will require ongoing surveillance of the rectum to assess for recurrence of CD as well as for evidence of dysplasia or cancer. Up to 40% to 50% of patients undergoing IRA will eventually require completion proctectomy with end ileostomy.

Total Proctocolectomy with End Ileostomy

Total proctocolectomy with end ileostomy is the treatment of choice for several presentations of CD, including penicillitis and perianal Crohn's, colonic dysplasia, and those with multiply recurrent disease. Removing the entire colon, rectum, and anus is associated with the lowest recurrence risk of any operation performed for CD. The operation is performed with the patient in the modified lithotomy position to allow the surgeon access to the abdomen and perineum. The perineal dissection is typically performed in the plane between the external and external sphincters as an intersphincteric proctectomy. This decreases the size of the perineal wound and minimizes the risk of poor wound healing and sexual dysfunction. The perineal wound is closed in layers with absorbable suture to provide multiple barriers in the event of superficial wound breakdown, which can happen in approximately 25% of patients.

Total Proctocolectomy with Ileal Pouch Anal Anastomosis

Patients with CC have a nontrivial lifetime risk of developing CD in the small intestine; therefore, a restorative procedure such as an ileal pouch anal anastomosis should generally not be performed in patients with CD. Patients may present with perianal or small bowel fistulizing disease after having had proctectomy for what was initially diagnosed as UC but subsequently determined to be Crohn's. Pouch complications from Crohn's may be successfully managed with medical therapy and frequent surveillance endoscopy, but significant complications may require excision of the pouch and conversion to end ileostomy.

Proctectomy

Completion proctectomy is often performed when there is recurrent disease in the rectum or severe perianal disease following subtotal colectomy for CC. Patients should undergo manometric dysfunction as described previously, unless there is suspicion or evidence of malignancy. In that case, patients should undergo a conventional abdominoperineal resection including removal of the internal and external sphincters. If a patient has isolated rectal disease or extraintestinal CD with the rectum as the only colonic site of disease, a proctectomy and end colostomy may be performed with the understanding that restoration may be necessary in the future should there be progression of the colonic disease.

Laparoscopic and Robotic Surgery for CC

The role of minimally invasive surgical techniques in treating CC is still evolving. Compared with open surgery, laparoscopy has short-term benefits of reduced wound morbidity, expedited recovery, and lower cost. Long-term benefits include lower rates of bowel obstruction and lower incidence of incisional hernias. When the appropriate expertise is available, laparoscopic or robotic surgical management is indicated. CD has been demonstrated to have comparable recurrence rates after open and laparoscopic surgery.

PERIOPERATIVE MANAGEMENT AND CARE AFTER SURGERY

Following surgical resection, multidisciplinary care with gastroenterology is essential. Endoscopic recurrence rates have been reported as high as 80% at 1 year following surgical resection. The yearly rate of recurrence approaches 10% to 15%. These statistics reemphasize that surgery is not a cure for CD, and returning patients on their maintenance medications and surveillance regimens is critical to their long-term outcomes. Patient should get repeat endoscopy at least by 6 months postoperatively to stage risk of recurrence and determine whether a change in therapy is indicated.

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Management of Ischemic Colitis

Ian Soisky, MD, MPH, and Farhad Nawras, MD

Ischemic colitis—a condition that occurs in settings when the blood supply to the colon is insufficient to meet cellular metabolic needs resulting in mucosal injury or full thickness necrosis—is the most common form of gastrointestinal ischemia. Although the incidence of ischemic colitis has previously been reported to range from 4.5 to 44 cases per 100,000 person-years, studies more recently have reported a range of approximately 15 to 18 cases per 100,000 person-years. These rates, however, may be underestimated because they tend to be based on hospitalized patients, and it is believed that a significant number of patients with mild disease are not captured because they never present for medical attention or are misdiagnosed. Ischemic colitis can present on a spectrum from self-limiting to life-threatening disease, and diagnosis requires a high index of clinical suspicion. Severity of disease dictates subsequent management. Most patients have a less severe form of disease (approximately 80%) and can be managed medically, whereas the remainder has a more critical form of disease requiring surgical intervention. Those treated medically have an overall mortality rate of approximately 6%, whereas those requiring surgery have a mortality rate nearing 50%. The wide difference in these mortality rates underscores the importance of early diagnosis and timely treatment. This chapter outlines the key considerations pertinent to the diagnosis and management of ischemic colitis.

ANATOMIC AND PATHOPHYSIOLOGIC CONSIDERATIONS

Understanding the presentation and pathophysiology of ischemic colitis requires a working knowledge of the blood supply to the colon. Fig. 1 shows the arterial supply to the colon. The superior mesenteric artery (SMA) via the ileocolic, right colic, and middle colic arteries supplies the right colon; the transverse colon is predominantly supplied by the middle colic artery, and the distal transverse colon to proximal rectum is supplied by the inferior mesenteric artery (IMA), which branches into the left colic, sigmoid, and superior rectal arteries. An extensive collateral circulation including the marginal artery of Drummond and the arch of Riolan (also referred to as the *meandering mesenteric artery*) connects the SMA and IMA, which is critical to ensuring that the colon is adequately perfused, even in cases of SMA or IMA stenosis or occlusion. The collateral circulation is of particular importance to the so-called watershed areas of the colon, which are the parts of the colon most at risk for hypoperfusion and thus ischemia because of their anatomic location at the distal end of an arterial supply. These watershed areas include the splenic flexure (Griffith's point), which receives its blood supply at the junction of the SMA and IMA, and the sigmoid colon (Sudeck's point), which receives its blood supply at the junction of the sigmoid and superior rectal arteries.

The colon has an inherently lower blood flow than the small bowel, which puts it at risk for ischemia. Colonic ischemia can develop as a result of two different processes, which can be described as nonocclusive and occlusive. The predominant mechanism is nonocclusive, which occurs in conditions that cause low flow states in the colon, and most commonly affects the watershed areas. However, the right side of the colon is also at risk from ischemia in low flow states because the vasa recta are believed to be less developed in the right colon compared with the left. Although many causes of nonocclusive disease have been identified (see the following section), in most cases, no specific cause is defined, and these cases are largely believed to result from small-vessel disease. Although less common, colonic ischemia can also result from embolic and thrombotic arterial occlusion. The straight take-off of the ileocolic artery from the SMA puts the right colon at risk for ischemia from embolic events. Whether the colon becomes ischemic because of an occlusive or nonocclusive process, the extent of disease can include transient ischemia, chronic ischemia, or gangrene. Transient ischemia tends to be limited to the colonic mucosa and often recovers. A chronic colonic ischemia picture may involve the muscularis layer, which can result in scarring and stricture. Transmural involvement of the colon, which can develop within 8 to 16 hours, can lead to perforation, peritonitis, sepsis, and death. The left colon is the most commonly affected segment, followed by the sigmoid colon, but right-sided and pan-colonic ischemia, colitis can occur and are associated with poorer prognosis.

It is important to understand the differences in pathophysiology between ischemic colitis and mesenteric ischemia (discussed elsewhere) because it dictates differences in management. In contrast to ischemic colitis, which tends to be a problem because of a low flow state, mesenteric ischemia is commonly caused by a vascular obstruction, which may require a revascularization procedure, thrombolysis, or anticoagulation, treatments that are rarely used for ischemic colitis.

CLINICAL PRESENTATION AND CAUSES

Identifying ischemic colitis can be a challenge because it often presents with nonspecific signs and symptoms requiring high clinical suspicion for diagnosis. It can also sometimes present in critically ill patients who may be misdiagnosed and missed, which can further complicate the identification of symptoms. Clinical presentation can vary based on whether a patient has acute or chronic colonic ischemia. In acute cases, patients may rapidly develop abdominal pain or cramping, which can also be associated with hematochezia or bloody diarrhea within 24 hours (usually transient and rarely requiring transfusion), as well as the sudden urge to defecate. Approximately half of the patients with ischemic colitis will have these symptoms. Others may have nausea, vomiting, and fever. Patients who present with right-sided ischemic colitis are more likely to have abdominal pain without associated bleeding, whereas bleeding is more common with left-sided disease. Although most cases of mild ischemic colitis resolve, approximately 10% of patients will have a recurrent episode that tends to be similar in intensity and location to the initial one. There is some debate about whether chronic ischemic colitis should be considered a unique entity. Chronic ischemic colitis is associated with a prolonged time course and milder symptoms, which may include recurrent abdominal pain and bloody stools that may last greater than 3 months. Chronic ischemic colitis can also be associated with malnutrition and recurrent episodes of sepsis.

Because the symptoms described above are not pathognomonic for ischemic colitis, consideration of patients' medical histories become equally as important in making this diagnosis. There are a number of medical, surgical, and pharmacologic risk factors, which should make clinicians suspicious for ischemic colitis when they are present in a patient who develops abdominal pain, hematochezia, or bloody diarrhea. Box 1 summarizes the common medical conditions, surgical conditions, and drugs associated with ischemic colitis.

Medical conditions that are commonly associated with ischemic colitis include myocardial infarction, renal disease requiring hemodialysis, and diseases of hypercoagulability. Colonic ischemia after myocardial infarction or dialysis is secondary to the low flow states caused by these conditions. Several hypercoagulable disorders including the presence of antiphospholipid antibodies and mutations in factor V Leiden and plasminogen activator inhibitor have been noted to be more prevalent in patients with colonic ischemia than the general population, but the extent to which hypercoagulable states contribute to this disease process has yet to be fully elucidated. Other medical comorbidities that have been reported to be prevalent in

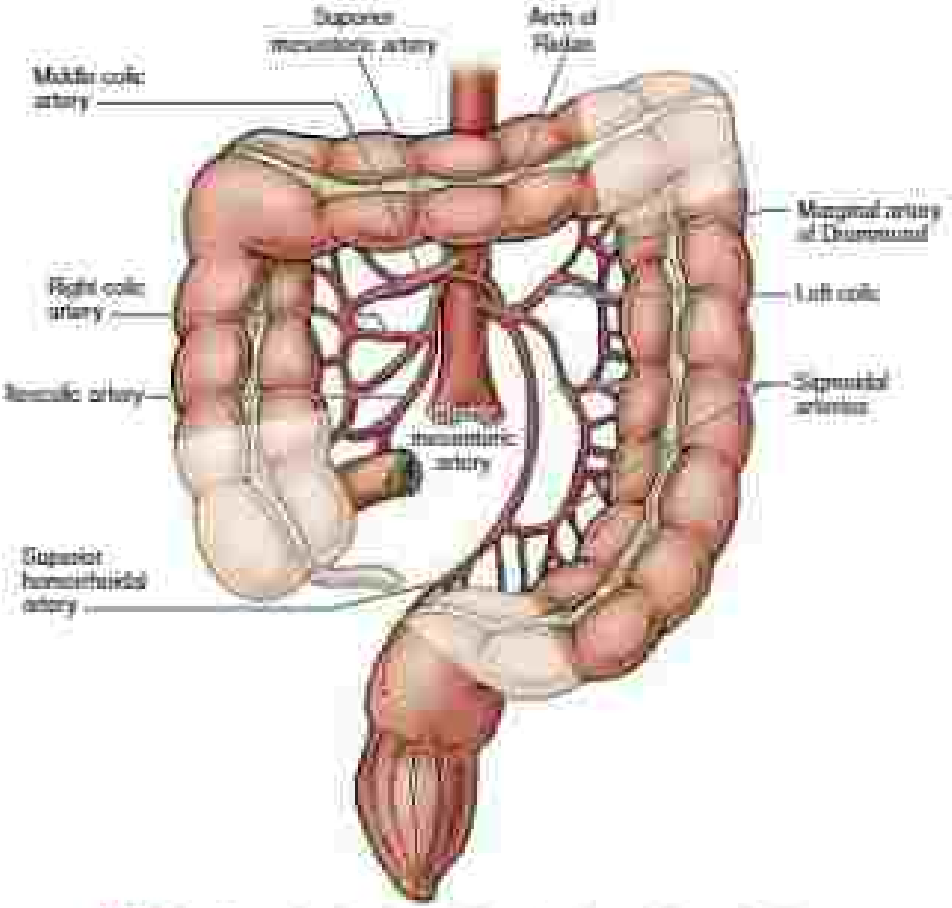

FIG. 1 Arterial supply to the colon. Dashed areas depict potential watershed regions.

patients with ischemic colitis include hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, chronic obstructive pulmonary disease, congestive heart failure, atrial fibrillation, and peripheral vascular disease, which makes sense given the occlusive and nonocclusive causes of colonic ischemia. One more rare but reported cause of ischemic colitis is extreme exercise as in marathon runners and is believed to develop as a result of blood flow being diverted away from the splanchnic circulation.

Surgical and procedural conditions that may predispose patients to colonic ischemia include aortoiliac surgery and surgeries involving cardiopulmonary bypass. Whether performed open or endovascularly, aortoiliac surgeries such as those performed for abdominal aortic aneurysms may involve ligation of vessels to the colon (such as the IMA or iliac artery), emboli events, hypotension, or surgical instrumentation leading to vascular compression, all of which can compromise the collateral blood flow to the left colon and result in ischemia. Whereas aortoiliac surgery can induce ischemic colitis through alterations to the collateral blood flow, procedures involving cardiopulmonary bypass can cause it through the induction of a low flow state. Bypass is also sometimes associated with the use of inotropic/vasoactive agents or intraaortic balloon pumps, which further can create a low flow state putting patients at risk for ischemia. Furthermore, bypass, in exposing the patient's blood to foreign surfaces, can result in hypercoagulability, microemboli, and the release of vasoactive substances. Also, although it is a rare phenomenon, colonic ischemia has been reported after colonoscopy, which is believed to be the result of excessive luminal distention via insufflation.

Many pharmacologic agents are also believed to contribute to the development of ischemic colitis. Although there are many classes of drugs that have been implicated, the offenders with the greatest supportive evidence include constipation inducing drugs, immunomodulators, and illicit drugs. Opioid and nonopioid drugs that induce constipation are believed to contribute to the development of ischemic colitis by causing increased intraluminal pressure, which can result in reduced blood flow. Immunomodulator drugs such as tumor necrosis factor α inhibitors for rheumatoid arthritis may trigger ischemic colitis through the release of cytokines that can affect thromboregulation. Illicit drugs such as cocaine and amphetamine can cause vasoconstriction, hypercoagulation, and direct endothelial injury, which also may contribute to the development of ischemic colitis. The wide spectrum of factors that may contribute to this disease emphasizes that the cause of ischemic colitis is likely multifactorial, requiring clinicians to take the patient's entire clinical picture into consideration when assessing for the presence of ischemic colitis.

DIAGNOSIS

Given the nonspecific symptoms and wide range of potential causes of ischemic colitis, clinicians who are considering ischemic colitis in a patient will often have a large differential diagnosis, which may also include acute mesenteric ischemia, diverticulitis, inflammatory bowel disease, infectious colitis, and colon cancer. As such, a workup, including laboratory testing, diagnostic imaging, and endoscopy, is usually performed to rule out other causes.

Routine laboratory studies such as complete blood count, basic metabolic panel, and coagulation studies will be ordered for patients and may show an elevated white blood cell count or decreased hemoglobin in cases of bleeding. Other studies that may aid in the assessment of disease severity include increased lactate dehydrogenase or creatinine phosphokinase. If an arterial blood gas is obtained in a critical patient, an elevated lactate and decreased bicarbonate may be indicative of a case of severe ischemic colitis. A decreased albumin may indicate malnutrition. Nonetheless, no laboratory findings are specific for ischemic colitis, and minimal abnormalities may be seen

BOX 1 Common Medical Conditions, Surgical/Procedural Conditions, and Drugs Associated With Ischemic Colitis

Medical Conditions

Cardiovascular/Pulmonary

Atherosclerosis
Atrial fibrillation
CHF
Hypertension
Vasculitis
Aortic dissection

[illegible]

Constipation
Colon cancer
Diarrhea
Irritable bowel syndrome

[illegible]

Septic shock
Congestive heart failure
Hemorrhagic shock
Hypotension

[illegible]

Diabetes mellitus
Dyslipidemia
Rheumatoid arthritis
Lupus

[illegible]

Hypercoagulable states
Sickle cell disease
Excessive exercise

Surgical/Procedural Conditions

[illegible]

Colectomy with IMA ligation
Aortoiliac surgery
Cardiovascular surgery
Cardiopulmonary bypass
Renal transplant

[illegible]

Colonoscopy
Chemoembolization
Dialysis

Drugs

Constipation-inducing drugs
- Opioids
- [illegible]

Immunomodulator drugs
- TNF-α inhibitors
- Type I interferons (α, β)

Chemotherapeutic drugs
- Taxanes

Illicit drugs
- Cocaine
- Methamphetamines

Hormonal therapies
- [illegible] hormones
- Oral contraceptive medications

Antibiotics
Laxatives
Thiazide diuretics
- Pseudoephedrine

Sympathomimetic drugs
- Ephedrine
- Sumatriptan

Diuretics

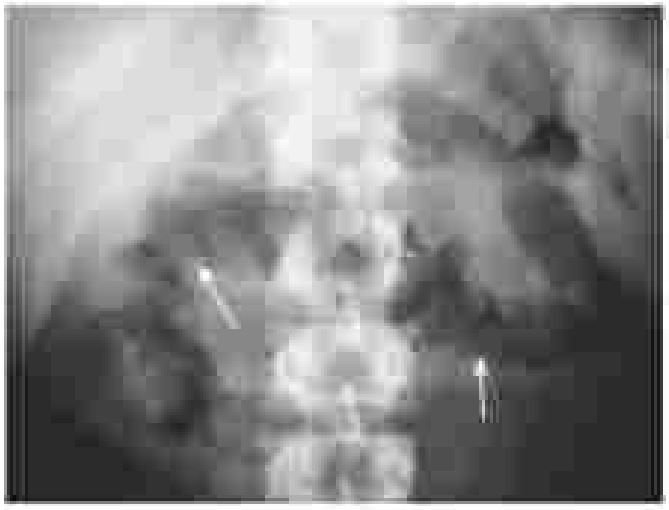

FIG. 1 Plain abdominal radiograph of patient with colonic ischemia showing sentinel and thumbprinting signs. [Text illegible] Am J Roentgenol Radium Ther Nucl Med. 1966;96:[illegible].

in mild cases. If there is a concern for a possible infectious colitis, it is also important to send off stool culture studies to evaluate for invasive bacteria, including *Escherichia coli* O157:H7, *Salmonella*, and *Shigella* species. A workup for *Clostridium difficile* colitis should also be considered in patients who have recently been hospitalized or used antibiotics.

Imaging studies also are generally obtained in patients who present with abdominal pain, hematochezia, and leukocytosis. Plain films such as a chest radiograph serve as a fast and appropriate initial study in cases when there is concern for perforation to identify pneumoperitoneum. Otherwise, obtaining an abdominal radiograph generally will show nonspecific findings that may not be helpful, but the presence of abnormalities may indicate more severe disease. The most common radiographic finding in ischemic colitis is thumbprinting (rounded densities along the side of a gas filled colon), which is indicative of submucosal edema (Fig. 2). Other findings on radiograph can include colonic dilation or mural thickening. Abdominal and pelvic computed tomographic (CT) scans are now the most common method for initial diagnosis and tend to be more helpful. They should be performed with both intravenous and oral contrast to identify the regions of involvement and the severity of disease. Findings from CT scans are also nonspecific, but those that are suggestive of ischemic colitis include segmental wall thickening, pericolonic fat stranding, thumbprinting, and ascites (Fig. 3). Worrisome findings that may prompt urgent surgical intervention include pneumatosis, portal venous gas, and stenosis. CT will also allow for the exclusion of other disease processes such as diverticulitis. CT angiography may be performed as part of a workup in cases where acute mesenteric ischemia is believed to be higher on the differential diagnosis to identify potential IMA occlusion; however, in general, this is not the appropriate test to evaluate for ischemic colitis, which is a disease of small vessels. Of note, isolated IMA occlusion typically is not believed to result in ischemic colitis because of the robust collateral blood supply, and, as such, this finding on CT angiography has uncertain significance. Other imaging modalities such as barium enema, ultrasound with Doppler flow, and MRI are available but have started to fall out of favor as CT imaging has improved.

The gold standard test for the diagnosis of ischemic colitis is lower endoscopy, typically with colonoscopy, which allows for the visualization of the colonic mucosa for signs of ulceration or ischemic change. Outside of extremely severe cases in which urgent surgical intervention may be warranted, such as peritonitis on clinical examination with imaging findings showing pneumoperitoneum, pneumatosis, or portal venous gas, early endoscopy should be performed to try to confirm the diagnosis. Although there do not seem to be higher rates of perforation for patients with colonic ischemia undergoing colonoscopy, insufflation should be minimized during the procedure, the scope should not be advanced beyond the distal extent of disease, and preprocedure bowel preparation should be avoided because this may induce toxic dilation or perforation. Endoscopy will usually reveal the segmental nature of ischemic colitis with an abrupt junction between normal and involved regions of the mucosa. Other endoscopic findings will vary based on the severity of disease. Mild disease may be associated with mucosal edema, erythema, ulceration, or petechial hemorrhage, whereas more severe disease may show dusky mucosa or hemorrhagic ulcerations (Fig. 4). The single stripe sign, a single linear ulcer along the longitudinal axis of the colon, may be more indicative of ischemic colitis than the other findings. During endoscopy, biopsies in areas of concern should be taken unless gangrene is present. The most common histologic changes include signs of inflammation, mucosal edema, hemorrhage, and destruction of crypt structures (Fig. 5). Although rarely seen, mucosal infarction and ghost cells on biopsy are pathognomonic for ischemic colitis. Endoscopy is also helpful in the evaluation of ischemic colitis because it will allow for the identification of other disease processes that could be confusing the clinical picture such as inflammatory bowel disease or infectious processes.

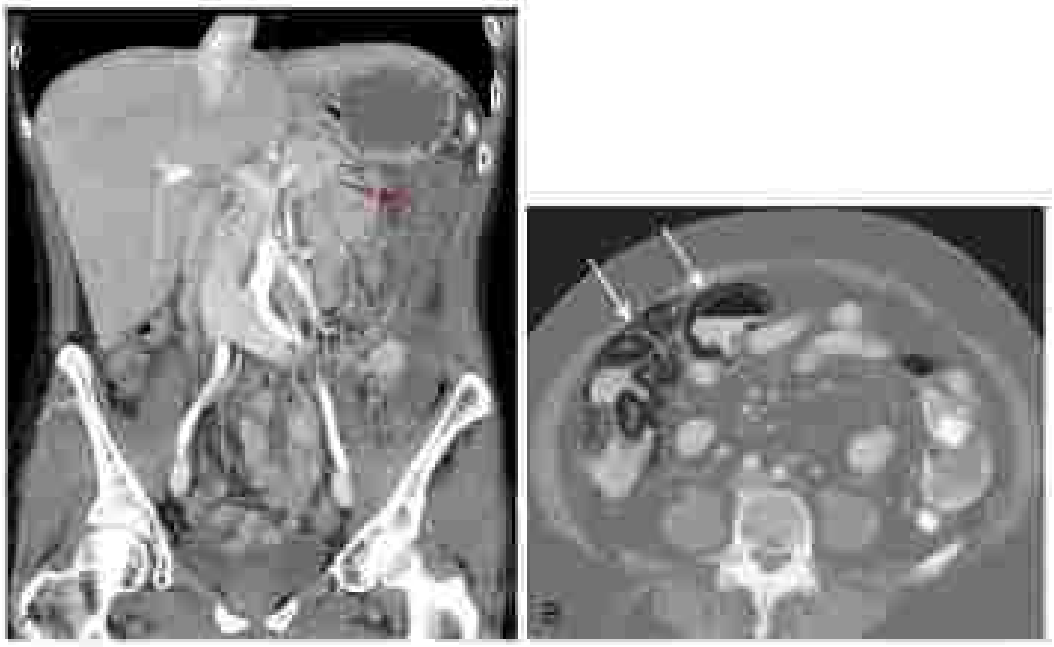

FIG. 3 CT findings of colonic ischemia. (A) Coronal reformatted image shows mural thickening with submucosal edema of the splenic flexure of the colon (arrow). (B) Pneumatosis intestinalis of the right colon (*) in a patient with extensive ischemic colitis and bacteremia. (From Corr P, Lahiri MK, Al-Zetoun M, et al. Gastrointestinal tract imaging. Adv Int Philadelphia: Elsevier; 2013.)

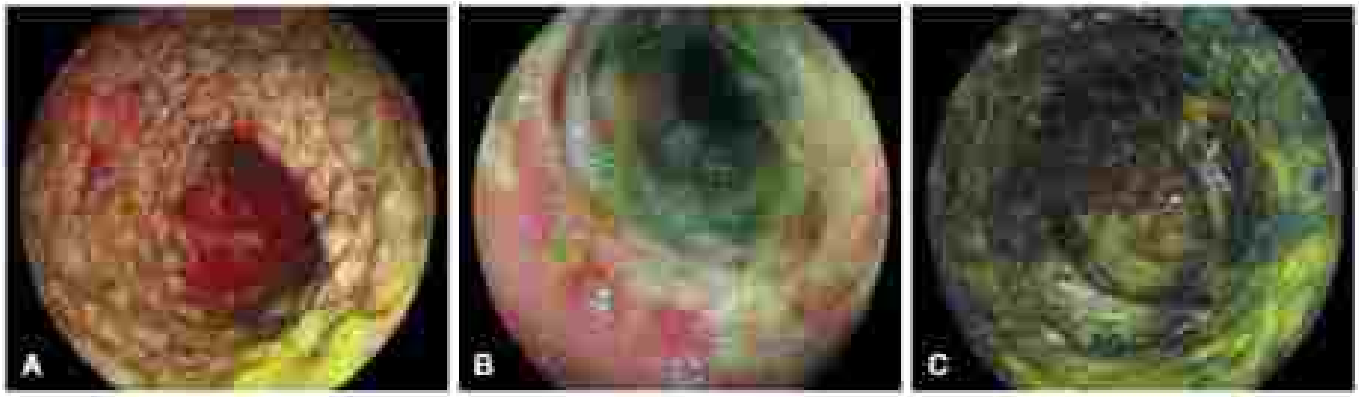

FIG. 4 (A) Ischemic colitis. (B) Ischemic colitis, boundary zone with normal mucosa. (C) Ischemic colitis at systemic stage. (From Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology. 2012;142(5):1258–1270.e1.)

TREATMENT

Treatment of colonic ischemia is dictated by the severity of disease and its cause. Even if the diagnosis of ischemic colitis is not confirmed from laboratory, radiographic, or endoscopic tests, treatment begins once it is determined whether a surgical intervention is needed. Patients with clinical or diagnostic signs of perforation, unstable bowel, or massive hemorrhage should proceed immediately to the operating room for exploration, even if the workup is not complete. Timely diagnosis and treatment are important to limiting morbidity and death associated with surgical treatment. If a patient is without these ominous signs, as is the case for most patients with ischemic colitis, supportive medical management is an appropriate approach, and remaining diagnostic tests can be performed. Fig. 4 shows the treatment algorithm for ischemic colitis.

For the majority of patients who can initially be managed nonsurgically, treatment begins with fluid resuscitation, bowel rest, and observation. Conditions that may induce ischemic colitis should be treated, and drugs that may trigger it should be stopped. Nasogastric tube decompression is not needed unless the patient has nausea and vomiting. Other important treatment principles to follow include the limitation of vasopressor use and the optimization of cardiac output to ensure adequate blood flow to the colon. Noninvasive hemodynamic monitoring tools are generally appropriate to guide fluid resuscitation. Parenteral nutrition may be needed in cases of prolonged bowel rest. While these supportive measures are being implemented, it is important for the clinical team to remain vigilant for signs of worsening bowel ischemia, which may warrant surgical intervention. Serial abdominal examination should be performed, careful monitoring of vital signs is needed, and repeat diagnostic testing may be appropriate in certain circumstances to evaluate for the resolution or worsening of disease. For example, patients who have undergone aortoiliac surgery and who develop fever, leukocytosis, hematochezia, or abdominal pain would require an urgent flexible sigmoidoscopy to assess for colonic ischemia. Early empiric broad-spectrum antibiotics have also been recommended for use in patients with ischemic colitis except in its mildest forms. Although there is limited evidence to support the use of antibiotics, this recommendation is based on studies that have suggested that colonic ischemia can disrupt the intestinal epithelial barrier leading to bacterial translocation and that antibiotics may thus play a protective role.

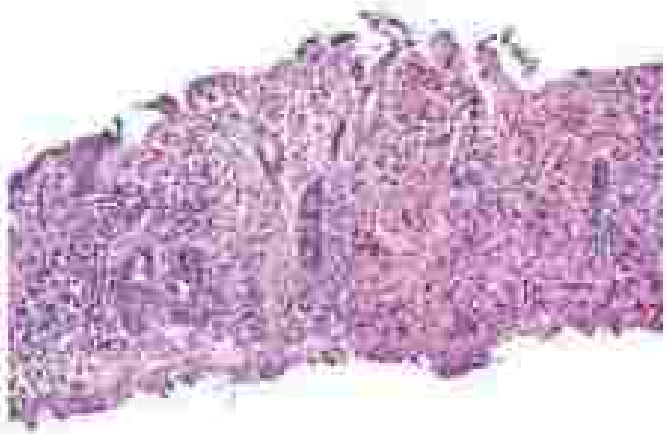

FIG. 1 Ischemic colitis histology. Injury and disturbance of the surface epithelium with preservation of the basal portion of the crypts and hyalinization and hemorrhage of the lamina propria are characteristic features of ischemia. Inflammatory cells may be present but are not a necessary component of the ischemic pattern. *(From [source].)* No other more definite diagnosis of acute colitis, such as [illegible] Clin Gastroenterol Clin. 2012;(1):[illegible].)

those patients who fail to improve with medical management or who initially present with signs of peritonitis, pneumoperitoneum, massive hemorrhage or gangrenous bowel would require urgent surgical intervention. Approximately 20% of ischemic colitis cases require surgical intervention. The standard surgical approach is to begin with a midline laparotomy incision to visualize the entire small intestine and colon from the ligament of Treitz to the peritoneal reflection over the rectum, but laparoscopic exploration may be appropriate in select cases to confirm the diagnosis. If laparoscopy is to be performed, lower than normally used intraperitoneal pressure (10 mm Hg) is sometimes advised to avoid the theoretical concern that pneumoperitoneum can further worsen blood flow. Grossly necrotic and perforated bowel should be resected. However, the viability of a spastic portion of the colon can sometimes be difficult to determine, especially if the bowel has a dusky appearance. In some instances, temporary abdominal closure with planned second look exploration after 12 to 24 hours is the appropriate next move. Intraoperative endoscopy can also be performed to assist with the determination of the extent of ischemia. Other adjuncts to the visual examination of bowel have been developed, which may assist with decision making regarding whether to resect a particular portion of bowel. The intravenous injection of indocyanine green coupled with a commercially available imaging system allows for the real-time evaluation of tissue perfusion (Fig. 2). This method, though still not universally practiced, has started to replace the older method of intravenous injection of

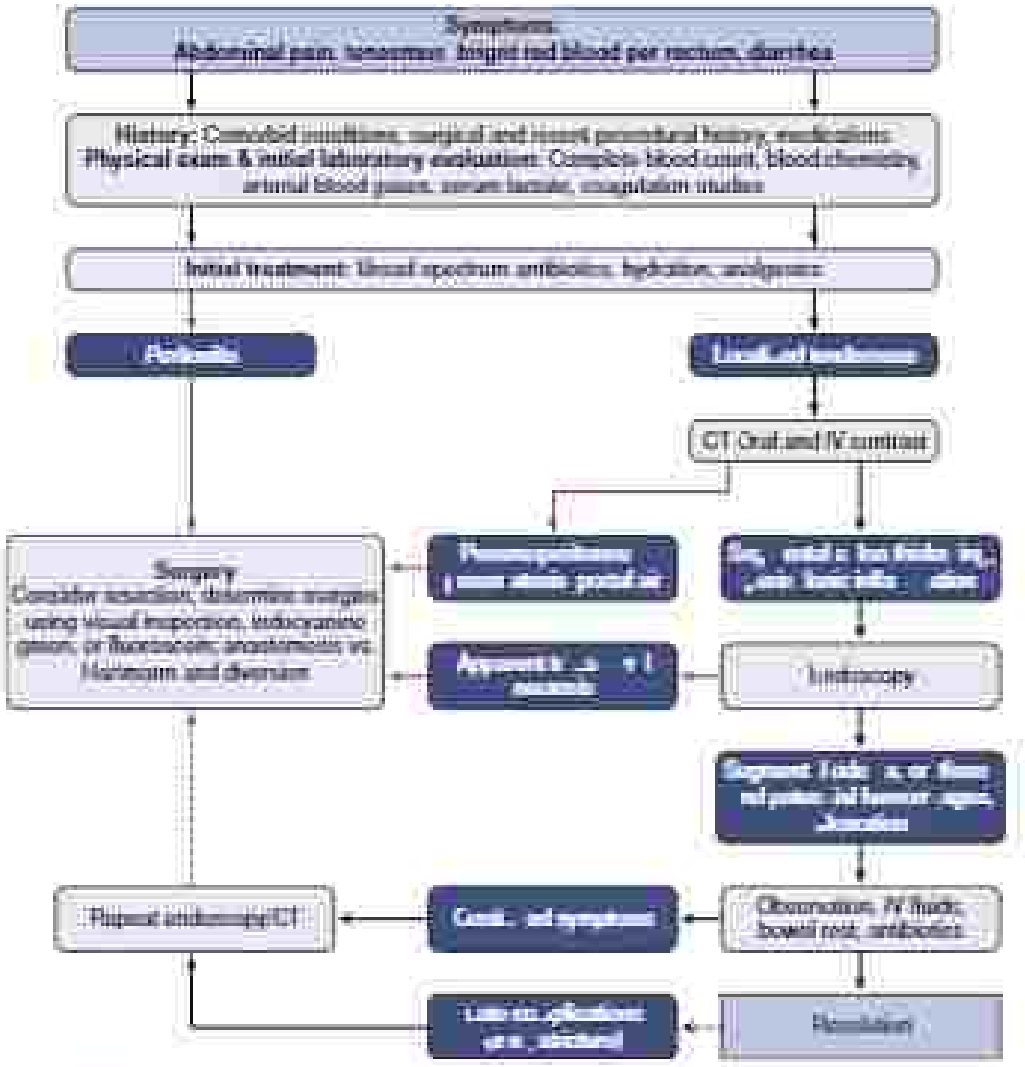

FIG. 3 Treatment algorithm for ischemic colitis. CT, Computed tomography; IV, intravenous.

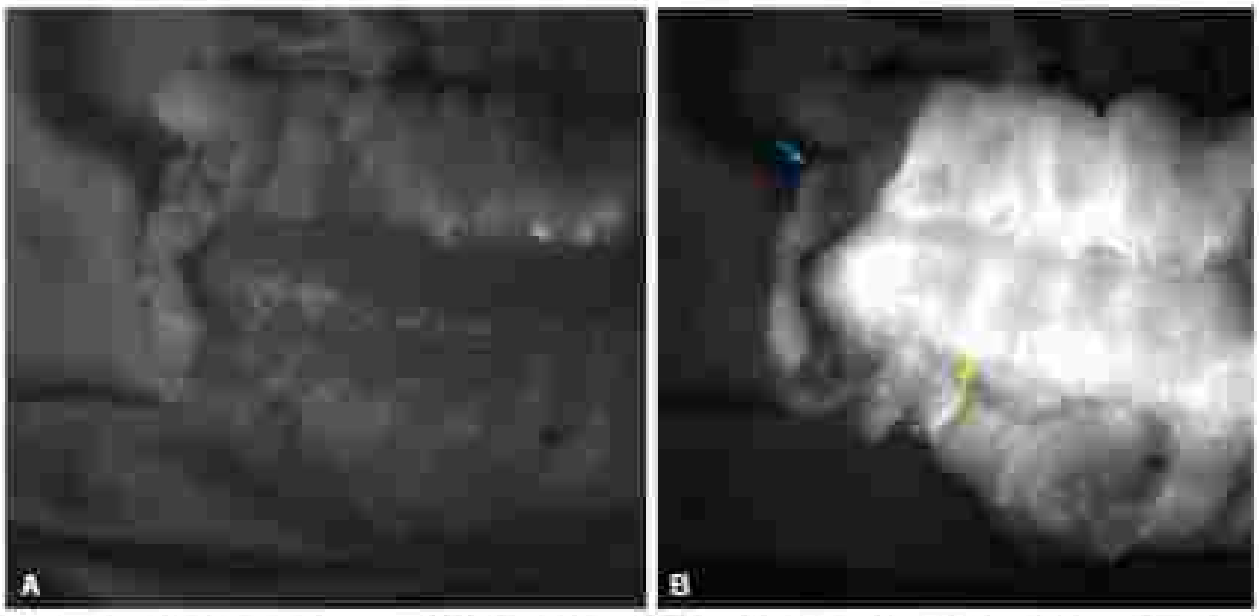

FIG. 7 Intraoperative green-based infrared angiography. (A) Colon before injection. (B) Colon after injection showing ischemia of resection margin (blue arrow) and normal perfusion of colon (yellow arrow).

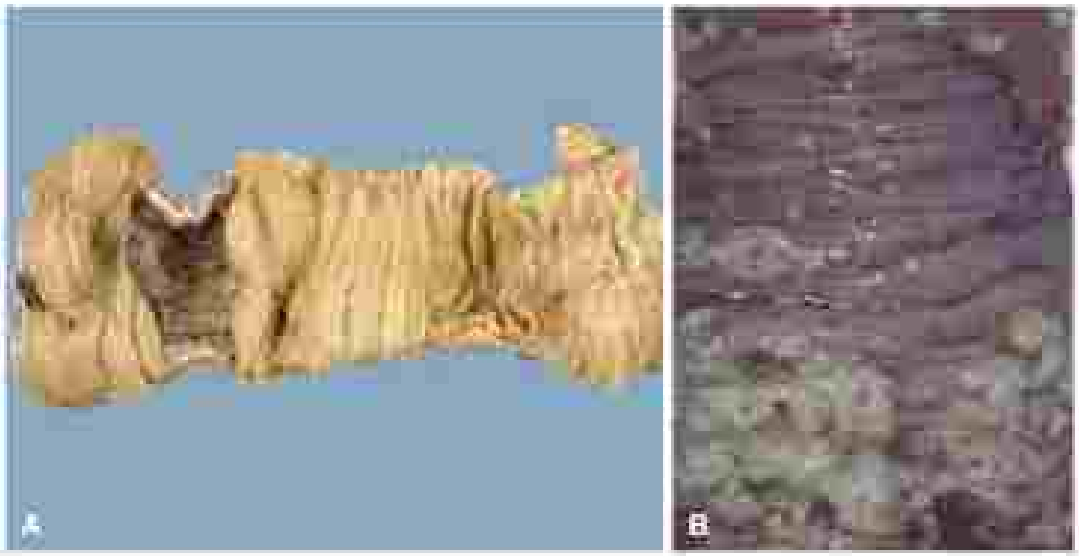

FIG. 8 (A) Surgical resection specimen displaying ischemic colitis. (B) Ischemic colitis with pseudomembranes. The luminal surface membrane must have an typical of ischemic whereas pseudomembranes of infectious processes tend to have a diffuse distribution. (B, from [illegible]; Mitchell R, Pathobiology of the Cell: An Illustrated Dynamic Encyclopedia of Disease Processes. Waltham, MA: Elsevier; 2015. B, from [illegible]. An differential diagnosis of acute colitis chart in a specific diagnosis. Surg Pathol Clin. [illegible].)

fluorescein, which was limited in that repeated assessments could not be performed because of the dye remaining in the tissue. Once the extent of ischemia is determined, resection can be performed. The surgical procedure performed is determined by the location of the affected colon. In general, it is advised that a primary anastomosis should not be performed because its integrity would be at risk due to inadequate blood flow and other physiologic derangements that exist in the setting of an emergency surgery. However, there may be circumstances in which a primary anastomosis would be appropriate given the patient's clinical condition. Right-sided disease is treated with resection followed by ileostomy and transverse colon mucous fistula or primary anastomosis. Left-sided disease is treated with segmental or left colon resection, followed by either a proximal colostomy and distal mucous fistula or a Hartmann's procedure. Subtotal colectomy with terminal ileostomy is indicated for cases of fulminant colonic ischemia. Fig. 8 shows the gross pathologic condition of patients with ischemic colitis.

After treatment, whether medical or surgical, it is important that patients be closely monitored to ensure resolution of ischemia. Most patients with mild, nonobstructive colonic ischemia clinically improve in 1 to 2 days. However, there are cases in which patients can continue to have prolonged symptoms. Some patients may have recurrent septic episodes if they have an unhealed segment of colon, which would require resection for cure. Others can develop a colonic stricture, which may be asymptomatic, but it can also lead to obstructive symptoms, which would require resection or stenting

for poor surgical candidates. Patients with chronic ischemic colitis need close attention paid to their nutritional status. For those patients who have undergone ileostomy or colostomy creation, reversal can be performed in healthy patients after 6 to 6 months. However, in this patient population, ostomy reversal was found to be associated with an in-hospitality mortality rate of 18%. For this reason, it is no surprise that approximately two-thirds of patients are never reversed due to their comorbidities.

SUMMARY

Ischemic colitis is a disease that can present with nonspecific symptoms and, on workup, is frequently associated with diagnostic results that are not pathognomonic. It can therefore be an extremely challenging disease to diagnose. Although most cases are mild in severity and can be managed medically, high clinical suspicion is needed to identify it early so that it does not escalate to a severe form requiring surgery, which is associated with much higher mortality and morbidity rates. Successful management of ischemic colitis requires the careful coordination of a healthcare team that may include internists, gastroenterologists, critical care specialists, radiologists, and surgeons.

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MANAGEMENT OF *CLOSTRIDIUM DIFFICILE* COLITIS

Rachel L. Chorun, MD, and Pamela A. Lipsett, MD, MHPE, MCCM

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EPIDEMIOLOGY

The incidence of *Clostridium difficile* infection (CDI) has increased rapidly in the past 2 decades. The Society for Healthcare Epidemiology of America (SHEA) estimates there are nine 500,000 cases of CDI in the United States each year compared with 139,000 cases in the year 2000. This expanding rate of CDI is due to the aging population, evolving usage of antibiotics, emergence of hypervirulent strains, and antibiotic resistance. Additionally, the risk of inpatient CDI has been directly related to hospital length of stay with a colonization rate of 13% at 2 weeks and 60% at 8 weeks. Overall, CDI results in $3 billion of hospitalization costs per year nationwide.

Not only has the incidence of CDI increased, but also the severity of disease and mortality has increased as well. The epidemic outbreaks of CDI in the 2000s were secondary to hypervirulent strains, most commonly ribotype 027, which caused increasingly severe infections and recurrence. Although ribotype 027 has declined markedly in parts of Europe, it is still one of the most commonly identified strains in the United States.

PATHOGENESIS

C. difficile is a gram-positive, spore-forming anaerobic bacillus that is highly resistant. It is the No. 1 cause of nosocomial infectious colitis and pseudomembranous colitis. Additionally, CDI is the major cause of nosocomial and antibiotic-associated diarrhea (10%–30%).

Transmission and Progression to Active Disease

C. difficile is transmitted by asymptomatic carriers (3% of adults) or by patients with active CDI via the fecal-oral route from hand-to-hand contact or indirectly from the colonization of patient environment. In the community, *C. difficile* has been cultured from soil, swimming pools, and both salt water and fresh bodies of water. Spores can survive weeks to years on inanimate objects. In the hospital, *C. difficile* has been cultured from telephones, call buttons, and shoes and can therefore be transmitted via healthcare providers from patient to patient.

Colonization with *C. difficile* can progress to CDI if the intestinal ecosystem is altered by antibiotics, antineoplastic agents, bowel preparations, or other agents. Postoperative patients are particularly at risk after perioperative antibiotic exposure, hospitalization, and relative immunosuppression.

Toxins

Patients with CDI typically have both toxin A and B, but they can have just one toxin. Toxin A, encoded by gene *TcdA*, is primarily an enterotoxin with many cytotoxic properties, whereas Toxin B, encoded by gene *TcdB*, is a cytotoxin that induces cytopathogenic effects. Both toxins interfere with actin cytoskeletons of intestinal epithelial cells and render them nonfunctional. They stimulate the inflammatory cascade and pro-inflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-1, IL-6, IL-8, IL-23), chemokines (CXCL1, CXCL2, IL-8), and the prostaglandin pathway leading to massive infiltration of neutrophils, macrophages, and lymphocytes in the colonic mucosa. This disrupts the intestinal epithelium with excessive leakage of fluid through the cytoskeleton and tight junctions. It also causes the appearance of pseudomembrane formation. The clinical manifestation of CDI is a result of the toxin production.

Hypervirulent Strains

The degree of toxin production is 16 to 20 times higher in hypervirulent strains of *C. difficile*. In turn, these hypervirulent strains have a fivefold increase in mortality. The most common hypervirulent strain, NAP1/027 or polymerase chain reaction ribotype 027, was discovered in 1981 and has been associated with fluoroquinolone resistance, a lower response to felodipine, epidemic outbreaks, and increased mortality. Cytolethal distending toxin, also known as binary toxin, has been found in 6% to 12% of toxinogenic strains and the ribotype 027 hypervirulent strain. There is a polymerase chain reaction test for cytolethal distending toxin that can help identify the ribotype 027 strain.

for poor surgical candidates. Patients with chronic ischemic colitis need close attention paid to their nutritional status. For those patients who have undergone ileostomy or colostomy creation, reversal can be performed in healthy patients after 6 to 6 months. However, in this patient population, ostomy reversal was found to be associated with an in-hospital mortality rate of 18%. For this reason, it is no surprise that approximately two-thirds of patients are never reversed due to their comorbidities.

SUMMARY

Ischemic colitis is a disease that can present with nonspecific symptoms and, on workup, is frequently associated with diagnostic results that are not pathognomonic. It can therefore be an extremely challenging disease to diagnose. Although most cases are mild in severity and can be managed medically, high clinical suspicion is needed to identify it early so that it does not escalate to a severe form requiring surgery, which is associated with much higher mortality and morbidity rates. Successful management of ischemic colitis requires the careful coordination of a healthcare team that may include internists, gastroenterologists, critical care specialists, radiologists, and surgeons.

SUGGESTED READINGS

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BOX 1 Risk Factors Associated with *Clostridium difficile* Infection

Primary Risk Factors

Age >65 years
Recent antibiotic use
Hospitalization

Secondary Risk Factors

Female gender
Double occupancy room
Intensive care unit admission
Long-term care facility admission
Acid-reducing therapy (proton pump inhibitors or histamine (receptor blockers)
Gastrointestinal procedures
Immunosuppression
Chemotherapy
Renal disorders
Organ transplantation
HIV infection
Autoimmune disease
Hypoalbuminemia
Inflammatory bowel disease

Primary Risk Factors

Patients are at increased risk for CDI if they have a source of colonization along with a change in their intestinal microbiogenesis, especially in the setting of immunocompromise or debility. Altered immunity can determine colonization versus clinical disease. Patients are also at greater risk for CDI when exposed to longer antibiotic durations, although a single antibiotic dose has been reported to cause CDI as well. Although initially attributed to clindamycin, any antibiotic can cause CDI; most commonly, penicillins, cephalosporins, and fluoroquinolones are responsible.

There is an epidemiologic association between proton pump inhibitor use and CDI; therefore, it is recommended to discontinue any unnecessary proton pump inhibitors.

The recurrence rate of CDI has been reported as high as 20%. Risks associated with recurrence are prolonged antibiotic use, prolonged hospitalization, age greater than 65 years, diverticulosis, and comorbid issues (Box 1).

Mortality

The incidence, severity, and mortality of CDI continue to increase over time. Predictors of mortality identified prospectively are older age, elevated lactate, delayed operative intervention, vasopressor use, and acute renal failure.

CLINICAL PRESENTATION

Because *C difficile* is a normal isolate from the gastrointestinal track, the stool presence does not signify the presence of disease. The clinical manifestations of CDI can vary with a wide spectrum of symptoms. Some patients have mild diarrhea compared with others with more severe disease, including toxic megacolon, multisystem organ failure, and death. Symptoms can manifest as early as the first day of antibiotic use; alternatively, symptoms can begin up to 4 weeks after completion of antibiotics.

CDI is now classified as nonsevere disease, severe disease, fulminant disease, and recurrence (Table 1).

Nonsevere Disease

Nonsevere disease has been described as diarrhea without systemic symptoms. Patients with nonsevere CDI typically have a white blood cell (WBC) count less than 15,000 cells/mL and a serum creatinine level lower than 1.5 mg/dL. These patients have less than 10 nonbloody stools per day and cramping.

TABLE 1 Differentiating CDI Based on Severity of Illness

Nonsevere CDI	Hemodynamically stable (HR <90 beats/min, SBP >100 mm Hg) Afebrile (<101.5°F) WBC 12,000–15,000 cells/mL Normal lactate Oliguria, but volume responsive Mild abdominal tenderness Pseudomembranes on colonoscopy Colonic thickening on CT scan
Severe CDI	Tachycardic without hypotension (HR >90 beats/min, SBP >100 mm Hg) Febrile WBC >15,000 cells/mL Creatinine >1.5 mg/dL Moderate abdominal tenderness
Fulminant CDI	Shock with hypotension Need for vasopressors Ventilator dependence Severe oliguria Perforation Toxic megacolon

CDI, *Clostridium difficile* infection; HR, heart rate; SBP, systolic blood pressure; WBC, white blood cell.

Severe Disease

Severe disease presents with profuse diarrhea, abdominal distention or pain, fever, tachycardia, oliguria, WBC greater than 15,000 cells/mL, and serum creatinine greater than 1.5 mg/dL. These patients are typically volume responsive to resuscitation.

Fulminant Disease

Fulminant disease has been previously called severe or complicated CDI. It is associated with hypotension or shock. Patients with fulminant CDI can also have an ileus, toxic megacolon, occult bleeding, or severe oliguria. These patients often require vasopressor support and mechanical ventilation. Fulminant disease has been increasing in incidence and severity and now accounts for 3% to 5% of all *C difficile* infections.

If not present initially, fulminant disease can lead to ileus, toxic megacolon, intestinal perforation, and death. Mortality rates for patients with fulminant CDI range from 30% to 90%. When fulminant CDI is concomitant with organ failure, shock, hypotension, ileus, or megacolon, CDI should be considered life threatening.

CDI does not always manifest with diarrheal symptoms and is often underdiagnosed in that patient population. CDI should be considered in patients with a fever without a known source, unexplained leukocytosis, distended abdomen, recent antibiotic use, or admitted to the intensive care unit. Up to 37% of patients with fulminant CDI can present without diarrhea secondary to an ileus.

Recurrence

Rates of CDI recurrence range between 6% and 67% within the first 2 weeks after completion of initial antibiotic treatment. The risk of recurrence increases further with each subsequent case of recurrence.

TABLE 2 Available Diagnostic Tests for CDI

Test	Sensitivity	Specificity	Substance Detected
Toxigenic culture	High	Low	*C. difficile* vegetative cells or spores
Nucleic acid amplification tests	High	Low/moderate	*C. difficile* toxin genes
Glutamate dehydrogenase	High	Low	*C. difficile* common antigen
Cell culture cytotoxicity neutralization assay	High	High	Free toxins
Toxin A and B enzyme immunoassays	Low	Moderate	Free toxins

CDI, *Clostridium difficile* infection.
Modified from the 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).

DIAGNOSIS OF CDI

Prompt diagnosis of CDI is imperative because a delay in diagnosis and treatment correlates with increased mortality. Current recommendations suggest diagnostic testing should be pursued in patients with three or more new, unexplained, unformed stools over 24 hours.

Stool Studies

There are multiple types of stool studies to detect CDI (Table 2). The Nucleic Acid Amplification Test (NAAT) is the most sensitive test for patients likely to have CDI based on their clinical symptoms; however, it can also detect *C. difficile* carriers without infection. The glutamate dehydrogenase (GDH) antigen test is less commonly used but is rapid, inexpensive, and easy to perform. It has poor sensitivity but a negative result strongly rules out CDI. A positive GDH result alone does not meet criteria to diagnose CDI. Enzyme immunoassays for toxins A and B are commonly used. This test has a specificity of 94% to 100% for the presence of clinically relevant CDI, but it is less sensitive (65%–94%).

Overall, stool studies in patients with CDI have the best positive and negative predictive values for detecting CDI. The use of a stool toxin test should be used in a multistep algorithm: GDH plus toxin, GDH plus toxin arbitrated by NAAT, or NAAT plus toxin.

Laboratory Tests

A leukocytosis greater than 30,000 is typically uncommon in most bacterial infection. An elevated leukocytosis of this magnitude should raise suspicion for CDI. An elevated lactate and abnormal albumin can help identify patients with severe and fulminant CDI.

Imaging

X-ray imaging can detect ileus, colonic dilation, colonic wall edema, thumb printing, haustral thickening, and toxic megacolon, which can be findings consistent with CDI. Computed tomography (CT) scan is a sensitive test for patients presenting with severe or fulminant CDI. Findings consistent with CDI found on CT scan include diffuse colonic thickening, pericolonic stranding, pancolitis, and megacolon. The entire colon may be involved with CDI even when fulminant CDI may be isolated to the right colon on imaging (Fig. 1). The accordion sign can also be identified on CT scan, which is intraluminal contrast or air outlined by a thickened mucosa.

Endoscopy

When evaluating the colon for CDI via endoscopy, colonoscopy is preferred over sigmoidoscopy because colitis, as noted previously can be limited to the right colon in up to one third of patients with CDI. Ulcers, plaques, and pseudomembranes can be seen in 50% of patients with fulminant CDI and 25% of patients with mild CDI. Pseudomembranes are pathognomonic and appear as raised, yellowish lesions that are 2 to 10 mm in size with skipped areas of normal mucosa. In fulminant CDI these lesions coalesce to form plaques. Colonoscopy can be diagnostic but also therapeutic when a large colonic decompression tube is placed that can also be used for vancomycin enema irrigation.

Diagnostic Recommendations

Current recommendations published in 2018 from SHEA and Infectious Diseases Society of America define CDI as the presence of symptoms (typically diarrhea) and either a stool test positive for toxin or new detection of toxigenic *C. difficile* or colonoscopic or histopathologic findings revealing pseudomembranous colitis.

A multidisciplinary approach with surgical consultation to evaluate the severity of CDI is a critical strategy to determine appropriate medical and surgical management. Literature has revealed early surgical consultation has shown to be beneficial even when not resulting in a surgical procedure.

MEDICAL TREATMENT

With the increase in resistance of *C. difficile*, there has been increased incidence, severity, and mortality of CDI over time. The treatment of CDI is based on the severity of disease (Table 3).

Infection Prevention and Control

A critical aspect of CDI management is a robust prevention program with two tiers. The first is focused on the avoidance of inoculation via measures such as hand washing and isolation precautions. The second is minimizing medical interventions that put patients at risk for developing CDI (Box 2).

Medical Therapy

Offending antibiotic agents should be stopped in patients with CDI if it is deemed medically safe and appropriate to do so; this will in turn decrease the risk of CDI recurrence. Antidiarrheals as well as narcotics should be avoided to minimize the development of toxic megacolon. Empiric antibiotic therapy should be initiated if there is high suspicion for CDI because delay in confirmatory diagnostic testing and treatment leads to increased mortality.

Nonsevere Disease

A patient with an initial episode of nonsevere CDI should receive oral vancomycin 125 mg every 6 hours or oral fidaxomicin 200 mg every 12 hours for 10 days. Although oral metronidazole is no longer considered a first-line agent for CDI, if vancomycin nor fidaxomicin is available, oral metronidazole 500 mg every 8 hours can be prescribed.

Severe Disease

In patients with an initial episode of severe CDI, oral vancomycin 125 mg every 6 hours or oral fidaxomicin 200 mg every 12 hours should be initiated for 10 days.

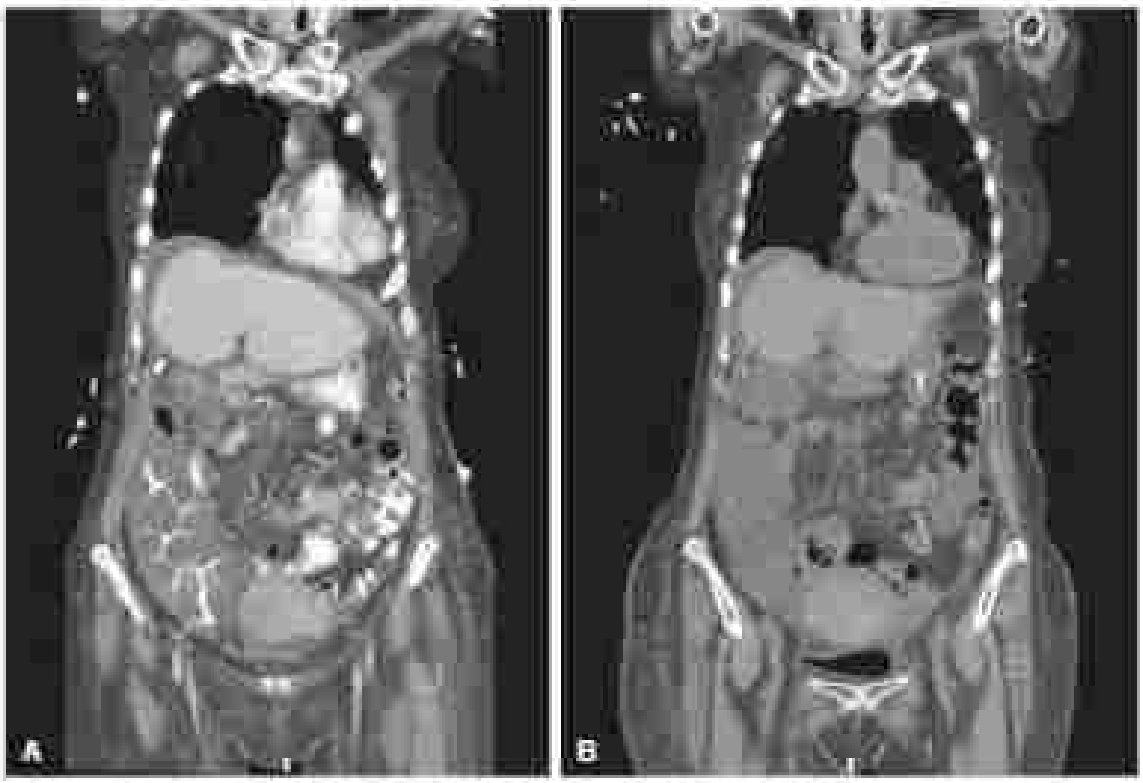

FIG. 1 Computed tomography scan showing fulminant Clostridium difficile infection of the right colon. (A) With contrast versus (B) without contrast reveals the importance of contrast utilization with imaging for diagnosis.

TABLE 3 Medical Management of CDI

Clinical Presentation	Recommended Treatment
Nonsevere, initial episode	1. Oral vancomycin 125 mg every 6 hours for 10 days, *or* 2. Fidaxomicin 200 mg every 12 hours for 10 days 3. If agents 1 and 2 are unavailable, oral metronidazole 500 mg every 8 hours for 10 days
Severe, initial episode	1. Oral vancomycin 125 mg every 6 hours for 10 days, *or* 2. Fidaxomicin 200 mg every 12 hours for 10 days
Fulminant, initial episode	1. Oral vancomycin 500 mg every 6 hours, and 2. Intravenous metronidazole 500 mg every 8 hours 3. If ileus present, consider rectal vancomycin
First recurrence	1. Prolonged tapered and pulsed oral vancomycin regimen if vancomycin was used for initial episode 2. Fidaxomicin 200 mg every 12 hours for 10 days if vancomycin was used for initial episode 3. Oral vancomycin 125 mg every 6 hours for 10 days if metronidazole was used for initial episode
Second or subsequent recurrence	1. Vancomycin in a tapered pulsed regimen, *or* 2. Vancomycin 125 mg every 6 hours for 10 days followed by rifaximin 400 mg every 8 hours for 20 days, *or* 3. Fidaxomicin 200 mg every 12 hours for 10 days, *or* 4. Fecal microbial transplantation

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Fulminant CDI

In the setting of fulminant CDI, the patient should be started on oral vancomycin 500 mg every 6 hours and intravenous metronidazole 500 mg every 8 hours. If the patient is unable to take oral medications, oral vancomycin can be administered via a nasogastric tube. If the patient has an ileus, the addition of rectal vancomycin enemas can be considered. In critically ill patients with fulminant CDI, studies have shown combination therapy decreases mortality.

Recurrence

Treatment of the first recurrence is based on what the patient was treated with during the initial episode. If oral vancomycin was used initially, oral fidaxomicin 200 mg every 12 hours for 10 days can be used or a prolonged taper of pulsed oral vancomycin (i.e., 125 mg every 6 hours for 10–14 days, every 12 hours for 7 days, every 2–3 days for 2–8 weeks). Although metronidazole is no longer recommended as a first-line agent in the treatment of CDI, if this was given

BOX 1 Infection Prevention and Control

Prevention/Avoidance of Inoculation

Minimize frequency and duration of antibiotics
Minimize number of antibiotics prescribed
Implement antibiotic stewardship program
- Consider restriction of fluoroquinolones, clindamycin, and cephalosporins (when not used for surgical prophylaxis)
- Discontinue unnecessary anti-acid reducing therapies

Patients With C. difficile Infection

Hand hygiene with soap and water before and after contact
Private room with dedicated toilet
If cohorting is required, cohort infected/colonized patients with the same organism
Preemptive contact precautions once C. difficile testing is ordered
Healthcare personnel must use gloves and gowns
Prolong contact precautions until discharge
Patients should wash their hands and shower to reduce spore burden
Use disposable patient equipment (stethoscopes, etc.)
Daily and terminal room cleaning with sporicidal disinfectant

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In patients that have a second or subsequent recurrence, there are three medical regimens (therapies currently recommended: a prolonged taper of pulsed oral vancomycin, oral vancomycin 125 mg every 6 hours for 10 days followed by rifaximin 400 mg every 8 hours for 20 days, or fidaxomicin 200 mg every 12 hours for 10 days.

Fecal Microbial Transplant

If antibiotic therapy has failed after multiple recurrences, fecal microbial transplant (FMT) has been reported as safe and effective. It was first described in 1983 and has a reported success rate of greater than 90%. Donor FMT has proved safe and more effective than autologous FMT and therefore careful donor selection is important when considering and managing a communicable disease.

FMT can be administered via nasogastric tube, upper endoscopy, enema, or colonoscopy. A randomized controlled trial published in 2017 determined FMT delivered via oral capsule was not inferior to delivery via colonoscopy in preventing CDI over 12 weeks.

SURGICAL TREATMENT

Although an average of only 1% of all patients with CDI undergo emergent surgical intervention, about 30% of patients with fulminant CDI require urgent surgery. Surgical intervention is becoming even more important in the setting of increasingly resistant *C. difficile* spores and hypervirulent strain evolution resulting in an increased incidence of fulminant CDI. A meta-analysis published in 2012 revealed 41% mortality in patients requiring emergency surgery for CDI.

Despite multiple attempts to create and identify early markers indicating the need for surgical intervention, high morbidity and mortality rates remain. Therefore, a multidisciplinary approach with early surgical consultation to evaluate severity of CDI and determine the need for surgical management is critical.

Decision to Operate

If aggressive surgical treatment is needed, early identification of this is imperative because delayed intervention results in increased mortality. Patients diagnosed with fulminant CDI should be adequately resuscitated and empiric combination antibiotic therapy should be initiated to decrease mortality.

The decision to operate on a patient with CDI should be well thought out. The strongest predictors of postoperative mortality are related to preoperative physiologic status. Patients presenting with preoperative acute renal failure, intubation, multisystem organ failure, or shock requiring vasopressor have high postoperative mortality and should therefore prompt serious consideration for early surgical intervention.

Indications

Immediate indications for operative intervention include peritonitis, perforation, toxic megacolon, and recalcitrant severe colitis. Typically, toxic megacolon that presents with a cecal diameter greater than 12 cm or a colonic diameter greater than 6 cm on radiographic imaging should warrant surgical consideration. Additionally, and not uncommonly, patients with CDI and toxic megacolon may lack diarrheal symptoms and can present atypically. Therefore, there should be a low threshold for surgical management in the setting of toxic megacolon.

Additional indications for surgical management that are not as well defined include fulminant CDI or failure of medical therapy within 48 to 72 hours in the setting of continued toxicity. In patients with fulminant CDI that also have inflammatory bowel disease or are older than 65 years, failure of medical therapy after 12 hours should warrant consideration for operation.

Preparation for Operative Intervention

When preparing a patient with CDI for the operating room, invasive cardiopulmonary monitoring with an arterial line and central venous access is recommended. Aggressive fluid resuscitation is critical and antibiotic delivery is imperative. Although it is not always possible, consultation with an interventional specialist is ideal for operative intervention planning. Additionally, reservation of an intensive care unit bed should be pursued for postoperative management of these critically ill patients.

Total Colectomy with End Ileostomy

Historically open total colectomy with end ileostomy has been the procedure of choice for fulminant CDI. It has been established segmental resection should not be considered even if disease is believed to be confined to one area of the colon. Ugwuh et al. found significantly improved mortality when total colectomy was performed in comparison to segmental resection.

Operative Approach

Open resection is typically recommended to facilitate the most expedient resection; however, a laparoscopic approach could be considered in a stable subset of patients. On entry into the abdomen, the colon typically will not appear necrotic; it can be edematous and boggy with significant inflammation and ascites. Nonetheless, a total colectomy should be performed by removing the intraperitoneal portion of the colon and dividing the rectum at the peritoneal reflection with a stapling device. The mesentery can be ligated with a clamp and tie technique or bipolar or ultrasonic tissue sealing and cutting devices. The omentum can be removed from the colon or divided and resected from the colon, whichever suits expedition.

In the setting of fulminant CDI in critically ill patients, anastomosis is not recommended. The distal ileum should be brought through a facial opening and maturation of the stoma completed after abdominal closure. Occasionally, a patient may have such edematous bowel that fascial closure cannot be accomplished and a damage control technique needs to be used. In this scenario, the abdomen should be temporarily closed with a vacuum device with delayed maturation of the stoma and abdominal closure on take-back laparotomy.

Stoma Reversal

The overall stoma reversal rates in patients' status after total colectomy and end ileostomy for CDI are only 29% to 35% with a 258-day median interval of closure. Although most patients do not undergo

reversal, patients that have undergone a total colectomy and ileostomy in the setting of fulminant CDI can be considered for stoma reversal after full recovery.

Mortality after Colectomy

Patients who undergo colectomy for CDI have a 34% to 57% mortality. Some of the contributing factors that result in this mortality rate are delay in initial diagnosis, delay in surgical consultation, poor patient selection, and delay to surgical intervention. Other factors that are associated with mortality after colectomy for CDI are preoperative shock, preoperative dialysis dependence, chronic obstructive pulmonary disease, wound class III, thrombocytopenia with platelets less than 150 × 10⁹/L, coagulopathy with international normalized ratio greater than 2, and renal insufficiency with blood urea nitrogen greater than 40 mg/dL. Patients older than age 80 years have a threefold increase in mortality and patients requiring intubation or vasopressors have a mortality rate greater than 50% after colectomy for CDI.

Although mortality rates remain high for patients with CDI undergoing total colectomy, treatment with colectomy improves outcome over medical management alone in patients with fulminant CDI. Emergency colectomy has been shown to improve mortality in critically ill patients with fulminant CDI.

Overall, total colectomy can be a time consuming operative course with blood loss intraoperatively, which is challenging in physiologically disturbed patients. Long-term 5-year survival after surgery for fulminant CDI has been reported as low as 36%. Of those survivors, only 20% had bowel continuity restored with stoma reversal.

Antibiotic Therapy After Colectomy

Currently, there are no established practice guidelines for postoperative antibiotic use in fulminant CDI after total abdominal colectomy. A multicenter retrospective study in 2015 compared four different antibiotic regimens: oral vancomycin, intravenous metronidazole and oral vancomycin, intravenous metronidazole alone, or intravenous metronidazole and vancomycin per rectum in postoperative fulminant patients with CDI status post total colectomy with end ileostomy. They found intravenous metronidazole with or without oral vancomycin was associated with shorter intensive care unit length of stay and more ventilator free days. They did not find evidence to support routine treatment greater than 7 days. They concluded patients should be treated with either oral vancomycin or intravenous metronidazole and proctitis can be treated with the additional of vancomycin per rectum.

Laparoscopic Diverting Loop Ileostomy

Although total colectomy with end ileostomy has a survival advantage over medical management alone in patients with fulminant CDI, it is still associated with high mortality rate and low stoma reversal rates; therefore, alternative surgical approaches to this problem have been studied. University of Pittsburgh developed a protocol for this population of critically ill patients with fulminant CDI. It involves emergency surgery to construct a diverting loop ileostomy, typically completed laparoscopically. This is followed by colonic irrigation with warmed polyethylene glycol 3350 electrolyte solution via the ileostomy intraoperatively. Postoperative antegrade irrigation with vancomycin solution through the ileostomy for 10 days is performed. Their data published in 2011 showed decreased mortality using this surgical strategy with high stoma closure rates.

The loop ileostomy with colonic washout and high-dose vancomycin enemas presents an attractive surgical option because it results in a less intensive surgical procedure in unstable patients. Additionally, it is associated with decreased operative times and decreased blood loss as compared to total colectomy. Neal et al. found this protocol allowed for ostomy reversal procedures with relatively easy surgical reconstruction after life-threatening disease was resolved. They reported a colonic preservation rate of 93%. Most importantly, when comparing study patients with historical patients that underwent traditional total colectomy with end ileostomy for fulminant CDI, there was significantly decreased mortality in the diversion group.

A retrospective multicenter American Association for the Surgery of Trauma trial published in 2017 reviewed 10 centers' surgical experience in patients with CDI from 2010 through 2014. They compared patients who underwent total colectomy vs loop ileostomy. After adjusting for preoperative confounders, the loop ileostomy group was found to have a significantly lower mortality (17.2% versus 39.2%). The loop ileostomy group required fewer intraoperative transfusions and had less intraoperative blood loss. Although not reaching significance, they found a higher absolute reoperation rate and unplanned operation rate in the loop ileostomy group. They concluded loop ileostomy has survival benefit and should be considered for patients without contraindications to loop ileostomy.

Although these studies promote the use of loop ileostomy and vancomycin enema therapy in fulminant CDI, there are downsides to this intervention as well. Several studies have shown patients are at risk for CDI recurrence after ostomy reversal and reanastomosis. There have also been studies that did not reveal any mortality difference between loop ileostomy and total colectomy but did reveal a higher recurrence of CDI with colonic preservation.

Currently the role for surgical intervention in the setting of CDI recurrence is unclear.

Ongoing Studies

Although the surgical standard of care for patients with fulminant CDI has historically been a total colectomy with end ileostomy, the 30-day mortality following surgical intervention remains high ranging from 30% to 70%. Alternative approaches to management have been studied using fecal diversion via laparoscopic loop ileostomy creation followed by direct colonic lavage with polyethylene glycol and vancomycin. This has demonstrated a relative mortality reduction of about 50%.

There is a study underway that is building on this foundation of literature. The protocol involves bedside lavage with polyethylene glycol and vancomycin via nasojejunal tube in addition to usual antibiotic management compared with antibiotic management alone.

CDI IN INFLAMMATORY BOWEL DISEASE

It is well established that CDI is increased in patients with inflammatory bowel disease (IBD), particularly in ulcerative colitis. Patients with IBD contract CDI more often as an outpatient than patients without IBD. Patients with IBD with CDI have increased hospital length of stay, greater need for surgical intervention, higher mortality, and higher mortality independent of surgical intervention.

An IBD flare can mimic the symptoms of CDI; therefore, CDI should be considered in relapsing or worsening IBD. Additionally, patients with IBD with restorative proctocolectomy or diverting ileostomy are not immune to CDI. It can cause enteritis on the small bowel or the ileal pouch.

Treatment of CDI in IBD

Although oral vancomycin is a first-line treatment for all patients with CDI now, it is also established as the first-line therapy for patients with IBD with CDI. In the setting of fulminant CDI, intravenous metronidazole can be added to oral vancomycin.

Patients treated with a combination of immunomodulators and antibiotics have more adverse outcomes than those treated with antibiotics alone. Steroids, immunomodulators, and broad-spectrum antibiotics should be minimized if possible. Additionally, biologic agents do not appear to increase the acquisition of CDI. Overall, there should be a low threshold for total colectomy with ileostomy in severe and fulminant CDI to be followed by restorative surgery after full recovery.

C. DIFFICILE ENTERITIS

Although it is uncommon, CDI of the small bowel can manifest in a number of ways. It can occur as pouchitis in patients with an ileal J pouch after restorative proctocolectomy for familial polyposis or ulcerative colitis. It can even occur in patients after colectomy with end ileostomy. Persistent CDI enteritis should be considered in patients with high ostomy output with unexplained systemic inflammatory response.

Treatment for patients with CDI enteritis involves oral vancomycin or metronidazole as well as supportive care. Additionally, fecal microbial transplantation has been reported as successful in treating patients with CDI pouchitis.

CONCLUSION

With increasing incidence and severity of CDI, surgeons need to be familiar with the management of CDI. CDI should be considered in any patient with recent antibiotic use, unexplained abdominal pain, distention, fever, or leukocytosis, even in the absence of diarrhea. The need for early recognition of CDI that requires surgical management is important to improve outcomes and mortality; therefore, a multidisciplinary approach with early surgical consultation should be used to establish diagnosis and treatment.

Surgeons should be familiar with medical treatment, fecal microbial transplantation, and surgical treatment for CDI. If patients present with peritonitis, perforation, or fulminant CDI, the first consideration should be operative intervention. Additionally, there should be strong surgical consideration in patients who fail medical management. Although historically total colectomy with ileostomy is the accepted procedure of choice, laparoscopic diverting ileostomy with polyethylene glycol lavage and antegrade vancomycin is emerging as a promising treatment option for fulminant CDI.

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Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P, West Midlands Research Collaborative. Systematic review and meta-analysis of outcomes following emergency surgery for *Clostridium difficile* colitis. *Br J Surg* 2012;99(11):1521–1531.

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MANAGEMENT OF LARGE BOWEL OBSTRUCTION

Susan L. Gearhart, MD, and Matthew P. Kelley, MD

Large bowel obstruction is a serious and common disorder that requires prompt attention. Emergency surgery for large bowel obstruction represents approximately 28% of the acute care surgeon's workload. The presentation is often inconsistent because of the variety of causes, and the diagnosis can easily be overlooked. The mortality associated with a large bowel obstruction is reportedly 14% to 17%. The surgeon should be able to establish a prompt diagnosis, be familiar with both benign and malignant causes, and be adept at determining the appropriate management plan.

ETIOLOGY

The cause of large bowel obstruction can be categorized broadly as mechanical or functional. Mechanical obstruction is more common and often results from a neoplastic process resulting in either an intrinsic or extrinsic compression. An intrinsic colorectal adenocarcinoma is the most common etiology and accounts for nearly 30% of large bowel obstructions. The most common site of an intrinsic malignant obstruction is the descending colon or rectosigmoid. Common etiologies for intrinsic and extrinsic lesions are shown in Box 1.

Diverticular disease is the second most common cause of large bowel obstruction. Chronic inflammation in the sigmoid colon can lead to a stricture in up to 17% of patients. The third most common cause of large bowel obstruction is volvulus and occurs in 5% of patients. Volvulus is the result of a long, redundant segment of colon that has developed an axial rotation of the bowel around the colonic mesentery. The most common location for volvulus is the sigmoid colon (60%–75%) followed by the cecum (25%–40%) and, rarely, the transverse colon (1%–8%).

Functional causes of large bowel obstruction include colonic pseudo-obstruction (Ogilvie's syndrome), narcotic-induced adynamic ileus, and an adynamic ileus caused by a systemic illness such as toxic ingestion from *Clostridium difficile* infection. Treating the underlying cause in functional large bowel obstruction often improves symptoms.

CLINICAL PRESENTATION

Large bowel obstruction can present with a wide range of symptoms depending on the acuity of the obstruction. The typical symptoms early on include lower abdominal pain, distention, and obstipation. Emesis is usually a late presentation of a large bowel obstruction and may not happen if the patient has a competent ileocecal valve. Often, acute large bowel obstruction is associated with signs of hypovolemia and electrolyte imbalances secondary to fluid sequestration in the intestines. Symptoms from chronic obstruction are typically mild and often associated with change in bowel habits, bloating, narrow caliber stools, and unintentional weight loss. The constellation of findings raises suspicion for malignancy.

DIAGNOSIS

History and Physical Examination

Rapid evaluation and diagnosis beginning with a focused history and physical examination should occur in patients presenting with signs and symptoms of a large bowel obstruction. Patients may report a rapid or slow progression of their symptoms depending on the etiology. Recent orthopedic or gynecologic procedures are commonly associated with the development of colonic pseudo-obstruction. A family or personal history of colonic neoplasms should be ascertained. A review of current medications may indicate prescription medications induced constipation.

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BOX 1 Common Etiologies for Intrinsic and Extrinsic Lesions

Extrinsic

Malignancy (e.g., ovarian cancer)
Endometriosis
Uterus
Pelvic abscess/inflammation

Intrinsic

Colon cancer
Diverticular stricture
Inflammatory bowel disease
Ischemia
Radiation

The physical examination classically reveals a tympanitic and distended abdomen. On occasion, a mass can be palpated through the abdominal wall. Diffuse tenderness is common and may raise the suspicion for possible peritonitis. Focal tenderness may suggest ischemia or localized perforation. Digital rectal examination should be performed on all patients to rule out fecal impaction, foreign body, or anorectal malignancy as the cause.

Imaging

When a patient presents acutely with abdominal pain, distension, obstipation, nausea, and vomiting, bowel obstruction is the leading consideration. Because of ease in accessibility, upright and supine abdominal (kidney, ureter, and bladder) radiographs are often the first images obtained. For the diagnosis of large bowel obstruction, kidney, ureter, and bladder radiographic images have a sensitivity and specificity of 88% and 72%, respectively. Abdominal radiographs can quickly assess the diameter of the colon and indicate the presence of pneumatosis coli or pneumoperitoneum, allowing for a quick decision regarding the care of the patient. Cecal dimension beyond 9 cm and colonic distension beyond 6 cm is indicative of a large bowel obstruction. Colonic volvulus can also be identified with abdominal radiographs. The classic findings of a sigmoid volvulus are seen in about two thirds of patients and are commonly described as the "bent inner tube" sign or "coffee bean" sign.

Contrast enemas (CEs) were once the gold standard in the diagnosis of large bowel obstruction. CEs have a 96% sensitivity and a 98% specificity for diagnosing large bowel obstruction. Classic findings is a "bird's beak" deformity at the site of a volvulus or an "apple core lesion" at the site of an obstructing cancer. However, because these tests are labor intensive and require additional time, CEs have mostly been abandoned. Computed tomography (CT) has become the most important imaging modality in the evaluation of a patient with signs and symptoms of a large bowel obstruction. CT confirms the diagnosis of large bowel obstruction with almost 100% sensitivity and 90% specificity, it also allows multiplanar reconstruction that further facilitates the definitive diagnosis. Finally, CT may have a substantial impact on the clinical management of a large bowel obstruction by demonstrating signs of intestinal ischemia, early perforations, or pneumoperitoneum leading to sooner interventions.

Although magnetic resonance imaging in the acute management of large bowel obstruction is not typically indicated, the emergence of magnetic resonance enterography with advanced cross-sectional characterization of the bowel particularly in inflammatory disease has been shown to be beneficial and correlates well with endoscopic findings. Furthermore, pelvic magnetic resonance imaging with rectal contrast is valuable in the diagnosis of rectal intussusception (dynamic imaging) and in the local staging of rectal cancer.

TREATMENT

Initial Management

In concert with the initial history and physical, laboratory assessment should include serum chemistry and electrolytes, complete blood count, and lactate level. Hypovolemia and electrolyte imbalances are common and should prompt aggressive resuscitation with accurate monitoring of intake and output with a urinary catheter. Decompression with a nasogastric tube should be performed early. If surgery is a consideration, preoperative antibiotics and stoma marking should occur as an entirety is frequently required.

Surgical Techniques: Colostomy

A diverting loop colostomy may be indicated if the patient is severely unstable, there is diffuse carcinomatosis, or a severe inflammatory/malignant process precludes resection. The best approach in this setting is a midline laparotomy that allows for decompression of the bowel, prompt identification of the lesion, and adequate exposure for a variety of procedures. Laparoscopic intervention may be difficult secondary to colonic distension. A loop colostomy is preferred over an end colostomy as the blind end that is left in the abdomen may perforate. A colostomy relieves patients of their symptoms and limits subsequent concerns for an anastomotic leak. However, colostomies can be associated with significant morbidity, including high rates of parastomal hernia (50%), decreased quality of life, and low rates of stoma closure.

Segmental Resection and Hartmann's Procedure

In patients with a right sided obstruction and the point of obstruction is proximal to the splenic flexure, urgent right hemicolectomy with primary anastomosis should be considered and can often be performed laparoscopically in a stable patient with limited bowel distension. This procedure is associated with low anastomotic leak rates (<5%) in a hemodynamically stable patient who has not undergone a bowel preparation.

There is more debate regarding the preferred surgical procedure for an obstructing lesion arising in the descending, sigmoid colon, rectum, or anus. Traditionally, primary anastomosis at the initial procedure was avoided because of the higher rates of anastomotic leak (20%). If the patient is unstable, has significant dilation of the proximal colon, or has multiple comorbidities (including pregnancy), Hartmann's procedure should be performed. Introduced in 1923 by Henri Hartmann specifically for the management of large bowel obstruction, Hartmann's procedure involves resection of the distal obstruction and the formation of an end colostomy. If the procedure is being performed for a suspected cancer, every attempt should be made to achieve and oncologic resection as this can enhance chances for cure.

To perform a Hartmann's procedure, the patient should be placed in the lithotomy position, which greatly enhances pelvic dissection and allows for access to the rectum if necessary. Following resection of the lesion, decompression of the colon is first achieved with an end colostomy (with or without a mucous fistula) In a review of 35 studies by van der Wall and colleagues, of the 4249 patients who underwent a Hartmann's procedure, only 48% underwent reversal with a mean time to reversal of 2.5 months. Morbidity rate was 3% to 60% (mean, 16.5%) and mortality rate from 0% to 7.1% (mean, 1%).

Segmental resection of the colon with primary anastomosis is a good option for carefully selected patients if the proximal colon is not dilated significantly. Retrospective reviews have shown similar rates of operative mortality and anastomotic leak in carefully selected patients undergoing left sided colectomy compared with right sided colectomy. Furthermore, quality of life is improved. A good option for a high risk patient is segmental colectomy, anastomosis, and a diverting loop ileostomy. This still allows for diversion of the fecal stream, and in the event of an anastomotic leak, intraabdominal

sepsis is contained and can usually be managed nonoperatively with percutaneous drainage and antibiotics. Loop ileostomy reversal is a less invasive operation and patients will more likely undergo this procedure to have their intestinal continuity restored as compared to reversing a Hartmann's procedure. The disadvantage is that ileostomy management in some patients (particularly the elderly) may be challenging with fluid and electrolyte shifts.

Colonic Lavage

In select patients, the use of an on table colonic lavage may permit a single stage surgery in the setting of a left sided large bowel obstruction. Following resection of the lesion, the colon should be fully mobilized at both flexures. Next, an appendectomy is performed and catheter passed into the cecum and secured with a purse string suture. This catheter is attached to a large bag of warmed saline and elevated on a pole. The staple line at the distal segment of colon is opened and a generous length of sterile corrugated tubing is placed into the lumen of the descending colon. The tubing is secured in place with umbilical tape or a purse string and then draped off the table into a basin. Warmed saline is then flushed through the colon. This is continued until the effluent clears and typically requires several liters. The catheter and tubing are removed and the site of the appendectomy is closed. Before the anastomosis, the colon is inspected for injuries that may have occurred during the lavage. The anastomosis is then performed in the standard fashion. A modified version of this method uses a Y shaped connector. One limb allows for retrograde infusion of saline through the descending colon and the other is attached to drainage tubing. This modification to appealing as it obviates the need for the appendectomy or ileostomy. In a study by Jung and colleagues, 171 patients with an obstructing left sided lesion received intraoperative colonic lavage with primary anastomosis. Compared with elective, nonobstructed patients during the same interval, anastomotic leakage and wound infection were not significantly different.

Subtotal Colectomy

Conversion from segmental resection to subtotal colectomy is rarely needed and determined by the integrity of the colon proximal to the obstruction. A subtotal colectomy is indicated when perforation, large serosal injuries or synchronous lesions are found at the time of exploration. When performing a subtotal colectomy in the emergent setting, creation of an end ileostomy is often necessary.

Endoscopic Stenting

In the past decade, endoscopic management of obstructing large bowel lesions has gained significant attention. In the appropriately selected patient, endoscopic stents can be tremendously beneficial. Indications for stent placement include palliation of an inoperable obstructing lesion (e.g., stage IV colorectal cancer) and as a temporizing "bridge" to definitive therapy in a patient with a curable, or potentially curable lesion. The ability to treat a curable, or potentially curable lesion, affords time for colonic decompression, medical optimization, endoscopic evaluation for synchronous lesions, and increases the likelihood of a single stage operation. Contraindications to stent placement include any of the previously discussed indications for emergent surgery, an abscess/infection closely associated with the lesion, short and tethered colon, and a lesion less than 5 cm from the anal verge.

Preoperative antibiotic coverage is unnecessary for stent placement. Gentle tap water enemas should be used to evacuate stool distal to the lesion. If an oral bowel preparation is desired, it may be attempted only if the obstruction is partial and the patient is closely monitored for the development of new or worsening symptoms. Colonoscopic evaluation of the lesion must be done with the utmost care; forceful attempts to traverse beyond the lesion are strictly avoided. Perforation is the most feared complication of stent placement. To mitigate the procedural risk of perforation, insufflation with carbon dioxide is preferred over room air because of the dramatically faster clearance time. The most common stents used in the United States are uncovered, self expanding metal stents. Through the scope (TTS) and over the wire, also referred to as non TTS, are the two conventional approaches to stent placement.

TTS is usually the first line approach (Fig. 1). The TTS system requires a colonoscope equipped with a working channel to pass the guidewire and stent. The scope is advanced and parked in an area immediately distal to the lesion. Contrast is administered and the lesion assessed with fluoroscopy. The guidewire is then advanced safely beyond the lesion followed by the stent (Seldinger's technique). Endoscopy and fluoroscopy confirm the correct location of the wire and the stent. Most TTS systems encourage a proximal and distal stent overlap of 2 cm. For longer lesions, additional stents can be placed in series. If assessment of the lesion shows anatomy unfavorable for TTS (e.g., available size of the stents), the procedure is converted to over the wire. With the guidewire fixed, the colonoscope is withdrawn entirely. The appropriate stent is selected and passed directly over the wire into position using fluoroscopy. Fluoroscopic or postprocedural abdominal films are obtained to confirm the typical wire appearance of a narrowed or waisted midportion with proximal and distal flaring. The flaring segments adequate overlap into normal, low resistance lumen. To reduce development of rapid restenosis, the luminal diameter at the mid portion of the stent should be at least 24 mm. Balloon dilation should not be attempted because of significant risk of perforation. If imaging does not demonstrate flaring at one or both ends of the stent, additional stenting is likely necessary and typically done to an end to end fashion.

Patients should expect gradual improvement of symptoms over 3 to 5 days as the stent reach maximal expansion and the colon decompresses. If the stented lesion was accurately or transitive colitis, patients can resume a regular diet immediately. For descending colon and beyond, patients are advised to consume a low residue, low fiber diet along with daily laxatives (e.g., polyethylene glycol) to promote soft stools that are unlikely to become impacted at the stent. It is important that definitive therapy is planned, it should be done within 7 to 14 days following placement of stent. Patients who receive stenting for palliation and the anticipated duration greater than 2 weeks have a significantly increased risk of perforation. Multidisciplinary discussion should weigh the possibility of surgical palliation in this high risk population.

Current literature reports successful stent placement for acute large bowel obstruction between 70% and 90%. In a pooled analysis by Sebastian et al., 25% of the 1198 patients who underwent stent placement for obstruction developed a complication. Most common complications include stent migration, restenosis, and perforation. The most serious complication is perforation and occurs in 4% to 5% of patients. Intrinsic factors that may increase the risk of stent related perforation include longer segment of obstruction (median length of 6 cm), benign etiology and extraluminal origin.

SPECIFIC SITUATIONS

Sigmoid Volvulus

Volvulus, from the Latin, volvere, means to roll. The classic patient with a sigmoid volvulus presents with sudden lower abdominal pain and obstipation. The demographic profile most affected by sigmoid volvulus is a black male older than 70 years with significant comorbidities. The gold standard in the management of sigmoid volvulus is endoscopic detorsion, gross inspection, and placement of a drainage catheter (successful in up to 80% of patients). Timing of definitive operation is based on the high rate of recurrence, most studies citing the rate in the 50% to 80% range. Atamanalp and colleagues published data from a single center review of 486 patients. They found morbidity and mortality of 35% and 16% for emergent surgery and 12.5% and 0% for elective surgery, respectively. Some suggest performing the definitive surgery as early as the index admission, but evidence for this is lacking. Regardless of timing, the approach can be either open or minimally invasive. The chronic process leading to

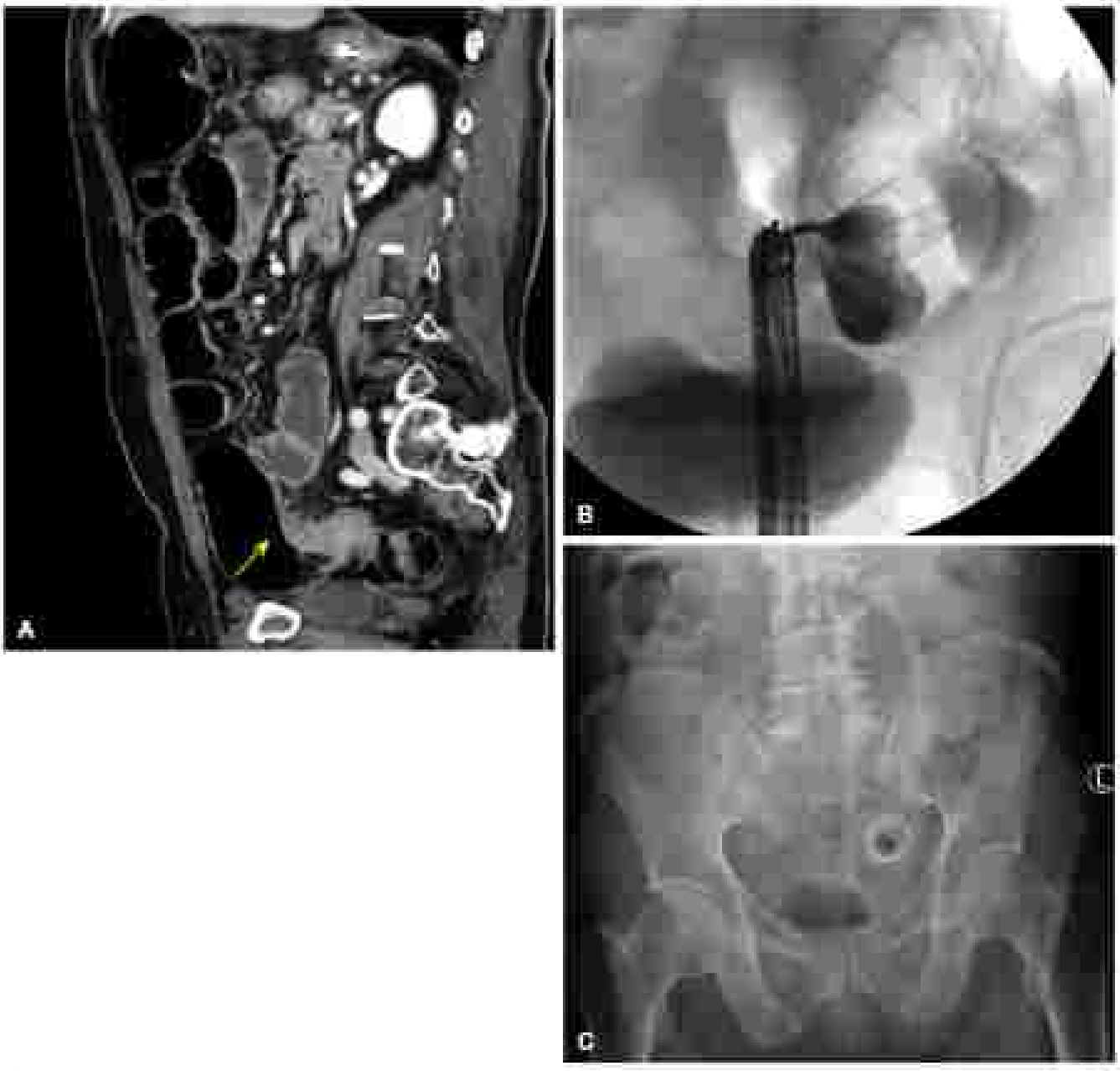

FIG. 2 Endoscopic stent placement for obstructing noncolorectal cancer. (A) Arrow indicates obstructing pelvic lesion. (B) Fluoroscopic guided passage of the wire across the obstructing lesion. (C) Poststent abdominal film with improvement of large bowel distention.

sigmoid volvulus results in an anatomical configuration that facilitates sigmoid resection with minimal difficulty. For isolated sigmoid volvulus and the elective sigmoid colectomy, the recurrence rates are very low.

Cecal Volvulus or Bascule

The second most common site of colonic volvulus is the cecum (Fig. 2). In patients with cecal volvulus, there is a female predominance, and typically patients are in the second and third decade of life. Presentation is similar to small bowel obstruction with abdominal distention, nausea, and vomiting; however, this can vary. There are three types of cecal volvulus.

1. Axial cecal volvulus. A twist of the mesentery on which the affected cecum remains in the right lower quadrant.
2. Loop cecal volvulus. The cecum and terminal ileum are twisted in the axial plane and the affected cecum typically lies in the left upper quadrant.
3. Cecal bascule. A redundant cecum folds in the sagittal plane onto itself and the proximal ascending colon leaving the affected cecum within the right upper quadrant.

All three types necessitate either an acquired or congenital hypermobile cecum and ascending colon. Types 1 and 2 are the most common, account for roughly 80% of cecal volvuli. Unlike types 1 and 2, type 3 does not exhibit torsion. Patients who present with type 3 typically have a much more tenuous presentation. Endoscopic management is not recommended for cecal volvulus or bascule because of a low rate of successful detorsion, and colonic ischemia can be missed in up to 25% of patients. For the patient presenting with a high probability of cecal volvulus, the operation of choice is

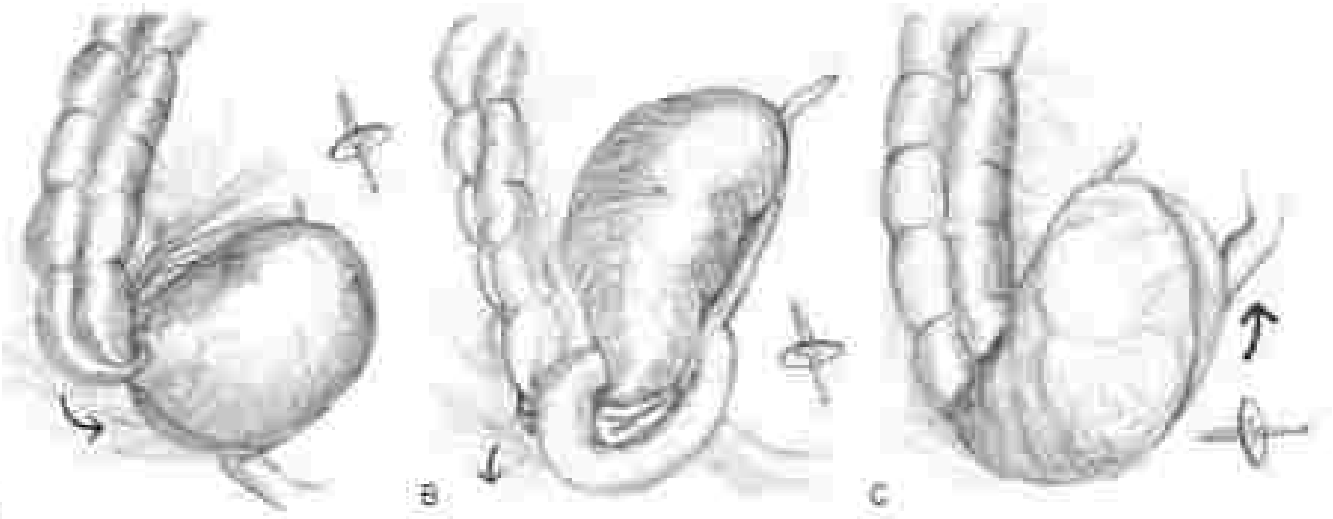

FIG. 1 Types of cecal volvulus. (A) Type 1, axial cecal volvulus. (B) Type 2, loop cecal volvulus. (C) Type 3, cecal bascule. (*Courtesy Matthew P. Kelly, MD.*)

an exploratory laparotomy. Severe ischemia, necrosis, or perforation occurs in up to 18% of patients with cecal volvulus; if present, mortality rates are equally as high. Management of the patient with nonviable cecum is resection and creation of end ileostomy, with consideration for mucous fistula. If the cecum is viable or with patchy ischemia, there is less consensus on the appropriate management. Nonresectional options include detorsion with cecopexy and cecostomy. Widely variable rates of recurrence, morbidity, and mortality have been demonstrated, although there is a paucity of recent data that compares these options and with respect to viable versus nonviable bowel. Devolution of the current data favors ileocecectomy with primary anastomosis for patients with acute cecal volvulus, even when bowel appears viable. Laparoscopic approach is an acceptable option in stable patients with limited bowel distension if performed by an experienced surgeon.

Acute Colonic Pseudo-obstruction

Acute colonic pseudo-obstruction (ACPO), is also referred to as Ogilvie's syndrome in homage to the British surgeon, Sir Heneage Ogilvie, who in 1948 identified two patients who presented with large bowel distension without an identifiable lesion. This syndrome is most commonly encountered in the hospitalized, elderly male patient. Hospitalization is usually unrelated to the presenting symptoms rather for unrelated surgical procedure (most commonly involving pelvic dissection) or traumatic brain injury. Additional predisposing factors include severe electrolyte disturbances, certain medications, and acute deconditioning. Presentation is consistent with other etiologies of large bowel obstruction, including nausea, vomiting, and persistent abdominal pain. A significant portion of these patients will continue to pass loose stool. Focal pericolonic confined to the right lower quadrant may be a warning sign of impending perforation because of the profound cecal distension. These findings should encourage expeditious intervention. Perforation at the time of presentation occurs in about 15% of patients and often is associated with abdominal tenderness, cecal diameter greater than 12 cm, fever, and leukocytosis.

Abdominal plain films are the best initial imaging study, although findings are nonspecific. Second line imaging has traditionally been with water soluble CE. Unfamiliarity with the technique coupled with the risk of perforation makes this option less favorable. The gold standard imaging modality is CT, findings include dilated colonic distension, possible transition point near splenic flexure, and importantly, no evidence of a mechanical obstruction.

Nonoperative management of ACPO is successful in more than two-thirds of patients. This consists of aggressive fluid resuscitation, repletion of serum electrolytes as necessary, cessation of possible offending medications (e.g., opioids, anticholinergics), and bowel rest. The use of nasogastric and rectal tubes for decompression may also encourage the passage of flatus. These principles of nonoperative management are continued for 2 to 4 days. During this period, it is essential to monitor the patient with the use of serial imaging and physical examinations.

Failure to improve over this period necessitates the next step in the algorithm, neostigmine. Neostigmine increases the availability of acetylcholine through its anti-acetylcholinesterase mechanism. In the colon, additional acetylcholine results in improved contractility and generalized motility. Before administration, the patient should be transferred to a unit with continuous cardiopulmonary monitoring and the ability to administer atropine, glycopyrrolate, or both. Neostigmine is contraindicated in patients in whom there is suspicion for ischemia or perforation, severe acute bronchospasm, poorly controlled cardiac dysrhythmia, or pregnancy. With the patient connected to continuous monitoring, the first dose of neostigmine of 2 to 3 mg given intravenously over 1 to 3 minutes. Success is achieved if passage of flatus, stool, or decreased abdominal distension. Patients are observed over the next 30 minutes. Atropine and glycopyrrolate should be readily available if there is development of bradycardia or bronchospasm, respectively. Neostigmine is successful at treating ACPO in more than 90% of cases. For patients who are partial responders or unresponsive after one dose, a second can be administered with high rates of success. For those who fail to respond to neostigmine, the next step in management is endoscopic decompression. Geller et al. reviewed 50 patients with ACPO treated with colonoscopic decompression and found clinical success in 92% following a single intervention, 18% needed at least one additional colonoscopy, for patients who did not receive a decompression tube at the time of the procedure, clinical success was only achieved in 25%. Regarding technical considerations, insufflation should be minimized and preferably with carbon dioxide. The scope should be advanced into the right colon. A decompression tube is strongly recommended and should originate from the right colon. The endoscopist should remove as much gas as possible during withdrawal of the scope. If endoscopic decompression is not possible or unsuccessful, percutaneous cecostomy can be used with variable success. When all these interventions have been unsuccessful, operative management is indicated. The surgery is dictated by the intraoperative findings. A cecostomy may be enough to assess the viability of the colon. If no evidence of perforation or ischemia, a tube cecostomy or surgical cecostomy may be sufficient. When ischemia is identified, the affected region should be

resected, including adrenal adenoma if indicated. Primary anastomosis is not recommended, but rather the creation of end colostomy with or without mucous fistula.

SUMMARY

Large bowel obstruction is a serious disorder that often necessitates surgical intervention. Rapid evaluation is essential to providing appropriate management. Emergent laparotomy should be performed on unstable patients with peritonitis and/or signs of symptoms of ischemia. Preoperative optimization of patients includes correction of electrolyte abnormalities with adequate hydration to correct acidosis. Segmental resection with primary anastomosis can be considered in patients who are stable and have minimal barriers to healing. Endoscopic stenting can be considered as a bridge to surgery or as palliation in select patients.

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ENTERAL STENTS IN THE TREATMENT OF COLONIC OBSTRUCTION

Wissam J. Halabi, MD, and Maher A. Abbas, MD, FACS, FASCRS

Colonic stents were introduced as a treatment option for colorectal obstruction by Dohmoto in 1991. When first described, the stents were used as a palliative method in patients with malignant left sided colonic or rectal obstruction to avoid stoma formation. The use of a stent was advocated to decrease the morbidity of emergency colorectal surgery and the need for a stoma. Over the past 2 decades, the implementation of stent technology has grown and now includes treating proximal malignant colonic obstructions. Although stent effectiveness is highest when dealing with an intrinsic malignant structure from colon carcinoma, there has been an increasing interest to stent use to palliate obstructions of extrinsic origin. In addition to their use as a definitive palliative measure, the role of stents has evolved to include their use as a bridge to surgery intervention, allowing bowel decompression and decreasing the risks associated with emergency operation in a dilated colon filled with stool. Under such circumstances, stent decompression provides an opportunity to optimize the patient's condition from a medical and nutritional standpoint and allows the administration of bowel preparation. From an oncologic perspective, additional staging workup can be undertaken to identify synchronous lesions and, in the case of a select group of patients with rectal carcinoma, consideration can be made for neoadjuvant chemoradiation. Beyond malignant obstruction, colonic stents have been used in the management of benign colonic obstructions or stenosis caused by diverticular disease or inflammatory bowel disease as well as the management of postoperative complications such as anastomotic leaks or strictures, as previously reported by the senior author (M.A.A.) (Fig. 1A–E).

INDICATIONS FOR STENTS

Stenting of Malignant Obstruction

The primary indication for colorectal stenting is to relieve intraluminal obstruction caused by large bowel cancer. In a retrospective analysis of 183 procedures performed in 165 patients over a decade, the senior author found that 90% of procedures were performed for malignant disease. The majority of patients had an intrinsic stricture from a primary colorectal adenocarcinoma (82%) (Fig. 2A–E). The remaining subgroup of patients had extrinsic obstruction caused by gynecologic malignancies, gastrointestinal cancers of noncolorectal origin such as gastric, esophageal, and hepatobiliary, and extraabdominal origin such as breast. Extrinsic obstructions are challenging to treat for several associated factors: often, they can be multifocal compressing a long segment of large bowel and are associated with carcinomatosis in many patients. Furthermore, some patients, especially those with gynecologic malignancy, have an extensive surgical history, dense pelvic adhesions, and in some cases prior exposure to radiotherapy. Put together, these factors yield a lower technical and clinical success rate of stent deployment in patients with extrinsic obstruction compared with patients with intraluminal malignancy (Fig. 3). Technical success (immediate or short-term success) is defined as the ability to safely deploy and properly position the stent across the stricture without any immediate complication. Clinical success (long-term success) is defined as the ability to achieve long-term decompression without the need for operative intervention to treat long-term failure of the stent or related complications such as migration or erosion of the stent, or the development of obstruction. Thus, although stenting can be considered for patients with extracolonic malignancy, proper patient and family counseling is key in setting a realistic expectation and to prepare the patient emotionally for the potential need for surgical intervention in case of an immediate technical failure or long-term clinical failure. This issue will become even more challenging in the future as cancer specific survival becomes longer with more effective chemotherapeutic agents.

Stenting of Benign Disease

The role of stenting has been more limited to benign conditions, but there is a growing interest in exploring the effectiveness and durability of colonic stents in this setting. The senior author has previously described the role of colorectal stents in treating benign disorders such as obstructing strictures from diverticular disease or prior radiation therapy, complex colorectal fistulas including colovesical and colovaginal, and management of acute or chronic anastomotic complications including leak and obstruction. Despite such interest, the scientific literature is scarce in that regard and overall there has been a limited experience with the use of stents for benign conditions. From a technical standpoint, benign strictures can be technically difficult to tackle because of the lack of proper instrumentation and the use of soft metal stents that have been designed to apply a radial force against tumor tissue. The morphology of benign strictures is quite different, and they are often associated with a significant degree of extraluminal scarring and fibrosis. However, with an increasing interest in endoscopic intraluminal surgery, newer technologies will undoubtedly become available in the future. These anticipated advances will provide a new horizon with a future generation of platforms that will allow surgeons and endoscopists to expand the role of enteral stents.

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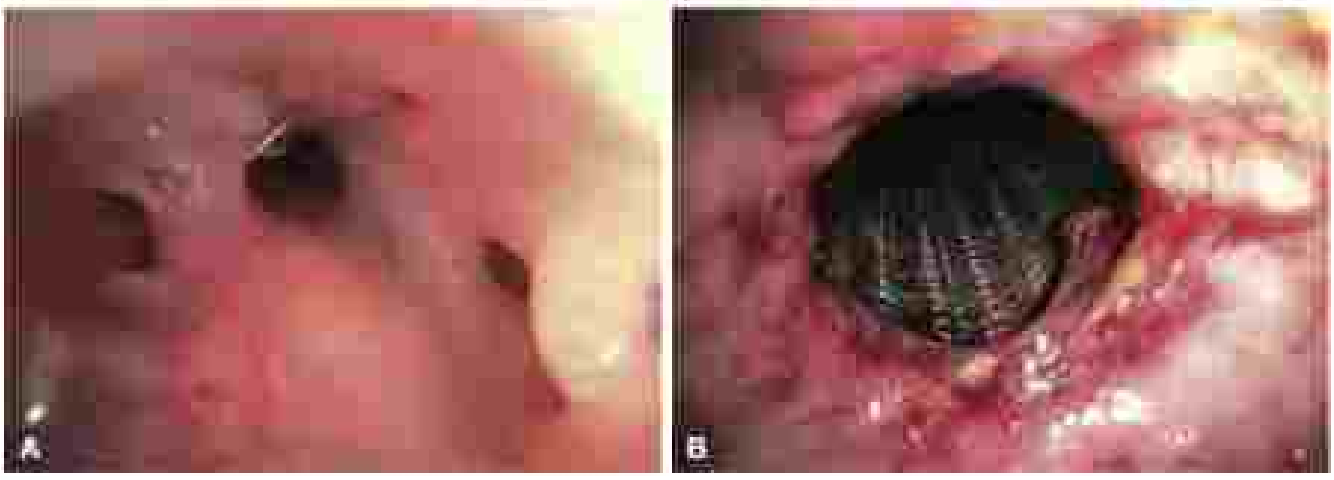

FIG. 1 (A) Endoscopic view of anastomotic ostium and stricture following high anterior resection for diverticulitis. (B) Endoscopic view after balloon dilation and stent deployment across the benign anastomotic ostium.

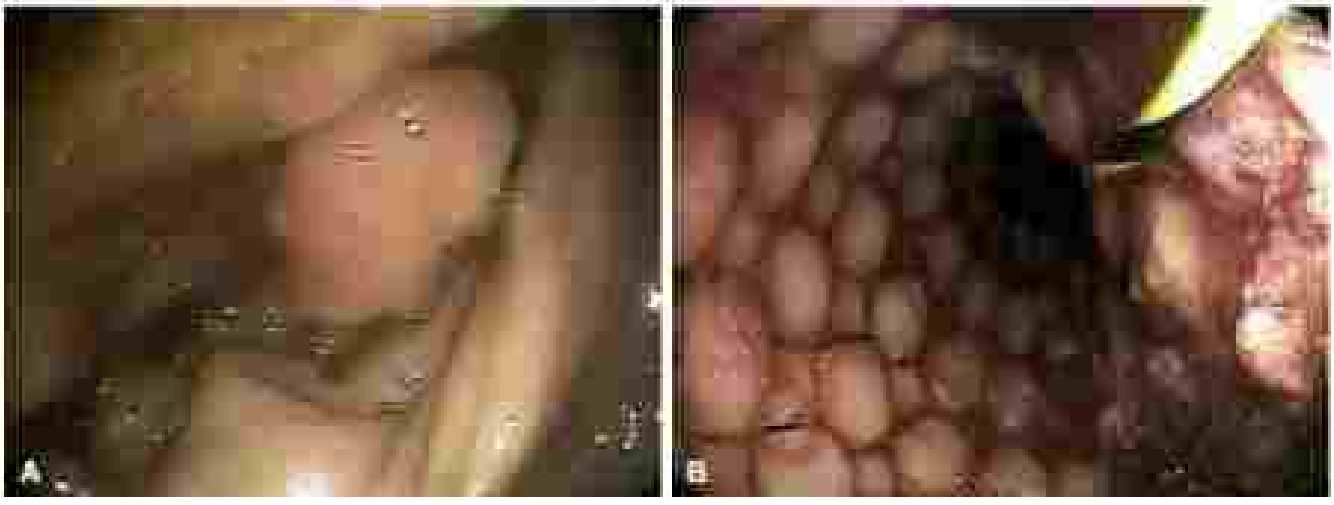

FIG. 2 (A) Endoscopic view of obstructing upper hemicolonic adenocarcinoma. (B) Immediate posterior deployment endoscopic view with decompression of the luminal obstruction.

Stenting as a Bridge to Surgery

The benefits of endoluminal stents inserted preoperatively as a bridge to a future definitive surgical intervention have been demonstrated in several series reporting on both malignant and benign disease. In patients presenting with acute large bowel obstruction from locally advanced disease with no evidence of metastasis or in the case of benign conditions such as a diverticular stricture, endoluminal stents provide an opportunity to convert the situation from an emergency setting into a more planned emergent or elective operation. Under such a scenario, stents confer a lower mortality and morbidity for patients in need of a curative or definitive operation. In the short term, stents are associated with a higher rate of primary anastomosis and avoidance of stoma in 42% to 77% of patients. Moreover, in patients with malignant obstruction, decompression with a stent allows for a proper staging workup to be performed as well as medical and nutritional optimization.

However, it is important to note that although numerous studies have advocated the use of stents as bridge to surgery in patients who are potentially candidates for a curative resection, the bulk of the data produced is limited by the retrospective nature of studies and small number of subjects. More recently, two multicenter randomized controlled trials comparing initial stent with surgery for acute left-sided malignant colonic obstruction were stopped because of a high rate of technical failure in the stent arm and a high perforation rate leading to an overall higher morbidity in the stent group. A further assessment of the available data on the outcomes of stents as a bridge to surgery at the meta-analysis level has yielded conflicting results. Endoluminal stents used as a bridge to surgery are associated with higher primary anastomosis rates and lower short-term stoma rates. Unfortunately, the reported permanent stoma rate is no different. Moreover, the morbidity and mortality rates in patients undergoing emergency surgery compared with those who had a stent were not significantly different. Complications inherent to stenting, such as colonic perforations, have been reported as 7% for clinical perforations and 10% for silent ones. Despite these complications, a relatively high technical success rate in the stent group has translated into a shorter hospital stay, lower rate of stoma formation, and lower mortality.

Beyond the technical and clinical success rates, it is important to appreciate the effect of stent placement on long-term oncologic outcomes in potentially curable patients. One of the concerns has been the potential risk of tumor spread in the bloodstream during endoscopic manipulation of the stent, and the potential for peritoneal seeding

in cases of clinical or silent perforations. Concerns expressed in the scientific literature include a higher rate of peritoneal invasion of the primary tumor in the stent group compared to the surgery group at time of resection. Furthermore, some studies have reported overall survival and a higher 5 year cancer specific mortality in patients receiving a stent compared with those managed with surgery. Such findings have led the European Society of Gastrointestinal Endoscopy to issue guidelines stating that the use of colonic self-expandable metal stent placement as a bridge to elective surgery is not recommended as a standard treatment for symptomatic left sided malignant colonic obstruction resulting from concerns of oncologic safety. These recommendations were subsequently endorsed by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Based on experience of the senior author and the currently available data, we believe that stents should not be used as a bridge to surgery in low risk patients with potentially curable disease. Such patient is better served with surgical intervention. However, a consideration for stent placement can be made in a patient who has a poor functional status resulting from significant medical comorbidities and/or severe malnutrition or a recent significant medical event such as a cerebrovascular or cardiovascular accident. Under such circumstance, the use of a stent may be justifiable as a bridge to surgery when considering the risk and benefits of morbidity and mortality versus long term oncologic outcome. Furthermore, even though the intent in such patients is a bridge to surgery, in many of these patients the stent becomes permanent as the patient may succumb to factors others than the colorectal malignancy.

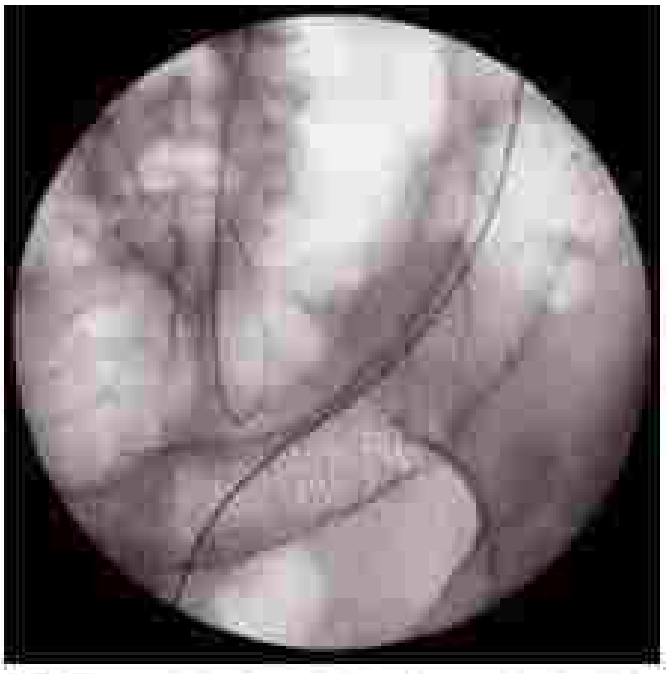

FIG. 3 Fluoroscopic view of successful stent decompression of anastomotic compression caused by recurrent ovarian cancer.

Stenting With Palliative Intent

Patients presenting with a malignant large bowel obstruction and metastatic disease often have a limited life expectancy especially in the setting of diffuse metastatic disease, cachexia, advanced age, and medical comorbidities. This patient population is often debilitated and considered as high risk for operative intervention. Under these circumstances, endoluminal stent placement is the intervention of choice in our opinion because it obviates the need for major surgery and associated recovery. Because chemotherapy is the mainstay of palliative treatment in patients with advanced cancer, it is of utmost importance to avoid delays in chemotherapy. There is a limited amount of data on the effect of stenting on the subsequent administration and timing of chemotherapy. As newer and more effective chemotherapeutic agents become available, this issue will become of increasing relevance. Before deploying a stent to patients with unresectable malignancy, a multidisciplinary discussion to build with medical oncology to determine which type of chemotherapy will be used. Bevacizumab is associated with a significant risk of colonic perforation and patients should be counseled regarding that risk.

The use of stents has been associated with a lower rate of short-term morbidity compared with palliative surgery. However, concerns remain about long term patency of stent in long term survivors. Several studies have reported on long-term complications of stent and the need for secondary endoscopic or surgical interventions (Fig. 4A–B). Such complications include perforation, occlusion, and migration (Fig. 5). Another important aspect of the team is consider is the patient's overall condition and life expectancy. Although in general most studies have failed to demonstrate a survival advantage of palliative stenting compared with surgery, it is important that future advances in chemotherapeutic agents will prolong survival that

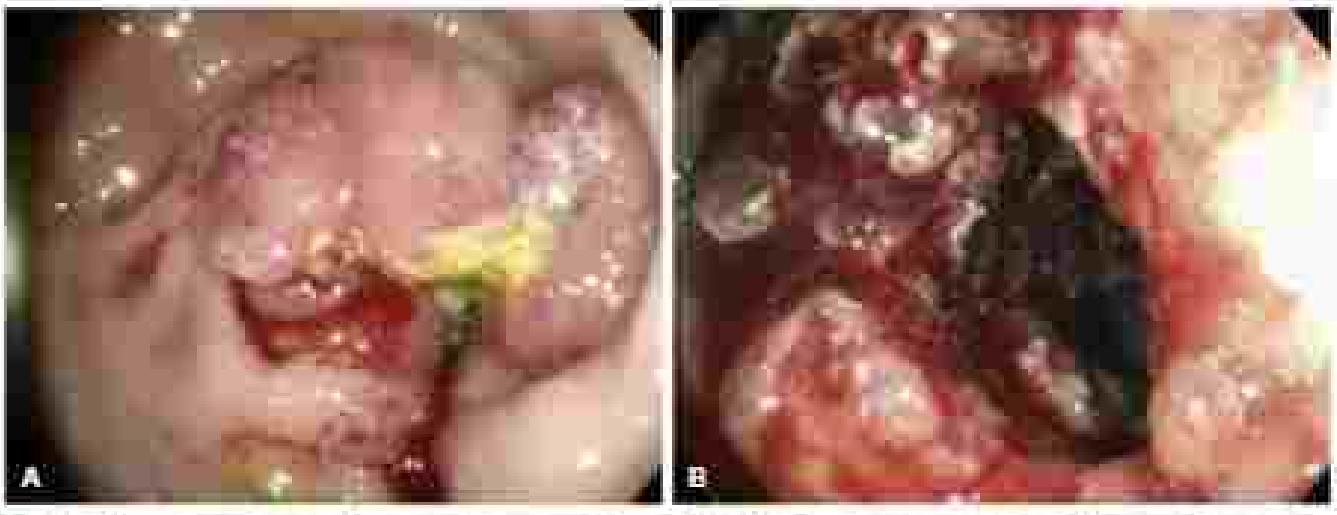

FIG. 4 (A) Endoscopic view of carcinoma ingrowth with obstruction of stent 4 months after initial deployment. (B) Successful fulguration of carcinoma ingrowth inside the stent using argon plasma coagulation.

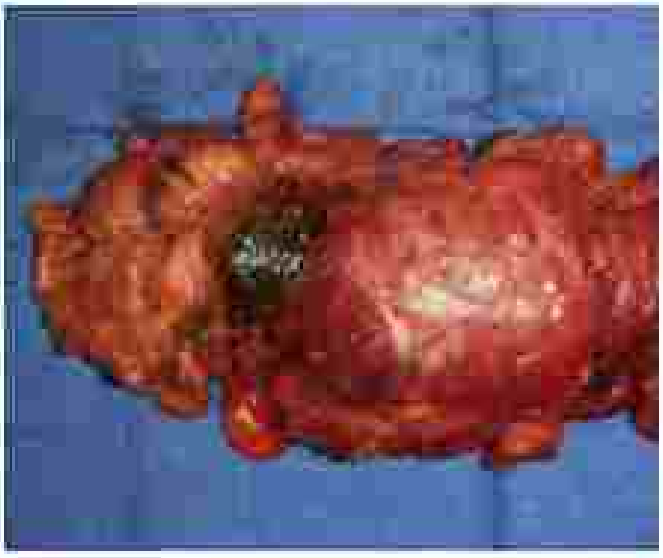

FIG. 5 Reconstructed transverse computed tomography image shows stent position.

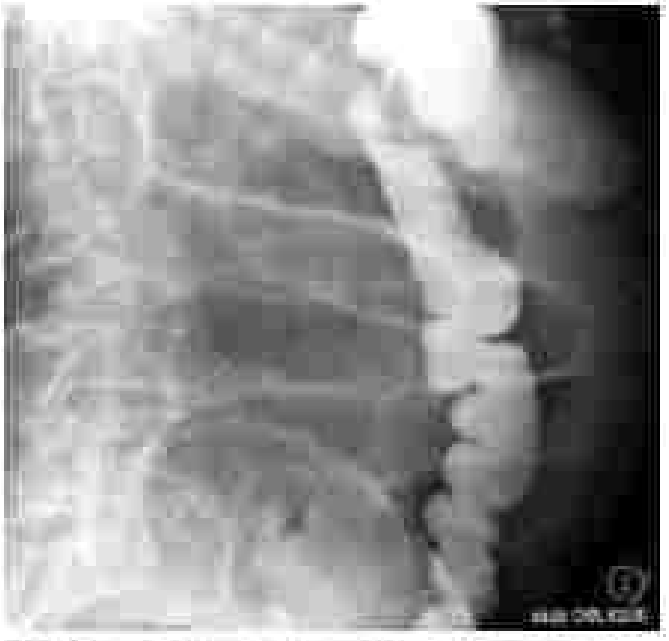

FIG. 6 Contrast enema demonstrates an apple core lesion at the splenic flexure. The angulation in this part of the colon can make stent deployment challenging with higher migration and perforation rates.

may increase the relevancy of long-term stent patency and secondary interventions. Finally, although no long-term survival has been demonstrated in general with stenting, palliative stenting of advanced colorectal cancer is associated with improved quality of life. Therefore, in patients with incurable malignant colonic obstruction, stenting should be reserved for those with limited life expectancy who are high-risk operative candidates, whereas operative intervention should be considered in patients who are better fit for surgery and have a longer life expectancy.

CONTRAINDICATIONS TO STENT PLACEMENT

Clinical or radiologic evidence of acute perforation of the colon or significant ischemia or necrosis constitute absolute contraindications to the use of colonic stents in the management of malignant large bowel obstruction. Relative contraindications are the presence of a long structure (although a long stent or two tandem stents can be placed), a functional proximal obstruction may ensue because of the inability of the colon to push stool through a long metal segment), proximal lesions in the ascending colon (often can be palliated surgically with a low rate of stoma), distal lesions within 5 cm from the anal verge (painful and high risk for migration), and the presence of diffuse carcinomatosis (higher failure rate). Lesions in tortuous or angulated portions of the colon can be technically challenging and may have a higher failure rate. Such areas include splenic flexure lesions and masses in an angulated and redundant sigmoid colon (Fig. 6). The risk for migration and perforation can be higher. Stents are not recommended in patients who may be considered for treatment with antiangiogenic drugs such as bevacizumab. The use of prophylactic stents in patients with metastatic disease to prevent potential obstruction is not recommended.

TYPES OF STENTS

Colonic stents are self-expandable and are made of radiopaque, woven, metal mesh that has the shape of a cylinder resulting in self-expansion forces. Different types of stents are available based on the material used to manufacture them. They each may have advantages and disadvantages based on a specific design. Z-Stent (Cook Medical) is a stainless steel stent available in both covered and uncovered forms. Stainless steel stents are relatively stiff and may affect the quality of imaging studies such as magnetic resonance imaging. Wallstent (Boston Scientific) is made of Elgiloy, an alloy of chromium, cobalt, and nickel. The stent is thinner, more elastic, and flexible and is MRI compatible with less imaging artifact. Alimaxx E stents (Alveolus) and Ultraflex (Boston Scientific) are made of Nitinol, which is an alloy of nickel and titanium. Nitinol stents may be difficult to visualize under fluoroscopy and are used in conjunction with radiopaque markers; however, their characteristic shape memory and superelasticity makes them more flexible than stainless steel or Elgiloy stents. Metal stents can be uncovered and thus have bare wires or covered (Fig. 7). The latter have a silicone membrane over the bare wires. Although covered stents may reduce the risk of tumor ingrowth and can be used in the management of fistulas or anastomotic complications, they tend to migrate more often compared with uncovered stents. To overcome the issues associated with tumor ingrowth, drug-eluting stents are in development.

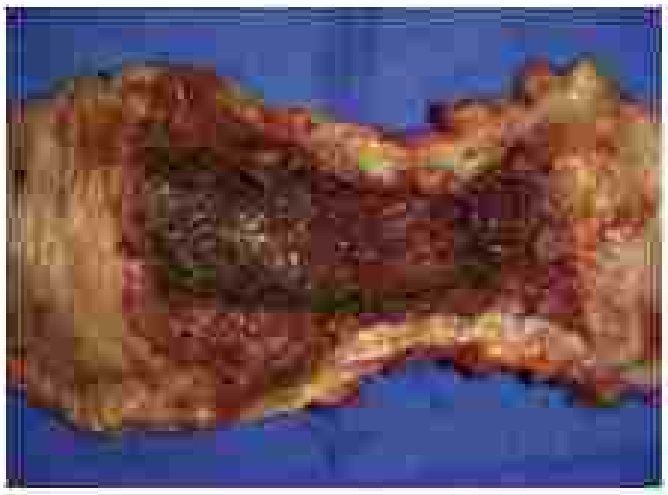

FIG. 7 Surgical specimen reveals the metal bare wires incorporated into the bowel wall and tumor.

In addition to metal stents, biodegradable stents made of polymers such as polydioxanone and biodegradable material (magnesium alloys) have recently been used to manage benign strictures such as

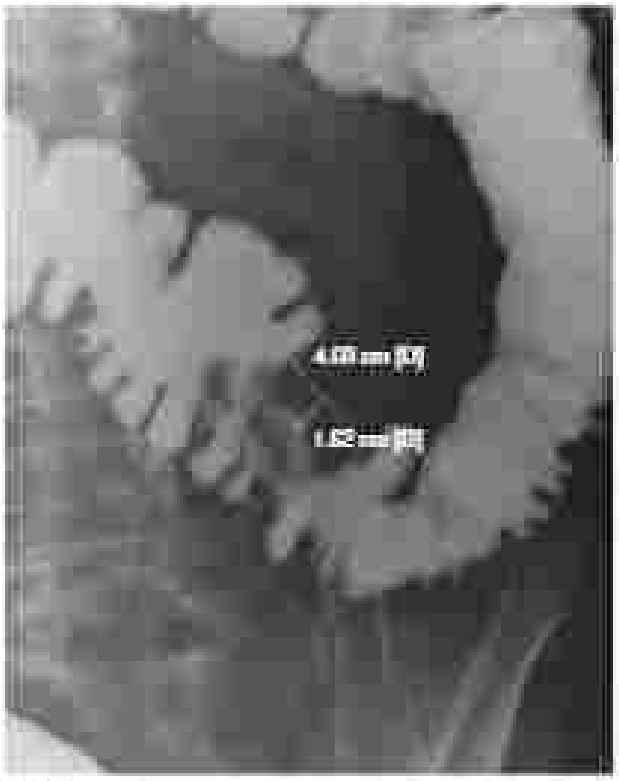

FIG. 8 Cancerous stoma now demonstrating the morphology of a malignant carcinoma.

in Crohn's disease or colorectal anastomotic strictures. These stents do not require surgical resection or endoscopic retrieval. The radial force of polyurethane stents is maintained for approximately 6 to 8 weeks following implantation and drops to 50% by week 9 with a mean degradation time of 4 months. Because most of these stents were designed to be used for esophageal pathology, their application to the colon while technically successful has had variable clinical success rates (0.4–100%) with a mean stent migration of 22% and symptom recurrence.

TECHNIQUES OF STENT PLACEMENT

Before placing a colonic stent, adequate assessment of the location, length, caliber, and morphology of the obstruction should be made (Fig. 8). Retrograde water soluble contrast enema can help delineate the anatomy and may sometimes reveal synchronous proximal lesions. It helps in evacuating retained luminal contents. Patients are usually given one or two cleansing enemas to prepare the distal colon. Oral mechanical bowel prep is discouraged because it may worsen the symptoms of obstruction.

In patients with complete obstruction and dilated colon proximally, intravenous antibiotics given prophylactically may be helpful because the insufflation during the procedure may cause microperforation and bacteremia. The procedure is usually performed in the operating room or the endoscopy suite under intravenous sedation. If the patient has severe abdominal distention with potential airway compromise, a general endotracheal anesthetic is safer. Before starting the procedure, the patient is placed in the left lateral decubitus position and the scope is inserted until the obstruction is reached. The patient is placed in the supine position for a better view under fluoroscopy, although this is not necessary with a rotating fluoroscope.

Stent insertion and deployment can be performed under endoscopic guidance without fluoroscopy if the distal aperture of the stricture is wide enough to allow passage of the endoscope and visualization of the colon proximal to the obstruction. A smaller caliber gastroscope may be used if needed. This approach is applicable mainly in distal left sided obstructions, however. Two techniques are used here: through the stent or over the wire technique. In the former, the endoscope is advanced to the level of the obstruction. A guidewire is placed through the scope and passed proximal to the lesion. The length of the stricture should be estimated based on pre-procedural contrast enema. The stent is passed through the scope channel and the scope is withdrawn to the level of the distal end of the stricture. The stent is deployed under direct visual guidance ensuring adequate proximal and distal overlap. In the over the wire technique, after passing the wire through the endoscope proximal to the lesion, the endoscope is withdrawn while the wire is left in place. The endoscope is then reinserted beside the guidewire and is used to observe the stent delivery device advancing. The stent crosses the stricture over the wire and is deployed under direct visualization. Typically, at least 1 to 2 cm of stent length should be kept distal to the lesion.

Stent insertion can be performed under fluoroscopy without endoscopy. This is mainly applicable for very distal left sided obstructions. In this approach, an angiography catheter is advanced over a guidewire proximal to the obstruction under fluoroscopy. Contrast is injected to confirm proper location and rule out perforation. The angiography catheter is then withdrawn and the stent is advanced over the guidewire and deployed across the lesion. This technique may be associated with higher radiation exposure. However, studies comparing it with the combined fluoroscopic endoscopic technique report similar technical and clinical success rates.

The combined fluoroscopic endoscopic approach for stent placement is currently our preferred method at surgeons. An endoscope is inserted to the level of the lesion. A hydrophilic, soft tipped guidewire is then loaded through an endoscopic retrograde cholangiopancreatography catheter passed through the endoscope channel. The guidewire is navigated across the obstruction under fluoroscopy. The endoscopic retrograde cholangiopancreatography catheter is then advanced over the wire through the obstruction and contrast is injected to confirm position and estimate the stricture length. A proper stent is chosen accordingly. The stent should be long enough to cover the entire obstructed area and have a 1 to 2 cm overlap proximally and distally. Symmetry is important because more coverage on one end versus another is associated with lower clinical success rate with the potential for migration and obstruction. If stent coverage is inadequate, an additional stent can be deployed in series to completely cover the lesion. This is rarely needed because most intrinsic malignant strictures are short. It is important to keep the wire in place across the lesion until the final position of the stent is assessed radiographically because trying to pass a wire through a newly deployed stent can technically challenging.

OUTCOMES

The technical success rate of endoluminal stents (defined as successful deployment across an obstruction without a complication) ranges between 70% and 100%. Clinical success (defined as long term resolution of the obstruction following stent placement) ranges between 70% and 100%.

Stent placement comes with its own set of complications, which can be divided into early and late. Early complications occur in less than 10% of cases. The most common early complications are bleeding and perforation. Overall, the rate of perforation in stents used for malignant obstruction is reported around 7% but is higher in patients with bevacizumab (17%). The perforation rate for benign etiology is higher at 18%. When perforations happen, they are difficult to treat endoscopically and are best managed operatively. Microperforation may be managed with bowel rest and intravenous antibiotics. Other early complications include failure of the stent to resolve the obstruction, which could be due to failure to cover the entire length of the stricture, synchronous colonic obstruction, early stent migration, fecal impaction, and early stent migration. Placing a second stent to

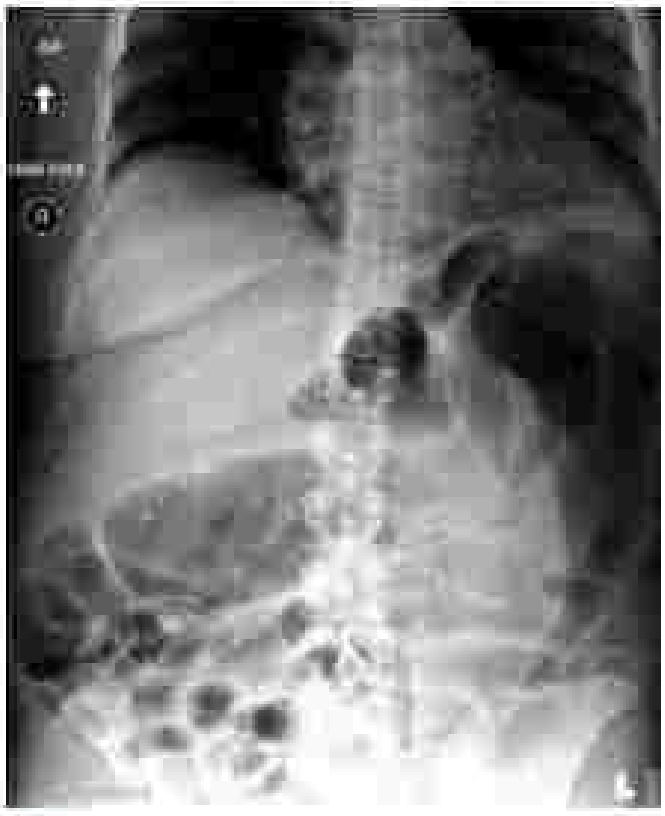

FIG. 9 Postprocedural abdominal radiograph demonstrating a well-positioned transverse colon stent across a malignant stricture.

correct this complication may be successful but is technically challenging. Pain and incontinence may occur if stents are placed within 2 cm of the anal verge. Such low placement is associated with a higher migration rate.

Late complications of stent placement are stent migration or occlusion by fecal impaction and/or tumor ingrowth. Tumor ingrowth has been reported in 15% of patients. Although most patients currently treated with palliative stents succumb to their disease before obstructing, the impact of newer chemotherapeutic agents on long-term survival may affect the rate of this long-term complication. Tumor ingrowth and fecal impaction of the stent can be managed endoscopically by placing another stent through the occluded stent, fulguration of the tumor, or disimpaction of the stent through balloon dilation.

Stent migration occurs in about 24% of cases and depends on several factors including treatment with chemotherapy or radiotherapy with subsequent tumor shrinkage, stent types, degree of stenosis, proximal and distant clearance, stent diameter impact the stent migration rate. Short stents, smaller diameter stents (<25 mm), and covered stents have higher rates of migration.

POSTSTENTING CARE AND SURVEILLANCE

The process of large bowel decompression starts after successful deployment of a stent. If a nasogastric tube is present, it can often be removed the following day. A postprocedural abdominal radiograph is obtained immediately after placement of the stent to check for location and exclude free air (Fig. 10). It is repeated within 24 to 48 hours when full expansion of the stent is expected. A liquid diet can typically be initiated within 24 to 48 hours of stent placement in most patients. Several days are needed for complete decompression in a normal size colon.

Suggested Readings

Abbas MA, Falk GW. Endoscopic stenting of colovaginal fistula: the transanal and transvaginal "kissing" stent technique. *JSLS*. 2008;12(1):68–72.

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Acute Colonic Pseudo-obstruction (Ogilvie's Syndrome)

David F. Hutcheon, MD

Acute colonic pseudo-obstruction (ACPO), or Ogilvie's syndrome, is an acute dilation of the colon in the absence of mechanical obstruction. William Ogilvie described two patients with malignant invasion of the preaortic ganglia and acute colonic pseudo-obstruction in 1948.

ACPO occurs in about 0.1% of hospitalized patients and carries a mortality of approximately 8%. About 15% of these patients develop colonic ischemia or perforation with an attendant mortality of 40% to 60%. The goal of therapy is to intervene before development of these complications.

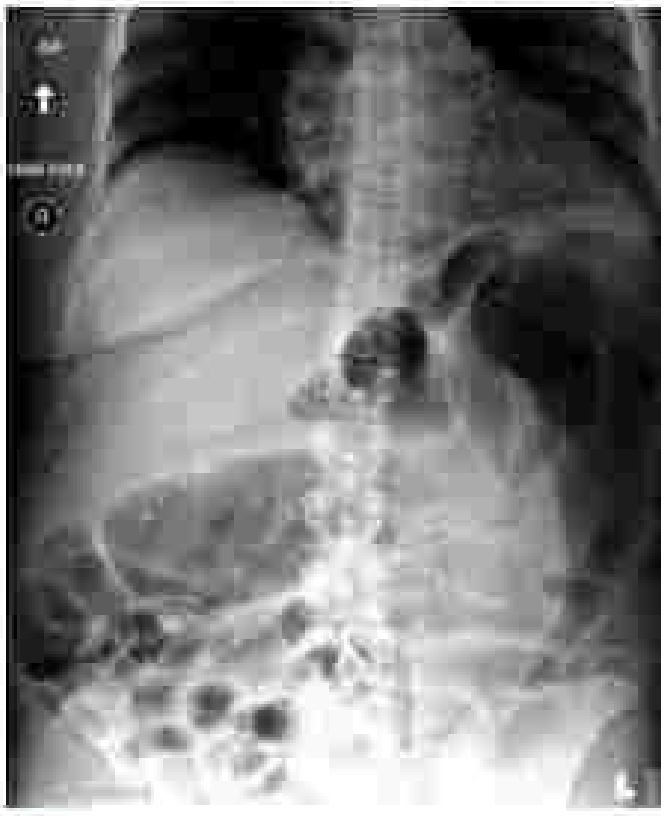
About one half of the patients have associated acute medical illnesses, the other half are postoperative patients. Ten percent of ACPO patients are postobstetric and postgynecologic procedures, with 93% of these presenting after cesarean section. Approximate incidences are various surgeries are: cardiac surgery, less than 1% and orthopedic surgery, 1% to 2%.

It is essential to differentiate ACPO from other causes of colonic dilation such as toxic megacolon, cecal or sigmoid volvulus, or chronic intestinal pseudo-obstruction. If there is a question of colonic obstruction, a limited water soluble enema is useful. Care must be taken not to fill the colon extensively—only through the site of possible obstruction.

Vanek et al. reviewed 400 patients in 1986. All patients had abdominal distention, and 83% had associated pain. Other associated symptoms and signs are listed in Table 1.

DIAGNOSIS

The diagnosis is usually made via abdominal and pelvis computed tomography (CT) scan without contrast. This can usually distinguish



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correct this complication may be successful but is technically challenging. Pain and incontinence may occur if stents are placed within 5 cm of the anal verge. Such low placement is associated with a higher migration rate.

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DIAGNOSIS

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ACPO from colonic volvulus, obstruction, and toxic megacolon. Cecal diameter has been a measurement used in consideration of therapy. Cecal dilation greater than 12 cm frequently prompts therapeutic intervention. Bowel dilation increases colonic wall tension and may lead to decreased perfusion, ischemia, and perforation. In one series, ischemia perforation occurred in 0% of patients with cecal diameters of less than 12 cm, 7% with cecal diameters 12 to 14 cm, and 23% with diameters greater than 14 mL. The therapeutic goal is to rectify the colonic dilation before ischemia and perforation. Fever, leukocytosis, abdominal tenderness, and cecal dilation greater than 12 cm are indicators of possible ischemia and/or perforation.

In the Vanek series, colonic dilation extended to the hepatic flexure in 17% of patients, splenic flexure in 56%, and left colon in 27%.

After initial CT scan, the patient is usually followed with every 12 to 24 hour abdominal radiographs with particular attention to cecal diameter (Figs. 1 and 2).

TABLE 1 Acute Colonic Pseudo-obstruction

Signs and Symptoms	% Patients
Abdominal distention	100
Abdominal pain	83
Nausea	63
Vomiting	37
Constipation	54
Diarrhea	46
Fever	37
Abdominal tenderness	
Performed	87
Not performed	64
Bowel sounds	
Normal to increased	80
Decreased	3
High pitched	17%

DIAGNOSTIC AND THERAPEUTIC OPTIONS

Conservative Management

- In all patients, correct metabolic abnormalities (i.e., serum sodium, potassium, calcium, phosphate, magnesium). Check thyroid stimulating hormone. Follow complete blood count, complete metabolic profile, magnesium, phosphate, and serum lactate levels. In patients with diarrhea, check stool for *Clostridium difficile*.
- Decompression with a nasogastric and rectal tube may be helpful. Diligent therapy of the underlying conditions is important.
- Maintain patient without food or water with adequate intravenous (IV) fluid hydration.
- Follow with serial physical examinations, serial abdominal radiographs, and CT scanning as clinically indicated.
- Discontinue or reverse medications that may contribute to colonic atony if possible. These include anticholinergics, antipsychotics, cytotoxic drugs, clonidine, and calcium channel blockers. Of particular importance, is the discontinuation of opiates if possible.

Methylnaltrexone is an opioid antagonist that binds to receptors in the gastrointestinal tract alone, without altering drug effect on pain. It is helpful in patients on narcotic agents who cannot have them discontinued, or that have just been discontinued recently, and are still having an effect. Dosing is subcutaneous and weight related: less than 38 kg, 0.15 mg/kg rounded off to the nearest 0.1 mL of volume; 38 to 62 kg, 8 mg subcutaneously; 62 to 114 kg, 12 mg subcutaneously; and more than 114 kg, 0.15 mg/kg rounded off to the nearest 0.1 mL of volume (Table 2).

A bowel movement frequently occurs within 30 minutes after methylnaltrexone administration, which may lead to colonic decompression. Side effects include abdominal pain, 14% to 29%; flatulence, 13%; and nausea, 9% to 12%.

Patients with progressive cecal dilation greater than 12 cm and/or those not responding to conservative therapy within 48 hours should be treated with neostigmine or colonic decompression.

Neostigmine Therapy

Neostigmine

Neostigmine is an acetylcholinesterase inhibitor that induces a potent parasympathetic response (Box 1). This leads to rapid restoration of colonic peristalsis and frequent resolution of ACPO. Controlled trials

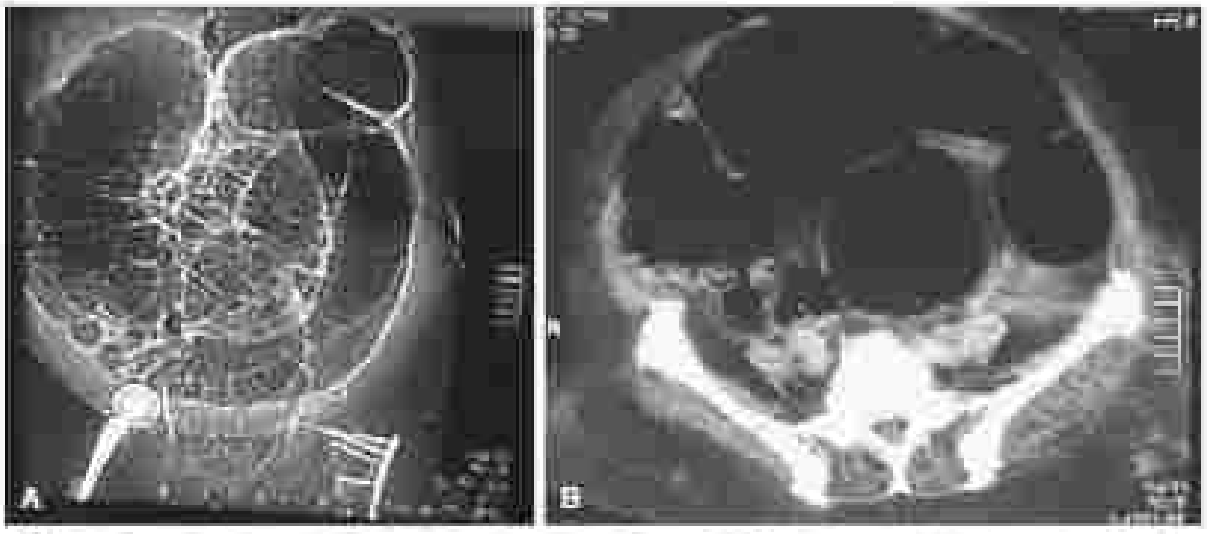

FIG. 1 CT scans illustrating marked dilation of the colon without significant wall thickening to suggest ischemia and without free air.

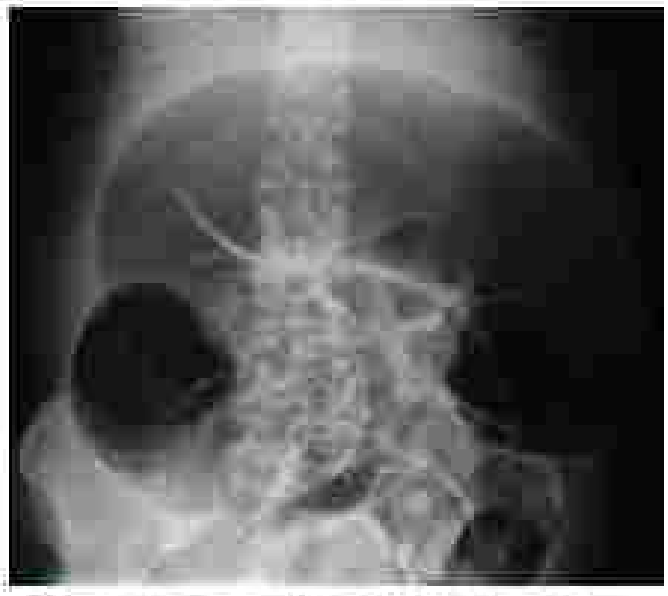

FIG. 2 Marked colonic dilation on upright radiograph of the abdomen.

TABLE 2 Dosing of Methylnaltrexone

38–<62 kg	8 mg subcutaneously
62–114 kg	12 mg subcutaneously
>114 kg	0.15 mg/kg, rounded off to the nearest 0.1 mL of volume

BOX 1 Neostigmine Therapy

Contraindications

- Mechanical colonic obstruction
- Bradycardia <60 beats/min, hypotension, systolic blood pressure <90 mm Hg
- Recent myocardial infarction
- Reactive airway disease
- β-Blocker therapy

Dosing

- 2 mg intravenously once, given slowly over 3 minutes, may repeat in 3 hours if inadequate response
- Consider simultaneous administration of glycopyrrolate 0.4 mg intravenously to attenuate side effects
- Decrease dose in setting of renal failure

Monitoring

- Continuous electrocardiogram, oxygen saturation, and blood pressure monitoring

have documented the effectiveness of neostigmine in the resolution of ACPO. Most series show successful colonic decompression in 85% to 90% after neostigmine administration. Dosing has varied in the series, from 2 to 5 mg administered over 1 to 3 minutes IV, 2 to 5 mg IV every 30 minutes, and 5 mg given over 1.2 hours. Most authors give 2.0 mg IV given slowly over 3 minutes. Patients usually respond with a large evacuation of gas and stool within 30 minutes of IV administration (Table 3).

TABLE 3 Neostigmine Dose Adjustments With Renal Impairment

Creatinine clearance 10–50 mL/min	Decrease dose by 50%
Creatinine clearance <10 mL/min	Decrease dose by 75%

Neostigmine should be avoided in patients with suspected perforation or ischemia, and in pregnant. Relative contraindications include bradycardia less than 60 beats/min, systolic blood pressure less than 90 mm Hg, reactive airway disease, recent myocardial infarction, and concomitant β-blocker therapy.

Side effects relate to cholinergic and parasympathetic stimulation and include abdominal pain in 5.9%, diarrhea in 3.9%, and vomiting in 1.6%.

The most concerning side effect is bradycardia, which occurs in 5% to 10% of patients. The patient should have continuous electrocardiography monitoring and oxygen saturation with frequent blood pressure measurements. Atropine and glycopyrrolate must be readily available in case of bradycardia or bronchospasm. Patients with a partial or poor response to neostigmine are frequently treated again 24 hours later.

ENDOSCOPIC COLONIC DECOMPRESSION

Decompression of the colon via colonoscopy is another nonoperative option. Colonoscopy is performed without colonic prepping and may be performed in the endoscopy suite or at the bedside in critically ill patients. Liquid stool is usually encountered, some of which can be aspirated. Care must be taken not to further distend the colon through air infusion, which may decrease perfusion to the right colon and lead to perforation. Use of CO_2 for insufflation is preferable to air.

Once the scope is passed into the right colon, air and fluid are aspirated. Abdominal distention usually improves acutely and dramatically. Reaching the ascending colon significantly increases the chances of adequate decompression, compared with aspiration of the transverse and left colon alone. Colonic decompression shows initial decompression rates of 61% to 95% with sustained decompression in 70% to 90% of cases.

Some endoscopists pass a guidewire through the colonoscope while in the right colon, with or without fluoroscopic guidance. The wire is left in place in the cecum or ascending colon while the colonoscope is removed. A decompression tube is passed over the guidewire into the right colon. Low intermittent suction is used for decompression.

A small nonrandomized study showed a 36% ACLO recurrence rate after colonic decompression alone, and no recurrences in the patients treated with decompression tubes. Colonic decompression has a complication rate of 5% including perforation (2%) and mortality (1%).

The initial intervention of ACLO, whether neostigmine or colonic decompression, has not been determined. Attendant medical conditions such as asthma, cardiac ischemia, arrhythmias, and heart block should be weighed in considering administration of neostigmine. A recent retrospective study by Peter et al. suggests that colonic decompression is more effective than neostigmine as initial therapy of ACLO (30% vs 48% initial response). Both forms of therapy appear to be effective and relatively safe.

Recurrent colonic dilation occurs in a small percentage of patients after initial successful decompression, either with neostigmine or colonoscopy. Recurrent therapy with neostigmine or colonic decompression is successful in these patients, with overall good success.

A small randomized, blinded, placebo-controlled trial demonstrated a decreased incidence of relapses in patients treated with polyethylene glycol 29.5 g daily by mouth or via nasogastric tube compared with placebo (9% vs 53.9%). Polyethylene glycol therapy is initiated after successful decompression.

In patients not responding to neostigmine or endoscopic decompression, endoscopic cecostomies have been performed with good success and few complications. Studies have been extremely small, and experience limited.

Cecostomy can be performed via colonoscopy, interventional radiology, or less frequently, surgically. Experience is extremely limited; however, success rates appear to be high, and complications low.

Surgery is required in patients with ischemia or perforation. Mortality rates range from 30% to 60%. Surgical options include laparoscopic or open cecostomy or colectomy, subtotal or total colectomy, with or without ileostomy.

SUMMARY

Acute colonic pseudo-obstruction is a disorder of colonic motility leading to massive colonic dilation without obstruction. It occurs almost exclusively in hospital patients postoperatively and with comorbid conditions. Diagnosis is made with CT scan of the abdomen and pelvis. The patients are followed with daily abdominal radiographs.

All patients receive supportive care with bowel rest, IV hydration, and attempts to resolve precipitating abnormalities. If the patient does not respond to conservative therapy within 48 hours, therapy with neostigmine or colonic decompression should be initiated to prevent complications of ischemia and/or perforation. Repeat therapy may be necessary for partial or nonresponders. Further options, such as cecostomy or surgery, are rarely necessary.

SUGGESTED READINGS

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Ponec RJ, Olson M. Colonoscopic decompression should be used before neostigmine in the treatment of Ogilvie's syndrome. *Eur J Trauma Emerg Surg* 2007;33:557–559.

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MANAGEMENT OF COLONIC VOLVULUS

Victoria Needham, MD, Renee Huang, MD, and Rebecca Lavinia, MD, FACS

Volvulus refers to twisting of a segment of the intestine. It can occur at any site in the gastrointestinal tract that is both mobile and long enough to rotate on a narrow based base. The twist of intestinal volvulus produces a closed loop bowel obstruction. Colonic volvulus accounts for 2% to 4% of all bowel obstructions in the United States, and 10% to 15% of all large bowel obstructions, with higher incidence in Africa, the Middle East, and South America. It most commonly occurs in the cecum and sigmoid colon because they are the most mobile parts of the colon, but has also been reported in the transverse colon, splenic flexure, and as the rare pathology of floating mesenteric knotting. Sigmoid volvulus accounts for 30% to 60% of colonic volvulus in the literature, whereas cecal volvulus accounts for 30%, although it has been documented to be increasing in incidence over the past decade. In the United States, patients with colonic volvulus tend to be older and have medical conditions that predispose them to chronic constipation or colonic dysmotility. They present with classic obstructive symptoms in a range of intermittent, slowly progressive, or acute forms, and the diagnosis can be differentiated from other types of large bowel obstruction by imaging studies or via operative exploration. Although management differs based on site of volvulus and patient factors, there are three cornerstones of treatment: detorsion (operatively in most cases, endoscopically in select sigmoid cases), resection of any ischemic or compromised colon, and their diversion or anastomosis of the remaining lower gastrointestinal tract. Rarely do fixation procedures serve as definitive operative treatment.

CECAL VOLVULUS

Cecal volvulus is the second most common type of colonic volvulus and exists in two distinct forms. A true cecal volvulus is an axial rotation of the terminal ileum, cecum, and proximal right colon, usually clockwise, around its mesentery, whereas a cecal bascule is an anterosuperior folding of the cecum, accounting for 10% of cases.

Several factors are thought to predispose patients to develop cecal volvulus. Foremost, increased mobility of the cecum is a feature of all volvulus, which can be either congenital or acquired. Approximately 10% to 25% of the population has a cecum and ascending colon mobile enough to form a volvulus on autopsy studies, which is thought to result from failed fusion of the ascending colon mesentery to the posterior parietal peritoneum. Adhesions from prior surgery or other iatrogenic anatomic abnormalities can result in acquired cecal mobility, with 30% to 70% of patients with cecal volvulus having a history of abdominal surgery. Additional factors associated with cecal volvulus include a female predominance (1.4:1), younger age, pregnancy or other colonic upward displacement by abdominopelvic structures or masses, and chronic constipation or colonic motility disorders such as Hirschsprung's disease.

Patients with cecal volvulus may present clinically with an intermittent, recurrent obstructive process or with an acute obstruction. Patients generally present with classic obstructive symptoms and signs including nausea, vomiting, anorexia, abdominal distention, constipation, tympany, and tenderness. Because volvulus is a closed loop obstruction, vascular compromise ensues, which may lead to diffuse peritonitis and even perforation.

Once volvulus is clinically suspected, imaging studies can help to confirm the diagnosis, distinguish a volvulus from other types of bowel obstruction or intraabdominal pathology, and determine the severity at presentation. Patients who present with frank peritonitis should be sent to the operating room. Otherwise, a workup of severe abdominal pain should begin with upright and flat abdominal radiographs, although abdominopelvic computed tomography (CT) scan is also commonly used as a first line imaging modality. Specific plain film and CT scan findings for volvulus are a "coffee bean" sign, with the apex of the distended, volvulized segment of right colon located in the left upper quadrant (Fig. 1), an "X marks the spot" sign of two crossing transition points in neighboring imaging slices, a "split wall" sign showing cecal wall separation by mesenteric fat in incomplete twisting, and small bowel distention and air fluid levels proximal to the cecal obstruction with distal colonic decompression. In contrast, a cecal bascule may appear as a "kidney bean" on the right side of the abdomen. In addition, a "whirl sign" on CT is pathognomonic for true (axial) cecal volvulus when associated with an abnormally positioned cecum, representing the mesentery twisted around the ileocolic vessels. Contrast enema is more specific for cecal volvulus. Despite these classic radiographic signs, volvulus is first revealed at the time of surgical exploration in 17% to 50% of patients.

A treatment algorithm for cecal volvulus has been described based on the level of bowel compromise and takes into account the patient's hemodynamic status. Both axial cecal volvulus and cecal

In patients not responding to neostigmine or endoscopic decompression, endoscopic cecostomies have been performed with good success and few complications. Studies have been extremely small, and experience limited.

Cecostomy can be performed via colonoscopy, interventional radiology, or less frequently, surgically. Experience is extremely limited; however, success rates appear to be high, and complications low.

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Volvulus refers to twisting of a segment of the intestine. It can occur at any site in the gastrointestinal tract that is both mobile and long enough to rotate on a narrow based base. The twist of intestinal volvulus produces a closed loop bowel obstruction. Colonic volvulus accounts for 2% to 4% of all bowel obstructions in the United States, and 10% to 15% of all large bowel obstructions, with higher incidence in Africa, the Middle East, and South America. It most commonly occurs in the cecum and sigmoid colon because they are the most mobile parts of the colon, but has also been reported in the transverse colon, splenic flexure, and as the rare pathology of floating mesenteric knotting. Sigmoid volvulus accounts for 30% to 60% of colonic volvulus in the literature, whereas cecal volvulus accounts for 30%, although it has been documented to be increasing in incidence over the past decade. In the United States, patients with colonic volvulus tend to be older and have medical conditions that predispose them to chronic constipation or colonic dysmotility. They present with classic obstructive symptoms in a range of intermittent, slowly progressive, or acute forms, and the diagnosis can be differentiated from other types of large bowel obstruction by imaging studies or via operative exploration. Although management differs based on site of volvulus and patient factors, there are three cornerstones of treatment: detorsion (operatively in most cases, endoscopically in select sigmoid cases), resection of any ischemic or compromised colon, and their diversion or anastomosis of the remaining lower gastrointestinal tract. Rarely do fixation procedures serve as definitive operative treatment.

CECAL VOLVULUS

Cecal volvulus is the second most common type of colonic volvulus and exists in two distinct forms. A true cecal volvulus is an axial rotation of the terminal ileum, cecum, and proximal right colon, usually clockwise, around its mesentery, whereas a cecal bascule is an anterosuperior folding of the cecum, accounting for 10% of cases.

Several factors are thought to predispose patients to develop cecal volvulus. Foremost, increased mobility of the cecum is a feature of all volvulus, which can be either congenital or acquired. Approximately 10% to 25% of the population has a cecum and ascending colon mobile enough to form a volvulus on autopsy studies, which is thought to result from failed fusion of the ascending colon mesentery to the posterior parietal peritoneum. Adhesions from prior surgery or other iatrogenic anatomic abnormalities can result in acquired cecal mobility, with 30% to 70% of patients with cecal volvulus having a history of abdominal surgery. Additional factors associated with cecal volvulus include a female predominance (1.4:1), younger age, pregnancy or other colonic upward displacement by abdominopelvic structures or masses, and chronic constipation or colonic motility disorders such as Hirschsprung's disease.

Patients with cecal volvulus may present clinically with an intermittent, recurrent obstructive process or with an acute obstruction. Patients generally present with classic obstructive symptoms and signs including nausea, vomiting, anorexia, abdominal distention, constipation, tympany, and tenderness. Because volvulus is a closed loop obstruction, vascular compromise ensues, which may lead to diffuse peritonitis and even perforation.

Once volvulus is clinically suspected, imaging studies can help to confirm the diagnosis, distinguish a volvulus from other types of bowel obstruction or intraabdominal pathology, and determine the severity at presentation. Patients who present with frank peritonitis should be sent to the operating room. Otherwise, a workup of severe abdominal pain should begin with upright and flat abdominal radiographs, although abdominopelvic computed tomography (CT) scan is also commonly used as a first line imaging modality. Specific plain film and CT scan findings for volvulus are a "coffee bean" sign, with the apex of the distended, volvulized segment of right colon located in the left upper quadrant (Fig. 1), an "X marks the spot" sign of two crossing transition points in neighboring imaging slices, a "split wall" sign showing cecal wall separation by mesenteric fat in incomplete twisting, and small bowel distention and air fluid levels proximal to the cecal obstruction with distal colonic decompression. In contrast, a cecal bascule may appear as a "kidney bean" on the right side of the abdomen. In addition, a "whirl sign" on CT is pathognomonic for true (axial) cecal volvulus when associated with an abnormally positioned cecum, representing the mesentery twisted around the ileocolic vessels. Contrast enema is more specific for cecal volvulus. Despite these classic radiographic signs, volvulus is first revealed at the time of surgical exploration in 17% to 50% of patients.

A treatment algorithm for cecal volvulus has been described based on the level of bowel compromise and takes into account the patient's hemodynamic status. Both axial cecal volvulus and cecal

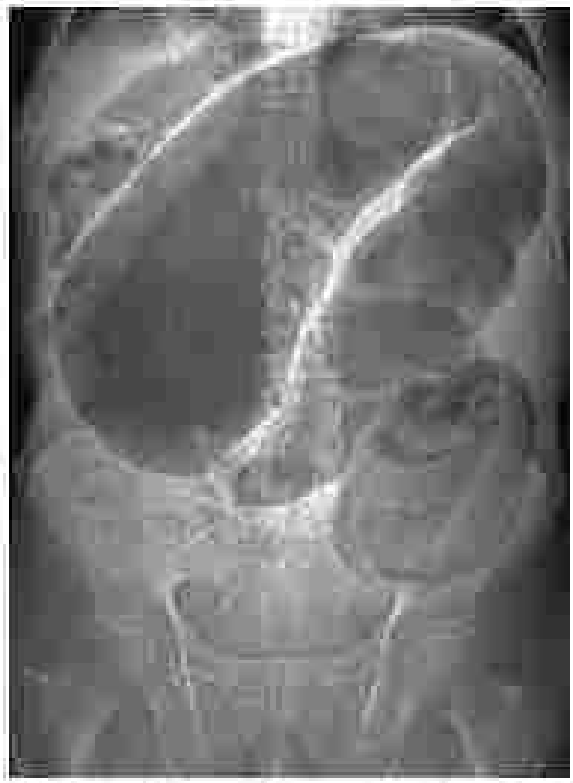

FIG. 1 "Coffee bean" sign, classically observed on plain film of sigmoid volvulus, with the apex of the distended, redundant segment of right colon pointed to the left upper quadrant. *(From Hobler J. Colonic volvulus. In: The ASCRS Textbook of Colon and Rectal Surgery. 3rd ed. Springer International; 2016:[in press].)*

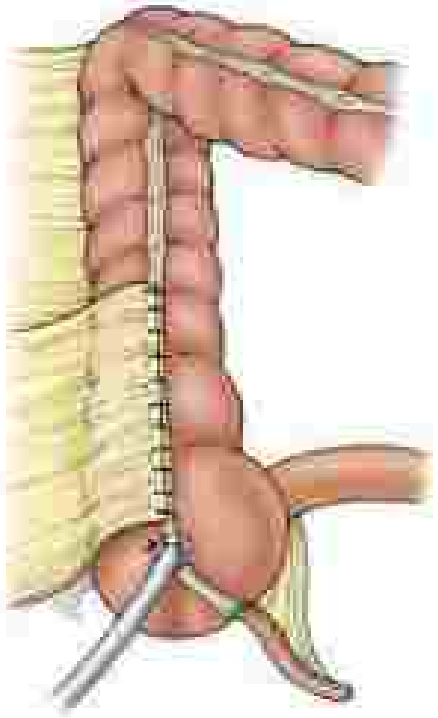

FIG. 2 *Colon fixation via cecopexy and percutaneous tube placement for treatment of cecal volvulus. (From Hobler J. Colonic volvulus. In: The ASCRS Textbook of Colon and Rectal Surgery. 3rd ed. Springer International; 2016:[in press].)*

fascicle are treated similarly. In contrast to select cases of sigmoid volvulus, endoscopic reduction of cecal volvulus, although described, is not a recommended treatment modality because of its technical difficulty, rate of missed ischemia, risk of perforation, and delay in more definitive surgical treatment. Surgical exploration with resection of the affected portion of intestine provides the lowest rate of recurrence. Both midline laparotomy and laparoscopic exploration have been described, with the latter having a lower mortality rate in a large retrospective dataset, but may be explained by a selection bias for patients with fewer medical comorbidities. On exploration, the bowel should first be examined for signs of compromise. If gangrene is evident, detorsion is not attempted because of the risk of bacteremia and sepsis from reperfusion. If the bowel appears viable, detorsion can be accomplished. In either case, the extent of resection is determined by the extent of bowel compromise plus the mobility of the ascending colon. Cases of nonviable or perforated bowel carry a higher rate of perioperative mortality and mandate resection. An ileocolectomy or a right colectomy are both appropriate operations if all compromised bowel is included. If redundancy of the right colon exists after ileocolic resection, literature has supported cecopexy of the right colon remnant to the posterior peritoneum to help prevent recurrent volvulus. For patients with significant perforation and soiling, extensive gangrene, hemodynamic instability, or severe underlying disease such as malnutrition or anemia, current guidelines support resection of the compromised portion with ileostomy (and or loop, and possible mucous fistula creation) if deemed necessary at the time of operation.

For patients with viable bowel, although definitive resection remains the most effective strategy for preventing recurrence, nonresectional operative techniques may be more appropriate in hemodynamically unstable patients and patients with risk factors for perioperative morbidity. Detorsion alone is associated with a recurrence rate of up to 23% and a high rate of perioperative mortality [138–139]; therefore, some studies have advocated against its use. Detorsion coupled with a fixation procedure is thought to reduce the risk of both recurrence and perioperative mortality in patients who would otherwise be poor candidates for operative resection. Fixation can be accomplished with either cecopexy, cecostomy tube placement, or both. A cecopexy is the suturing of the serosa of the distended, mobile segment of cecum (plus flexure and/or right colon), to a raised flap of adjacent retroperitoneal tissue, reducing colonic mobility. This can be done alone or in conjunction with cecostomy tube placement (Fig. 2). Recurrence rates approach that of detorsion alone, whereas mortality ranges from 0% to 14%. A cecostomy tube can be placed to decompress the distended colon and provide fixation. A tube, typically a Malecot drain, is placed via percutaneously along the anterior cecum, sutured in place with a purse-string suture, and then brought out to drain externally (Fig. 2). Although cecostomy tube placement can be faster and simpler than formal resection and therefore may be preferred in hemodynamically unstable patients, the potential perioperative complications are significant, including fecal spillage and cutaneous fistula, with a recurrence rate up to 10% and double the mortality of resection. The current literature provides no consensus regarding the best operation for this subset of patients; therefore, patients' perioperative risk should be weighed with their risk of recurrence and appropriate management chosen accordingly.

SIGMOID VOLVULUS

The sigmoid colon is the most common location for colonic volvulus. There is a male predominance of 2:1 and the age at presentation is often older (>70 years of age) than for cecal volvulus. Increased incidence of sigmoid volvulus is seen in regions where a high fiber diet predominates, such as Africa, India, and the Middle East. A high-residue diet is thought to lengthen the intestine and its mesentery, making it more prone to twisting. Other risk factors include black race, diabetes, pregnancy, colonic dysmotility, chronic constipation

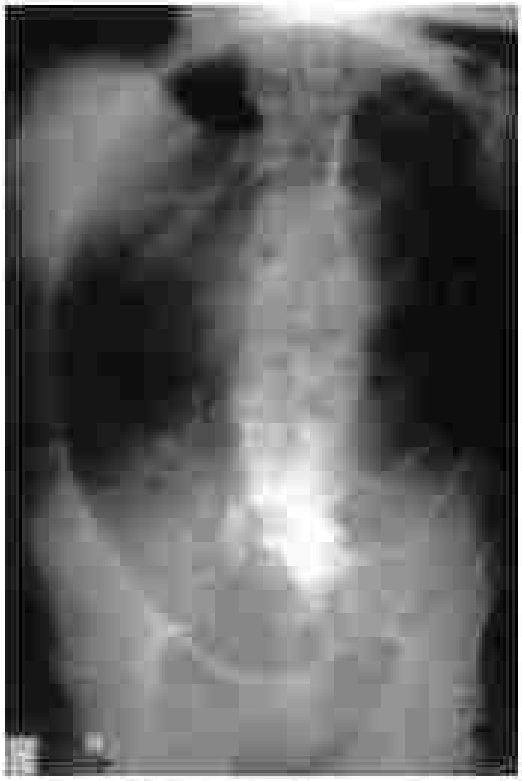

FIG. 3. "Bent inner tube" or "coffee bean" appearance of a dilated sigmoid colon with the apex of the bend pointing toward the right upper quadrant. [From Kumar J, Kumar Abhishek M, Das Abhijit, Sreenivas V, Shukla R. Endoscopic management of sigmoid volvulus: a review of 30 cases. Dis Colon Rectum. 2010;53:1]

and megacolon. Higher rates are also seen in institutionalized patients and those with disability via neurologic and psychiatric disorders. Overall, patients with sigmoid volvulus have a higher degree of medical comorbidities compared with those with cecal volvulus and have an overall higher mortality rate (9.4% vs 6.7%).

Although the exact pathophysiology has not been fully described, these associated conditions all in some way predispose the sigmoid colon to become elongated and redundant, which leads to twisting on a narrow mesenteric attachment, most often in a counterclockwise direction. Once the colon twists 180 degrees, a clinically significant large bowel obstruction occurs and generally presents with a slow, insidious onset of abdominal pain, distention, nausea, and constipation, with vomiting following days after the initial symptoms. As the twisting persists or progresses, vascular compromise ensues, which can lead to necrosis and perforation. More acute presentations of severe pain with fulminant colonic gangrene have also been described, attributed to rapid colonic distention. Symptoms and signs may be less clinically apparent in the older population.

Participants on examination mandates operative exploration. Otherwise imaging studies can be obtained to further elucidate the diagnosis and cause of the obstruction. The classic radiographic finding of a "bent inner tube" or "coffee bean" appearance of a dilated sigmoid colon with the apex of the bend pointing toward the right upper quadrant confirms the diagnosis in 90% of cases (Fig. 3). If plain film is equivocal, either a CT scan or a contrast enema, which is a less common yet highly specific modality, should be performed. Similar to cecal volvulus, CT scan findings sensitive and specific for sigmoid volvulus include the coffee bean sign, the appropriately located X marks the spot sign, the split wall sign, and the whirl sign, along with the absence of rectal gas. In addition, the adjacent twisted colonic segments may show a "bird's beak" appearance, a sign that is also apparent on the afferent end of a volvulus in a water soluble contrast enema. Although some describe enema as both a diagnostic and therapeutic tool, its use for the latter is very infrequent (<1% in a cohort of >3 million cases in the United States over 10 years), and surgical expertise should be available at the time of the enema because of risk of perforation. Ogilvie's syndrome (colonic pseudo obstruction) is a common differential diagnosis for sigmoid volvulus because it often presents in a similar patient population and may appear similar on initial clinical presentation and plain film. CT scan should be able to differentiate between the two diagnoses, with the absence of whirled mesentery and distal transition point to pseudo obstruction.

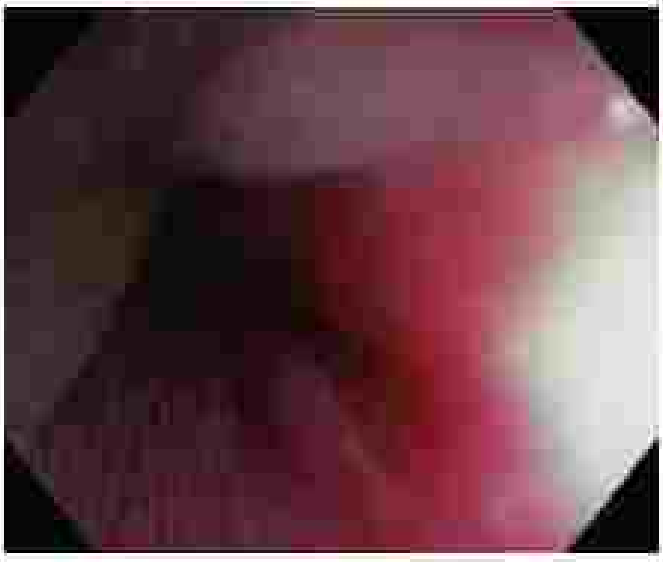

FIG. 4. Spiraling appearance of colonic mucosa in sigmoid volvulus at the site of obstruction. [From Ang S-J, Wu E-J. Endoscopic decompression, reduction and resection of sigmoid volvulus. Volvo J Hepatobiliary GI Oncol Sci. 2014;7:22]

As with any intestinal volvulus, the goals of treatment are to reduce the twisted bowel and prevent recurrence. In the presence of peritonitis or sepsis, or if gangrene or bowel perforation is suspected from laboratory findings and imaging studies or found on endoscopic evaluation, an emergent operation is required. Nonviable bowel should not be drawn. Voluminal, redundant, and any nonviable or suspected ischemic sigmoid colon should be resected. No statistically significant differences in perioperative morbidity and mortality have been observed in the literature between Hartmann's procedure and primary anastomosis with or without proximal diversion for resectable cases of sigmoid volvulus. Selective use of Hartmann's procedure may be appropriate and is described for patients with hemodynamic instability, coagulopathy, severe acidosis, hypothermia, or significant medical comorbidities (increased American Society of Anesthesiologists score). Patients with sigmoid volvulus in the setting of megacolon should undergo subtotal colectomy as sigmoid resection alone has been shown to have a higher rate of recurrence.

In the absence of emergent characteristics, current guidelines recommend proceeding in a stepwise fashion to achieve the lowest rate of recurrence with the lowest risk of perioperative mortality, first with endoscopic decompression and detorsion of the sigmoid volvulus and second by definitive sigmoid resection during the index admission. Endoscopy is both diagnostic and therapeutic because it offers an assessment of bowel viability and is successful in decompressing, detorting, and reducing the colon in 55% to 95% of patients. It is performed most commonly by flexible sigmoidoscopy, although both rigid sigmoidoscopy and colonoscopy can be used. First the distal colon is examined, maintaining low and low-pressure insufflation of air. The first, distal point of twisting should be recognized as a converging or spiraling of colonic mucosa, usually near the rectosigmoid junction (Fig. 4). If mucosal ischemia, gangrene,

or perforation are apparent on examination, reduction should not be attempted, and emergent surgical resection becomes necessary. If the colonic mucosa appears viable, the scope can be gently advanced into the dilated loop of sigmoid colon. Successful decompression is confirmed by the evacuation of copious flatus and stool with decreased abdominal distention. The endoscope can then be advanced toward the proximal point of the volvulus, again identifying and detorting the area of spiraling mucosa. The scope is then withdrawn to continue the reduction (shortening) of the bowel loop. A rectal tube can be placed for maintenance of decompression, prevention of recurrence, and facilitation of bowel preparation for definitive resection within the index admission. Endoscopic placement of the rectal tube over a guidewire has been described. A plain film is obtained post-procedure to evaluate for resolution of volvulus and to rule out free air. If reduction is unsuccessful, the patient requires urgent operative sigmoid resection.

Endoscopic decompression alone has a recurrence rate of 60% to 75%, with particularly high risk in the first 30 days postprocedure, and should therefore be followed by definitive sigmoid resection during the same admission. Elective resection after endoscopic decompression has a mortality rate less than 10% and a recurrence rate of nearly zero. Patients should undergo bowel preparation and preoperative optimization of comorbid medical conditions. A completion colonoscopy should be considered either at the first or subsequent endoscopy to evaluate for other colonic lesions that could alter the planned operation. Both open and laparoscopic approaches have been described, with use of the latter increasing over the past decade. Open resection can be approached via lower midline laparotomy. After mobilization, the colon can be exteriorized either through the laparotomy wound or through a wound protector in laparoscopic cases, the remainder of the field can be covered with towels to control contamination. Hartmann volvulus is most commonly presented by performing a sigmoid colectomy with colorectal anastomosis. Proximally, resection should include all redundant and ischemic sigmoid and descending colon, with the distal margin at the rectosigmoid junction. Ostomy creation (either Hartmann's procedure with end colostomy or a primary anastomosis with a diverting loop ileostomy) is less commonly performed in the nonemergent setting but may be necessary in the setting of a deteriorating clinical picture, significant colonic distension or fecal spillage, insufficient length, compromised blood supply, or significant comorbidities that could predispose a patient to anastomotic breakdown. Operative detorsion alone or combined with fixation procedures (extraperitoneal sigmoidopexy or peexy to the abdominal wall with prosthetic, parallel colopexy to transverse colon, and mesosigmoidoplasty) have been described for sigmoid volvulus, but are uncommonly performed and not recommended because they are associated with significant perioperative complications as well as high recurrence rates (at least 20%), and offer no benefit over formal resection particularly because morbidity for the latter has decreased substantially in recent years.

Endoscopic reduction and decompression convert an emergent pathology into an indication for elective surgery, ideally within the index admission after additional decompression and resuscitation for 24 to 72 hours. Endoscopic therapy alone has a high recurrence rate (Table 1). Although some have advocated for one-stage endoscopy and resection or an elective colonic lavage and resection, no randomized control trials exist to determine their efficacy and outcomes. Regardless, in the case of cecal or sigmoid volvulus, the operating room should be equipped with endoscopic equipment and expertise should the need arise.

Another procedure supported by increasing evidence is the percutaneous endoscopic colostomy technique for fixation of the sigmoid colon to the anterior abdominal wall following endoscopic detorsion and decompression. The procedure is indicated primarily for patients who are poor candidates for operative resection as a result of comorbid conditions because it can be done under minimal sedation. The colon is fixed to the abdominal wall either by tube colostomy or with T fasteners, at one or two points. From the available studies, recurrence rates for this procedure are low, and perioperative mortality is variable but potentially acceptable when weighed against these patients' comorbidities.

Overall, outcomes for sigmoid volvulus with necrotic are poor. Operation in the emergent setting carries a 20% mortality rate. Both peritonitis and gangrenous colon are strong predictors of perioperative complications and mortality, followed by the use of a stoma. In the literature, Hartmann's procedure is used in 15% of elective cases and 24% of emergent cases, and any stoma (end or diverting) is used in one half of all operations for sigmoid volvulus. Anastomotic complications occur in up to 15% of cases.

OTHER COLONIC VOLVULUS

Splenic flexure and transverse colon volvulus are rare, accounting for 1% to 3% and 1% to 4% of all colonic volvulus, respectively. These patients are generally younger than those with cecal or sigmoid

TABLE 1 Management and Outcomes of Endoscopy Therapy for Sigmoid Volvulus

Study	No. of Patients	% Male	Age (y)	Success Rate of Endoscopic Detorsion (%)	Rate of Performance of Emergency Operation (%)	Recurrence Rate After Endoscopic Treatment (%)	Mortality Rate (%)
Ballabio et al. (2014)	19,238	65.5	71.0 (62–82)*	ND	ND	ND	9.4
Ulmer et al. (2007)	827	83.2	72.9 (0–98)*	78.1	47.5	34.9	15.8
Soloklaus et al. (2007)	33	54.5	ND	78.8	21.2	41.7	5.9
Tan et al. (2010)	73	68.6	73.0 (17–96)*	80.1	9.9	68.9	6.2
Akamangwa (2013)	902	82.4	58.6 (0–98)*	79.7	42.8	42.6	8.1
Larkin et al. (2009)	27	70.4	75.3 (48–99)*	55.6	25.9	86.7	22.2
Total	21	71.4	76.0 (54–80)*	61.9	38.1	84.2	4.8

*Mean (range).
†Median (range).
ND, not described.
From Ada S, Nakagaki S, Sarah S, et al. Clinical outcomes of sigmoid colon volvulus: classification of the factors associated with successful endoscopic detorsion. Intest Res. 2017;15(2):219.

volvulus, with a female predominance. Transverse colon volvulus has been associated with a higher comorbidity score than its cecal and sigmoid counterparts, despite resection at a younger mean age. As with other types of colonic volvulus, a history of chronic constipation, high fiber diets, and redundancy of the colonic segment are associated with their development, with the additional risk of prior abdominal surgery attributed to both splenic and transverse colonic volvulus. One half of cases present as acute and severe large bowel obstructions, whereas the other half have subacute or recurrent presentations. Plain films may show two air fluid levels. Similar to cecal volvulus, endoscopic decompression is not recommended, with resection of the involved segment necessary to relieve the twisted intestine and prevent recurrence. Transverse colon volvulus can be addressed via a transverse colectomy or an extended right colectomy, whereas a splenic flexure volvulus requires extended resection with theoretical anastomotic. Transverse colon volvulus has up to a threefold increase in mortality after resection compared to cecal and sigmoid volvulus.

Sinusgmoid knotting is a rare etiology of colonic volvulus in the United States, but is more commonly seen in Africa, Asia, and the Middle East. It involves wrapping of the ileum around itself or around the sigmoid colon, causing a double obstruction of both segments of intestine. Patients tend to be young, with a male predominance. These patients present with severe, acute bowel obstruction and require urgent operative exploration with detorsion (if possible) and resection of both segments. Hartmann's procedure, or en bloc resection of the knotting with ileocolic anastomosis. These cases carry a high mortality rate (10%–30%), which is increased if gangrene is present (up to 50%). Endoscopic reduction should not be attempted and has no documented success in the literature.

In addition, synchronous cecal and sigmoid volvulus has been documented (27 of 3,779 total cases of colonic volvulus over a 10-year period in the United States). In this cohort, patients had the highest level of medical comorbidities compared with other types of colonic volvulus, and a mortality rate of nearly 19%.

COLONIC VOLVULUS IN PREGNANCY

Pregnancy is an established risk factor for intestinal volvulus. Of all cases of bowel obstruction in pregnancy, although rare overall, 45% are caused by sigmoid volvulus. Ten percent of all patients with cecal volvulus are pregnant. This predisposition to volvulus likely occurs secondary to upward displacement of bowel loops by the gravid uterus, making them more mobile. The diagnosis has been shown to be delayed or made to the operating room after clinical deterioration, leading to a high mortality rate for volvulus in pregnancy. All available diagnostic options should be considered if there is clinical suspicion for volvulus up to and including safe radiologic techniques and diagnostic laparoscopy. In the absence of frank perforation or severe sepsis and peritonitis indicating emergent operation, treatment can be stratified by trimester for sigmoid volvulus. It is less well described for other types but in general warrants a careful analysis of the risks and benefits. In the first trimester, if the colon is deemed viable, endoscopic detorsion should be performed. Definitive resection can occur in the second trimester when peri-operative risks to the fetus are lessened. For sigmoid volvulus that occurs during the third trimester, nonoperative management including endoscopic decompression is preferred with definitive resection postpartum.

SUMMARY

Colonic volvulus accounts for approximately 13% of all large bowel obstructions in the United States, with sigmoid and cecal volvulus being the most common. It most frequently affects elderly patients with significant comorbidities, and therefore portends a poor outcome overall. Signs and symptoms of obstruction generally lead to an imaging diagnosis, whereas some cases can present as acute sepsis, peritonitis, or perforation and are diagnosed intraoperatively. Treatment method is determined by the viability of the involved bowel, the hemodynamic stability of the patient and the patient's overall perioperative risk. Endoscopic decompression can be achieved for sigmoid volvulus with viable bowel. Recurrence is best prevented by definitive operative resection of the involved colonic segment for all types of colonic volvulus, although fixation procedures have been described. Colonic volvulus is not uncommon in the setting of pregnancy and should be considered early in the differential for obstructive signs and symptoms, with treatment stratified by trimester.

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Management of Rectal Prolapse

Katerina Wells, MD, MPH, and James Hashemari, MD

Rectal prolapse occurs when the rectal wall invaginates through the anus. This is a rare disorder that occurs in approximately 0.5% of the population. Typically, women in the fifth to eighth decades of life are affected; however, this disorder is also seen in a very different subset of younger patients, usually with psychiatric illness, developmental delay or autism, and severe constipation. Men with rectal prolapse tend to present earlier, in the third to fourth decades of life.

Historically, multiparity was thought to contribute to the pathogenesis of rectal prolapse. Yet, 30% of women with rectal prolapse are nulliparous, suggesting a different etiology compared to anterior (cystocele and uterine) prolapse.

PRESENTATION

The symptoms of rectal prolapse include rectal pressure or pain resulting from the prolapsing tissue through the anus and drainage of mucus and blood from the exposed friable mucosa. Patients may experience constipation (25%–50%) thought to be due to mechanical blockage of the rectum or associated pelvic dysfunction, fecal incontinence resulting from stretch-induced denervation, and subsequent atrophy of the external anal sphincter. In addition to the physical complications of prolapse, this can be an emotionally traumatic and socially isolating disease.

EVALUATION

Evaluation of a patient begins with a thorough evaluation for modifiable risk factors, exacerbating factors, and symptoms related to the prolapse. A surgical history must detail any prior abdominal surgery, rectal resection, or pelvic radiation that may influence surgical management. Physical examination includes digital rectal examination to assess sphincter tone and proctoscopy to evaluate for alternative diagnoses that can be confused with rectal prolapse, including prolapsing hemorrhoids or prolapsing masses. Full-thickness prolapse is distinguishable by the appearance of concentric circular folds, whereas prolapsing hemorrhoids will have radial grooves on either side of the hemorrhoidal columns. It is important to document the maximum extent of prolapse when the patient strains to distinguish between distal rectal mucosal prolapse and full-thickness rectal prolapse. A prolapse of less than 3 cm may be limited to the mucosa and is treated differently.

Patients with rectal prolapse frequently have a pudendal neuropathy with decreased resting tone. The prolapse will typically reduce to the prone jack-knife position but can be induced with Valsalva maneuvers. The best method for eliciting prolapse is to have the patient sit on the commode and bear down to simulate defecation. In some cases when the prolapse is more conditional, patients can be asked to photograph the prolapse in the comfort of their home. Anterior prolapse including cystocele or uterine prolapse may accompany the rectal prolapse up to 20% of the time. This combination of disease should be fully assessed with pelvic imaging (computed tomography, magnetic resonance imaging, cystography) because correction often requires a multidisciplinary approach. Additional diagnostic testing including defecography may be helpful in the case of occult prolapse or distal rectal mucosal prolapse.

TREATMENT

Rectal prolapse is a surgical disease. Nonoperative measures are used to temporize the surgical patient or provide palliation in the prohibitively morbid patient. In the case of acute prolapse without strangulation, the prolapse should be reduced. Topical application of table sugar to the incarcerated edematous rectum may decrease edema of the rectum and allow return of the rectum to the pelvis until surgery is planned. For those without a surgical option, attention to a bowel regimen and skin care can offer some improvement in quality of life.

Patients who are deemed fit for surgical intervention should proceed with surgery without delay to avoid irreversible fecal incontinence. Before the surgical procedure, oral antibiotic and mechanical bowel preparation should be prescribed as part of an enhanced recovery pathway. Standard prophylaxis for venous thromboembolism and surgical site infections are also administered.

Perineal vs Transabdominal Repair

There is no consensus on the best surgical approach for rectal prolapse and it remains a matter for debate. Traditionally, transabdominal repairs are preferred over perineal repairs in the fit patient because of the lower rate of recurrence and perineal repairs are recommended for comorbid patients because of a lower operative impact and morbidity. Recurrent prolapse has been reported after abdominal rectopexy in 7% to 9% of patients and after perineal procedures in 10% to 30% of patients. However, more recent evidence from the Prospective Study of Pneumatic in the Elderly at Risk randomized trial finds that functional outcomes and rates of recurrence (12%–21%) are similar between perineal and abdominal procedures, with a higher rate of recurrence for abdominal procedures than previously reported. The majority of patients reported significant functional improvements, suggesting that perineal proctectomy is an acceptable strategy even in the younger subset. The importance of recurrent prolapse may also be overemphasized in the comorbid population with a limited life expectancy. Minimally invasive techniques and advances in perioperative management have improved enough to mitigate the operative morbidity of a transabdominal repair. In a National Surgical Quality Improvement Program analysis of 2188 matched patients undergoing prolapse surgery by either a perineal or abdominal technique, no significant difference was found in the rate of any complication or mortality (0.9%). The hazard ratio for major morbidity after an abdominal approach relative to a perineal approach was only 1.30 (95% confidence interval, 0.92–2.10, $P = .15$). The authors concluded that many patients treated with perineal repair may have also done well if treated with a transabdominal repair. A 2012 Cochrane review included approximately 1000 patients, but the clinical data were found lacking to determine "clinically important differences between alternative surgical operations." Limitations of available data to direct choice of treatment mean that the approach for prolapse repair can be less motivated by outcomes of recurrence and more oriented to provide immediate reduction of the prolapse while addressing associated incontinence or bowel dysfunction.

Perineal Procedures

Prolapse procedures that employ a perineal approach are traditionally considered for those with short segment rectal prolapse (<3 cm) or for those with comorbidities precluding abdominal surgery. Anal encirclement (Thiersch wire) procedures that work by confining the prolapsed rectum within the anal canal are mostly mentioned for historical interest owing to associated high rates of fecal impaction and perineal sepsis. Currently, sleeve resection of the rectal mucosa (Delorme's procedure), Stapled Transanal Rectal Resection, and perineal rectosigmoidectomy with or without levatorplasty (Altemeier's procedure), are most commonly performed.

Mucosal Sleeve Resection (Delorme's Procedure)

First introduced in 1900, Delorme's procedure is safe and effective for the treatment of short segment (<5 cm) full thickness distal rectal prolapse or mucosal prolapse. The procedure is also an option for patients with previous rectal resection or pelvic radiation because no anastomotic resection or full thickness incision is required. This procedure consists of a circumferential resection of the prolapsing sleeve of mucosa to expose the distal muscularis propria. Placement of plicating stitches on at least three of the four quadrants to "accordion" and reduce the prolapsing muscularis propria to a thickened ring of muscle at the anal outlet.

Operative Technique

The patient can be positioned in either lithotomy, left lateral decubitus, or prone jackknife positions (Fig. 1A–F). A Lonestar retractor (Cooper Surgical), with hooks placed outside the anal verge, is used to expose the operative site. Using atraumatic clamps, the rectum is prolapsed as completely as possible to identify the proximal extent of planned mucosal resection. Tumescent solution of saline and epinephrine is injected circumferentially in the submucosa, creating a plane between the submucosa and muscularis propria and aiding in hemostasis. Using flush electrocautery, the mucosa is released from the circular muscles of the muscularis propria all the way to the anal transition zone above the dentate line. Plicating stitches are then placed in three or four quadrants from the proximal cut edge of the mucosa, in linear array serially through the muscularis (three to four bites), to the distal edge of the mucosa just proximal to the dentate line. Because quadrant plicating stitches are tied, the prolapse reduces into the anal canal to create a thickened rim of muscle that serves to create a barrier to prolapse and provides some continence support. The now adjacent cut edges of mucosa can be approximated as an anastomosis using a running or interrupted suture. Careful proctoscopy is performed at the end of the procedure to ensure patency of the rectum and completeness of the anal mucosal anastomosis.

Outcomes

Delorme's procedure is considered to be very safe with postoperative mortality approaching 0%. Complications occur in 0% to 12% of patients. The most common short-term complications include urinary retention, bleeding, infection, fecal impaction, fecal urgency, and tenesmus. In a manometric study of patients undergoing Delorme's procedure, increases in mean rest and squeeze pressures and rectal sensation were seen. Incontinence improved in 63% and constipation improved in 38%.

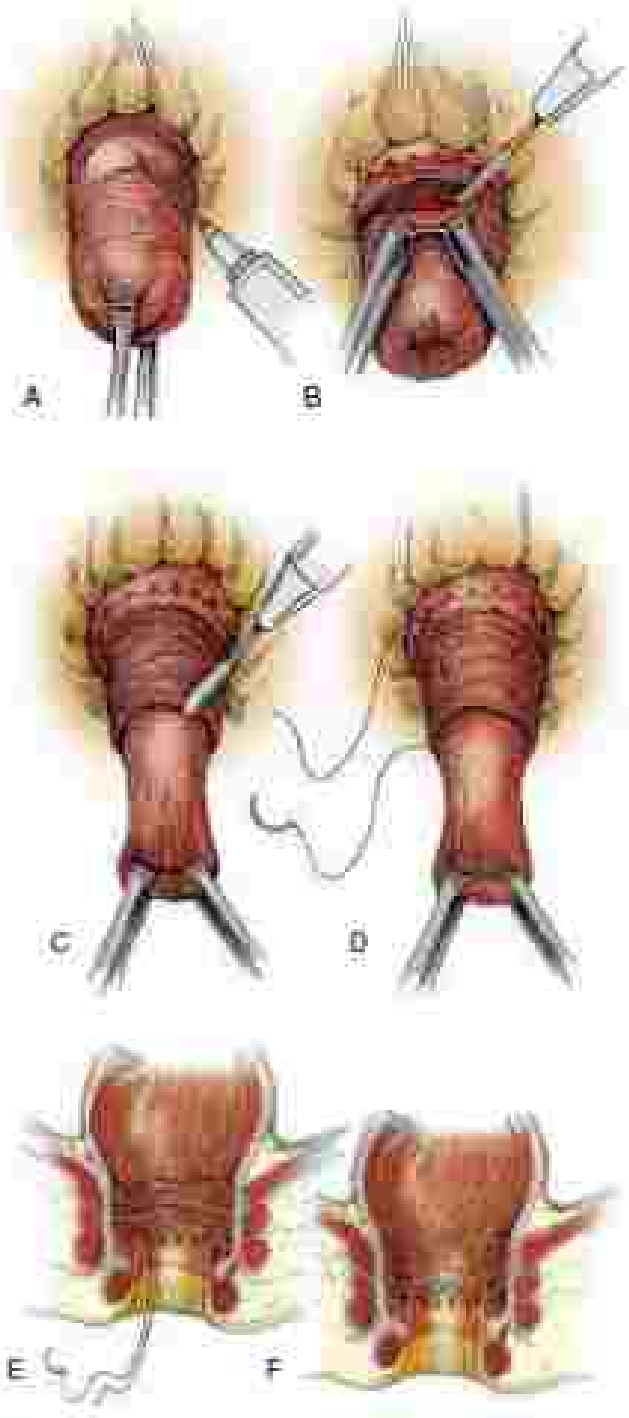

FIG. 1 Delorme's procedure. (A) Submucosal infiltration is carried out with saline or local anesthetic with epinephrine. (B) Partial-thickness circumferential incision is made 1–2 cm proximal to the dentate line. (C) The incision is carried through the mucosa, and the mucosa is dissected off the underlying muscularis. (D–E) Plication sutures is placed. (F) Mucosa is amputated and anastomosis is completed.

Perineal Rectosigmoidectomy (Altemeier's Procedure)

Perineal rectosigmoidectomy was first introduced by Miles in 1933 and then repopularized by Altemeier in the 1970s as a one stage repair for full thickness rectal prolapse.

Full thickness rectal prolapse greater than 5 cm is best treated with perineal rectosigmoidectomy and colorectal anastomosis. The approach can also be considered in the rare male patient with prolapse because it avoids dissection at the pelvic brim and potential postoperative sexual dysfunction. The procedure is essentially a transanal full thickness resection of the prolapsing portion of the rectum and entire sigmoid colon with a left colorectal anastomosis.

Operative Technique

The patient can be positioned in either lithotomy, left lateral (Sims'), or prone jackknife position (which we prefer) (Fig. 2A–F). A Lonestar retractor (Cooper Surgical), with hooks in the anal canal, is used to expose the operative site. The rectum is prolapsed, the tone of the anal sphincter inspected and estimated, and a full thickness circumferential incision in the rectal wall is created at a level 1 to 2 cm proximal to the dentate line. Anteriorly the cut is extended and the apex of the pelvic floor peritoneum marked with a suture. The lateral peritoneal attachments to the rectum are incised on both sides of the pelvis to expose the mesorectum. The lateral vascular attachments are divided with energy (monopolar or bipolar). The rectum is then progressively withdrawn from the body by incising the posterior attachments of the mesorectum in a cephalad direction.

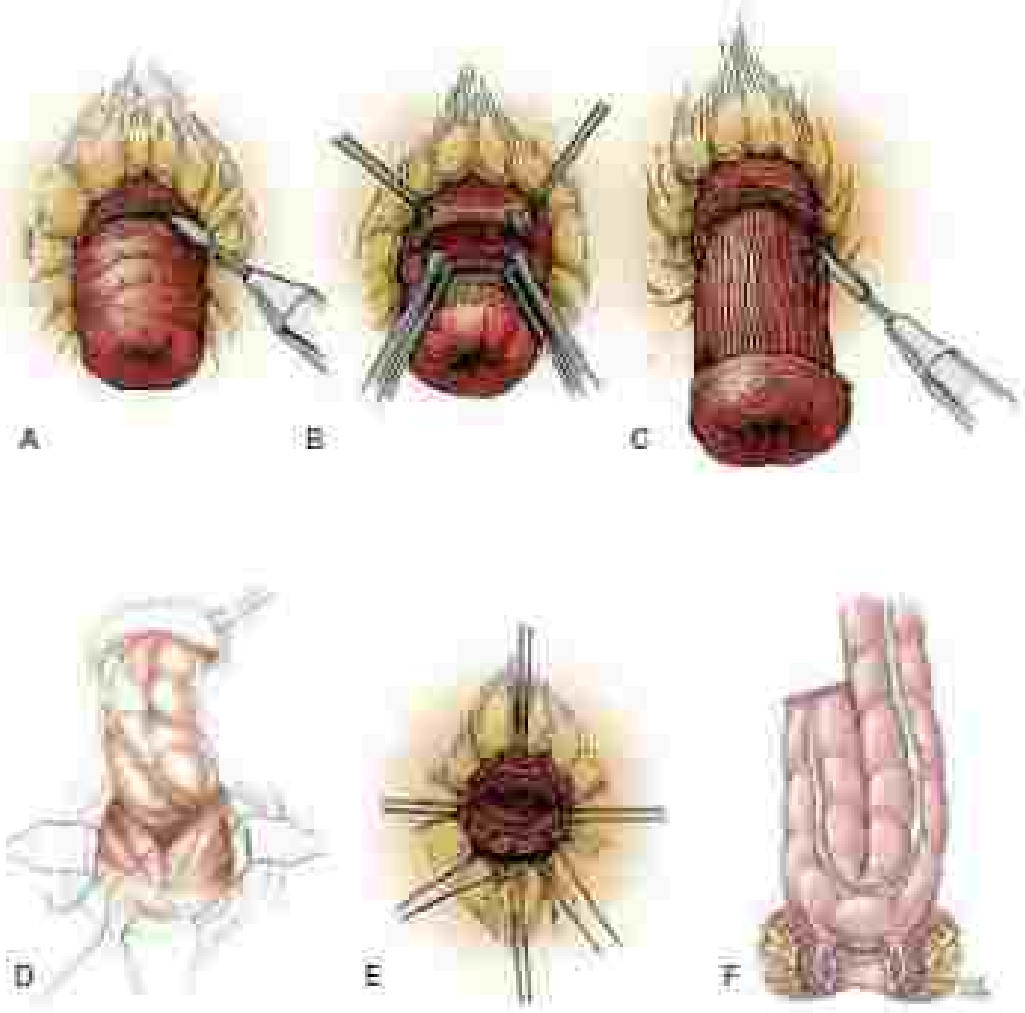

FIG. 1 Perineal rectosigmoidectomy. (A–C) Full-thickness excision of redundant bowel. (D) Levatoroplasty is performed with several figure-of-8 sutures. If possible, (E) excision of bowel at level of mucus anastomosis after redundancy is removed. (F) If adequate length is present, colonic J pouch is performed. (A–C, Modified from Corman ML: Rectal prolapse. In Corman ML, Nivatvongs S, eds: *Principles and Practice of Surgery for the Colon, Rectum, and Anus*. 3rd ed. New York: Informa Healthcare; 2007. p. 615–632. D–F, Modified from Wexner SD, Heitmann JM: Anal and Rectal Surgery. In Beckford RJ, ed: *Atlas of Operative Gynecologic Surgery*. Philadelphia: Lippincott Williams and Wilkins; 2011.)

Tethering vessels of the mesorectum are divided sequentially as the rectum is extracted. A finger through the anterior pubic opening can find the redundant sigmoid. The proximal rectum and distal sigmoid colon are released from the posterior vessels and drawn through the anus until no further redundancy of the colon occurs, yet a tension-free colorectal anastomosis can be created. The bowel and mesentery are then divided at this level, being mindful to preserve the mesenteric vessels supplying the left colon to prevent devascularization of the anastomosis. Using a laparoscopic-length bipolar sealing energy device is helpful to reach the distal vessels at the level of the sacral promontory as the dissection transitions to the sigmoid colon mesentery. A levatoroplasty is then performed by placing the levator ani muscle anteriorly and posteriorly to recreate the pelvic floor sutures with figure of 8 sutures of nonabsorbable material. Before creation of the colorectal anastomosis, the orientation of the mesentery and colon are checked to prevent torsion. Creation of the handsewn colorectal anastomosis is performed to either a straight or colonic J pouch configuration. A circular stapler technique can be applied by creating a purse-string closure of the top of the anal canal and securing the anvil to a purse-string in the cut end of the left colon. Removal of the entire rectum and sigmoid is essential to reduce bowel frequency and urgency. The sigmoid colon to anal anastomosis without a colonic pouch is almost intolerable.

Outcomes

As with Delorme procedure, mortality is low (0%–4%). Morbidity of the procedure is reported at 2% to 24% and largely secondary to patients' specific comorbidity. Technical complications are reported at 12% and include bleeding, anastomotic dehiscence, pelvic sepsis, and colorectal stricture. An oral antibiotic and complete mechanical bowel prep may reduce contamination, anastomotic leak, and pelvic sepsis.

Levatoroplasty is recommended in the case of preoperative fecal incontinence and a large pudendal canal with chronically stretched sphincter because it has been shown to afford greater gains in postoperative continence and a lower rate of recurrence compared to resection/rectopexy alone. In a prospective study by Kim et al., patients also gain an improved subjective state of health and quality of life in the areas of mobility, activity, pain and discomfort, and anxiety and depression at 49 month follow up.

Transabdominal Procedures

Many transabdominal procedures are described for the treatment of rectal prolapse. Ultimately, the goals of transabdominal rectal prolapse surgery are to completely mobilize the rectum to the pelvic floor with preservation of the lateral stalks and to reattach the rectum to

the rectum. Recurrence is eightfold higher among patients treated with mobilization alone compared with mobilization with fixation; however, limited evidence is available to support a benefit of fixation in the posterior or anterior structures.

In a 2015 Cochrane review, division of the lateral stalks to the low pelvis was associated with decreased rates of recurrence (0%–10%) but an increased rate of constipation (67% vs 0%).

Minimally invasive techniques have gained a foothold as the standard of care for most colorectal procedures. Laparoscopic techniques should be applied to transabdominal repairs of rectal prolapse whenever possible. Laparoscopic port sites are used for mobilization of the rectum with a small Pfannenstiel port extended to place fixation sutures. A minimally invasive approach offers similar rates of recurrence (4%–8%) and morbidity (10%–33%) with shorter length of stay, earlier return of bowel function, and better pain control compared with an open approach.

Abdominal Suture Rectopexy With or Without Resection

Abdominal rectopexy with sigmoid resection was first introduced by Frykman in 1963 as a composite of surgical procedures of the time for patients with massive prolapse requiring a "radical" and more permanent approach. The essential steps of this procedure included: (1) mobilization of the rectum; (2) elevation of the rectum as high as possible and suture fixation of the lateral stalks to the periosteum of the sacrum; (3) suture of the endopelvic fascia anterior to the rectum and obliteration of the cul de sac; and (4) sigmoidal resection of the excess sigmoid colon, without compromising the blood supply of the rectum, with end to end anastomosis. The suture rectopexy is performed on the anterior surface of S1 with a circle taper needle carrying permanent suture. The best point for suture placement is just off the midline on each side of the sacral promontory, just below the course of the common iliac vein. The peritoneal wings of rectum at the level of the peritoneal reflection are pulled up to the sacral promontory and the resulting stretch of the rectum eliminates the redundancy that starts rectal prolapse in the deep pelvis. The modern iteration of this procedure has omitted obliteration of the cul de sac.

Combined sigmoid resection carries minimal additional morbidity and is indicated for patients with constipation as it has been found in randomized controlled trials to reduce the rate of recurrence and improve constipation compared to rectopexy alone. Conversely, resection should be avoided in patients with preexisting incontinence. Resection should also be avoided in combination with mesh procedures due to the risk of superinfection of mesh and is absolutely contraindicated in the case of prior perineal rectosigmoidectomy since critical vascular supply has already been removed. A diverting ileostomy is only used if ongoing bleeding cannot be stopped.

Outcomes

Rectopexy carries acceptable morbidity; major complications of 6% to 21% and minor complications 10% to 20%. In a National Surgical Quality Improvement Program review of 560 patients, takeback to the operating room was 2.8%, and organ space infection was 2.3% (likely secondary to anastomotic leak). Minor complications included urinary tract infection and superficial site infection.

Functional outcomes are favorable with significant improvement in reported incontinence (67%–73%) and increased maximal anal resting pressures. Huber et al. showed a reduction of constipation from 81% to 26% postoperatively. However, other studies report de novo constipation as high as 41%, which may reflect lack of appropriate preoperative evaluation or failure to perform sigmoidectomy when indicated.

Ventral Rectopexy

Ventral rectopexy is an adaptation of the Orr Loygue mesh procedure as an alternative method for rectal prolapse repair that uses an anterior rectal dissection with only a limited posterior dissection to expose a site of fixation on the sacral promontory. An incision is made to the right lateral peritoneal wings all the way to the vagina. Following anterior dissection, separating rectum and vagina, to the pelvic floor, a synthetic or biological mesh is sutured as distally as possible to the anterior rectal wall and the proximal portion of the mesh is secured to the sacral promontory. The low anterior rectum is stretched and prevents intussusception. The pelvis is then reperitonealized and the mesh is covered by the peritoneum along the rectum to the right pelvic peritoneum. In doing so, the mesh is excluded from other intraperitoneal structures.

Outcomes

Morbidity (<7%), mortality, and rates of recurrence are similar to suture rectopexy; however, the fear of mesh related complications is the driver of criticism toward this technique in the United States. In a systematic review of 2856 patients (2517 synthetic/439 biologic), the mesh erosion rates were exceedingly low (3.87% synthetic/0.22% biologic), respectively, with mean ranging from 1.7 to 12.8 months. However, more long-term, controlled studies are needed to better understand the true effect of synthetic mesh material on rectum and the impact of the potentially devastating complication of erosion.

The main benefit of ventral rectopexy over traditional rectopexy is a significant and durable decrease in postoperative constipation due to avoidance of the posterior dissection that causes autonomic denervation. In a study of 45 consecutive patients by Boons et al., constipation was improved in 72% of patients at 3-month follow up, with a very low rate of de novo constipation (2%). In long-term follow up of 61 months, Williams et al. reports resolution of constipation in 64% (16 of 19) of patients without any cases of new onset constipation following this procedure. Continence is also improved in 82% of patients.

Recurrent Prolapse

In the case of recurrent prolapse, the choice of repair is dictated by the remaining blood supply to the rectum. Patients who have undergone a previous sigmoid resection risk ischemia to the remaining distal rectum if re resection is performed. It is imperative to review previous operative notes for history of resection. An algorithm for approaching repair of recurrence is provided in Fig. 3; however, the literature to fully inform decision making and outcomes is lacking.

Steele et al. reviewed 78 of 685 patients who underwent repeat prolapse surgery for recurrent prolapse by various approaches; recurrence occurred more often following a perineal approach (19 of 51) compared with a transabdominal approach (4 of 27), $P = .03$, at mean follow up of 9 (range, 1–82) months. This disparity is widened further following a third surgery with a recurrence rate of 50% following perineal repairs versus 8% following transabdominal repairs ($P = .07$). These findings support the general assertion from previous studies that second time recurrence is higher following perineal repair. However, selection bias may have affected this comparison. Ultimately, the choice of recurrence surgery must weigh these and other factors.

CONCLUSIONS

Rectal prolapse is a surgical disease that challenges the colorectal surgeon. The choice of surgery should address both the mechanical and functional disorders that underlie the diagnosis with an acceptable risk and recurrence profile in the typically comorbid patient. Outcomes of recurrence and function do not appear to differ largely between perineal and transabdominal approaches. The management of recurrent prolapse also lacks clear evidence to guide decision making. Perineal repair is associated with a higher rate of re recurrence. Despite limitations of available data, surgical decision making should ultimately provide the best treatment for reduction of the prolapse while addressing associated incontinence or bowel dysfunction.

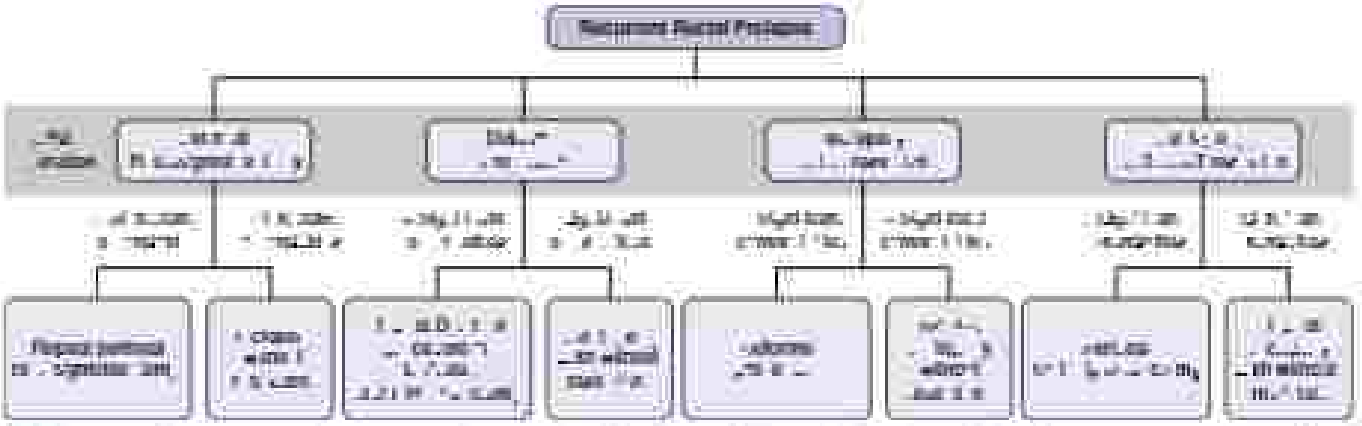

FIG. 3 Algorithm for treatment of recurrent rectal prolapse. (Modified from Watson... [Fulgenzi P. Approaches to adult rectal prolapse: surgery or... our. In: Mellgren M., Wilson Lynch. Reconstructive Surgery of the Rectum, Anus and Perineum. London: Springer; 2012. p. 53–63.)

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Management of Solitary Rectal Ulcer Syndrome

Shlomo Yellinek, MD, FACS, FRCS, FRCS(Ed), and Steven D. Wexner, MD, PhD(Hon), FACS, FRCS(Eng), FRCS(Ed), FRCSI(Hon), FRCS, Glasg(Hon)

Solitary rectal ulcer syndrome (SRUS) is a rare and underdiagnosed benign rectal disorder that represents a spectrum of rectal wall abnormalities, ranging from ulcers to nodules or polypoid lesions. The term "solitary" is misleading because the ulcers can be multiple and can be anywhere between the rectum and the cecum. The prevalence of SRUS is less than 1 to 100,000 per year, with equal gender distribution and a median age of 50 years at time of diagnosis. The syndrome, characterized by Madigan and Morson in 1969, is a combination of clinical symptoms, endoscopic appearance, and histologic findings. The treatment is multidisciplinary and should be tailored to each patient.

PATHOPHYSIOLOGY

The underlying pathophysiology of SRUS is not fully understood and is probably multifactorial. There are several clinical pathologies associated with SRUS, including rectal prolapse, strenuous defecation, and paradoxical contraction of the pelvic floor muscles. In some individuals, these conditions may cause a chronic reduction in blood perfusion to the rectal mucosa and, over time, ischemia and ulceration. However, these conditions are probably only predisposing factors and most patients do not suffer from SRUS.

Chronic rectal mucosal prolapse is the most common pathology associated with SRUS. In a series of 58 patients with diagnosed SRUS, radiographic evidence of prolapse was present in 94%. Prolapse, either partial or full thickness, results in areas of focal ischemia in the rectal mucosa resulting from reduced blood flow and local inflammatory reaction.

Chronic local rectal trauma from strenuous defecation and hard stools may cause SRUS. The physical injury to the rectal mucosa may cause scarring and inflammation that eventually leads to local ischemia and ulceration. The high pressure in the rectum resulting from strenuous defecation may cause a reduction in mucosal perfusion. The uncoordinated contraction of the pelvic muscles in paradoxical puborectalis muscle syndrome and the resultant ineffective defecation can result in local ischemia and ulceration in the same mechanism.

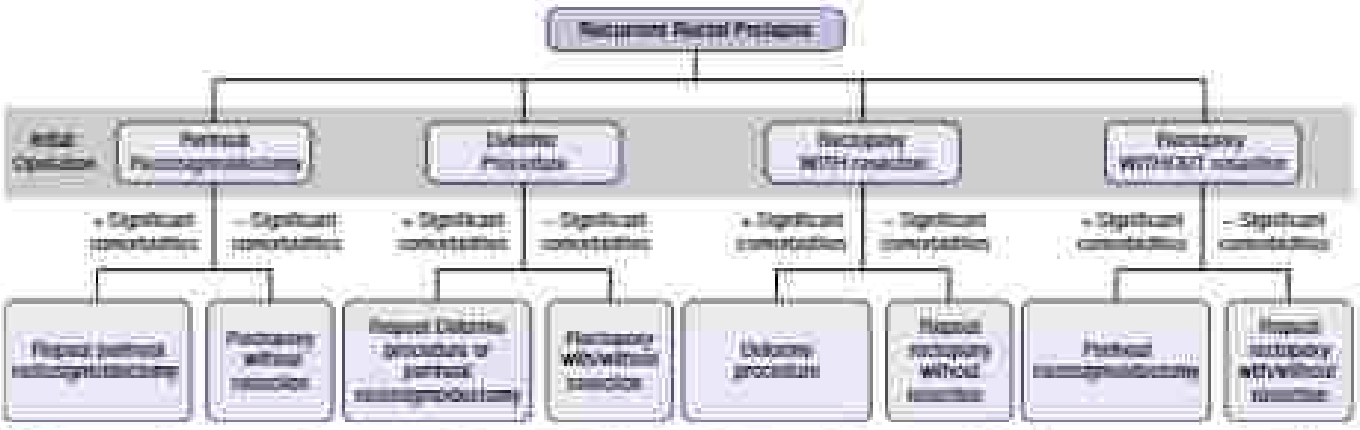
DIAGNOSIS

The diagnosis of SRUS requires a high level of suspicion and is mainly based on clinical features, endoscopic findings, and typical histopathologic findings. Imaging studies can be useful in diagnosing the underlying pathology. It is imperative to exclude other causes of rectal ulcers such as malignancy, inflammatory bowel disease, HIV, syphilis, and stercoral ulcerations before making a diagnosis.

The clinical presentation of patients with SRUS is variable and reflects the symptoms of the ulcer and the symptoms of the underlying pathology. Frequent unproductive straining and incomplete evacuation are common and frustrating symptoms. Rectal bleeding and mucus discharge are also common symptoms. Other symptoms include prolapsed tissue, tenesmus, pelvic pain, and fecal incontinence.

External signs on physical examination are usually not present, unless there is a full thickness rectal prolapse. Digital rectal examination may reveal nodular and friable rectal mucosa and occasionally blood per rectum. It is possible to sense a lack of relaxation of the puborectalis muscle when the patient bears down.

Endoscopic findings may vary from hyperemic friable mucosa to mature ulcers covered by white or gray slough (Fig. 1). The



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Endoscopic findings may vary from hyperemic friable mucosa to mature ulcers covered by white or gray slough (Fig. 1). The

FIG. 1 Endoscopic imaging of a 17-year-old male with solitary rectal ulcer syndrome (SRUS). A polypoid lesion was found in the first rectal valve. Biopsy showed fragments of rectal mucosa with focal erosion, granulation tissue replacement, and glandular reactive changes consistent with SRUS.

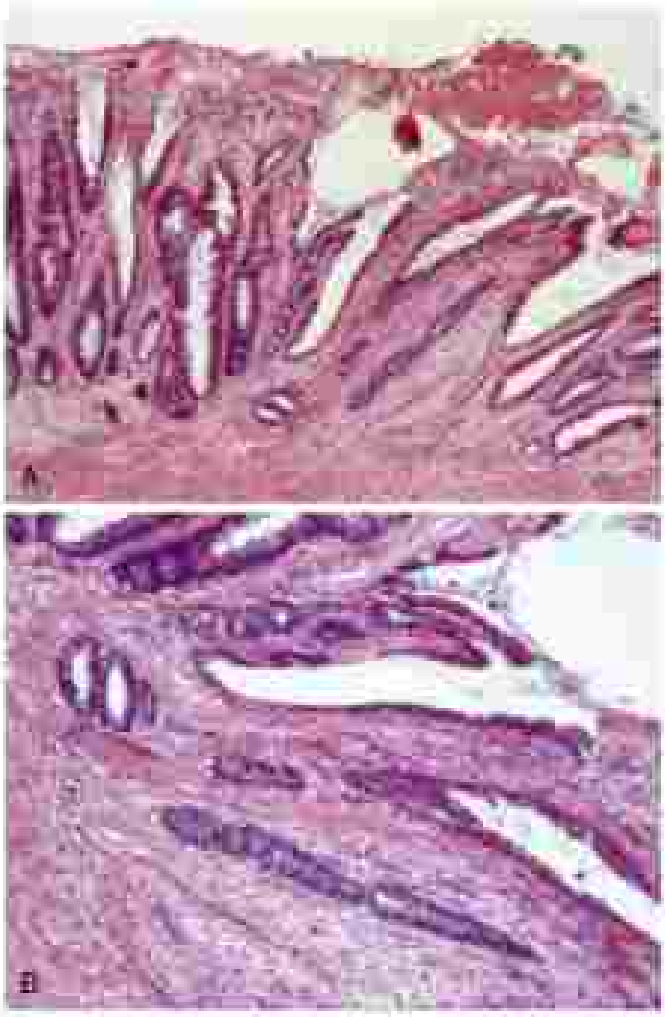

FIG. 2 Solitary rectal ulcer syndrome. (A) Erosion of the surface epithelium, vascular congestion, and irregularity of the glandular crypts. In addition, extra bundles of myofibroblasts projecting from the base to the upper areas of the lamina propria (hematoxylin and eosin, ×100). (B) Myofibroblastic hyperplasia was between the glandular crypts (hematoxylin and eosin, ×200).

macroscopic appearance of SRUS is often classified into three types: ulcerative (50%–60%), polypoid (25%), and flat (25%). The lesions are typically located 4 to 12 cm from the anal verge on the anterior rectal wall. It is important to obtain biopsies of the lesions and the surrounding area to make the diagnosis and exclude other pathologies as well as perform a full colonoscopy.

Morphologic findings in the pathology specimen include fibromuscular obliteration of the lamina propria, hypertrophied muscularis mucosa, and glandular crypt abnormalities. Secondary changes such as surface erosion, inflammation, hemorrhage, congested vessels, deep cyst formation, or misplaced glands in submucosa may be seen (Figs. 2 and 3).

Defecography and anorectal manometry may help in diagnosis the underlying pathology. Defecography is helpful in the diagnosis of rectal prolapse, intussusception, and paradoxical puborectalis syndrome. Manometry defines the pressure profiles, rectoanal inhibitory reflex, and sensory thresholds, and is helpful in the diagnosis of paradoxical puborectalis syndrome.

MANAGEMENT

Several options for treatment of SRUS are available. The decision must take into account the underlying pathology. Initially, a trial of conservative treatment is initiated and includes patient education, dietary modifications, topical agents, and biofeedback therapy. Patients should be educated to avoid straining and to regulate toilet habits. Dietary modifications should include a high fiber diet, fiber supplements, and stool softeners. Topical treatments with either anesthetic or mucosa occlude agents such as sucralfate, salicylates, steroids, salicylates, and mesalamine, with varying degrees of improvement. If symptoms fail to improve, especially in patients with documented paradoxical puborectalis syndrome, a trial of biofeedback therapy should follow. Biofeedback therapy focuses on reducing excessive straining and strenuous defecation by correcting abnormal pelvic floor behavior and by eliminating agitation and suppository use. In patients with paradoxical puborectalis syndrome who have failed to improve, botox injection to relax the sphincter muscle complex may be helpful.

The use of argon plasma coagulation (APC) has shown good results in with patients with SRUS who have failed medical and behavioral treatment. APC is especially useful in bleeding control, which can be significant in some patients and may manifest blood transfusion. In a series of 99 patients (41 treated with APC vs 58 treated conservatively), a significant difference in bleeding cessation in the APC group was noted, but there was no significant difference between the two groups in terms of pain relief.

If conservative treatment fails to improve the patient's symptoms, a surgical approach may be considered. Common indications for surgery include intractable pain, significant bleeding, and prolapse. There are various surgical procedures for repair of rectal prolapse that are mainly divided into two approaches: perineal and abdominal. Although the perineal approach is typically easier, it tends to be more difficult because of scarring and ulcerations in the setting of SRUS. The abdominal approach, which includes rectopexy with or without excessive sigmoid resection and with or without mesh placement, has higher success rates and is considered the gold standard given that there are no severe comorbidities. In patients without mucosal prolapse or intussusception who have failed conservative treatment and suffer from intractable pain or persistent bleeding, a proctectomy and/or fecal diversion may be warranted. Fig. 3 outlines a stepwise approach to the management of SRUS.

In a series from Cleveland Clinic Florida, 46 patients with SRUS underwent surgical procedures. There was a combined improvement

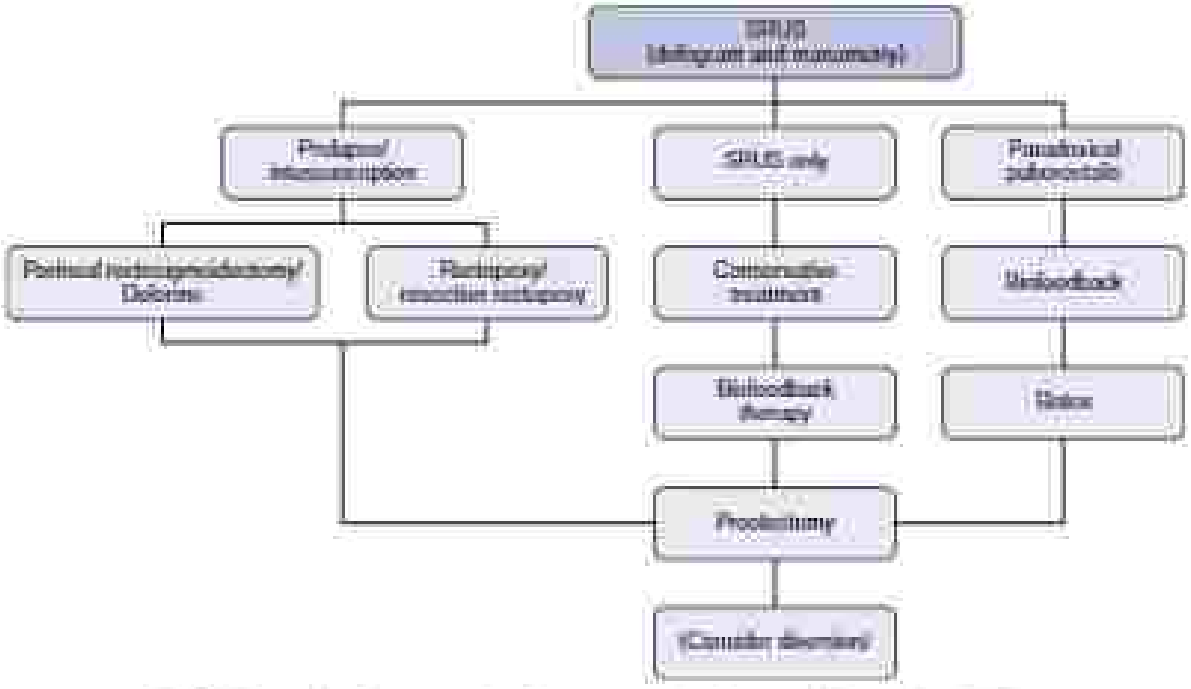

FIG. 3. Suggested stepwise approach for the management of solitary rectal ulcer syndrome (SRUS).

rate of 76% for all surgical procedures. The authors noted that, for SRUS without prolapse, a resection or local diversion was followed by a significantly higher improvement rate than local excision of the ulcer.

CONCLUSION

SRUS is a rare underdiagnosed condition with highly variable clinical presentation and can be the result of several underlying pathologies. The diagnosis of SRUS is challenging, mandating a high level of suspicion, and must be made only after excluding other pathologies such as malignancy or inflammatory bowel disease. The diagnosis is a combination of clinical presentation, endoscopic appearance, and pathologic findings. Treatment options depend on the underlying pathology and include conservative treatment, endoscopic treatment, and surgery. Surgical options include perineal repair procedures, proctectomy and/or fecal diversion. Local excision of SRUS is not recommended.

SUGGESTED READINGS

Chat H, Shin G, Hwang YH, Kim HC, Shigeeda T, Wexner SD. Clinical presentation and surgical outcome in patients with solitary rectal ulcer syndrome. Surg Innov. 2005;12(4):307–313.

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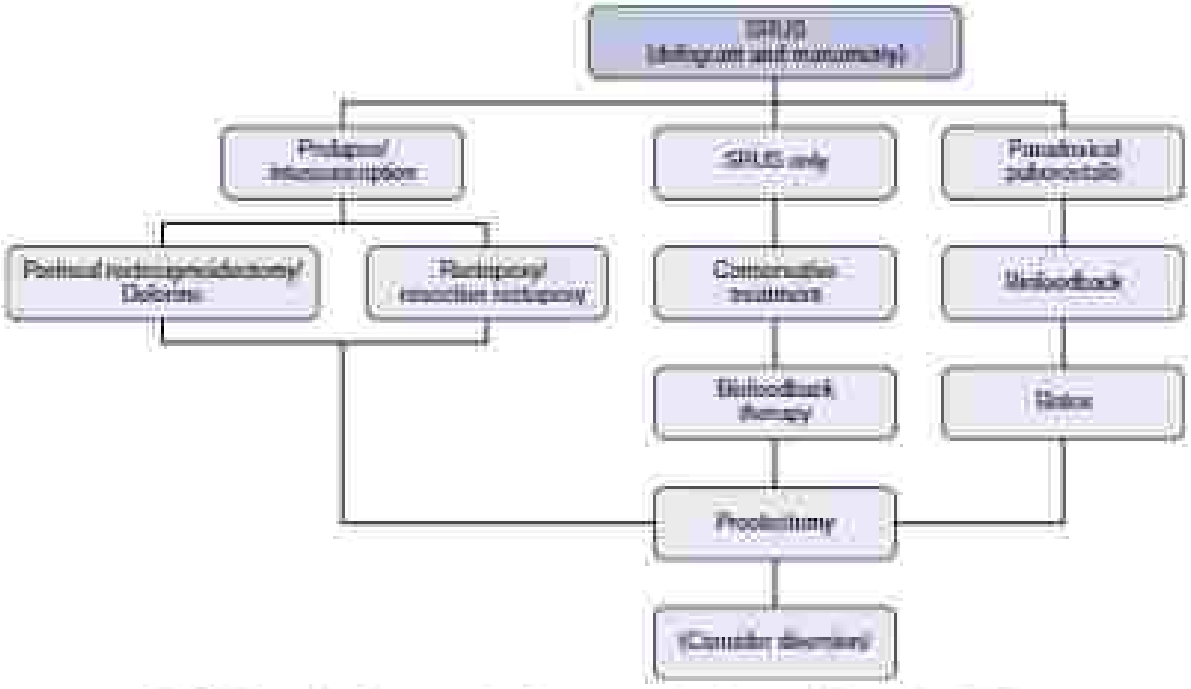
SURGICAL MANAGEMENT OF CONSTIPATION

Lisa Park, MD, and Jeremy M. Lipman, MD, MHPE, FACS, FASCRS

Constipation is a multifactorial and intricate diagnosis that remains one of the most common reasons for an office visit to a physician. It is a substantial clinical problem, affecting an estimated 3% to 11% of the population in Western countries, with an increased prevalence in women, children, and the elderly. In addition to leading to an estimated 2.5 million office visits, this common complaint has led to an increasing number of emergency department visits and hospitalizations. Between 2006 and 2011, the frequency of constipation-related emergency department visits increased by 41.5% and the aggregate national cost of constipation-related emergency department visits increased by 121.8%, making constipation among the top 10 digestive disorders in attributable costs of $1.4 billion annually.

ANATOMY AND PHYSIOLOGY

Defecation is a complex physiologic process that relies on the coordinated interplay between anatomic and neurologic features of an individual's colonic musculature, neurorectal reflex, and sphincter complex. As stool enters the rectum, the internal anal sphincter, comprising smooth muscle under autonomic control, involuntarily relaxes while the external anal sphincter simultaneously contracts, allowing rectal contents to reach the upper anal canal. Feedback from terminal sensory fibers in the anal canal, distinguishing liquids from solids and gas, allows the process of defecation to occur as the anal canal pressure increases. The puborectalis muscle, which is tonically contracted at rest but also under



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BOX 1 Rome IV Criteria for Constipation

Requires Two or More of the Following:

- Straining with more than 25% of defecations
- Lumpy or hard stools (Bristol stool form scale 1 or 2) more than 25% of defecations
- Sensation of incomplete evacuation more than 25% of defecations
- Sensation of anorectal obstruction/blockage more than 25% of defecations
- Manual maneuvers to facilitate more than 25% of defecations (such as digital evacuation or support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

Plus:

- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

From Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–1407.

BOX 2 Rome IV Criteria for IBS-C

Recurrent abdominal pain, on average, at least 1 day per week in the past 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis
- Patient reports that abnormal bowel movements are usually constipation (such as type 1 or 2 Bristol stool form scale)

From Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–1407.

IBS-C, irritable bowel syndrome with predominant constipation.

voluntary control, relaxes to straighten the anorectal angle, and the striated external anal sphincter muscle also relaxes. Defecation occurs when the intrarectal pressure exceeds the anal canal pressure.

DIAGNOSIS

Constipation is generally defined by bowel symptoms such as difficulty passing stools, infrequent or hard stools, or a feeling of incomplete evacuation. Because of the subjectivity and variation of patient-reported symptoms, objective criteria to define this condition and more importantly, to distinguish and treat the underlying cause of constipation, have led to the creation of several scoring systems. The Rome Criteria for Gastrointestinal Disorders, introduced in 1988 and most recently updated to a fourth edition in 2016, is a commonly used tool to diagnose functional constipation as shown in Box 1. It is important to differentiate constipation from irritable bowel syndrome (IBS) as operative management is never recommended for IBS. Criteria for IBS with predominant constipation are shown in Box 2.

PREOPERATIVE EVALUATION

Once the diagnosis of constipation is made, it is critical to ensure it is functional and not from other causes. Structural and metabolic etiologies for constipation must be excluded because they will require therapy directed at these underlying causes. Thus, the evaluation of any patient with constipation should begin with a detailed history and physical examination to identify modifiable behavioral factors such as diet, medications, and contributing medical disorders such as hypothyroidism, electrolyte derangements, and diabetes, which can slow bowel function. Laboratory evaluations should only be done to assess for these conditions. Rectal bleeding, change in caliber of stools, unintentional weight loss, or a family history of colorectal cancer are red flags that should warrant further investigations to determine whether an underlying colorectal malignancy is the reason for associated constipation symptoms.

Functional constipation can be divided into two main categories based on the underlying pathophysiology: (1) disorders of colonic motility and (2) disorders of defecation. In terms of motility, constipation is categorized as either normal transit or slow transit constipation based on the rate of stool passage through the colon. Obstructed defecation syndrome, also referred to as dyssynergic defecation, is a generalized diagnosis used for various pathophysiologic disorders resulting in impaired defecation such as pelvic floor dysfunction. However, history and physical alone may be inadequate to clearly establish a diagnosis because overlap between the subtypes is not uncommon. In a study of more than 1000 patients with functional constipation who were evaluated at the Mayo Clinic, 19% were found to have normal transit constipation, 25% had defecatory disorders, 13% had slow transit constipation, and 3% had a combination of a defecatory disorder and slow transit constipation.

A careful anorectal examination is critical to evaluate for outlet obstruction constipation and should involve a digital evaluation of anal sphincter tone and coordination of function. Evaluation for pelvic floor dysfunction such as perineal descent, pelvic organ prolapse or the presence of rectal or cystoceles should also be performed.

Slow-Transit Constipation

The exact etiology of slow transit constipation is unknown but arises from disordered colonic motor function with neuronal and muscular factors implicated in its pathogenesis. As such, it is on the spectrum of disordered gut brain interactions. It is most common in young women and is characterized by infrequent bowel movements. Operative management should be reserved for patients whose symptoms are refractory to all available medical treatments. Because slow transit constipation can exist in concert with other functional gastrointestinal (GI) disorders, it is critically important to evaluate for these prior to considering an operation. This is particularly important with slow transit constipation because operative management may worsen coexistent motility disorders.

Preoperative evaluation for slow transit constipation should include a colonic transit study such as Sitzmark's study, Smart Pill study, or scintigraphy, to confirm the diagnosis. Also, amplification evaluation to exclude outlet obstruction and a colonoscopy should be performed to exclude luminal disease.

Sitzmark's Test (Radiopaque Marker Testing)

The Sitzmark's or radiopaque marker test can be used to measure colonic transit time by performing abdominal radiographs at predetermined times after the patient ingests radiopaque beads or rings. Patients are typically instructed to swallow the markers on a Sunday, and then undergo plain abdominal radiographs on Monday, Wednesday, and Friday to observe progression through the GI tract. The number and location of retained markers are used to assess overall GI transit time.

During the study, the patient should be maintained on a high-fiber diet and avoid laxatives, enemas, or medications that may affect bowel function. This can be problematic for some patients because of the severity of symptoms when off laxatives.

Retention of more than 20% of the ingested markers on day 5 suggests slow transit constipation. A typical positive test result for slow transit constipation would show more than 20% of ingested markers scattered throughout the colon on the fifth day of the test (Fig. 1). If all markers have not progressed to the colon by the first

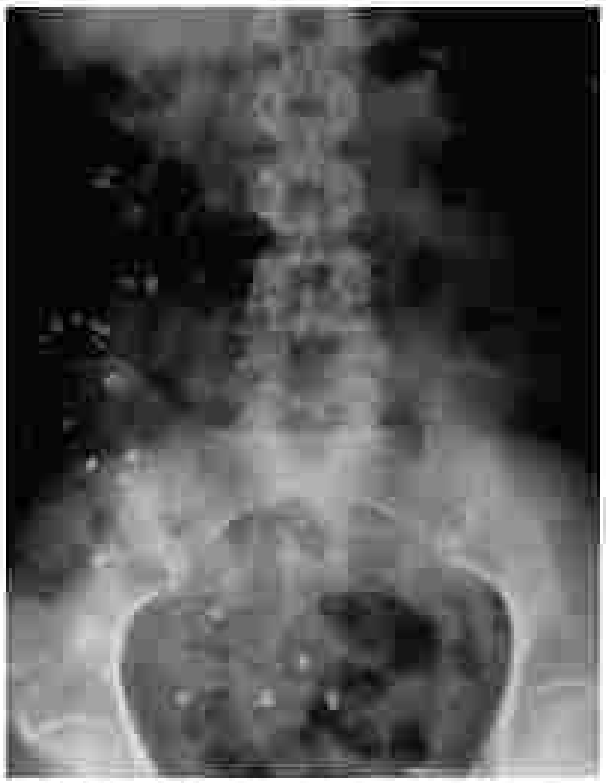


FIG. 1 Stomach study suggesting slow-transit constipation.

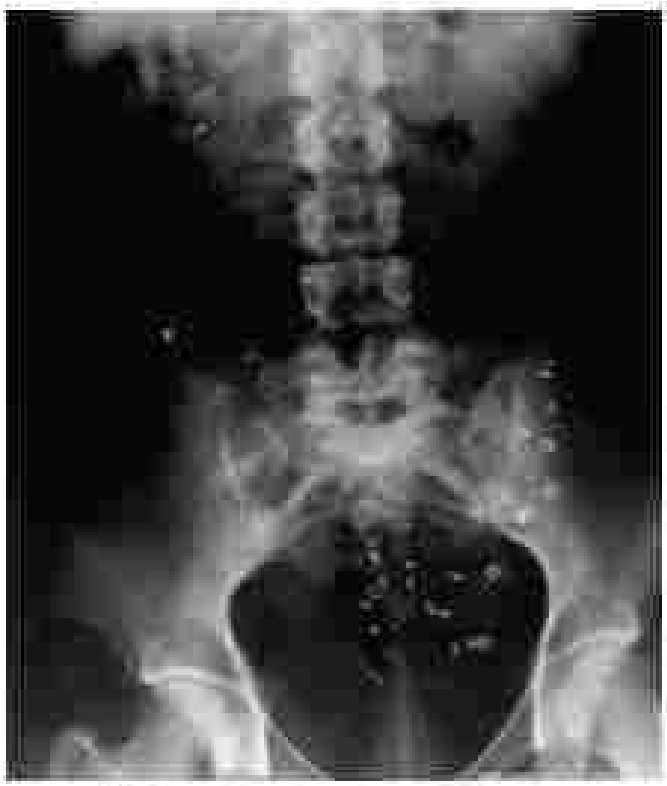


FIG. 2 Stomach study suggesting outlet dysfunction.

day, this is suggestive of small bowel or gastric dysmotility and further investigation should be initiated. If, on the fifth day, all the test markers are retained exclusively in the sigmoid colon and rectum, this is suggestive of (but not diagnostic of) outlet dysfunction as an etiology for symptoms (Fig. 2).

Wireless Motility Capsule

The wireless recording capsule is a single use device used to distinguish normal from slow colonic transit. It can also be used in patients with a suspected motility disorder of the upper GI tract because it measures gastric emptying and small bowel transit in addition to colonic transit times. The capsule continuously sends temperature, pH, and pressure measurements as it moves along the GI tract. This is transmitted to a data receiver worn on the waist for 5 days. Patients also keep a log of daily activities, meals, sleep, and bowel movements. Normal colonic transit time using the wireless motility capsule is 10 to 59 hours, with delayed colonic transit considered greater than 44 hours in men and 59 hours in women. A typical study result is shown in Fig. 3. An advantage of the wireless motility capsule test is its use in patients being considered for a colectomy or diverting ileostomy as treatment for severe constipation when assessment of upper GI transit is also recommended. Moreover, the wireless motility capsule is well tolerated by most patients and is a more convenient ambulatory test than the Sitzmark's test because it does not require serial imaging. It is contraindicated in patients with pacemakers or defibrillators, swallowing disorders, or suspected strictures or fistulas.

Scintigraphy involves patients eating a radiolabeled meal and following its transit through the GI tract using a gamma camera. This provides an accurate assessment of GI motility but is more time intensive than other methods.

Outlet Obstruction Constipation

Defecatory disorders related to outlet dysfunction are primarily characterized by impaired rectal evacuation. As noted previously, defecatory disorders can occur in the presence of normal or delayed colonic transit times. Incomplete rectal evacuation results when there is an inadequate rectal propulsive force because of an inability to coordinate the abdominal, perineal, and pelvic floor muscles. In addition, an increased resistance to evacuation such as high anal resting pressures, incomplete relaxation, or paradoxical contraction of the pelvic floor can contribute to this. Less frequently, defecatory disorders are associated with structural abnormalities such as rectal intussusception, obstructing rectocele, megarectum, pelvic organ prolapse, or excessive perineal descent.

There is a significant coincidence of emotional, physical, and sexual trauma in patients with outlet obstruction constipation. A careful social history is important for identifying and treating this component of the disease.

A meticulous perineal and rectal examination is critical in diagnosing defecatory disorders. Patients may have high anal resting tone and increased resistance to insertion of the examining finger during a digital rectal examination. Findings may also include impaired relaxation or paradoxical contraction of the sphincter complex with reduced perineal descent (normal 2–4 cm descent) during a simulated evacuation test when they are instructed to "expel the examining finger." Other findings may include the quality of stool in the rectal vault, presence of fecal soiling, hemorrhoids, rectocele, or pudendal neuralgia tenderness. When a defecatory disorder is suspected, or before considering operative management for constipation, diagnostic testing may be used to supplement the history and physical examination in making the diagnosis. These include anorectal manometry, defecography, and electromyography (EMG).

Anorectal Manometry

Manometry is a functional test that can assess the resting and squeeze pressures of the anal sphincters, the neorectal inhibitory reflex, rectal sensation, and compliance. The results of anal manometry may be used to guide further testing or treatment. Although manometry findings may be supportive of a diagnosis of dyssynergic defecation,

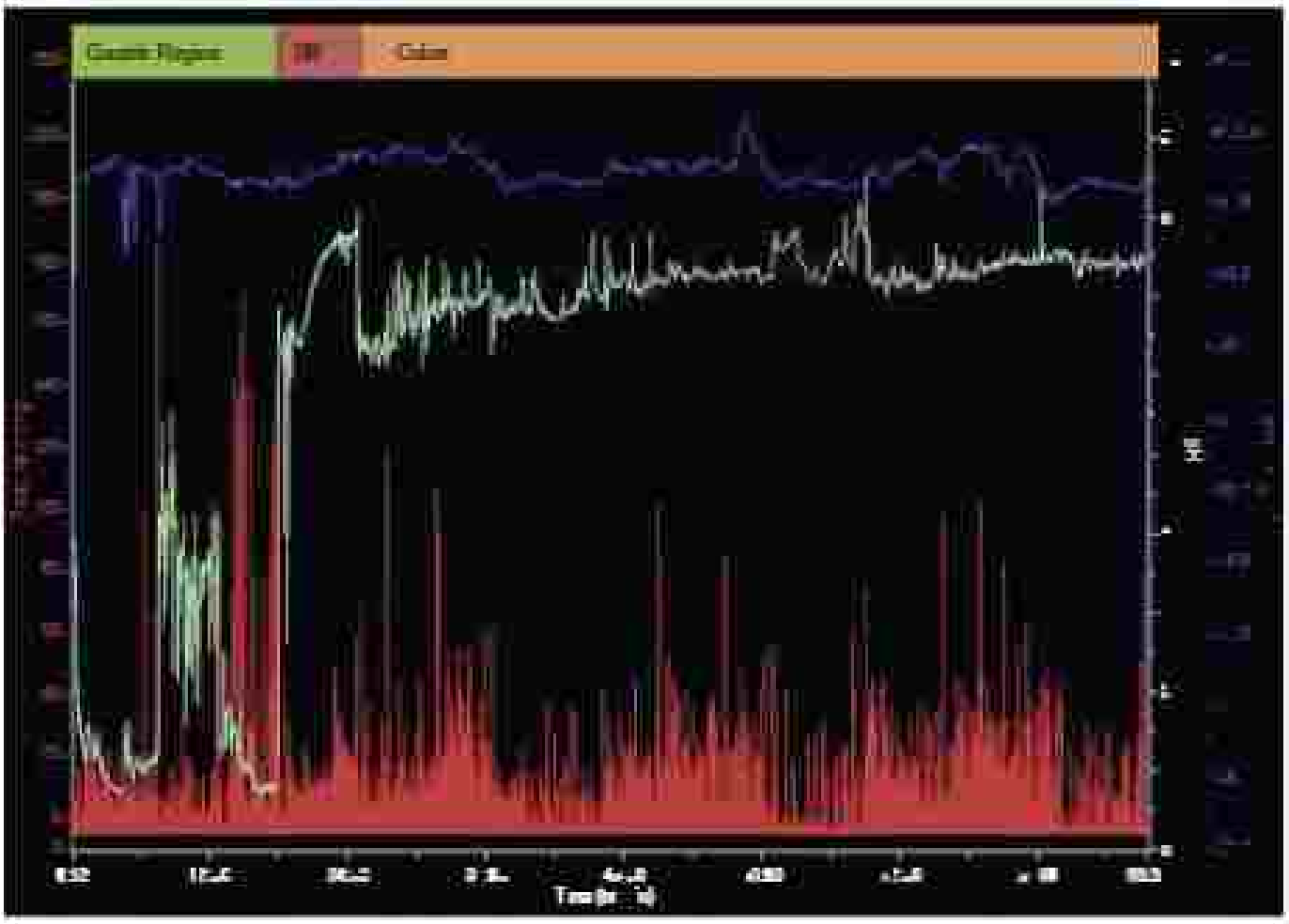


FIG. 3 ...colonic inertia transit study [illegible]

it is not conclusive by itself, and this result should be used in conjunction with other physiologic testing such as defecography as outlined below. A representative example of manometry findings is shown in Fig. 4.

Defecography

Defecography is a dynamic study that evaluates the rate and completeness of rectal emptying, anorectal angle, and length of perineal descent. Structural abnormalities that may contribute to outlet obstruction can also be seen such as rectocele, internal rectal prolapse and intussusception. Defecography can be performed as a fluoroscopic or magnetic resonance (MR) imaging study. MR defecography is advantageous in its ability to show the anatomy of the pelvic floor musculature including the puborectalis and external and internal sphincters. The disadvantages of MR imaging are the expense of the procedure, prolonged testing time, and the need for a dedicated radiologist with experience in reading dynamic MR imaging (Fig. 5).

EMG Testing of Striated Muscle Activity

EMG is used to assess the contraction of the external anal sphincter by measuring depolarization and the activity of both the external anal sphincter and puborectalis. Needle, surface, and anal plug EMG can be used based on indication and clinical preference. EMG activity may be recorded at rest and with squeeze and push efforts. During defecation, EMG activity should be absent now as the resting activity during defecation may point to a diagnosis of paradoxical puborectalis contraction causing difficult evacuation.

Management of Patients With Slow-Transit Constipation

Patients with refractory colonic slow transit constipation without coexisting outlet obstruction should first exhaust all medical options to treat the disease. This should include optimization of underlying metabolic derangements and trial of all appropriate laxative medications. Operative intervention should be reserved only for those who have no other options.

Operative management of slow transit constipation should be a total abdominal colectomy with ileorectal anastomosis (TAC IRA). The anastomosis should be performed at the level of the convergence of the taenia to the upper rectum to ensure an adequate resection.

A minimally invasive approach is preferred to reduce rates of postoperative complications, length of hospital stay, and time away from work. Port site placement is at the surgeon's preference but should consider the need for manipulation and visualization to all four quadrants of the abdomen. A high ligation of mesenteric vessels is not necessary, although some may find that plane of dissection easier. It is also not necessary to resect the omentum, and there may be some benefit to leaving it in place. At the level of the convergence of the taenia, the rectum is transected with an endoscopic stapler and the bowel is exteriorized through the preferred extraction site. Recent data suggest that extraction sites away from the midline have a lower

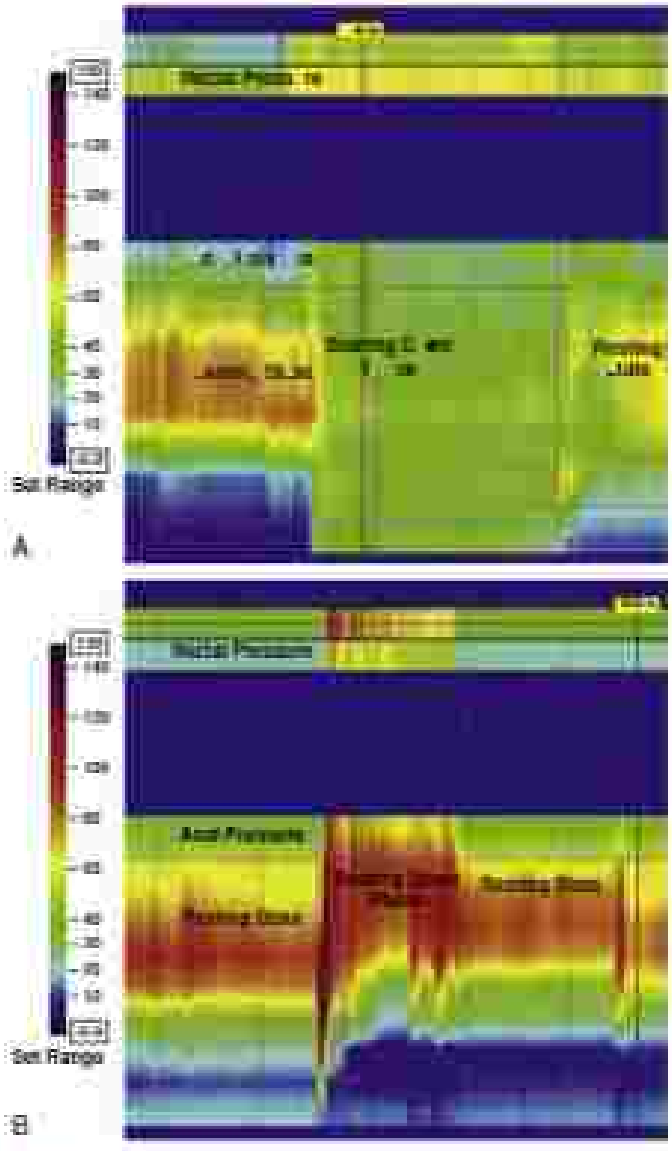


FIG. 4 Anorectal manometry (A) normal manometry (Sensor = 20 mm Hg pressure. (B) Dyssynergic defecation. Scale = 100 mm Hg pressure. (From Rao SS, Bharucha AE, Wald A, et al. American Gastroenterological Association medical position statement on anorectal testing techniques. Gastroenterology. 2019;144(1):211–217.)

incidence of hernia formation. The ileorectal anastomosis can be completed as an end to end, side to side, end to side, or side to end at the surgeon's preference. Proximal fecal diversion above the anastomosis is typically not indicated after this operation.

Recurrent constipation is uncommon. More often, patients will report diarrhea postoperatively, with some series reporting a rate as high as 46%. Diarrhea can often be managed with dietary modification, including a higher fiber diet. In some cases, patients may require the use of antimotility agents to control their bowel movements. Fecal incontinence is also reported, particularly in those with diarrhea. This can also usually be controlled by thickening the bowel movements through diet modification, fiber supplementation, and medications.

Alternative operative procedures have been proposed for the treatment of slow transit constipation, but data are lacking to support any resection other than TAC: IRA. Reports of experience with segmental colon resections in an attempt to preserve bowel have resulted in nearly universal failure to treat the underlying condition. This stands in sharp contrast to those who undergo TAC: IRA, in which 50% to 100% rates of clinical improvement are reported. Perhaps most important, more than 90% of patients state they would undergo the procedure again to treat their constipation. Subtotal colectomy with ileoproctostomy (ileorectal anastomosis) has been proposed because of the theoretical reduction of postoperative diarrhea due to preservation of the ileocecal valve. Sufficient data are lacking, however, to support this theoretical advantage.

As an alternative to resection, a diverting loop ileostomy (DLI) alone is another reasonable option to treat slow transit constipation. This may be recommended for patients who are poor operative candidates for a larger resection or for those whose symptoms cannot be definitively attributed to functional constipation. A DLI can prove to be both a therapeutic option as well as a diagnostic measure. It is important to communicate to the patient, however, that by performing a DLI alone the colon is still at risk for neoplasia and requires routine surveillance.

For patients who present with refractory slow transit constipation associated with outlet obstruction, constipation because of functional or structural abnormalities, treatment for the outlet obstruction is recommended before considering TAC: IRA. Resection in the presence of untreated outlet obstruction can result in significant worsening of symptoms because of the high stool burden coming from the small bowel. In addition, there is increased risk for anastomotic leak because of the functional obstruction distal to the anastomosis.

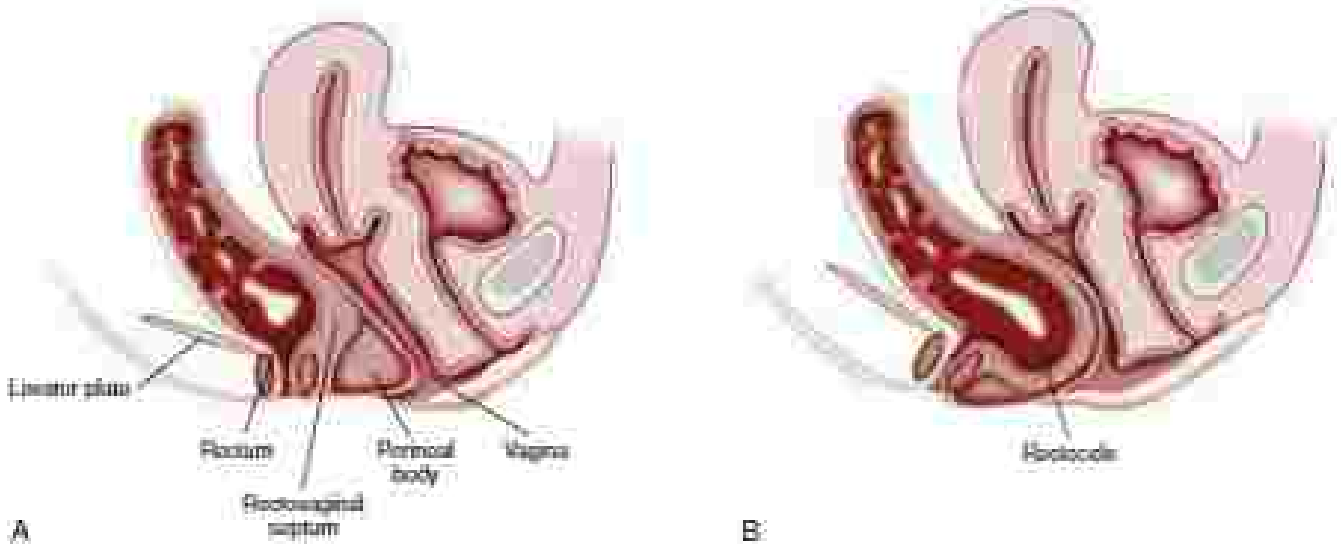
MANAGEMENT OF PATIENTS WITH NORMAL-TRANSIT CONSTIPATION AND OUTLET OBSTRUCTION

Functional disorders leading to outlet obstruction rely heavily on nonoperative treatments such as bowel retraining programs, pelvic floor physical therapy, and biofeedback. Structural abnormalities such as rectoceles, enteroceles, sigmoidocele, intussusception, and prolapse should be addressed with operative intervention as appropriate. These mechanical etiologies for outlet obstruction may occur concurrent with functional abnormalities; therefore, a thorough evaluation of the rectum and anus is valuable to aid decision making regarding a treatment plan.

Rectocele operations can be performed via transanal or transvaginal approaches. Equivalent complication rates have been shown for both approaches. According to the American Society of Colon and Rectal Surgeons' Clinical Practice Guideline (2016), transanal stapled repair of rectocele and rectal intussusception is not recommended because of the high rate of observed complications including proctalgia, urgency, incontinence, constipation, rectovaginal fistula formation, and bleeding. Rectopexy alone, resection rectopexy, and Delorme's procedure have been described for the successful management of rectal intussusception.

For patients with outlet obstruction constipation who have failed nonoperative therapy or are not candidates for other available treatment options, an ostomy can be considered. Patients with normal colonic transit can usually be treated with a descending colostomy. A loop colostomy is beneficial because it provides a means for proximal decompression of the distally obstructed, dysfunctional rectum/sigmoid remnant, but this comes at the cost of an increased risk for parastomal hernia. An end descending colostomy is also a reasonable alternative. Rarely, patients will continue to have pain or other ongoing symptoms related to the retained rectosigmoid colon. These very infrequent situations may benefit from an abdominoperineal resection of the rectum.

In patients who have both slow transit and outlet obstruction constipation refractory to nonoperative management, total proctocolectomy can be considered. It is reasonable, in these patients, to first offer a trial of a DLI alone to determine if their symptoms improve. This may also provide an improved quality of life while working to improve functional outlet constipation with nonoperative therapies. If effective, this could provide an option for restoration of intestinal continuity with an eventual ileorectal anastomosis. If amenable to ongoing endoscopic surveillance of the remaining, dysfunctional



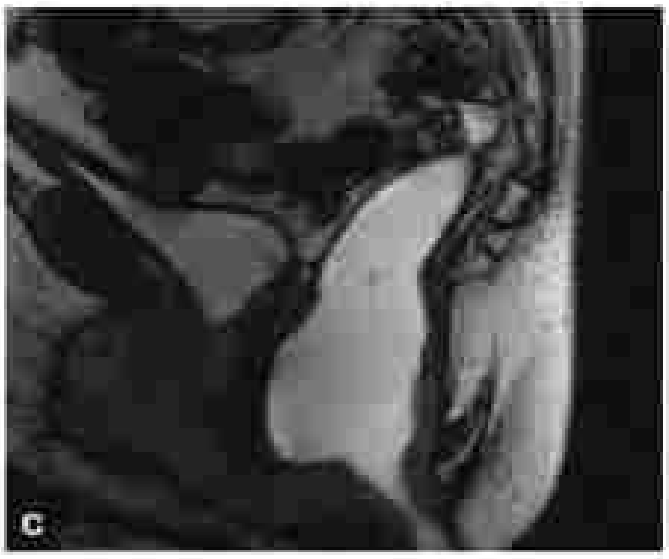


FIG 5. Rectocele. (A) Normal anatomy. (B) Rectocele. (C) Magnetic resonance defecography of rectocele. (A, B, from Hedrick M, Herman D, Shnaid D, Jackson and Hardiman Gastrointestinal and Liver Disease. Philadelphia: Elsevier; 2016. p. 796.)

colon, dressing alone can serve as definitive management. Some patients with fecal diversion alone will be troubled by mucous and stool production from the remaining colon. This can leave them with symptoms similar to those they experienced before fecal diversion. In these cases, total proctocolectomy is an appropriate option.

Total proctocolectomy with ileal pouch anal anastomosis has been described for patients with combination slow transit and outlet obstruction constipation. There are limited data on this approach, but some have reported as high as a 50% pouch failure rate after this procedure.

Malone Antegrade Continence Enema

Malone antegrade continence enema is another treatment modality, adapted from pediatric surgery, that involves the creation of a continent catheterizable appendicostomy or cecostomy through which antegrade enemas can be administered. This flush can overcome the dysmotility in the colon and in the anus. The Malone antegrade continence enema is an especially attractive option in patients who wish to avoid permanent external ostomy creation. This is a reasonable alternative to consider in those patients unfit for a colectomy. A retrospective study of 32 patients who underwent this procedure and were followed for a median of 36 months (range, 13–180 months) reported satisfactory long-term results in about 50% of the patients. Revisions were frequently required for complications such as leakage around the umbilicus site and stricturing, however.

Adult Hirschsprung's Disease

Adult Hirschsprung's disease is caused by the congenital absence of submucosal and myenteric ganglion cells in the internal anal sphincter. The length of proximal aganglionosis is variable but typically is a short segment in adults accounting for the delayed diagnosis. The resultant impaired rectoanal inhibitory reflex leads to stasis and distention in the more proximal bowel. The adult patient usually presents with a history of lifelong constipation. Anal manometry can be used as a diagnostic adjunct, but the diagnosis is confirmed with a full thickness rectal biopsy.

Posterior anorectal strip myectomy can be both diagnostic and therapeutic for those with short segment disease. This involves excising the rectal mucosa proximal to the dentate line to expose the underlying muscularis, which is excised for pathologic analysis of the ganglion cells. If myectomy is unsuccessful as a therapy, patients are usually recommended to undergo a bypass or resection of the dysfunctional rectum.

In a meta-analysis and review of adult Hirschsprung's disease from 2018, a total of 840 patients were identified in the literature. The most common surgical procedure performed in this cohort were Duhamel's (47%), Swenson's (19%), myectomy alone (9%), Soave's (8%), and low anterior resection (5%). There are no recently published comparative data to evaluate the relative success of these techniques in adults.

Duhamel's procedure is a retro-rectal transanal pull-through operation, in which the posterior wall of the rectum and anterior wall of the colon form a wide anastomosis. It has been adapted several times and has been simplified by surgical staplers. The main advantage of this approach is the avoidance of rectal mobilization and associated morbidity. The disadvantage is the preservation of a blind rectal stump with the diseased segment left in situ. In contrast, Swenson's procedure involves sequential biopsies along the anti-mesenteric border of the colon and rectum, until the most proximal aganglionic segment is identified. This then is mobilized fully, transected through the anus, and resected. The colon is pulled through for a colorectal anastomosis. Soave's procedure involves a rectal mucosectomy up to the level of the peritoneal reflection and retraction of the colon through the remnant sleeve of rectal muscle. The colon is anastomosed to the anal canal after confirming the presence of ganglion cells on frozen biopsy.

CONCLUSION

Constipation can be a disabling disease with multiple contributing etiologies. The majority of patients are effectively treated with non-operative therapies. A thorough diagnostic evaluation is critical to ensuring the correct management is prescribed. Careful patient selection is crucial to successful operative management, when indicated.

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MANAGEMENT OF RADIATION INJURY TO THE LARGE AND SMALL BOWEL

Scott R. Kelly, MD, FACS, FASCRS, and Christopher L. Hallemeier, MD

Ionizing radiation is an important part of multimodal treatment for a variety of pelvic malignancies (anorectal, gynecologic, urogenital) and is administered in both electromagnetic (x-rays, gamma rays) and particulate (protons, neutrons, electrons, carbon ions, and alpha and beta particles) forms. Radiation directly affects cells and their microenvironments. Rapidly dividing cells such as those of the gastrointestinal tract are most sensitive, which is a major limiting factor affecting treatment tolerance. Cells of the mucosa are affected first, followed by the submucosal, muscularis, and serosa. Radiation-induced acute intestinal injury occurs during therapy and usually resolves weeks to months following cessation. Acute injury typically includes mucosal sloughing, glandular hypersecretion, and bowel wall inflammation and edema. Late or chronic tissue manifest months to years after treatment and are the result of occlusive endarteritis/obliterative endarteritis that leads to tissue ischemia/hypoxia, mucosal atrophy, transmural fibrosis, and impaired angiogenesis and tissue repair. Chronic changes are irreversible and can be challenging to treat.

Scoring systems for grading radiation toxicity have been developed by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer. Grading is separated into acute (up to 90 days) and late (after 90 days) and is summarized in Table 1. Other scoring systems available include the Late Effects Normal Tissue/Subjective Objective Management Analytic and the National Cancer Institute Common Terminology Criteria for Adverse Events.

It is imperative to have a thorough understanding of the radiation (duration of radiotherapy, target fields, dosing regimen, complications during therapy) and operative history before pursuing any surgical intervention. An inadequate understanding will result in unfavorable surgical outcomes. Patients need to understand before any procedure that surgery will not cure the disease, but rather palliate symptoms/complications of the disease process. Preoperative enterostomal therapy education and site marking is imperative. Placement of enteral stents should be considered. Patients with severe protein calorie malnutrition (weight loss >15% of ideal body weight or serum albumin <2.5 g/dL) should be nutritionally optimized and may require total parenteral nutrition prior to surgery.

RISK FACTORS

Both tumor and normal tissue have radiation dose response relationships. Increasing doses of radiation delivered to the tumor are

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RISK FACTORS

Both tumor and normal tissue have radiation dose response relationships. Increasing doses of radiation delivered to the tumor are

TABLE 1 RTOG/EORTC Radiation Toxicity Grading

Grade	0	1	2	3	4	5
RTOG; acute radiation morbidity score[a]	None	Increased frequency or change in quality of bowel habits not requiring medication Rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs Mucus discharge not necessitating sanitary pads Rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support Severe mucus or blood discharge necessitating sanitary pads Abdominal distension	Acute or subacute obstruction, fistula, or perforation GI bleeding requiring transfusion Abdominal pain or tenesmus requiring tube decompression or bowel diversion	NA
RTOG/EORTC late radiation morbidity score	None	Mild diarrhea and cramping Bowel movement <4 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >4 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, or fistula	Death resulting from radiation late effects

[a]The acute morbidity criteria are used to scoregrade toxicity from radiation therapy. The criteria are relevant from day 1 through day 90, thereafter the RTOG/EORTC late radiation morbidity index is to be used.

GI, gastrointestinal; NA, not available; RTOG/EORTC, Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer.

typically associated with a greater degree of tumor cell kill and clinical response. However, increasing doses of radiation delivered to normal tissues are associated with increased likelihood and severity of toxicity. Higher doses administered in fewer fractions and/or over a shorter time interval are associated with increased rates of toxicity. Extended treatment areas (e.g., both abdomen and pelvis as pelvis or abdomen alone) result in higher rates of radiation-induced injury because more normal tissue is included in the treatment field. Those who have undergone pelvic and abdominal surgeries are at increased risk of intestinal injury as a result of visceral fixation and scarring. Factors that compound radiation-induced bowel injury include disease processes that affect vascularity and limit tissue perfusion/recovery genetics such as smoking, diabetes mellitus, hypertension, collagen vascular disorders, atherosclerosis, coronary artery disease, and vasculitis. A thin body habitus has also been associated with a higher rate of toxicity. Chemotherapeutic agents that potentiate the effects of radiation (radiosensitizers) are also culprit, such as fluoropyrimidines (5-fluorouracil and capecitabine), platinum agents (cisplatin and oxaliplatin), taxanes (docetaxel and paclitaxel), anthracyclin C, gemcitabine, methotrexate, actinomycin D, irinotecan, and dactinomycin.

CARCINOGENESIS

Ionizing radiation can increase the risk of subsequent cancer formation. Typically, there is a long latency period (>5 years) between treatment with ionizing radiation and the development of cancer, and different tissues have different rates of radiation-induced carcinogenesis. The most vulnerable is the hematopoietic cell line, followed by the thyroid, breast, lung, and salivary glands. The skin, bone, and gastrointestinal tract are less vulnerable. Multiple hypotheses have been postulated for radiation-induced carcinogenesis including mutation of tumor suppressor genes, activation of proto-oncogenes, genomic instability, and bystander effect (cells that have not been directly irradiated). A thorough evaluation for malignancy should always be part of the algorithm for patients with radiation-induced bowel injury.

SMALL BOWEL RADIATION INJURY

An undesirable side effect of treating abdominal and pelvic malignancies with ionizing radiation is injury to the small intestine. Acute radiation-induced small bowel disease, also known as radiation enteritis, is common if there is small intestine in the treatment field. It is typically transient and subsides following discontinuation of therapy. Common symptoms include nausea/emesis, diarrhea, bloating, and colicky abdominal pain. Late or chronic small bowel injury affects between 5% and 10%, of which 30% to 50% will require surgical intervention, and can result in malabsorption, unintended weight loss, stricture/obstruction, fistula formation, infection (abscess), perforation, and refractory bleeding/hemorrhage. Secondary to their fixed locations, the duodenum and terminal ileum are the most common areas of the small intestine affected.

Diagnosis

Acute radiation injury is typically diagnosed based on symptoms. For chronic issues, evaluation commonly includes imaging with computed tomographic or magnetic resonance enterography, which allows simultaneous evaluation of the small bowel and extraintestinal anatomy. Small intestine contrast studies (enteroclysis) are also an option, though rarely used. For suspected duodenal injury, upper endoscopy may be pursued. Lower endoscopy and barium or water soluble contrast enemas typically fail to reach the area of interest. Capsule endoscopy should be pursued with significant caution secondary to the risk of capsule obstruction at a right radiation stricture.

Medical Management

There is no proven effective medical treatment for radiation-induced small bowel disease. Symptoms can be controlled with a host of measures including dietary modifications (low residue, low fat, lactose free, elemental diet, hydration) and medications (antidiarrheals, antispasmodics, bile acid binding agents, antidiarrheals, antisecretory agents, analgesics).

Patients with chronic radiation enteritis often have disease that has been progressing for years and can present with infection (abscesses), fluid and electrolyte derangements, protein/calorie malnutrition, and debility. Optimization should occur prior to any elective surgery. Malnourished patients with fistulas often benefit from total parenteral nutrition, although spontaneous closure is unlikely.

Surgical Management

Secondary to increased morbidity (30%–50%) and mortality (10%), surgery for radiation–induced small bowel disease should be avoided other than for specific indications such as perforation, fistulae, obstruction, bleeding/hemorrhage, persistent abscess, and intractable pain.

Limited resection of the involved segment is the procedure of choice, although bypass and exclusion are options when dense adhesions or pelvic fixation make resection impossible. Secondary to diffuse adhesions and bowel fibrosis, it can be difficult to distinguish between normal and involved intestine and anastomosing irradiated segments of bowel is associated with leak rates upward of 50%. Incidence of nonirradiated bowel to the anastomosis or bypass is advisable. Ligation of the mesentery with vessel sealers or a clamp, cut, and tie technique is often inadequate secondary to mesenteric foreshortening, thickening, and friability. Oversewing the mesentery with heavy sutures between clamps is preferable.

Adhesiolysis during resection is associated with an increased risk of fistula formation and should only be performed if the area of resection can be resected if necessary. Injecting saline with a fine needle (50 g) into dense interloop adhesions (hydrodissection) can help delineate tissue planes and decrease the risk of serosal injuries.

Compared with bypass, resection will remove the affected segment, reduces the rate of reoperation, and is associated with increased survival. Bypass is more simplistic and decreases the risk of anastomosis or bowel injury but leaving an affected segment behind increases the risk of blind loop syndrome (bacterial overgrowth) and fistula formation. For dense adhesions and tethering in the pelvis, bypass is typically a better option.

Stricturoplasty can be considered in patients with strictures located within long segments of bowel where resection or bypass would exclude a large portion of the intestine and lead to metabolic and nutritional deficiencies.

Patients with enteric fistulas (e.g., enterovaginal, enterovesical, enterocutaneous) should be optimized before pursuing any surgical intervention. Time should be provided for fistula maturation while controlling output, enhancing nutrition, treating any underlying infection (abscesses), and restoring fluid and electrolyte balance. Fistulograms can help define the extent and area of intestine involved.

If unable to resect and anastomose the segment of bowel containing the fistula, it can be totally excluded by transecting proximally and distally leaving the short segment of well vascularized fistulating bowel attached to the bladder/vagina/skin for continued mucus decompression.

LARGE BOWEL RADIATION INJURY

Secondary to fixation, radiation induced injury affects the sigmoid colon more frequently than the small intestine but is less likely to require surgery and overall has a better prognosis.

Acute symptoms typically include diarrhea with or without bleeding, mucus discharge, abdominal cramping, and tenesmus. Chronic issues can result in obstruction, persistent bleeding/hemorrhage, intractable pain, fistulization, and perforation.

Diagnosis

As with the small intestine, acute colonic radiation injury is typically diagnosed based on symptoms alone. Endoscopy allows for the identification of edema, friability, ulcerations, telangiectasia, and strictures (Fig. 1). Barium and water–soluble contrast enemas can reveal shortening, narrowing, lack of distensibility, absence of haustral mucosal folds, and loss of normal curvature. Computed tomography or magnetic resonance enterography provide the ability to assess not only the colon and rectum, but also the small bowel and extraintestinal anatomy (Fig. 2). Identification of fistulas can require fistulograms, cystograms, and gynecologic examinations.

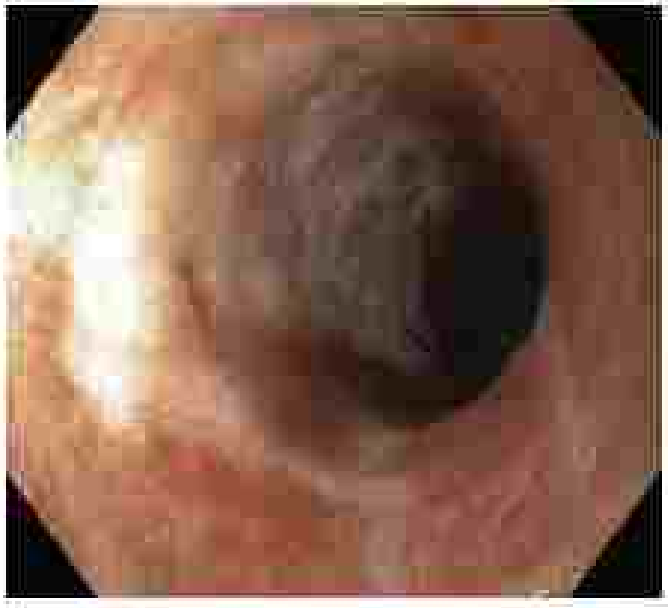

FIG. 1 Endoscopic view of sigmoid colon edema and erythema. (Courtesy Mayo Foundation for Medical Education and Research.)

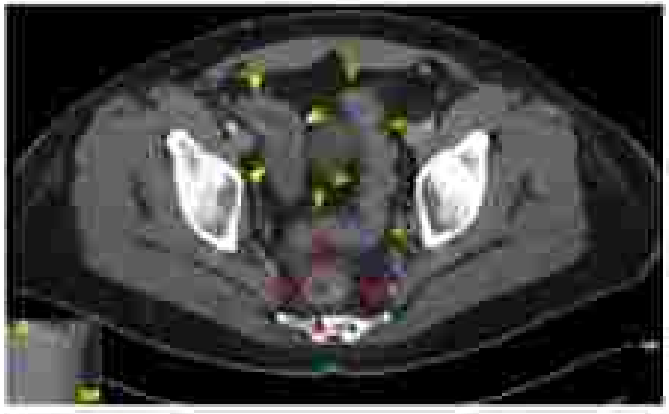

FIG. 2 Axial cassette of contrast filled gallbladder (yellow arrows), sigmoid colon (orange arrows), and rectum (red arrows). (Courtesy Mayo Foundation for Medical Education and Research.)

Medical Management

As with radiation induced small bowel disease there is no effective medical treatment for radiation induced colitis. Symptoms can be controlled with dietary modifications (low residue) and medications (anticholinergics, antispasmodics, antidiarrheals, stool softeners, sucralfate enemas, analgesics).

Surgical Management

Other than for specific indications (perforation, fistula, obstruction, persistent bleeding/hemorrhage, intractable pain, incontinence), the majority of patients with radiation induced colonic injury do not require operative intervention.

A segmental resection and anastomosis with a nonirradiated proximal colonic conduit, with or without temporary diversion, is effective in most cases. For those who are not surgical candidates, a permanent diverting ileostomy or colostomy is recommended. Using nonirradiated bowel is preferable to decrease issues with stoma structure, bleeding, and necrosis.

Fistulae involving the urinary tract (colovesical) or vagina (colovaginal) can be treated in a similar manner. Interposition of

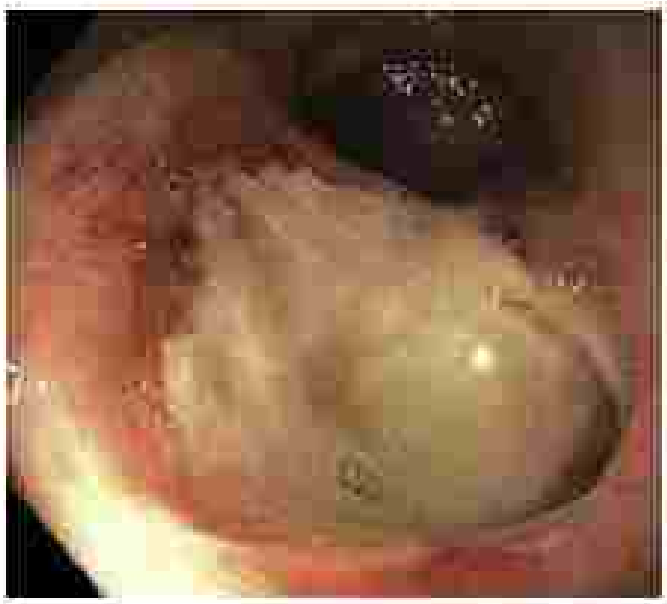

FIG. 3 Endoscopic view of rectal ulcer. (Courtesy Mayo Foundation for Medical Education and Research.)

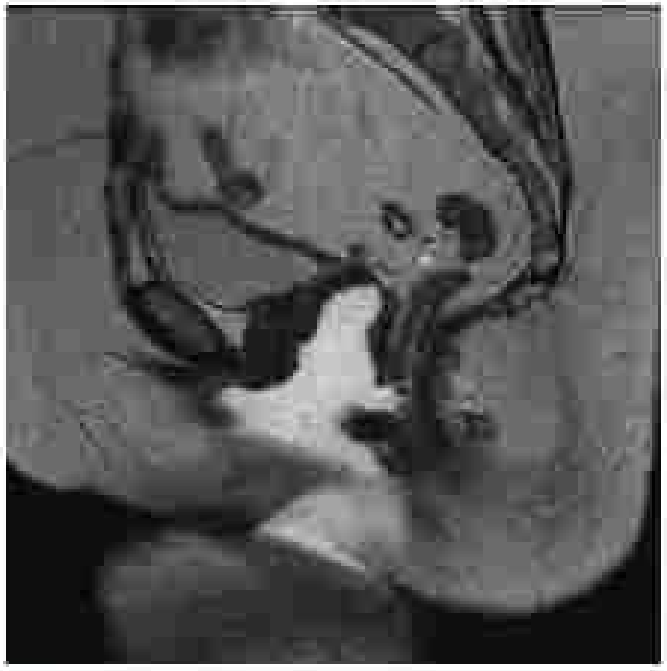

FIG. 4 MRI of pelvis showing a low rectovaginal fistula. (Courtesy Mayo Foundation for Medical Education and Research.)

well vascularized nonirradiated tissue (omental or rectus pedicle flap) between the affected organs and instruments should be considered. A protective stoma should always be entertained. If unable to resect and reanastomose, the segment of bowel containing the fistula can be transected proximally and distally, leaving a short segment of well vascularized bowel attached to the offending organ, which may result in persistent mucous discharge.

RECTAL RADIATION INJURY

Rectal injury is unavoidable in most patients who receive pelvic radiation. With the increased use of radiation to treat pelvic malignancies, radiation proctopathy, also called radiation proctitis, has become more commonplace over the decades. The incidence of both acute and chronic radiation proctitis correlates with the dose and fractionation regimen and the volume of rectum receiving exposure. Acute self-limiting symptoms affect a majority of patients and typically include diarrhea with or without bleeding, urgency, tenesmus, mucus discharge, and abdominal cramping. A minority of patients will require temporary cessation of treatment or dose modification. Chronic radiation proctopathy, affecting up to 20%, can result in rectal bleeding from telangiectasias, bowel dysfunction (diarrhea, obstipation, urgency, frequency with or without incontinence, loss of compliance), pain, strictures, ulcerations, and fistulas (Fig. 3).

Diagnosis

Endoscopic findings alone are not directly correlative with symptoms because more than one half of asymptomatic patients will have mucosal congestion and telangiectasias, although it provides the ability to thoroughly evaluate the luminal integrity of the rectum. Unless there is concern for malignancy, deep biopsies should be avoided to decrease issues with bleeding, perforation, and fistulization. On imaging, the presacral space can appear wider than normal secondary to rectal scarring. Fistulous evaluation can require dedicated pelvic magnetic resonance imaging, cystograms, and gynecologic examinations (Fig. 4).

Medical Management

Minor to moderate rectal bleeding can be treated with a multitude of noninvasive modalities, including bowel regimens, enemas, topicals, and endoscopic treatments. For many patients, improving issues with constipation or diarrhea is all that is needed. Sucralfate (2 g in 20 mL tap water) administered as an enema twice daily has been shown in some studies to decrease issues with bleeding and promote healing.

For patients with moderate or severe bleeding symptoms, argon plasma coagulation (APC) is the primary treatment modality. APC uses inert argon gas at a flow rate from 1.2 to 2.1 L/min, an electrical power setting ranging from 45 to 50 W, and a probe size from 2.7 to 3.2 mm in diameter to treat bleeding by creating a superficial coagulation. Targeted pulse treatment is preferred to extensively painting the rectal mucosa to decrease the risk of postprocedure ulceration. Repeat treatments may be required and APC is less effective in sites with active bleeding. Bipolar or heater probes can also be used when a visible vessel is identified.

Dilute formalin (4% solution) prepared by mixing 200 mL of 10% buffered formalin with 300 mL water has been used to control sites of bleeding (chemical cauterization) using either gauze or direct instillation through a sigmoidoscope. Gauze soaked formalin sponges are placed through a rigid proctoscope and held in direct contact with bleeding areas for 2 to 3 minutes. Alternatively, aliquots of 30 to 50 mL can be instilled through a sigmoidoscope, allowing the solution to remain in contact with the rectal mucosa for 30 seconds. In addition, topical treatment with a 10% formalin soaked long jumbo tip (obstetrics/gynecology) cotton swabs placed through a rigid proctoscope can be used to treat spot areas of bleeding. Saline should be used liberally to irrigate the rectum between each treatment, and the perineum should be washed thoroughly if exposed because formalin is a severe irritant. Vaseline gauze can be used to protect the perineum, and the rectum can be packed with gauze proximal to the treatment area. Weekly/biweekly applications are typically necessary until cessation of bleeding. Worsening rectal strictures, ulcerations, and chronic pain can occur following treatment. Additional treatments that have been used for chronic radiation proctopathy include hyperbaric oxygen treatments, cryoablation, radiofrequency ablation, sunfinatrex, and probiotics.

Surgical Management

Surgical intervention is necessary in less than 1% of patients with radiation proctopathy and typically indicated for obstruction, stricture,

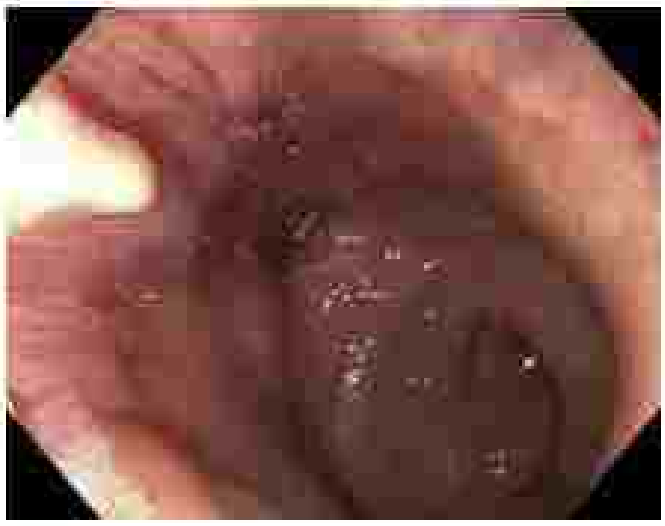

FIG. 5. Endoscopic view of urinary catheter visible through a low rectovaginal fistula. (Courtesy Mayo Foundation for Medical Education and Research.)

perforation, fistulization, intractable pain, persistent bleeding, and incontinence. In most cases, fecal diversion will improve pain, allow rectal mucosal edema to subside, and result in cessation of bleeding. In young patients with good sensation, function, and control, a proctectomy with coloanal anastomosis can be considered. To decrease issues with staple line ischemia, a handsewn coloanal anastomosis is preferred.

Mid- to upper rectal fistulas (rectovaginal, rectourethral) can be treated with resection and anastomosis of healthy colon to distal rectum or anus. Interposition of well-vascularized nonirradiated tissue (omental or rectus pedicle flap) between the affected organ and anastomosis should be considered.

Low rectal fistulas can be treated in a similar manner or managed in a perineal, transanal (Kraske) or transsphincteric (York Mason) approach (Fig. 5). Compared with using native tissue, interposition of well-vascularized healthy tissue (omentum, rectus, gracilis, bulbocavernosus) is associated with higher rates of healing.

For those with comorbidities precluding surgery, bowel diversion and placement of a suprapubic urinary catheter may be necessary. A loop ileostomy is easier to manage and does not interfere with the possibility of a future proctectomy and coloanal anastomosis. To decrease the risk of a Hartmann's stump disruption (blow out), an anal colostomy should be avoided.

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Surgical Management of the Polyposis Syndromes

Erik R. Nelson, MD, MS, and Sang W. Lee, MD, FACS, FASCRS

Colorectal polyps can be classified as adenomatous, hamartomatous, hyperplastic, neoplastic, and inflammatory based on their morphology and histologic features. Several polyposis syndromes have been described, each with unique presentation, genetic basis, extracolonic manifestations, and malignancy risk. Most of the identified syndromes carry increased risk for development of colorectal cancer. Suspicion is the key to making the diagnosis of hereditary polyposis syndrome. A detailed family history and genetic evaluation are important to allow siblings and offspring the opportunity for genetic counseling and testing. Management options include strict surveillance for the early detection of cancer, chemopreventive medications, and surgery. Multidisciplinary care, including clinical services, support and counseling, as well as referral to a polyposis registry is recommended. This chapter discusses the most common polyposis syndromes with a focus on recommendations for management (Table 1).

ADENOMATOUS POLYPOSIS SYNDROMES

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease resulting from a germline mutation to the adenomatous polyposis coli (APC) tumor suppressor gene located on chromosome 5q21. Most mutations are found between codons 1relt and 1640, with two of the most significant being 1061 and 1309. FAP is characterized by the endoscopic identification of greater than 100 synchronous adenomas. Severe cases often manifest thousands of adenomatous lesions, sparing little normal colon and rectal mucosa. Patients with fewer than 100 adenomatous polyps are considered to have attenuated FAP. Approximately 25% to 30% of APC mutations occur de novo and will not have a family history of FAP. Patients diagnosed with FAP should be referred to a polyposis registry and genetic counseling specialist to identify at-risk family members and coordinate testing.

Adenomatous polyps in FAP are found predominantly in the rectum and left colon. They develop in adolescence and are present in up to 15% of patients by 10 years of age and 75% by age 20. The risk of colorectal malignancy is nearly 100% by 40 years of age for patients with untreated FAP. Overall, FAP is estimated to account for just 1% of overall colorectal cancer diagnoses. The most common presenting symptoms are bleeding, diarrhea, abdominal pain, and mucous discharge. For those with a family history or identified APC mutation, a screening should be performed at 12 years of age and can be started with a flexible sigmoidoscopy. If polyps are detected, a full colonoscopy should be performed and repeated annually.

Extracolonic Intestinal Disease

Extracolonic intestinal disease is a common manifestation of FAP. More than 80% to 90% of patients will have gastric fundic gland hyperplastic polyps with very low malignant potential. Gastric adenomas are rare (10%), typically occur in the antrum, and are associated more commonly with Japanese and Korean heritage.

Duodenal adenomas, most commonly found around the ampulla of Vater and macroscopically different than colonic adenomas, are found in more than 90% of patients with FAP and develop approximately 15

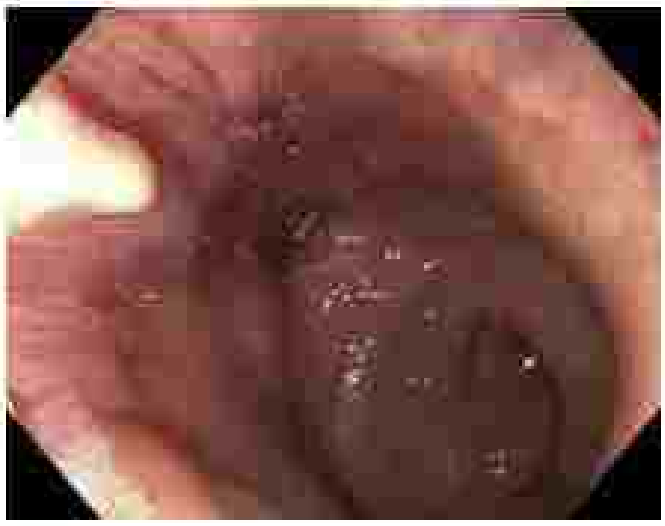

FIG. 5. Endoscopic view of urinary catheter visible through a low rectovaginal fistula. (Courtesy Mayo Foundation for Medical Education and Research.)

perforation, fistulization, intractable pain, persistent bleeding, and incontinence. In most cases, fecal diversion will improve pain, allow rectal mucosal edema to subside, and result in cessation of bleeding. In young patients with good sensation, function, and control, a proctectomy with coloanal anastomosis can be considered. To decrease issues with staple line ischemia, a handsewn coloanal anastomosis is preferred.

Mid- to upper rectal fistulas (rectovaginal, rectourethral) can be treated with resection and anastomosis of healthy colon to distal rectum or anus. Interposition of well-vascularized nonirradiated tissue (omental or rectus pedicle flap) between the affected organ and anastomosis should be considered.

Low rectal fistulas can be treated in a similar manner or managed in a perineal, transanal (Kraske) or transsphincteric (York Mason) approach (Fig. 5). Compared with using native tissue, interposition of well-vascularized healthy tissue (omentum, rectus, gracilis, bulbocavernosus) is associated with higher rates of healing.

For those with comorbidities precluding surgery, bowel diversion and placement of a suprapubic urinary catheter may be necessary. A loop ileostomy is easier to manage and does not interfere with the possibility of a future proctectomy and coloanal anastomosis. To decrease the risk of a Hartmann's stump disruption (blow out), an anal colostomy should be avoided.

Suggested Readings

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TABLE 1 Summary of CRC Polyposis Syndromes

Syndrome	Gene	Inheritance Pattern	Clinical Presentation	CRC Risk (%)
FAP	APC	Autosomal dominant	>100 adenomas Duodenal adenomas (90%) Fundic gland hyperplasia (90%) Desmoid tumors (30%) CHRPE (75%) Osteomas (80%)	100
Attenuated FAP	APC	Autosomal dominant	<100 adenomas Fundic gland hyperplasia Duodenal polyps	100
MUTYH	MYH	Autosomal recessive	6–100 adenomas Fundic gland hyperplasia Duodenal adenomas (20%) CRC <50 years	75
Serrated polyposis	Unknown	Unknown	>20 serrated polyps Any serrated polyps and family history >5 serrated polyps proximal to sigmoid colon and two >1 cm in diameter	25–40
Peutz-Jeghers polyposis	STK11	Autosomal dominant	Hamartomatous polyps (90%) Perioral pigmentation (95%)	40
Juvenile polyposis	SMAD4 BMPR1A	Autosomal dominant	>5 hamartomatous polyps in the colon or rectum (100%) gastric polyps (50%) Cleft lip and palate, polydactyly, genitourinary anomalies, intestinal malrotation, hydrocephalus, and congenital heart disease	40
PTEN hamartoma syndrome	PTEN	Autosomal dominant	Hamartomatous polyps, lipomas, fibromas, ganglioneuromas, juvenile hamartomas, trichilemmomas Thyroid cancer (10%) Breast cancer (50%)	10 (Cowden)

CHRPE, congenital hypertrophy of the retinal pigment epithelium; CRC, colorectal cancer; FAP, familial adenomatous polyposis; MUTYH, mutation Y-homolog-associated polyposis.

years later than colonic polyps. Duodenal cancer, typically diagnosed around 50 years of age, occurs in 5% to 10% of patients and is the second leading cause of death associated with FAP. A screening esophagogastroduodenoscopy (EGD) is recommended around 20 years of age, and the Spigelman severity score and staging system (Table 2) is used to determine surveillance intervals (Table 3). The risk of developing cancer after 10 years of follow up for stage I to II, stage II and III to IV, and 36% for stage IV. Small tubular adenomas, as well as those with low grade dysplasia, can undergo biopsies and be observed. High risk adenomas (villous, >1 cm), severe duodenal polyposis, high grade dysplasia, or stage IV disease should be offered a pancreas preserving duodenectomy, and those with cancer a pancreaticoduodenectomy. Chemoprevention with nonsteroidal antiinflammatory agents (sulindac, celecoxib) can result in polyp regression in those with a lower polyp burden, although overall the effect is minimal at best.

Extraintestinal Manifestations

The APC gene protein is expressed in organs throughout the body, but at lower levels than the colonic mucosa. Common extraintestinal manifestations of FAP include osteomas, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermoid cysts, and desmoids. Benign osteomas of the mandible, skull, and tibia are the most common extraintestinal finding occurring in more than 80% of patients. Although CHRPE is not specific to FAP, having four or more areas of large, patchy fundic discoloration is pathognomonic and will be present in around 75% of individuals. Epidermoid cysts occur approximately 20% of the time.

TABLE 2 Spigelman Staging System for Upper Gastrointestinal Manifestations of FAP[a]

Points	1	2	3
Number of polyps	1–4	5–20	>20
Size of polyps	1–4 mm	5–10 mm	>10 mm
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

[a]Spigelman stage I, score 1–4; stage II, score 5–6; stage III, score 7–8; stage IV, score 9–12.

Other extraintestinal manifestations, although rare, include supernumerary teeth, cerebellar medulloblastoma, and cancers of the liver, biliary tree, adrenal glands, and thyroid. The risk for thyroid cancer for patients with FAP is approximately 2%, which is double that of the general population. Screening thyroid ultrasound is recommended annually, also starting at 20 years of age. Thyroid nodules larger than 1 cm warrant fine needle aspiration.

Desmoid Tumors

Desmoids are rare in the general population but develop in up to 30% of FAP patients. These locally invasive abdominal wall and intraabdominal/retroperitoneal myofibroblastic tumors typically develop 2

TABLE 3 Derivation of Spigelman Stage From Scores

Total Points	Spigelman Stage	Suggested Interval to Next Duodenoscopy
0	0	5 y
1–4	I	3–5 y
5–6	II	3 y
7–8	III	1 y
9–12	IV	Consider duodenectomy vs endoscopy in 6 mo

to 3 years after surgery and occur around 30 years of age. Etiology and pathogenesis are not well understood. Desmoids can develop spontaneously, are the third most common cause of death associated with FAP and have been noted to be associated with trauma. Risk factors associated with the development of desmoids are mutations in the 3′ end of the APC gene, female gender, extraintestinal manifestations, and a family history of desmoid disease. Of desmoids, 30% grow rapidly, 10% resolve spontaneously, 30% oscillate between cycles of growth and regression, and 50% remain stable or grow very slowly.

Extraabdominal desmoids are best treated with surgical extirpation with a 1-cm margin, although recurrence is high with documented rates of 20% to 50%. Early excision is recommended to decrease the size of the resultant abdominal wall defect.

Intraabdominal/intraperitoneal desmoids can invade the mesentery and surrounding structures resulting in obstruction, hemorrhage, ischemia, and perforation. The primary treatment is medical and includes nonsteroidal antiinflammatory agents (sulindac, celecoxib), estrogen antagonists (tamoxifen, toremifene, raloxifene), and chemotherapy (vinblastine, methotrexate, doxorubicin, dacarbazine). Surgical removal is difficult and often impossible if the root of the mesentery is involved. Resection with completely uninvolved margins (R0) will result in recurrence 50% of the time. If possible, noninvasive procedures such as dilatation and bypass are preferable for palliation. Ureteral obstruction is best treated with stenting.

There is not a defined screening regimen for desmoid tumors, although computed tomography and magnetic resonance imaging can be used, especially for patients with an increased risk of developing desmoids.

Attenuated FAP

In contrast to classic FAP, attenuated FAP (aFAP) occurs at a later age (30s and 40s), with fewer than 100 polyps, found predominantly in the right colon. If untreated, the risk of colorectal malignancy is 70% and cancer develops later in life (58 years of age on average). Fundic gland polyps and duodenal adenomas occur frequently, but other extracolonic and extraintestinal manifestations, including gastric adenomas, desmoids, and CHRPE, typically are not seen in aFAP.

For those with a family history or identified APC mutation suggestive of aFAP, screening colonoscopy should begin at 20 years of age and be repeated every 1 to 2 years. With the predilection for polyp development in the right colon, a formal colonoscopy is recommended.

Mutation Y-Homolog–Associated Polyposis

Mutation Y homolog (MYH) associated polyposis (MAP) is the only polyposis syndrome with an autosomal recessive inheritance pattern. It results from a biallelic mutation in the MYH gene located on chromosome 1p34. The number of polyps associated with MAP is variable from to hundreds with a median around 50. Polyps are found most commonly in the left colon and occur at a median age of 48 years. Polyposis is not required for the diagnosis of MAP. Up to 30% of such patients present with colorectal cancer without history of synchronous polyps. If untreated, the risk of colorectal malignancy is around 75% for males and 72% for females by 70 years of age. Extraintestinal manifestations can be associated with MAP, although these are exceedingly rare.

Because of the phenotypic overlap with FAP, genetic testing for the MYH mutation is typically performed when no APC mutation is detected. There are fewer than 100 adenomatous polyps, and the family history is irrelevant or does not reveal a dominant mode of inheritance.

Although there are no defined endoscopic screening criteria for MAP, an initial endoscopic (colonoscopy and EGD) evaluation should be performed starting around 25 to 30 years of age. If no polyps are appreciated, endoscopy should be repeated every 3 to 5 years and more frequently if present. As in the case of FAP, patients have an increased risk for developing thyroid malignancy, and annual screening ultrasound of the thyroid is recommended.

CHEMOPREVENTION

Although clinic trials have shown that nonsteroidal antiinflammatory drugs (sulindac, celecoxib) and aspirin can reduce the size and number of adenomas in the colon and rectum, there was not an appreciable reduction in cancer. Chemoprevention is not recommended as a primary therapy for polyposis syndromes and is not an appropriate alternative to prophylactic surgery. Situations in which chemoprevention can be entertained include treating ileal pouch and anastomosis polyps, a high family risk of desmoid tumors, delayed surgery, and unwillingness or inability to tolerate polypectomy or completion proctectomy.

SURGERY

The goal of prophylactic surgery for polyposis syndromes is to prevent colorectal cancer. The timing and type of surgery offered depends on a multitude of factors, including clinical presentation, family history, and, if known, the site of the chromosomal mutation. Severe polyposis (more than 1000 colonic or 20 rectal polyps) and APC mutations between codons 1250 and 1464 carry a higher risk of cancer, and surgery should be offered as early as possible. Surgery also should be pursued early for symptomatic disease. For those with a high risk of desmoid disease (family history, mutation in the 3′ end of the APC gene, female gender, extracolonic manifestations), surgery should be delayed as long as possible to decrease the chance of desmoid tumors developing. Young patients should have surgery delayed, if possible, to allow for adequate physical, rectal, and intellectual maturity. For patients with classic FAP, surgery typically occurs around 16 to 20 years of age.

Surgical options include open or minimally invasive total proctocolectomy with creation of an end or continent ileostomy, total abdominal colectomy with creation of an ileorectal anastomosis (IRA), and a total proctocolectomy with creation of an ileal pouch anal anastomosis (IPAA). A thorough preoperative discussion of the advantages and drawbacks to each approach is necessary to achieve the best patient outcome.

PROCTOCOLECTOMY WITH END-ILEOSTOMY

A proctocolectomy with end ileostomy has a low rate of complications. Most patients do not elect for creation of an incontinent stoma if they are candidates for other continence restoring approaches. Indications for this approach are patient preference, low rectal cancer requiring an abdominoperineal resection, rectal cancer requiring postoperative pelvic radiation, inability to create an IPAA (inadequate mesenteric length), and poor sphincter function. In

some cases, patients with chronic pouch dysfunction may elect for conversion to an end ileostomy.

The procedure is carried out in an oncologic approach secondary to the risk of a preoperatively unrecognized cancer. A perineal intersphincteric dissection is carried out preserving the external sphincter and levator ani muscles. The perineum is closed in layers and the greater omentum, if present, is mobilized and placed in the pelvis to prevent future bowel obstructions. After closure of the abdomen the ileostomy is matured to a standard end-stoma fashion.

Proctocolectomy With Continent Ileostomy

The continent ileostomy was initially described by Nils Kock (Kock's pouch) in 1969; it allows patients an option for an ileostomy without need for a cumbersome bag. Modifications and revisions to the original Kock's continent ileostomy have been described (Barnett continent intestinal reservoir and T-pouch). Each features an ileal pouch reservoir and valve mechanism to prevent leakage of accumulating stool. Although the technique lost favor when IPAA was established as the first choice technique, continent ileostomy remains an option for select patients undergoing proctocolectomy for FAP, including those with inadequate sphincter function, insufficient small bowel mesentery, a history of low rectal or anal cancer, failed existing IPAA, and/or in whom traditional ileostomy is undesirable. Contraindications to construction of a continent ileostomy include Crohn's disease, morbid obesity, marginal small bowel length, and a psychologic or physical disability that would preclude understanding or being able to perform daily stoma catheterization.

Total Abdominal Colectomy With IRA

Colectomy with IRA should be considered only in cases of attenuated or mild polyposis (fewer than 20 rectal or 1000 colonic adenomas), rectal polyps smaller than 3 cm, no colorectal dysplasia or cancer, a distensible and compliant rectum, and in patients with an intact sphincter mechanism that are willing to adhere to strict follow up. This rectal sparing approach is an appealing alternative to younger patients of reproductive age to decrease the risk of impotence and reduced fecundity. Strict rectal surveillance (every 6–12 months) must be adhered to because of the increased risk of future neoplastic changes. The risk of rectal carcinoma can reach up to 40% by 30 years, although this is based on literature from the pre-1980s era. In patients who require a completion proctectomy, an end ileostomy, restorative IPAA, or continent ileostomy remain viable options.

Restorative Proctocolectomy With IPAA

Initially described in 1978 by Parks and Nicholls, the restorative proctocolectomy has become the most common continence preserving procedure performed in patients who are appropriate candidates. Indications include severe polyposis (>20 rectal or >1000 colon adenomas), rectal polyps larger than 3 cm in size, colonic dysplasia or cancer, dysplastic rectal polyps, and in patients with an intact sphincter mechanism willing to adhere to strict follow up. The restorative pouch can be fashioned in two limbs (J), three limbs, four limbs, or isoperistaltic configurations. The J pouch, because of its ease of construction and excellent functional outcomes, has become the most common choice for surgeons.

A total colectomy is performed in an oncologic fashion, and the ileum is transected flush with the cecum. To provide adequate perfusion to the pouch, it is imperative to preserve the ileal branches of the ileocolic and distal mesenteric arteries. Evaluation for adequacy of reach of the small bowel to the deep pelvis should be undertaken before creation of the pouch. If the proposed apex of the pouch and mesentery can be advanced 3 to 4 cm below the inferior edge of the pubis, one can feel confident of successful reach for anastomosis. Strategies to decrease tension at the anastomosis include complete mobilization of the small bowel mesentery to the root of the superior mesenteric artery cephalad to the head of the pancreas, proximal division of the ileocolic artery, and relaxing incisions of the mesentery over tension points along the superior mesenteric artery. Rectal dissection to completion in the total mesorectal excision plane, and transection of the rectum with a 30 mm transverse stapler should occur 2 to 3 cm above the dentate line in the anal transition zone. After reach has been verified, a J configuration is fashioned with each limb measuring between 12 and 15 cm in length. The limbs are parted in an antimesenteric fashion and are held in orientation with interrupted stay sutures. For those without evidence of adenomas in the anal transition zone, or dysplasia in the lower rectum, a double stapled IPAA can be fashioned; otherwise, an anal mucosectomy and handsewn IPAA is recommended. After creation of the IPAA, an air insufflation leak test is performed and, if necessary, a protective loop ileostomy fashioned, which should be created as close to the pouch as possible to decrease issues with high output. In selected patients, the operation can be completed with good results without the creation of a diverting loop ileostomy.

Double-Stapled Technique

An enterotomy is made to the antimesenteric apex of the pouch, and a linear cutting stapler is used to divide the walls of the two limbs, creating a common channel (Fig. 1). A pursestring suture then is fashioned around the enterotomy, and the anvil from a circular stapler is placed inside the pouch, where it is held in place by tightening the purse string (Fig. 2). The circular stapler then is placed transanally. After appropriate orientation, the circular stapler cartridge spike is advanced either above or below the transverse rectal staple line and attached to the anvil. The stapler then is closed, approximating the pouch and anus (Fig. 3).

Handsewn Technique

An anal mucosectomy is performed starting at the dentate line. Raising the mucosa with a submucosal injection (Fig. 4) of dilute saline and epinephrine (1:200,000) facilitates dissection of the mucosa away from the internal sphincter muscle (Fig. 5), which can be completed sharply or with electrocautery. After the mucosa and

FIG. 1 J pouch creation. *(Courtesy Mayo Foundation for Medical Education and Research.)*

FIG. 2 **Ileal J pouch.** (Courtesy Mayo Foundation for Medical Education and Research.)

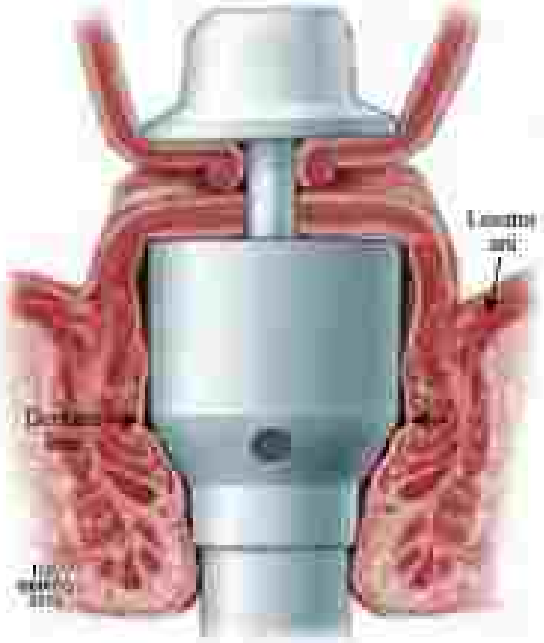

FIG. 3 **Stapled ileal pouch anal anastomosis.** (Courtesy Mayo Foundation for Medical Education and Research.)

proximal rectum have been removed circumferentially, the pouch is brought down gently to the level of the dentate line. An enterotomy is made in the apex of the pouch, if not already created, and anchored in position by placing a suture in each of the four quadrants, incorporating a full thickness bite of the pouch, internal sphincter muscle, and mucosa. Sutures are placed between the anchoring stitches to complete the anastomosis (Fig. 4).

FIG. 4 **Submucosal injection.** (Courtesy Mayo Foundation for Medical Education and Research.)

FIG. 5 **Ileal transection.** (From Kelly SB, Thekkinkattil D, Cahill RA, et al. Colorectal surgery: A companion to specialist surgical practice. 5th ed. Edinburgh: Elsevier; 2014. p. 141.)

Postoperative Surveillance

After creation of an ileal J pouch, IPAA, or IRA, annual surveillance with flexible endoscopy facilitates early detection and removal of adenomas, dysplasia, and carcinoma. The patient must understand the need for a lifelong surveillance regimen. Histologic evaluation of random biopsies and polyps should be performed to exclude dysplasia and cancer, particularly in any areas of chronic scarring. More frequent surveillance is performed for increased numbers or size of polyps. Severe dysplasia and villous adenomas more than 1 cm in size should prompt a completion proctectomy in those with an IRA.

HAMARTOMATOUS POLYPOSIS SYNDROMES

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant inherited disease resulting most commonly from a mutation in the *LKB1* (*STK11*) tumor suppressor gene located on chromosome 19p13. Approximately 30% to 80% will occur de novo. Hamartomatous polyps are found throughout the gastrointestinal tract, although most

FIG. 8 Giant cow fetal pouch and anencephaly. (Courtesy Allegra Foundation for Health & Education and Research.)

commonly in the small intestine. Polyps vary in size and tend to become pedunculated as they grow larger. Extraintestinal manifestations are common, with the hallmark phenotypic feature in adolescence being mucocutaneous hyperpigmentation that can affect the perioral and buccal region, eyes, nostrils, perianal region, fingers and toes, and hands and feet. Hyperpigmentation dissipates as a patient ages. Hamartomatous polyps and mucocutaneous pigmentation confirms a diagnosis of Peutz-Jeghers syndrome. Although the overall number of polyps tend to be small (<20), the large polyp size tends to cause abdominal pain, alteration in bowel habits, weight loss, bowel intussusception, anemia, hematochezia and melanotic stools, and small bowel obstruction. The risk of malignancy is substantially higher than the general population and increases with age. The most common cancers are colorectal, breast, pancreatic, and genitourinary.

Colonoscopy and UGD should be initiated around 10 years of age. If polyps are detected, endoscopic evaluation should continue every 2 to 3 years. If no polyps are found, repeat endoscopy and small bowel follow through or capsule enteroscopy should be initiated by 20 years of age and repeated every 2 to 3 years. Other surveillance recommendations with low levels of evidence include an annual clinical examination, annual testicular examination starting at birth with ultrasound for abnormalities detected, monthly breast examination starting at age 18, and annual breast magnetic resonance imaging and cervical smear starting at age 25 years.

Gastrointestinal surgery is reserved for symptomatic disease, endoscopically uncontrollable polyp burden, high grade dysplasia, or cancer. Any polyp larger than 1.5 cm should be removed, if possible, at the time of surgery. Intraoperative on table endoscopy can be used to evaluate the entire gastrointestinal tract. Laparoscopic total abdominal colectomy and IRA is the operation of choice for management of colonic disease.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome is an autosomal dominant inherited disease resulting most commonly from mutations in the *SMAD4* and *BMPR1A* genes, which are located, respectively, on chromosomes 18q21 and 10q22. Polyps can be found throughout the gastrointestinal system, the colon is affected 100% of the time and gastric polyps found in approximately 50%. Extraintestinal manifestations occur around 15% of the time and can include cleft lip and palate, polydactyly, genitourinary anomalies, intestinal malrotation, hydrocephalus, and congenital heart disease. Hereditary hemorrhagic telangiectasia and bleeding arteriovenous malformations in the gastrointestinal, pulmonary tracts, brain, and mediastinum are associated with some *SMAD4* mutations. Diagnosis of juvenile polyposis syndrome is confirmed when five or more juvenile polyps are found in the colon or rectum, multiple polyps are appreciated in other regions of the gastrointestinal tract, or after identification of polyps with a positive family history. Presenting symptoms can include hematochezia and melanotic stools, anemia, intussusception, obstructing, and passage of autoamputated or prolapsed polyps. Colorectal cancer is the most common associated malignancy with lifetime rates as high as 50%. Other malignancies include gastric, duodenal, and pancreatic.

Asymptomatic patients should begin with screening colonoscopy by 15 years of age, and earlier for those with symptoms. If no polyps are detected, evaluation can be repeated every 2 to 3 years, otherwise annually. UGD is recommended by age 25 years. Those with an *SMAD4* mutation should have periodic screening for arteriovenous malformations.

Colorectal surgery is reserved for symptomatic disease, dysplasia, cancer, or polyp burden not amenable to endoscopic management alone. For those with a relatively spared rectum, a total abdominal colectomy with IRA can be pursued. Patients must be cautioned about the need for lifelong surveillance of the remaining rectum. If the rectum is significantly involved, a total proctocolectomy with IPAA is advisable. Surgeries to the remaining gastrointestinal tract may also be warranted.

Cowden's Syndrome

Cowden's syndrome is an autosomal dominant disorder resulting from a mutation to the *PTEN* tumor suppressor gene located on chromosome 10q23. Ninety five percent of patients will manifest colon polyps, most commonly hamartomas, though fibromas, adenomas, lipomas, and neurofibromas are also found. Extraintestinal manifestations include pathognomonic trichilemmomas, macrocephaly, and a wide variety of tumors and hamartomas of various organ systems (oral mucosa, small bowel, breast, thyroid, uterus).

The risk of developing colon and rectal cancer is thought to be no greater than the general population, although the risk for thyroid and breast cancer is noted to be around 10% and 50%, respectively. Screening recommendations are not standardized, but some recommend colonoscopy, mammography, and thyroid ultrasound beginning around 30 years of age. Treatment is based on symptoms. Polyp burden unable to be controlled endoscopically is an indication for prophylactic colectomy.

Bannayan-Riley-Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba syndrome is an autosomal dominant disorder resulting from a mutation in the *PTEN* tumor suppressor gene located on chromosome 10q23. Hamartomatous polyps of the colon and ileum are characteristic of the disorder. Other common findings associated with Bannayan-Riley-Ruvalcaba syndrome include pigmented penile macules, macrocephaly, hemangiomas, and mental retardation in more than 10% of patients.

The risk of developing colon and rectal cancer is thought to be no greater than the general population. Treatment is focused on symptom reduction and supportive care.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is a nonhereditary disorder resulting from a mutation to the *PTEN* tumor suppressor gene located on

chromosome 10q23. Hamartomatous gastrointestinal polyps in addition to alopecia, macrocephaly, myxolipoma, and cutaneous pigmentation are common findings. Diffuse gastrointestinal inflammation resulting in malabsorption, diarrhea, and protein losing enteropathy can occur.

The risk of developing colon and rectal cancer is thought to be no greater than the general population. Treatment is focused on symptom reduction and supportive care.

OTHER POLYPOSIS SYNDROMES

Serrated Polyposis Syndrome

Serrated polyposis syndrome is characterized by the presence of multiple or large serrated or hyperplastic polyps throughout the colon. Sessile serrated polyps are premalignant lesions that progress to cancer via a pathway of *BRAF* mutation and DNA hypermethylation. A heritability pattern and causative germline mutation have not been identified. The World Health Organization has proposed three criteria for diagnosing serrated polyposis syndrome. Fulfillment of any one of the criteria is sufficient for diagnosis. The criteria include the following:

- Twenty or more serrated polyps of any size distributed throughout the colon.
- More than five serrated polyps proximal to the sigmoid colon, at least two of which are larger than 10 mm in diameter.
- Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis.

The risk of developing colorectal cancer is increased with rates of up to 50% documented in those with synchronous serrated polyps. The average age for developing colon and rectal cancer is 48 to 60 years.

Strict surveillance with colonoscopy every 1 to 2 years is advisable. First-degree relatives are at a fivefold increased risk of developing colon and rectal cancer and should be offered surveillance starting at 40 years of age or 10 years younger than the earliest age that a relative was diagnosed with a neoplastic lesion.

Treatment is focused on decreasing the patient's risk for developing colorectal cancer by removing premalignant polyps before they progress to cancer. Endoscopic removal and histologic evaluation of all polyps 5 mm in size or larger is recommended. Histologic diagnosis of carcinoma, dysplasia identified within a lesion that cannot be completely removed endoscopically or cases of extensive polyp burden that cannot be eradicated endoscopically are indications for surgical resection. Traditionally, any patient with a complex polyp not amenable to simple endoscopic removal, even those with a benign appearance, was recommended to undergo colon resection. Development and utilization of advanced endoscopic techniques and combined endoscopic and laparoscopic surgery now allows many such patients with ultimately benign polyps to avoid colectomy.

Hereditary Mixed Polyposis Syndrome

Hereditary mixed polyposis syndrome (HMPS3) is an autosomal dominant inherited syndrome associated with mutation in the *GREM1* gene. Patients with HMPS manifest multiple different colon and rectal polyps including adenomatous, hamartomatous, hyperplastic, and serrated lesions.

HMPS is most frequently described in patients of Ashkenazi Jewish descent and genetic screening is recommended for members of affected families as the risk of developing colorectal cancer is thought to be greater than the general population.

SUGGESTED READINGS

Church J, Gilad S, Burke C, et al. Understanding MYH-associated neoplasia. Dis Colon Rectum. 2013;56:359–362.

Hamig D, Hardiman K, Weiser M, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of inherited polyposis syndromes. Dis Colon Rectum. 2017;60:881–894.

Kalady MF, Gould JJ. Diagnostic approach to hereditary colorectal cancer syndromes. Clin Colon Rectal Surg. 2013;26:205–214.

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Stoffel S, Gilad SD, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–262.

SURGICAL MANAGEMENT OF COLON CANCER

Winson Jiantong Tan, MBBS(Hons), MRCS(Ed), MMed(Surg), FRCS(Ed), and José G. Guillem, MD, MPH

Colorectal cancer is the fourth most commonly diagnosed cancer in the United States. An estimated 4.3% of the US population will be diagnosed with the disease in their lifetime. Fortunately, the disease-associated mortality has been declining over the years. While much of the improvement in outcomes can be attributed to the increase adoption of screening, advancement in colorectal cancer treatment also plays a major role. The colonic adenocarcinomas approximately 70% of all colorectal cancer cases. In the management of colon cancer, surgery remains the mainstay of treatment for patients with resectable and nonmetastatic disease. In this chapter, we outline the major principles behind the surgical management of adenocarcinoma of the colon. Since most of our primary colon cancer resections are performed using the enhanced recovery after surgery (ERAS) approach and the robotic minimally invasive surgery (MIS) platform, we highlight these modifications.

PREOPERATIVE EVALUATION AND STAGING

The evaluation of patients referred with a diagnosis of colon cancer begins with a complete history and physical examination. While the presenting symptoms can usually shed light on the location of the cancer, it is the severity of those symptoms that offer practical information and dictates the urgency of surgical intervention necessary to prevent the development of complications. In addition, a detailed family history is also critical and this should encompass both colorectal malignancies and extracolonic malignancies of endometrial and urothelial origin that can be associated with Lynch syndrome. This potentially influences the surgical plan, as extended resections can be offered as a treatment option for patients with Lynch syndrome since the rate of metachronous colorectal cancer ranges from 22% to 30%. In addition, these individuals may benefit from referral to a clinical genetic service to facilitate counseling and genetic testing for the patient and the family.

Physical examination is usually normal in patients with early stage colon cancer. In advanced disease, an abdominal mass may be palpable and fixation may indicate invasion into the abdominal wall and the need for an en bloc abdominal wall resection. The presence of hepatomegaly, ascites, Virchow's node enlargement, Blumer's shelf, and Sister Mary Joseph nodule, and so forth may also indicate metastatic disease and alter the therapeutic intent and treatment plan.

chromosome 10q23. Hamartomatous gastrointestinal polyps in addition to alopecia, macrocephaly, myxofibroma, and cutaneous pigmentation are common findings. Diffuse gastrointestinal inflammation resulting in malabsorption, diarrhea, and protein losing enteropathy can occur.

The risk of developing colon and rectal cancer is thought to be no greater than the general population. Treatment is focused on symptom reduction and supportive care.

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A colonoscopy with complete visualization of the entire colon to the cecum should be performed in all patients not only to exclude the presence of synchronous colon lesions but also to ratify the location of the cancer, which is helpful for localization during an MIS approach. Synchronous colon benign polyps have been reported in 17% to 62% of cases, whereas synchronous cancers have been reported in 2% to 8% of cases. In a scenario where a stenotic tumor precludes passage of an endoscope, computed tomography (CT) colonography can be utilized to exclude synchronous lesions in the proximal colon.

Staging of colon cancer is performed using CT of the chest, abdomen, and pelvis. CT of the chest assesses for pulmonary metastasis, while the abdominal and pelvic scans provide information on the local extent of the tumor and the presence of lymphatic and liver metastases. In the presence of liver lesions deemed indeterminate for metastases, magnetic resonance imaging (MRI) of the liver can be utilized to better characterize the lesions. Positron emission tomography scans do not appear to provide additional information compared to CT scans. Carcinoembryonic antigen (CEA) levels should be included, when possible, in the preoperative evaluation, as it has prognostic significance and baseline values provide a useful adjunct for surveillance after curative resection.

STAGING OF COLON CANCER

The tumor node metastasis (TNM) system as described by the American Joint Committee on Cancer is currently used to stage colon cancer (Table 1).

TABLE 1 Tumor-Node-Metastasis Staging for Colon Cancer

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the • Subserosa • Mesentery • Or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs (this category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Continued

TABLE 1 Tumor-Node-Metastasis Staging for Colon Cancer—cont'd

AJCC Prognostic Stage Groups			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1–	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1–N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

From Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*, 8th ed. New York: Springer; 2017.

SURGICAL MANAGEMENT

General Principles

Preparation

We use a mechanical and antibiotic bowel preparation prior to elective colon resection. Mechanical bowel preparation involves a clear liquid diet and the administration of polyethylene glycol on the evening prior to surgery. Oral neomycin and metronidazole are administered concurrently with the bowel prep. In malignant polyps and small lesions, it is important to ensure that the tumor location has been marked with an endoscopic tattoo to facilitate intraoperative identification. This is particularly pertinent if the MIS approach is intended.

All suitable patients are currently managed perioperatively via an enhanced recovery protocol. Most patients undergoing elective colorectal surgery are included, unless the operation is a major tumor debulking or complex multivisceral resection (e.g., pelvic exenteration, primary tumor resection with synchronous liver metastasectomy), or if the patient's physiologic status precludes safe inclusion in an enhanced recovery protocol. Protocols vary between institutions, but our program focuses on goal-directed fluid administration, enhanced pain management while minimizing narcotic use, and early postoperative feeding and mobilization. Specific interventions include preoperative carbohydrate loading 2 hours prior to admission and administration of gabapentin, and a peripheral acting μ receptor opioid antagonist (alvimopan) prior to surgery. Opioid sparing strategies are employed, using preoperative epidurals or transversus abdominis plane blocks with liposomal bupivacaine, intraoperative nonopioid infusions (e.g., ketamine or dexmedetomidine), and maximizing antiinflammatories and nonopioid adjuncts throughout the perioperative period, as clinically appropriate.

On the day of surgery, patients are given an intravenous dose of a second generation cephalosporin prior to skin incision. Sequential compression devices are placed prior to induction of anesthesia for deep venous thrombosis prophylaxis. For left sided resections, the modified lithotomy position using Lloyd-Davies stirrups is preferred. This position provides versatility for the surgeon to stand between the legs during open procedures for mobilization of the splenic flexure and facilitates intraoperative colonoscopy or the use of circular stapling devices during both open and MIS procedures. For right sided resections, supine positioning is usually adequate. For distal colon and sigmoid lesions, the rectum is irrigated with saline solution until clear in the operating room prior to skin preparation. An orogastric tube and Foley catheter are placed after induction of anesthesia.

Operative Approach

Both open and MIS (laparoscopic or robotic) approaches can be employed for colon cancer resection. Multiple randomized trials (COST, COLOR, and CLASICC) have demonstrated that long term oncologic outcome of the MIS approach is not inferior to that of open surgery. In addition, MIS confers benefits of a shorter length of stay with reduced analgesia requirements and postoperative ileus. However, it is important to emphasize that the oncologic adequacy of a laparoscopic resection should be identical to that of open surgery, and in instances whereby this may not be possible (e.g., locally advanced tumor necessitating multivisceral resection), an open approach may be more prudent.

Surgery for colon cancer should begin with a thorough abdominal exploration to assess the extent of local involvement and to detect any occult metastatic disease. This includes inspection of the liver, peritoneal surfaces, omentum, retroperitoneum, and ovaries. When feasible, metastatic disease should be documented histologically.

Lymphadenectomy

An adequate lymph node dissection entails the removal of the tumor en bloc with the mesentery up to the origin of the primary feeding vessel. Suspicious apical lymph nodes should be marked for pathologic analysis, as involvement is a negative prognostic indicator. Efforts should be made by the pathologist to examine a minimum

of 12 lymph nodes to ensure adequate nodal sampling. In recent years, some surgeons are advocating an extended lymphadenectomy, whereby nodes beyond the primary feeding vessel and associated central lymph node basins are removed as well. This is commonly performed as part of "complete mesocolic excision," which in right-sided colon cancer involves ligation of the mesenteric vessels at the base of the superior mesenteric artery and vein with dissection and removal of any overlying lymphatic tissue. However, the oncologic benefit of such extended lymphadenectomy is not widely accepted by the surgical community.

Tumor Handling

Excessive manipulation of the tumor during resection should be avoided. Adjacent organs that are adherent or grossly involved should be resected en bloc with the tumor to minimize cancer spillage. Proximal and distal margins of resection should be at least 5 cm in cancer at risk pericolonic lymph nodes are resected with the specimen. The actual margins are usually greater as an adequate vascular ligation often defines a larger devascularized segment.

Anastomoses

During creation of a colonic anastomosis, two key principles ought to be emphasized. The anastomosed bowel ends should be well vascularized, and the anastomosis should be created without tension. The alignment of the resultant small and large bowel should be checked prior to anastomosis to ensure there is no internal herniation or torsion around the bowel mesentery. This is of particular concern when using the MIS approach. Both hand-sewn and stapled anastomoses can be performed with randomized studies showing no difference in outcomes between the 2 modalities. For handsewn, we commonly perform a two-layer anastomosis (interrupted inner seromuscular rows and an outer row of running full-thickness sutures) in a side-to-side or end-to-end fashion. In MIS extracorporeal anastomosis, we use a two-layer closure (inner full-thickness and outer serosal running V-lock stitch). Single layer handsewn colon anastomoses have been shown to be effective as well. When we perform stapled colon anastomoses, we most commonly perform either an end-to-end anastomosis or a side-to-side anastomosis using the GIA-80 stapler (anastomosis to antimesenteric border) to create the anastomosis and a TA-90 stapler to close the defect.

Drains

We do not use drains (open or closed) following an elective colon resection. Temporary surgical drains may be utilized in select cases whereby significant intraperitoneal spillage was encountered.

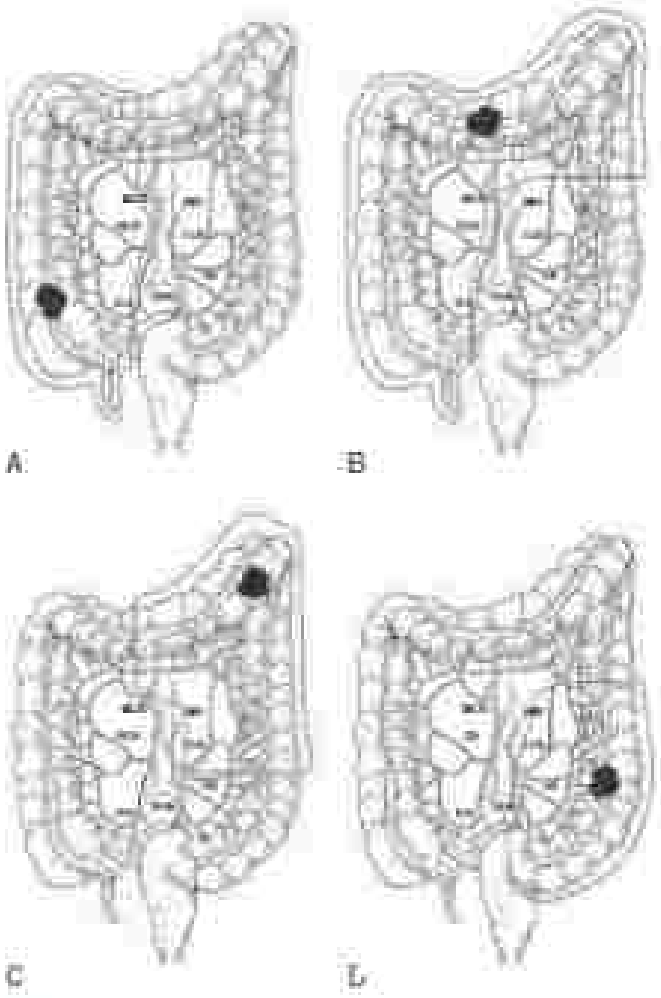

FIG. 1 Extent of resection for colon carcinoma. (A) Cecal or ascending colon cancer; (B) transverse colon cancer; (C) splenic flexure colon cancer; (D) sigmoid colon cancer. ICA, ileocolic artery; IMA, inferior mesenteric artery; LCA, left colic artery; MCA, middle colic artery; RCA, right colic artery; SA, sigmoidal arteries; SHA, superior hemorrhoidal artery. (From Nelson H, Gallinger JL. Cancer of the colon. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, eds. Abeloff's Clinical Oncology. 5th ed. Philadelphia: Churchill Livingstone Elsevier; 2014.)

Right-Sided Colon Cancers

Cancers of the right colon account for up to 15% of primary colorectal cancers. Patients with adenocarcinoma involving the cecum or ascending colon who do not have hereditary nonpolyposis colorectal cancer or other synchronous lesions should be treated with a right hemicolectomy (Fig. 1A). The ileocolic, right colic, and right branch of the middle colic arteries and veins should be ligated near their origin in order to ensure an adequate lymphadenectomy. Approximately 7.5 to 10 cm of distal small intestine should be resected in continuity with the right colon to ensure well-vascularized small bowel is available for the ileocolic anastomosis.

Transverse Colon Cancers

Transverse colon cancers are relatively uncommon, accounting for only 8% of colorectal primaries. Lesions of the proximal and midtransverse colon are usually best managed with an extended right hemicolectomy involving ligation of the ileocolic, right colic, and middle colic vessels (Fig. 1B). The cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure are removed with anastomosis of the ileum to the descending colon. Blood supply to the colon is based on the ascending branch of the left colic artery. We generally avoid an anastomosis at the hepatic or splenic flexure because of concerns over its vascularity and tension at the anastomosis, as the ascending and descending colon tend to migrate to and lie in their anatomic position within the lateral gutters.

Left-Sided Colon Cancers

Lesions of the splenic flexure and descending colon are also uncommon, accounting for less than 9% of colorectal primaries. Splenic flexure cancers may be managed with an extended right or left hemicolectomy (Fig. 1C). Cancers in the descending colon may be managed with a left hemicolectomy involving division of the left colic artery, preservation of the left branch of the middle colic artery, and anastomosis of the distal transverse colon to the sigmoid following a full splenic flexure mobilization. Alternatively, a left hemicolectomy may be performed with ligation of the inferior mesenteric vessels and an anastomosis between the transverse colon and the upper rectum.

Sigmoid Cancers

Tumors of the sigmoid colon are the most common. These tumors are usually removed by means of an anterior sigmoid colectomy, which usually involves division of the inferior mesenteric artery and vein with anastomosis of the descending colon to the upper rectum (Fig. 111). Large, bulky sigmoid cancers located above the peritoneal reflection but at the level of the pelvic inlet as defined by a sagittal MRI view present a unique challenge. Anteriorly they can invade the bladder and form a colovesical fistula. Posteriorly they abut important structures such as the ureters, hypogastric nerves, and iliac vessels. Proper preoperative planning based on optimal imaging (CT scan and/or MRI) is essential. In carefully selected cases, preoperative chemoradiation has proven helpful by down-staging the tumor to facilitate negative resection margins while preserving vital structures.

Postoperative Care

Antibiotics are not routinely continued for more than 24 hours postoperatively, and appropriate thromboembolism prophylaxis should be maintained until the patient is ambulating sufficiently. Postoperative course is largely governed by an ERAS protocol, as mentioned previously, which encourages early feeding and ambulation, removal of the Foley within the first 24 hours after surgery and early discontinuation of intravenous fluids. Patients on the ERAS protocol are usually discharged within 3 to 5 days.

SPECIAL SCENARIOS

Malignant Polyp

With the implementation of colonoscopic screening, colon cancers are increasingly being detected as malignant polyps. This often happens when a polyp, initially thought to be benign, is resected endoscopically only to be found to contain a focus of invasive adenocarcinoma after pathology review. The propensity for lymph node metastasis is related to several histopathologic features. Adverse risk factors include deep invasion of the submucosa, high tumor grade, poor degree of differentiation and the presence of perineural or lymphovascular invasion. Classification systems for pedunculated and sessile polyps are available to quantify the depth of invasion in malignant polyps.

The Haggitt classification system is used to quantify the depth of invasion for a malignant pedunculated polyp (Fig. 28). The risk of lymph node metastasis in Haggitt level 0, 1, and 2 lesions is less than 1% in the absence of the other adverse prognostic factors mentioned previously. Endoscopic removal is deemed to be sufficient if the lesion was removed en bloc and with clear margins of at least 2 mm, even though in recent years many regard margins 1 mm or greater as adequate. Haggitt level 4 malignant polyps should be offered oncologic segmental resection, as the risk of lymph node metastases is estimated to be close to 30%.

The Kikuchi classification divides the extent of submucosal invasion into thirds and is used to quantify the depth of invasion for a sessile malignant polyp (Fig. 28). The risks of lymphatic metastases increase with the depth of submucosal invasion and range from: 2% for Sm_1 lesions to 23% for Sm_2 lesions. In general, only Sm_1 and select Sm_2 lesions can be adequately treated with complete endoscopic removal. Sessile malignant polyps that are Sm_2 or with other adverse prognostic factors should be offered oncologic segmental resection. The practical implementation of the Kikuchi classification may be difficult, as the muscularis propria layer is usually not included in the resected polyp, which limits the accurate division of the submucosal layer into thirds. Hence, some have used the depth of invasion beneath the muscularis mucosae as an alternative measure of submucosal involvement. A malignant sessile polyp with depth of submucosal invasion 1 mm or greater is considered low risk for lymphatic metastases in the absence of other adverse features and can be managed with endoscopic resection.

Patients with malignant polyps who opt for nonsurgical management should, however, be adequately counseled that even though the risk of lymph node metastasis is low, it is not zero, and close surveillance for cancer local recurrence/persistence or distant metastases would still be required.

Locally Advanced Colon Cancers

Approximately 5% to 10% of colon cancers will present as locally advanced lesions with invasion of contiguous organs. The most commonly involved organs include the small bowel, spleen, pancreas, duodenum, and stomach. In these situations, an en bloc multivisceral resection of contiguous structures with histologically negative margins should be attempted whenever feasible.

Unlike the rectum, which is confined to the pelvis, the location of the colon within the abdominal cavity precludes the use of radiation as a modality for neoadjuvant treatment due to concerns regarding collateral damage to the surrounding viscera. Neoadjuvant chemotherapy is an option for tumor downstaging and has been shown in a randomized study (FOxTROT Collaborative Group) to be effective in downstaging the primary tumor with acceptable morbidity and toxicity. However, improvement in long-term oncologic outcomes is yet to be established.

Synchronous Colon Cancers

Synchronous colon cancers are estimated to occur in 4% of patients, with incidence ranging from 0.3% to 11% in various studies. For synchronous cancers located in different segments of the colon, both extended resections and two separate resections are viable options. Extended resection offers the benefit of a single anastomosis with the trade-off for possible increased daily bowel movements associated with inferior functional outcomes and quality of life in patients with underlying colonic disease predisposing to cancer formation such as ulcerative colitis or Lynch syndrome–associated colon cancer, an extended resection may be preferred to address the underlying diseased at risk colon.

Stage IV Colon Cancer

Approximately 20% of colorectal cancer patients present with stage IV disease at the point of diagnosis. Patients with colon cancer and limited metastatic disease confined to one organ (liver or lung) can be surgically resected with curative intent if adequate residual organ function is preserved after metastasectomy. These patients can experience 5-year survival rates ranging from 40% to 60% after curative surgery and systemic chemotherapy. Hence, stage IV colon cancer patients with resectable single-site metastases in the lung and liver should be recommended curative surgical resection if they are suitable surgical candidates. The management of stage IV colon cancer patients with isolated peritoneal metastases remains controversial. Cytoreductive surgery with intraperitoneal chemotherapy is performed in some centers, but it remains unknown if outcomes are superior compared to modern systemic chemotherapy and biologic agents. Hence, it is not recommended as a routine treatment option in the current National Comprehensive Cancer Network guidelines.

The management of stage IV colon cancer with unresectable metastases must be individualized. Factors such as the patient's fitness for surgery, extent of symptoms from the primary, and the life expectancy ought to be considered during decision-making regarding resection of the primary colon tumor. Surgical resection may not be indicated in patients with an asymptomatic colon lesion. This is most commonly encountered in right-sided lesions where an obstruction is less likely. In patients with symptomatic lesions, palliative resection of the primary can provide symptom relief and quality of life improvement. In patients with limited life expectancy, the surgical approach should be tailored toward the least invasive procedure to achieve symptom relief (e.g., diverting ileostomy instead of resection in a patient with obstructive symptoms).

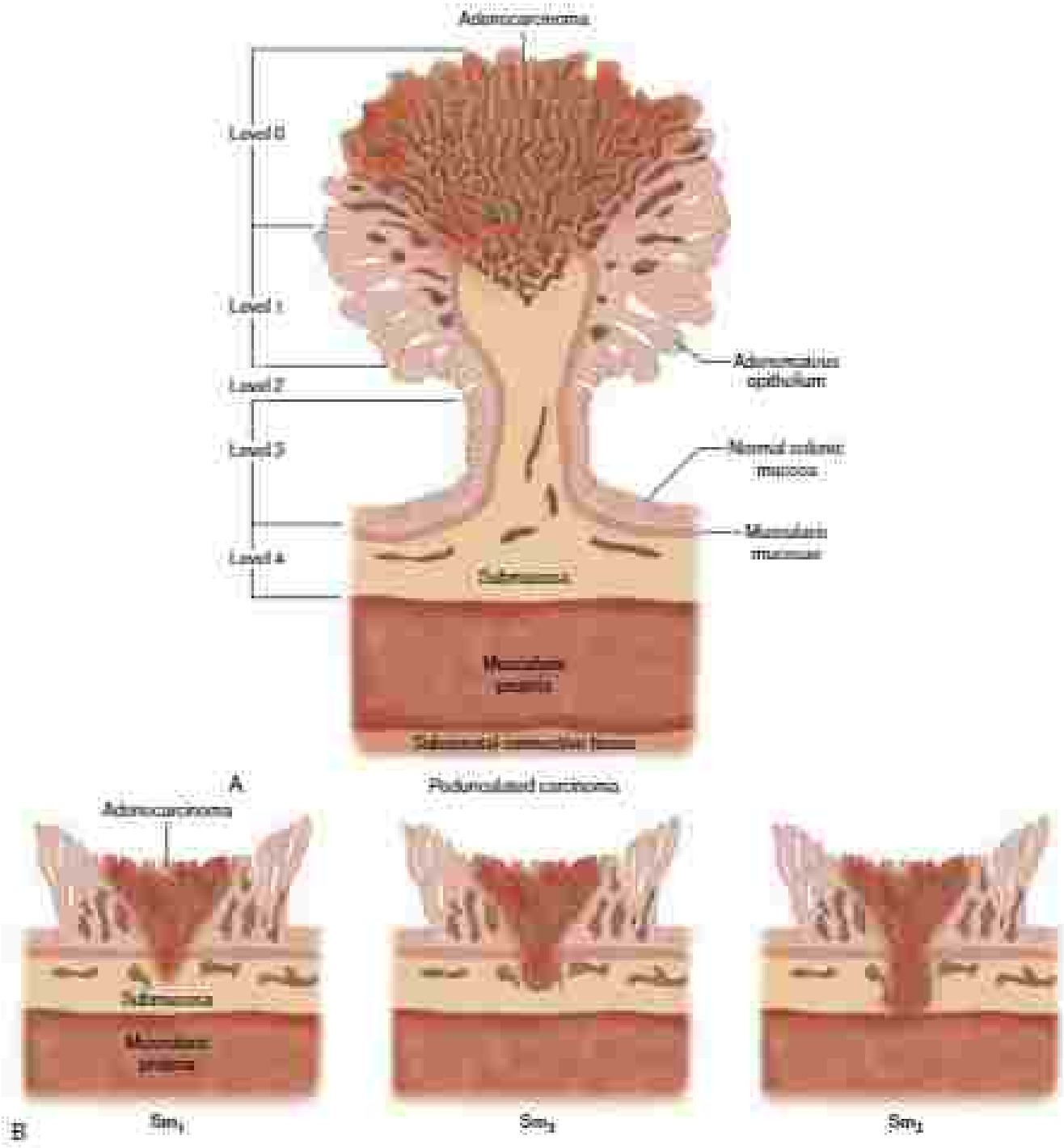

FIG. 2 Depth of invasion of malignant polyps. (A) Haggitt's classification for pedunculated polyps. (B) Kikuchi classification for sessile polyps. [illegible]

Emergency Presentation of Colon Cancer

Perforated Colon Cancers

Perforated colon cancers pose a management conundrum for the colorectal surgeon. Patients often present with peritonitis and hemodynamic instability, and the emergent nature of the surgery may preclude adherence to surgical oncology principles since the priority may be damage control in these potentially unstable patients. The resection should adhere to established oncologic principles whenever possible.

The goals of surgical management are to remove the diseased segment of colon and prevent ongoing peritoneal contamination. Following resection and thorough irrigation of the peritoneal cavity, options for subsequent management include proximal diversion with creation of a mucous fistula/Hartmann pouch or primary anastomosis with proximal diversion via loop ileostomy. Perforated colon cancer is associated with a high rate of local recurrence and poor overall survival.

Obstructing Colon Cancers

Bowel obstruction can be the presenting symptom in up to 30% of newly diagnosed colon cancer. Obstructing lesions tend to be more common in the left colon, although lesions in the cecum can sometimes also cause small bowel obstruction by occluding the ileocecal valve.

Obstructing right and transverse colon cancers can generally be managed with a right hemicolectomy or an extended right hemicolectomy and primary anastomosis. In frail and malnourished patients or those with hemodynamic instability requiring inotropic support, a defunctioning or end stoma may be indicated with intestinal continuity reestablished in a separate elective setting.

The surgical approach for obstructed left sided tumors can be an either single stage or two stage approach. Factors influencing a single stage or two stage approach include the patients' nutritional status, clinical stability, and life expectancy.

Single stage management usually includes subtotal colectomy with ileosigmoid or ileorectal anastomosis. This has the benefit of incorporating well vascularized small bowel in the anastomosis and removes the uncertainty of retained synchronous tumors in the proximal colon. However, bowel function may be compromised after surgery. Segmental resection with a colocolonic anastomosis is another option but it entails anastomosis of dilated and edematous proximal colon to the distal colon, which may increase the risk of anastomotic dehiscence. In addition, synchronous lesions in the proximal colon may be left in situ.

A two stage procedure involves resection of the primary tumor with proximal diversion and creation of a mucous fistula (Hartmann's pouch or a sigmoid resection with primary anastomosis and proximal ileal diversion with a loop ileostomy). Bowel continuity is reestablished at a separate elective setting.

In recent years, colonic stenting has emerged as a viable option for patients who present emergently with a malignant colon obstruction. Stenting can be used as a bridge to surgery by converting an emergent situation to an elective one. Successful deployment of a colonic stent allows bowel decompression and medical or nutritional optimization prior to elective resection, which can be performed via the minimally invasive approach. It also allows evaluation of the proximal colon for synchronous lesions prior to resection. Clinical success rates of approximately 80% have been demonstrated in various reviews and meta analysis. However, stenting does have its complications and perforation can occur in 6% to 7% of cases. There are also concerns regarding inferior long-term oncologic outcomes after stenting, although this has not been consistently demonstrated.

CHEMOTHERAPY FOR COLON ADENOCARCINOMA

The need for adjuvant therapy following resection of a colon cancer is best determined in a multidisciplinary manner with a member of the medical oncology service. In general, adjuvant chemotherapy is indicated in stage III colon cancer, as disease recurrence is reduced by 30% and mortality by 20% to 30% with treatment. Adjuvant chemotherapy generally utilizes a fluoropyrimidine backbone (intravenous 5-fluorouracil with leucovorin or oral capecitabine) with oxaliplatin given for 3 to 6 months duration. In frail or elderly patients, oxaliplatin may occasionally be omitted due to concerns regarding toxicity.

In stage II colon cancer, adjuvant chemotherapy is generally not indicated unless adverse risk factors for recurrence are present. These factors include poorly differentiated histology, T4 stage, perforated or obstructed tumors, perineural or lymphovascular invasion, close margins, or less than 12 lymph nodes examined at pathology. In these patients, chemotherapy may be indicated to reduce the risks of recurrence, and therapy usually involves fluoropyrimidine monotherapy.

In stage IV disease, advancements in chemotherapy have markedly improved survival. A fluoropyrimidine backbone with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are the usual first line choices. Targeted therapies such as bevacizumab (monoclonal antibody targeting vascular endothelial growth factor) and cetuximab/panitumumab (monoclonal antibody targeting epidermal growth factor) are also part of the current treatment armamentarium in stage IV disease. The response to treatment of these targeted agents can be predicted with tumor mutational status and whenever possible should be determined for all metastatic colon cancers. Tumors with *KRAS* or *BRAF V600E* mutations respond poorly to monoclonal antibodies targeting epidermal growth factor (cetuximab/panitumumab).

SURVEILLANCE FOLLOWING RESECTION OF COLON ADENOCARCINOMA

The goal of postoperative surveillance following resection of colon adenocarcinoma is the early identification of asymptomatic recurrences to allow early treatment and improvement in survival. While many studies on intensive surveillance have shown benefits in terms of the rate of curative resection of the recurrence, survival benefit has not been consistently demonstrated.

The current American Society of Clinical Oncology recommend history and physical examination with CEA monitoring every 3 to 6 months for 5 years, CT chest, abdomen, and pelvis annually for 3 years and surveillance colonoscopy within 1 year after curative resection of stage II and III colon cancers. Surveillance for stage I colon cancer is currently not recommended, although this may be of value in high risk cases such as those with poor prognostic factors like lymphovascular invasion, positive margins, poor tumor differentiation, and T2 disease. While these recommendations serve as a reference, the surveillance strategy for each patient should be individualized. Factors such as the patient's preference, functional status, comorbidity profile, and lifetime to tolerating resection of any detected recurrent disease might to be considered when deciding the optimal surveillance strategy.

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Management of Rectal Cancer

Junior Salgado Pagacnik, MD, and Michael A. Choti, MD, MBA, FACS

The complexity of care and treatment choices facing the clinician managing rectal cancer is more than with most surgical diseases. Surgical treatment options can vary from radical transabdominal operations to local excision. Newer techniques are being applied to reduce the necessity for permanent colostomy, improve functional results, and reduce local recurrence. Multimodality treatment strategies, including expanded use of preoperative therapy, are being advocated more commonly. Changing treatment algorithms in this disease make evidence based management particularly important.

Approximately 40,000 new cases of rectal cancer are diagnosed annually in the United States accounting for about 30% of large bowel malignancies. While colon cancer is nearly equal in men and women, more men are diagnosed with rectal cancer. Deaths from colorectal cancer in the United States number approximately 50,000 per year. Unfortunately, reliable data on deaths specifically from rectal cancers are not known, as almost 40% of deaths from rectal cancer are misclassified as colon cancer.

Surgeons generally consider the rectum to begin at the level of the sacral promontory. It descends along the curvature of the sacrum and coccyx and ends by passing through the levator ani muscles, turning downward and backward to become the anal canal. It differs from the colon in that the outer layer is entirely longitudinal muscle. It measures 12 to 15 cm in length and lacks a mesentery, sacculations, and appendices epiploicae.

This chapter reviews the preoperative evaluation and clinical staging of patients with rectal cancer and management options based on stage of disease, highlighting a multidisciplinary approach, careful preoperative planning, and sequential multimodal therapy when indicated.

PREOPERATIVE PLANNING

The evaluation of a patient with rectal cancer should be performed in a multidisciplinary, integrated approach, addressing the medical, surgical, and psychosocial needs of the patient. Determination of an ideal treatment plan in a patient with rectal cancer is a complex process. Guidelines must be followed, focusing on the diagnosis, pathologic staging, neoadjuvant therapy, surgical management, adjuvant management, management of recurrent metastatic disease, and patient surveillance. Multimodality (MDT) approach includes integrating primary care physicians, gastroenterologists, surgeons, radiation and medical oncologists, radiologists, interventional therapy nurses, pain specialists, and social workers. In European countries, MDT approach has resulted in lower rates of permanent stoma, reduced rates of local recurrence, greater delivery of evidence based care, and improved overall survival.

CLINICAL EVALUATION AND PREOPERATIVE STAGING

The general physical examination is crucial for determining the extent of local disease, unveiling distant metastases, and evaluating the operative risk of the patient regarding nutritional, cardiovascular, pulmonary, and renal status. A thorough digital rectal examination allows the surgeon to identify the extent and location of the mass, mobility or fixity, size, and macroscopic configuration, involvement in relation to the anorectal ring, extension to adjacent viscera or fixation to the sacrum. These are all key features in establishing the nature of the problem and target the appropriate testing and therapy.

A full colonoscopic evaluation should be done in rectal cancer patients in order to rule out synchronous lesions and other associated pathologic conditions of the colon and rectum. These patients may also require rigid or flexible proctoscopy by the surgeon in selected cases in order to assess and confirm macroscopic characteristics of the tumor, including size, location, and extent of circumference of the tumor affected.

Biopsy with histopathologic examination is important to confirm adenocarcinoma and determine any unique histologic features that may be of value prior to therapy, such as microsatellite status. Endoscopic biopsies obtained at an outside institution should be confirmed and reviewed when possible. Additional testing should include routine serum laboratory studies, including liver function tests and carcinoembryonic antigen.

Preoperative imaging for rectal cancer is essential to adequately stage the disease and plan the treatment approach. Computed tomographic (CT) scan of the chest, abdomen, and pelvis is recommended to determine absence or presence of regional or distant metastatic disease. Transrectal endoscopic sonography (EUS) was considered important for staging, specifically to delineate the depth of tumor penetration through the rectal wall and determine whether local regional lymph nodes are involved. Pelvic high resolution magnetic resonance imaging (MRI) has largely replaced EUS as the preferred locoregional staging modality. MRI has similar accuracy to EUS with regard to T and N staging accuracy but with less operator dependency. In addition, MRI is better at accurately assessing the circumferential resection margin and identifying other prognostic features such as extramural venous invasion. EUS also has limited utility in high rectal cancer or stricturing lesions.

Fluorodeoxyglucose positron emission tomography (PET)-CT can be considered in some cases when evaluating a patient with rectal cancer, but its routine use for staging is controversial. Several studies have shown an overall accuracy in detecting distant disease in excess of 90%. However, reports challenge the value of PET in changing surgical management. Most guidelines recommend the use of PET/CT selectively to evaluate an equivocal finding on CT or in patients with contraindication to intravenous contrast.

RADICAL RESECTION WITH TOTAL MESORECTAL EXCISION

Most patients with intermediate stage rectal cancer will require radical resection. This is defined as resection of the tumor and rectum en bloc with its blood and lymphatic supply and surrounding mesorectum. Traditionally during transabdominal resections, much of the pelvic dissection below the peritoneal reflection was performed in a blind fashion. In 1982, Heald et al. published the first description of dissection of the mesorectum in a sharp fashion. This technique, called total mesorectal excision (TME), involves the sharp dissection between the parietal and visceral planes of the endopelvic fascia (Figs. 1 through 4). Such a technique minimizes the risk of a positive circumferential margin, a factor of strong prognostic significance for local recurrence. Along with the TME, the other tenets of adequate surgical resection include achieving negative distal and circumferential resection margins, preservation of autonomic nerves, and restoration of gastrointestinal continuity if possible.

In the early 2000s, the laparoscopic minimally invasive technique emerged as an acceptable surgical approach for the treatment of rectal cancer. In recent years, newer surgical techniques such as robot assisted procedures and transanal TME have been developed as part of our surgical armamentarium. Robotic assisted surgery can reduce some of the limitations of conventional laparoscopy with improved visualization and better maneuverability. In some reports, robotic techniques were associated with comparable short term oncologic outcomes, but operative times and costs are higher compared with laparoscopic colorectal surgery. The role of robotics in rectal surgery remains to be defined.

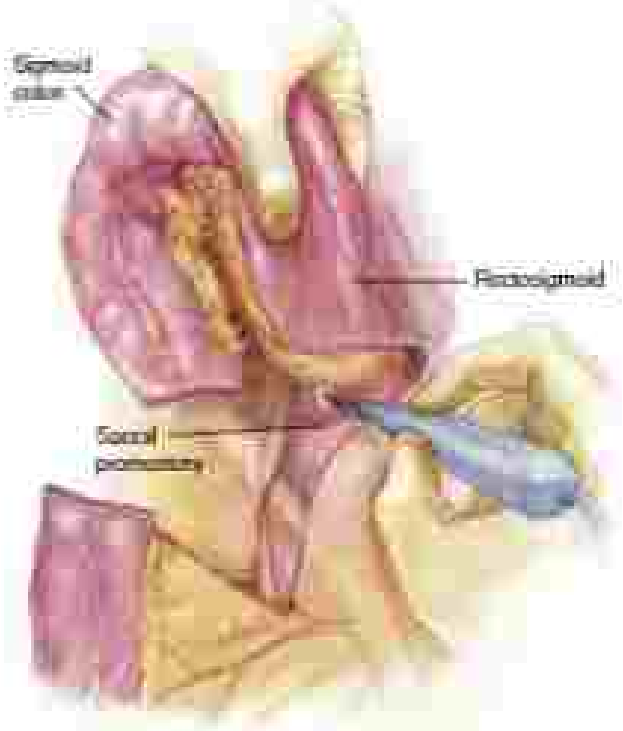

FIG. 1 Total mesorectal excision is between parietal fascia and fascia propria. (Courtesy Cleveland Clinic Foundation, Department of Colorectal Surgery.)

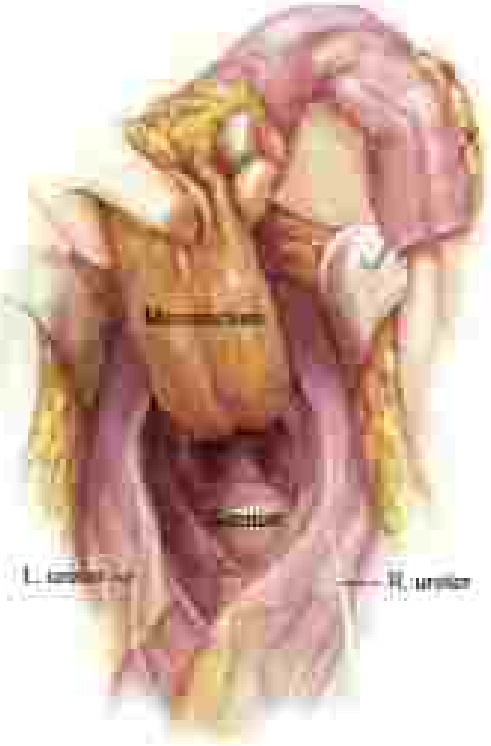

FIG. 2 Total mesorectal excision plane. Posterior rectal dissection. (Courtesy Cleveland Clinic Foundation, Department of Colorectal Surgery.)

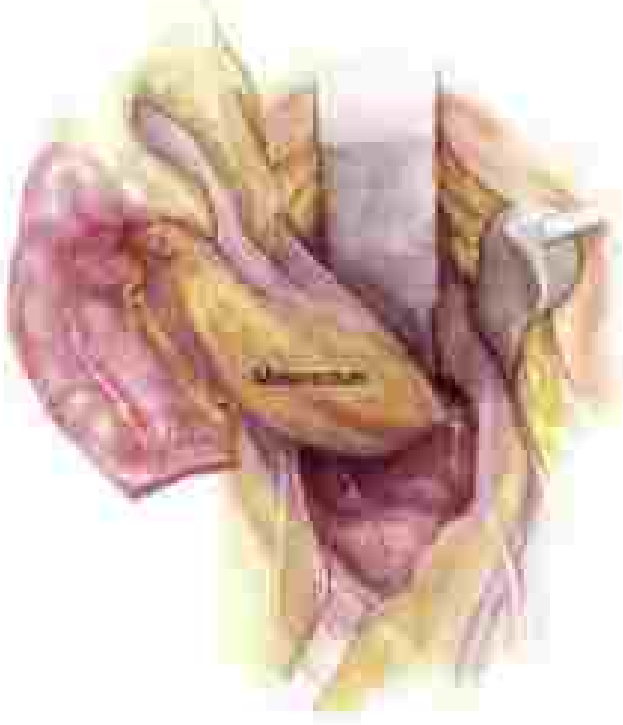

FIG. 3 Lateral peritoneal reflections divided. (Courtesy Cleveland Clinic Foundation, Department of Colorectal Surgery.)

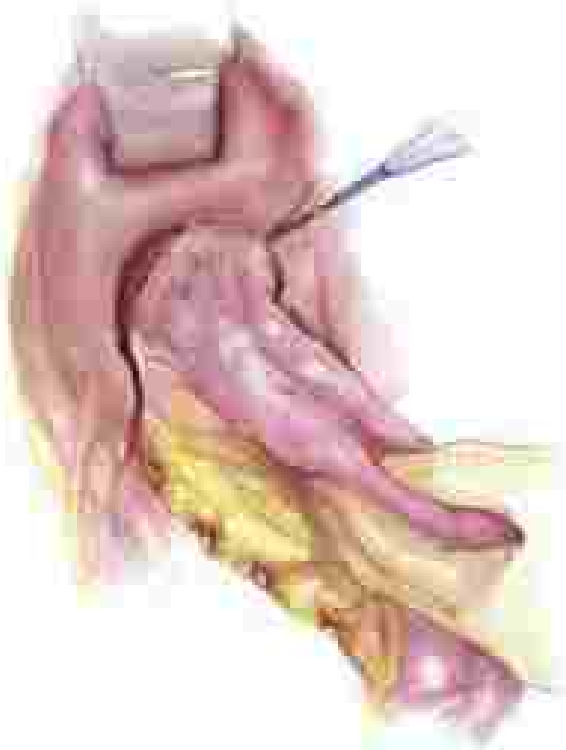

FIG. 4 Anterior peritoneal attachments divided. (Courtesy Cleveland Clinic Foundation, Department of Colorectal Surgery.)

In rectal cancer surgery, achieving a negative distal resection margin is the principal factor when deciding between a sphincter-preserving procedure and an abdominoperineal resection (APR). Historically, margins of greater than 2 cm were considered oncologically adequate. More recent studies have challenged the need for such a wide margin. However, reports comparing distal margin distance find that narrow margins of 0 to 10 mm are associated with higher risk of local recurrence. Therefore, a distal margin of greater than 1 cm is recommended when possible.

NEOADJUVANT THERAPY

Over the last 30 years, treatment of clinical stage II or III locally advanced rectal cancer has moved to an almost universal use of neoadjuvant therapy, with demonstration of reduced local recurrence rates improved sphincter preservation, even among those patients undergoing transabdominal TME surgery. Most neoadjuvant regimens include combined chemotherapy and radiation. The Swedish Rectal Cancer Trial, when comparing preoperative radiation therapy versus surgery alone, found a significant reduction in local recurrence (11% vs 27%) and an increase in 5-year survival (58% vs 48%). In another large randomized trial from the Netherlands, investigators found the long-term incidence of local recurrence was 5% in those patients receiving preoperative short-course chemoradiation therapy compared with 11% in the TME surgery alone group. Based on these and other randomized trials, treatment for clinical stage II or III should include preoperative chemoradiotherapy followed by transabdominal resection with TME.

The standard of care in patients who have undergone resection following neoadjuvant chemoradiation therapy is additional postoperative adjuvant chemotherapy with oxaliplatin-based regimen. More recently, the concept of total neoadjuvant therapy (TNT) has gained some appeal, with the administration of systemic chemotherapy and chemoradiation prior to surgery. This approach has been particularly encouraged in locally advanced rectal cancer. In most reports, induction chemotherapy is oxaliplatin based for 2 to 3 months prior to chemoradiation. Findings suggest that those patients undergoing TNT were more likely to receive the planned chemotherapy, had higher rates of complete pathologic response, and were more likely to have early reversal of the temporary ileostomy.

ROLE OF LOCAL EXCISION OF RECTAL CANCER

In treating rectal cancer, the surgeon's goal is curative resection of the tumor with minimal morbidity and mortality. Sometimes, the best operation for this is a local excision, most commonly through a transanal approach. Proper selection of patients is the key factor here. Ideal rectal tumors for this approach are below the peritoneal reflection, less than 4 cm in diameter, take up less than 40% of the rectal circumference, have no palpable or radiologically visible perirectal nodes, are mobile on digital exam, and have a well differentiated histology. Transanal excision is most commonly utilized to manage early stage rectal cancer (Tis, T1 N0) with the objective of performing a full-thickness excision of the lesion with negative margins without the intent to remove regional lymph nodes. It can be achieved with a number of surgical techniques, including the traditional Parks transanal excision, transanal endoscopic microsurgery, transanal minimally invasive surgery and, more recently, transanal robotic surgery utilizing different robotic platforms including Da Vinci surgical system and a Flex Robotic System.

RESTORATION OF GASTROINTESTINAL CONTINUITY

The emphasis of surgery for low rectal cancers is to achieve adequate oncologic outcomes in addition to obtaining good functional result and the importance of maintaining quality of life. Different surgical techniques have been described to restore intestinal continuity in patients undergoing a sphincter preserving operation (low anterior resection). These techniques include a straight colorectal anastomosis, the creation of a colonic J-pouch, or coloplasty. Evidence suggests that the J-pouch is associated with improved bowel function, particularly in the first year after surgery.

Fecal diversion by the creation of a temporary ileostomy is generally performed when performing proctectomy, particularly in patients following neoadjuvant radiation therapy. It is believed to protect or mitigate the risk of an anastomotic leak after a colorectal anastomosis. It is most beneficial when used selectively in high-risk patients with low pelvic anastomoses that are at an increased risk for leak. As some have challenged its routine use, better methods are needed to identify patients at high risk for anastomotic failure after low anterior resection. When performed, the timing of reversal or closure is also controversial. In some recent randomized trials, early closure (8–12 days) may be associated with less suffering and improved satisfaction compared with late closure (after 12 weeks).

In spite of significantly increased success of sphincter-preserving approaches, complete resection of the rectum and anus with permanent colostomy, the APR, is still required for many patients with low rectal cancers. As with restorative proctectomy, the APR must also be performed with a total mesorectal excision.

NONOPERATIVE TREATMENT

As discussed, the standard treatment for rectal cancer is neoadjuvant chemoradiotherapy followed by major resection surgery. However, there has been increasing interest in whether a nonoperative or watch and wait strategy instead of routine surgery is an option in selected patients with complete clinical response following chemoradiation therapy. Recent reports from Brazil and the Netherlands provide some support for this approach. Preoperative chemoradiation results in pathologic complete response rates of about 10% to 20% in rectal cancer, potentially avoiding the need for surgery in these patients. However, questions remain regarding the potential for increased salvage in those who have regrowth. Even with an apparent complete tumor response within the bowel wall, up to 17% can still have disease in the mesorectal lymph nodes. Moreover, the ability to adequately determine complete response clinically in most centers, as well as the challenges associated with aggressive posttreatment surveillance, limit the recommended use of this approach outside of a clinical protocol.

CONCLUSIONS

Improved imaging techniques and increased use of multidisciplinary treatment strategies have led to improved outcomes of those patients with rectal cancer. Neoadjuvant chemoradiation therapy has clearly been associated with significantly decreased local recurrence and the addition of induction combination chemotherapy, total neoadjuvant therapy, will likely be used with increased frequency. A nonoperative watch and wait strategy in selected patients with complete response after neoadjuvant therapy has been proposed, but this bold approach awaits long-term results. Improved operative results have been achieved with TME as the standard technique, with an expanding use of laparoscopic and robotic assisted techniques. Most importantly, management of rectal cancer can be challenging and is best managed when approached in a coordinated way by an experienced multidisciplinary cancer treatment team.

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Management of Tumors of the Anal Region

Miriam W. Tsao, MD, and David Shibata, MD

OVERVIEW AND ANATOMY

Appreciation of the anatomic landmarks and histologic features of the anorectal region is essential to understanding management of tumors of the anal region. The anal canal measures approximately 4 cm in length and extends proximally from the dentate line (anorectal canal) or the anorectal ring (surgical anal canal) to the anal margin located at the intersphincteric groove (Fig. 1). The dentate line can be identified macroscopically by the anal valves and bases of the anal columns, while the anal margin coincides histologically with the mucocutaneous junction between nonkeratinizing squamous mucosa and keratinizing squamous epithelium with hair follicles, sebaceous glands, and sweat glands. The anal canal itself can be microscopically separated into three zones: an upper zone proximal to the dentate line featuring columnar and cuboidal cells similar to colorectal mucosa, a middle anal transition zone (ATZ) near the level of the dentate line/valves of Morgagni comprised of transitional epithelium, and finally, a distal zone containing squamous epithelium (Fig. 2). The ATZ can also contain reactive, endocrine, and melanocytic cells. This variation in cell histology throughout the three zones accounts for the array of neoplasms that may arise from the anal canal.

The proximal anal canal is supplied by the superior rectal artery and venous drainage occurs via the superior rectal veins (tributaries of the inferior mesenteric vein), as well as the middle rectal veins (into the internal iliac veins). The distal anal canal is supplied by the inferior rectal branch of the pudendal artery, and venous drainage occurs to the inferior hemorrhoidal vessels then to the internal iliac veins. Lymphatic drainage from the proximal anal canal (above the dentate line) is into the mesorectal, internal iliac and inferior mesenteric lymph nodes. In contrast, the lower anal canal drains to the inguinal lymph nodes. This is particularly important when considering regional spread of anal lesions.

Although anal cancer is rare, its incidence is increasing and it now accounts for 2.4% of all newly diagnosed gastrointestinal malignancies within the United States. Most (80%) anal canal malignancies are of squamous origin, 10% are adenocarcinomas, and 5% are other types, such as melanoma and small cell. Although patients with anal tumors may present with symptoms such as bleeding, pain, and discharge, they are frequently asymptomatic and lesions are diagnosed incidentally.

SQUAMOUS NEOPLASMS

Human Papillomavirus and Anal Squamous Neoplasia

Human papillomavirus (HPV) is the most common sexually transmitted infection, with a prevalence of 42% among all adults within the United States and up to 93% among human immunodeficiency virus (HIV)–positive men who have sex with men (MSM). Over 100 HPV types have been identified, with over one third affecting the anogenital region; however, only a few types have been associated with anal carcinoma, mainly HPV 16 and 18. Additionally, HPV infection is associated with squamous cell carcinoma (SCC) of other areas of the genital tract but also of the oropharynx. Epidemiologic studies worldwide have identified the presence of HPV in up to 94% of anal carcinomas and up to 100% of premalignant anal lesions. The development of HPV vaccines targeting oncogenic HPV types has subsequently been associated with decreased rates of anogenital malignancy. The Centers for Disease Control and Prevention (CDC) currently recommends a two dose HPV vaccination schedule for all children at age 11 to 12 and a three dose vaccination schedule for women up to age 26, men up to age 21, and for high risk patients, such as patients with HIV. Within the United States, however, vaccine uptake remains suboptimal, and therefore anogenital malignancies will likely continue to be a relevant issue in the foreseeable future.

Condylomata Acuminatum (Anal Warts)

Condylomata acuminata, or anal warts, occur when a patient is infected by certain types of HPV, with nononcogenic types 6 and 11 accounting for approximately 90% of lesions. Lesions typically appear as flat or raised flesh-colored papules or plaques associated with discomfort or pruritus. The lag time between HPV infection and the appearance of condylomata can range from weeks to months, and spontaneous regression, mediated by the patient's own immune system is common, even in the setting of HIV/AIDS (acquired immunodeficiency syndrome).

Management of condylomata can include medical and surgical approaches; however, there are limited data to guide optimal therapy. Evaluation should always include a thorough anogenital examination, including anoscopy to examine the anal canal, and women should be referred for a Papanicolaou (Pap) smear. Biopsy should be considered if lesions are pigmented, indurated, bleed spontaneously, or ulcerated, or if there is no response to standard therapy.

Treatment of condylomata consists of topical patient administered treatments and provider administered treatments. Topical therapies include imiquimod cream, podophyllotoxin, 5-fluorouracil (5-FU) and sinecatechins, all of which have moderate efficacy, with clearance rates of 40% to 60%. Their use for larger lesions is limited, however, due to significant local irritation and systemic toxicity. Current CDC recommendations for provider administered treatment include 80% to 90% trichloroacetic acid (TCA) cryotherapy, or surgical fulguration/excision and are typically employed when other medical therapy fails. Surgical excision for condylomata is typically reserved for giant condylomas. Recurrence rates for all provider administered treatment, however, remain between 20% and 40%, likely as a result of persistent HPV infection.

The Buschke-Lowenstein tumor (BLT), verrucous carcinoma or giant condyloma acuminatum is a rare, slow growing lesion characterized by exophytic, ulcerative, and cauliflower like tumors most commonly in the anogenital region with a tendency for local invasion and frequent fistula or abscess formation (Fig. 3). It differs from SCC in that it lacks lymphatic involvement and is unlikely to metastasize, but rather spreads laterally. As with condylomata acuminatum, BLT is thought to be caused by HPV infection, most commonly types 6 and 11. Wide local excision (WLE) remains the mainstay of treatment, with abdominoperineal resection and pelvic exenteration reserved for extensive disease. Unfortunately, even with optimal management recurrence rates are from 40% to 70% with a 30% to 50% rate of malignant transformation.

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Treatment of condylomata consists of topical patient administered treatments and provider administered treatments. Topical therapies include imiquimod cream, podophyllotoxin, 5-fluorouracil (5-FU) and sinecatechins, all of which have moderate efficacy, with clearance rates of 40% to 60%. Their use for larger lesions is limited, however, due to significant local irritation and systemic toxicity. Current CDC recommendations for provider administered treatment include 80% to 90% trichloroacetic acid (TCA) cryotherapy, or surgical fulguration/excision and are typically employed when other medical therapy fails. Surgical excision for condylomata is typically reserved for giant condylomas. Recurrence rates for all provider administered treatment, however, remain between 20% and 40%, likely as a result of persistent HPV infection.

The Buschke-Lowenstein tumor (BLT), verrucous carcinoma or giant condyloma acuminatum is a rare, slow growing lesion characterized by exophytic, ulcerative, and cauliflower like tumors most commonly in the anogenital region with a tendency for local invasion and frequent fistula or abscess formation (Fig. 3). It differs from SCC in that it lacks lymphatic involvement and is unlikely to metastasize, but rather spreads laterally. As with condylomata acuminatum, BLT is thought to be caused by HPV infection, most commonly types 6 and 11. Wide local excision (WLE) remains the mainstay of treatment, with abdominoperineal resection and pelvic exenteration reserved for extensive disease. Unfortunately, even with optimal management recurrence rates are from 40% to 70% with a 30% to 50% rate of malignant transformation.

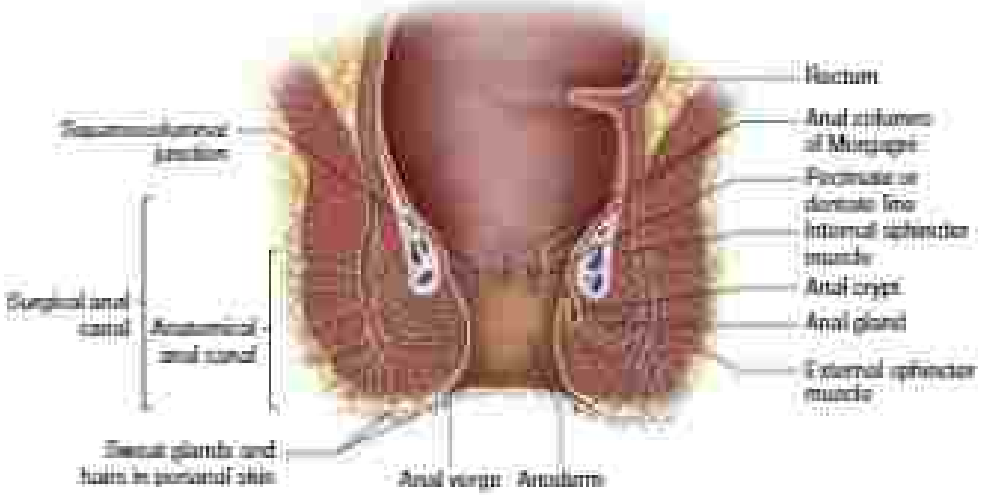

FIG. 1 Anatomy of the anal canal. (From Jones DJ, et al. The ASCRS Textbook of Colon and Rectal Surgery. 3rd ed. Springer; 2016.)

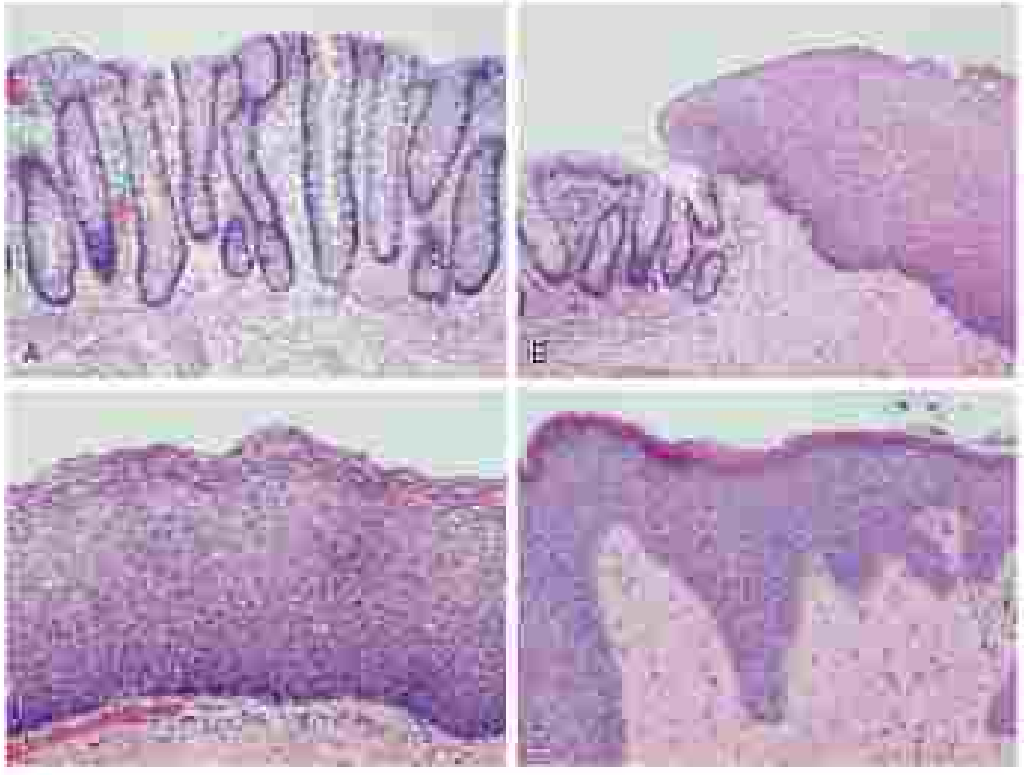

FIG. 2 (A) Normal columnar epithelium lining the upper zone of the anal canal. (B) Normal mucosa transition from proximal to distal (left to right). Normal, metaplastic (C) and keratinized (D) stratified squamous epithelium of the distal anal canal.

Anal Intraepithelial Neoplasia

Epidemiology and Histologic Features

As with cervical intraepithelial neoplasia and the development of cervical cancer, anal intraepithelial neoplasia (AIN) is considered a precursor to SCC of the anus and has historically been graded according to the degree of dysplasia: AIN I (low grade), AIN II (moderate grade) and AIN III (high grade or SCC in situ). These lesions can involve the perianal skin, anal canal, and are strongly associated with HPV types 16 and 18 for high grade lesions and types 6 and 11 for low grade lesions. In 2012, however, the Lower Anogenital Squamous Terminology Standardization project attempted to unify nomenclature across all HPV-related lesions. This consolidated the three categories into two, with low grade squamous intraepithelial lesion (LSIL) corresponding to AIN I and high grade squamous intraepithelial lesion (HSIL) corresponding to AIN II/III. The use of the term *flowerik disease*, which has traditionally referred to squamous cell carcinoma in situ, has been discouraged by the same coalition. This classification is intended to reduce interobserver variability and is currently the most commonly used terminology. Cytologic specimens collected by anal Pap smear utilize the Bethesda classification system, which classifies cells as atypical squamous cells of undetermined significance (ASCUS), LSIL, HSIL, and atypical squamous cells cannot exclude HSIL.

Histologically squamous intraepithelial lesions (SIL) are characterized by cellular and nuclear abnormalities in squamous epithelial cells, not extending into the basement membrane. SIL abnormalities include loss of epithelial stratification and nuclear polarity with development of nuclear polymorphism, hyperchromasia, mitosis, and increased mitotic activity. SIL may also demonstrate koilocytes—enlarged cells with a cytoplasmic halo surrounding the nucleus indicating active HPV replication. LSIL is defined as the replacement of the lower third of the

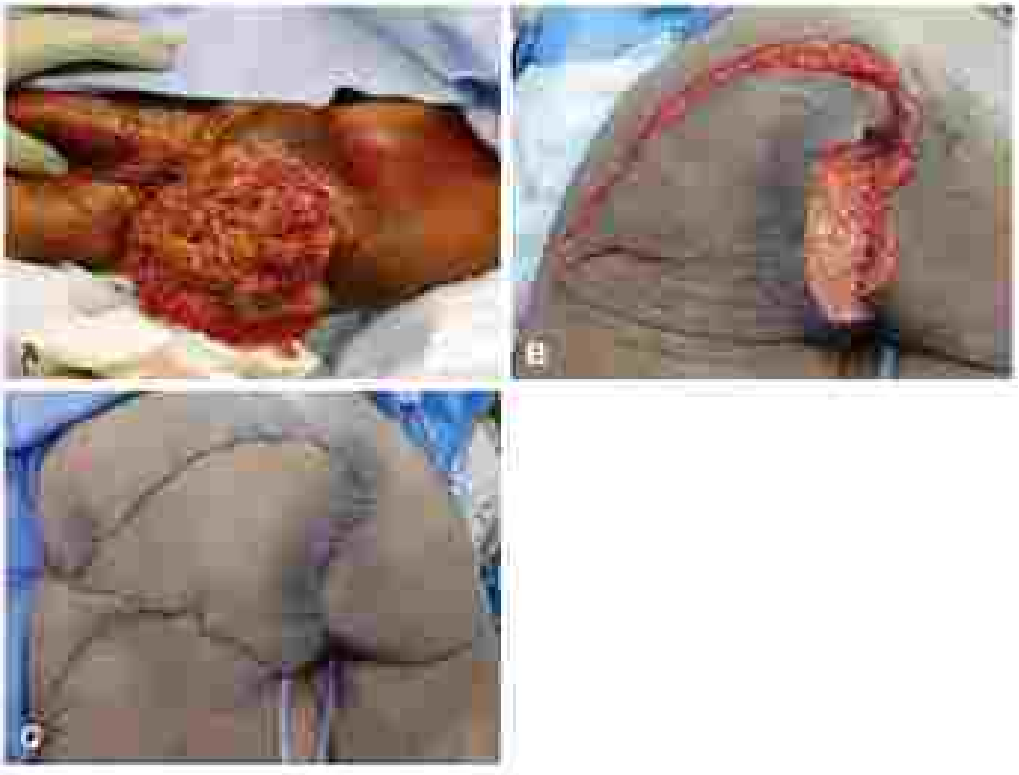

FIG. 3 (A) Exophytic anal lesion: clinical presentation. (B) Wide local excision. (C) 1-Up review.

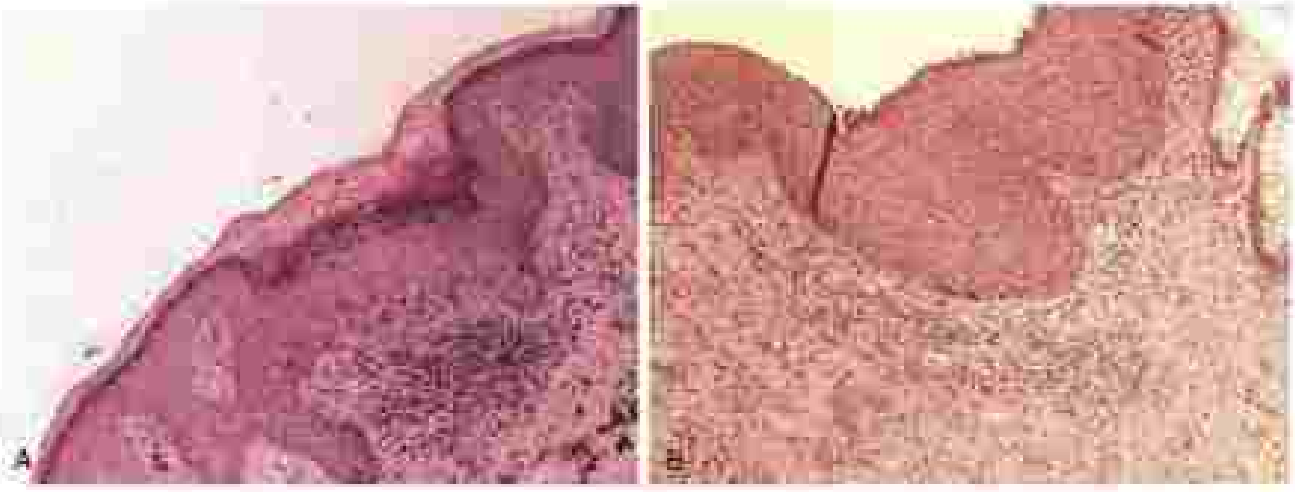

FIG. 4 (A) Low-grade squamous intraepithelial lesion demonstrating atypia limited to the lower third of the epithelium characterized by increased nuclear: cytoplasmic ratio and nuclear irregularity. (B) HSIL showing dysplastic cells throughout the epithelium. Note there is no keratinized basal layer with the top of the epithelium identical in appearance to the bottom. (Courtesy Dr Dennis O'Brien, Memphis, TN.)

epithelium by abnormal cells, while in HSIL the middle/upper thirds of the epithelium are also comprised of abnormal cells (Fig. 4). P16 is a cyclin dependent kinase inhibitor that is overexpressed in HPV-associated carcinogenesis, and its immunohistochemical expression has been utilized to better differentiate between benign/LSIL lesions and HSIL. HSIL demonstrates strong and diffuse nuclear staining of p16, while in LSIL benign lesions the expression is focal or patchy with minimal nuclear staining. Other markers of interest include Ki-67 and ProEx C, with some studies supporting improved sensitivity and specificity when used in combination with p16.

Diagnosis

The true burden of anal SIL is difficult to estimate in the general population due to a lack of population-based screening and validated testing; nonetheless, it is thought to be less than 1%. The risk factors typically associated with HPV infection include multiple sexual partners, anal receptive intercourse, immunosuppression (particularly HIV positivity), smoking, and genital dysplasia. Patients with SIL are typically asymptomatic, with lesions often presenting as an incidental finding after minor surgery. Symptomatic patients can present with rectal bleeding, irritation, pruritus, discharge, and/or soreness, with associated skin changes such as plaques, pigmentation or erythema.

There is limited literature on the natural history of SIL; however, both LSIL and HSIL have been noted to regress with observation alone. The estimated risks of progression have generally been derived from small cohort studies. In immunocompetent patients, the risk of progression from HSIL to SCC is not well documented, while

progression from LSIL to HSIL has been described to occur in less than 50% of HIV-positive MSM after 2 years and SIL to SCC in 10% to 15% of HIV-positive patients.

Anal cancer screening in high-risk populations such as HIV-positive and MSM patients remains controversial as there are false-negative rates of up to 42% and no definitive studies showing improved outcomes. Conversely, it has been suggested that targeted screening may be potentially cost effective by preventing anal SCC, and has been implemented suitably with annual anal Pap smear followed by high-resolution anoscopy (HRA) for any ASCUS or dysplasia.

HRA involves the application of high-magnification colposcopy to the anal canal. Enhancement of visualization is achieved by the use of 3% acetic acid solution with dysplastic areas demonstrating acetowhite staining. The mucosa is also inspected for characteristic HSIL-associated changes that consist of punctation and mosaicism of the vasculature as well as hyperpigmentation of the epithelium. Lugol's iodine solution can also then be applied to the anal canal, causing browning of the normal mucosa and yellowing of areas with HSIL due to the absence of glycogen (Fig. 5). This approach can facilitate targeted biopsies and subsequent therapeutic management.

Management

LSIL, and possibly even select cases of HSIL, can be managed with surveillance every 3 to 6 months, with or without HRA, as there is a reasonably low risk of disease progression and directed treatment is not without associated morbidity. Nevertheless, directed therapy has been reported to clear up to 80% of HSIL with less than 5% progression to SCC, and therefore local therapy is currently recommended for HSIL, while the role of local therapy for LSIL remains controversial. The Anal Cancer HSIL Outcomes Research study is a multicenter, randomized phase III trial that is currently accruing patients and aims to clarify whether topical therapy, ablative therapy, or observation should be used to manage HSIL in HIV-positive patients.

Topical therapies include 3% imiquimod cream, 5-FU, or TCA. Imiquimod is an immune modulator with cohort and case studies demonstrating 77% to 86% response rates; however, there are substantial recurrence rates, and side effects such as irritation, burning, and erosions may affect compliance. Similarly, topical 5-FU has demonstrated response rates up to 80% with recurrence in 50%, while TCA has been reported in retrospective studies to result in a 71% to 79% response rate. Although well tolerated, there are a significant proportion of nonresponders and high recurrences after topical therapy, and they should therefore be considered adjuncts to local therapies. Photodynamic therapy, which involves the application of photosensitizing creams to the affected area followed by laser treatment, has also been described; however, data are too limited to draw any conclusions regarding its efficacy.

Local ablative therapies include radiofrequency ablation (RFA), infrared coagulation, and electrocautery. Electrocautery has been reported to result in 66% response rates in HIV-positive MSM, with higher response rates after multiple sessions, although recurrence rates were 25% at 30 months. Studies examining RFA's initial efficacy are limited at this point; however, they typically show high initial response rates from 68% to 80% followed by more than 40% recurrence. These studies demonstrate that HIV-positive patients consistently experience significantly higher rates of recurrence, potentially due to ongoing exposure to predisposing risk factors.

Although surgical therapy continues to remain a viable option, particularly for lesions occupying less than 30% of the anal circumference, its utility is limited in SIL, despite 1 cm margins and the use of frozen section, clearance of all disease is difficult and recurrence rates are high. Historically, perianal mapping was routinely used in the setting of perianal SIL and currently continues to be applied; however, it is more recently considered potentially unnecessary. Frequently, WLE results in high rates of wound complications such as stenosis and incontinence as well as in significant deficits requiring the use of local flaps.

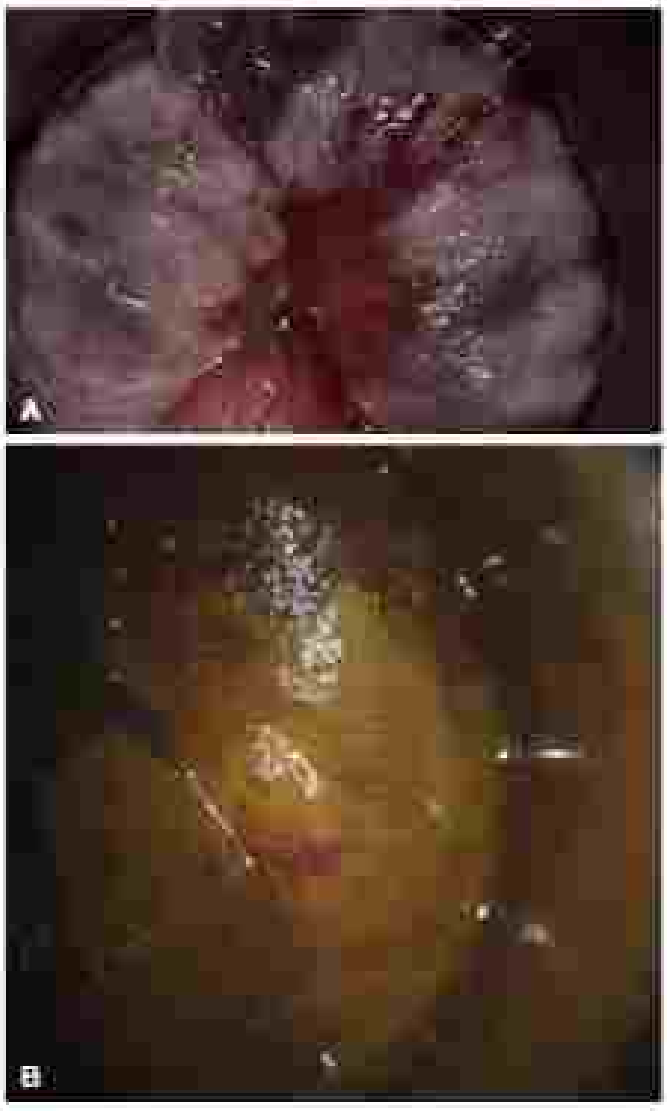

FIG. 5. High-resolution anoscopic view of high-grade squamous intraepithelial lesion (HSIL). (*A*) Acetowhite staining of dysplasia with vascular punctation. (*B*) Mustard yellow staining of HSIL with Lugol's solution (arrow). Note normal mucosa stains brown. (*Courtesy Dr Stephen Goldstone, New York, NY.*)

Recurrence rates for SIL are not insignificant, and therefore ongoing surveillance is paramount. The ideal surveillance interval and modality, however, remains up for debate. The American Society of Colon and Rectal Surgeons recommends 3- to 6-month intervals in the setting of dysplasia, with follow up consisting of digital rectal exam and office-based anoscopic examination with or without HRA, acetic acid, or Lugol's (Fig. 6).

Superficially Invasive Squamous Cell Carcinoma

Superficially invasive squamous cell carcinoma of the anus is a minimally invasive form of anal cancer defined by the College of American Pathologists as a completely excised anal cancer with 3 mm or less basement membrane invasion and a maximal horizontal spread of 7 mm or less. It is typically diagnosed incidentally on excisional biopsy and is unique in that excision alone is associated with good outcomes, with rates of 90% success reported after 4 years.

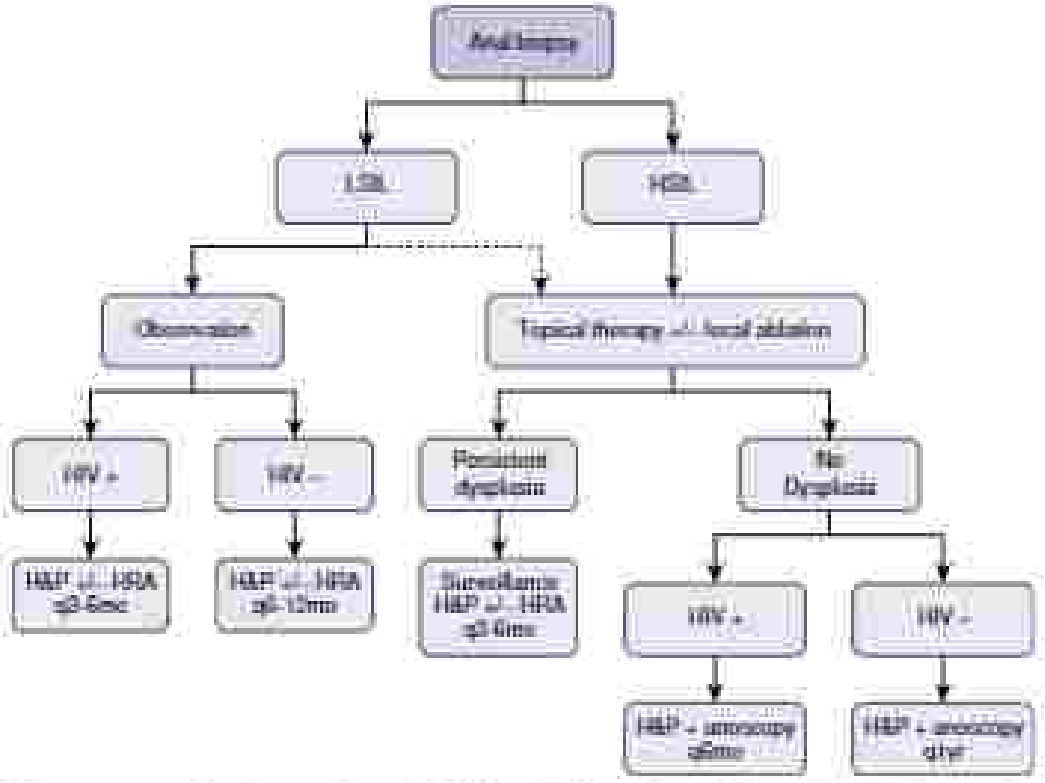

FIG. 6 Algorithm for the management of anal squamous intraepithelial lesions. HIV, Human immunodeficiency virus; H&P, history and physical examination; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Squamous Cell Carcinoma

Presentation

At the time of diagnosis, 68% of anal carcinomas are confined to the primary site, 32% involve regional lymph nodes and 3% are associated with metastatic disease. Anal cancers are frequently diagnosed late, as 20% of patients are asymptomatic and 45% present with anorectal bleeding, which is commonly attributed to hemorrhoids (Fig. 7). Thirty percent of patients experience anorectal pain and fullness, while others experience narrowing of stool caliber, a change in bowel habits, and tenesmus. Initial evaluation involves a detailed history to assess for risk factors such as MSM, receptive anal intercourse, and immunosuppression, as well as details of local regional symptoms such as groin pain/discomfort. The patient's baseline sphincter continence should be established, and any anorectal bleeding should be quantified. A history of poorly controlled HIV or previous radiation is important to elicit, as this may limit subsequent therapeutic approaches. Physical examination should involve thorough inspection of the perianal skin/anal margin and a digital rectal exam. Attention should be paid to sphincter tone, size and location of the tumor as well as fixation to nearby structures such as the vagina and prostate. The bilateral inguinal basins should be examined for lymphadenopathy. Women should undergo cervical and vulvar evaluation, while men should receive a penile/scrotal exam.

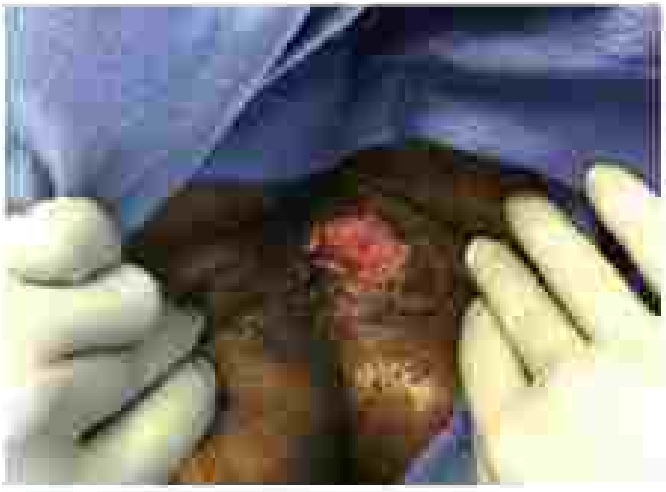

FIG. 7 Anal squamous cell carcinoma targeting mass at the anal verge.

Staging

According to the American Joint Committee on Cancer 8th edition, anal cancers are staged according to tumor size and involvement of adjacent structures, nodal involvement, and distant metastases. All staging occurs prior to initiation of any treatment and begins with digital rectal exam, anoscopy, and biopsy of the primary tumor. Histologically, SCC is defined by invasion of tumor cells into the basement membrane, which differentiates it from SIL. Any concerning groin lymphadenopathy on physical exam should be biopsied with fine needle aspiration to rule out lymphatic spread. Radiologic staging involves computed tomography (CT) of the chest, abdomen, and pelvis as recommended by the National Comprehensive Cancer Network (NCCN) guidelines. Magnetic resonance imaging of the pelvis can be used for more detailed local regional evaluation but is not mandatory. Similarly, positron emission tomography/CT (PET/CT) may provide additional information for staging verification, but it is not mandatory nor is it a replacement for standard CT imaging. The use of PET/CT for the enhancement of radiation oncology treatment planning has also been described.

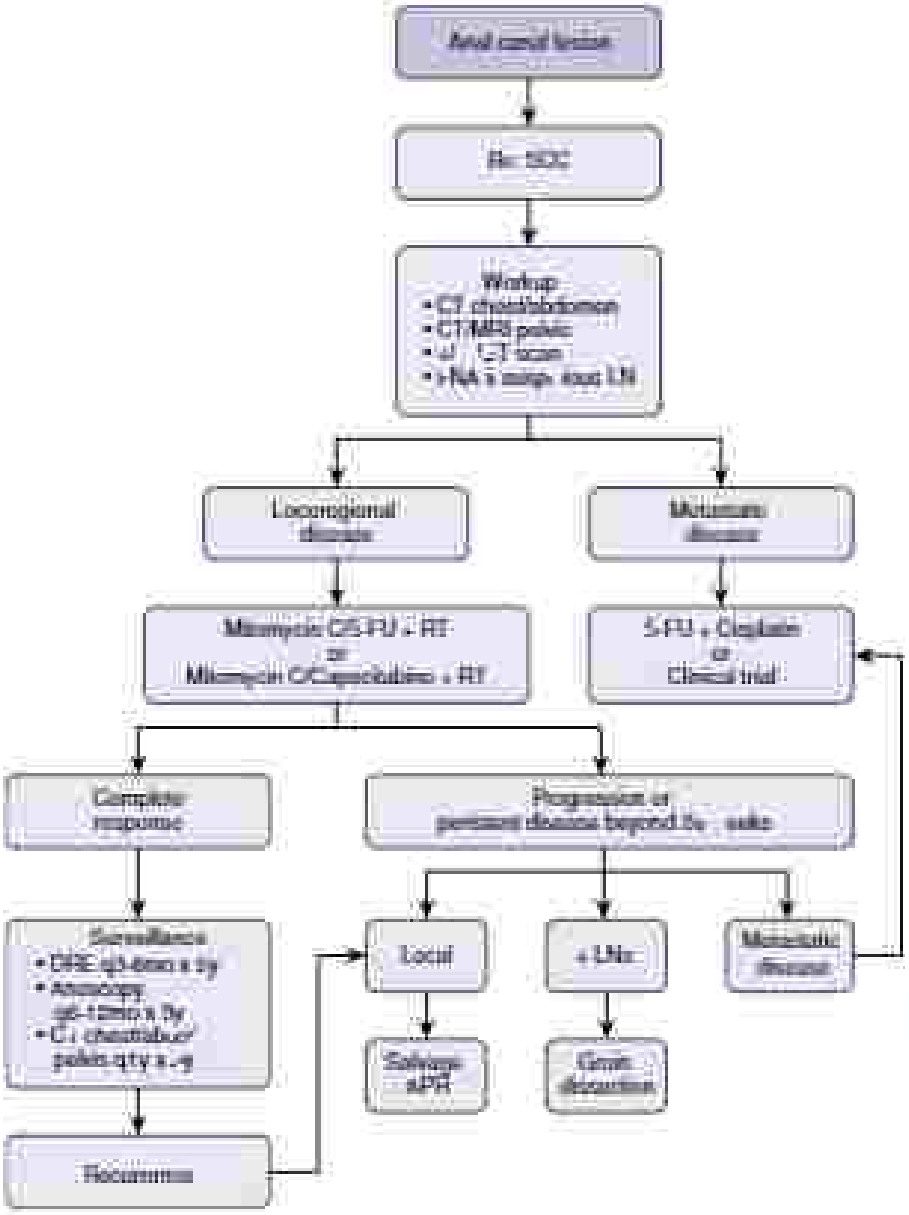

FIG. 8 Algorithm for the workup and management of anal canal squamous cell carcinoma (SCC). Abbr: AAdenocarcinoma; APR, abdominoperineal resection; Bx, biopsy; CT, computed tomography; DRE, digital rectal examination; FNA, fine needle aspiration; LN, lymph node; MRI, magnetic resonance imaging; PET, positron emission tomography; RT, radiotherapy; 5-FU, 5-fluorouracil.

Treatment

Prior to the 1980s, SCC of the anal canal was treated definitively with radical surgical resection. This involved an abdominoperineal resection (APR), which left patients with a permanent end colostomy, a perineal wound at significant risk for complications, and a 3% risk of perioperative mortality, all with a 5-year overall survival rate between 40% and 20%. In 1974, Dr. Norman Nigro and colleagues sought to decrease surgical failure rates by administering neoadjuvant chemoradiation with 5-FU, mitomycin C (MMC) and 30 Gray (Gy) of radiation to the full pelvis over 3 weeks in 3 patients. It was subsequently observed that following APR, specimens very frequently revealed no evidence of tumor on final pathology. This led to a substantial paradigm shift towards the nonsurgical management of anal cancer. Since then, numerous randomized controlled trials (RCTs) have confirmed the efficacy of concurrent 5-FU and MMC with radiation, even in the setting of HIV positivity, resulting in the preservation of surgery as a salvage option for persistent/recurrent disease after definitive chemoradiation (Fig. 8).

Continued modality therapy has undergone several revisions since the initial Nigro protocol. Current protocols typically involve 5-FU based concurrent chemotherapy (infusional or orally as capecitabine) with MMC on days 1 or 1 and 29 with a minimum of 45 Gy radiation administered over 5 weeks. The radiation fields include the pelvis, anus, perineum and inguinal nodes, with boosts based on areas of involvement, combined modality therapy is the treatment of choice for local regional disease. The radiation potentiating effects of chemotherapy are significant, as this regimen leads to complete tumor regression in 80% to 90% of cases compared with 45% to 65% with radiation alone, and 5-year operative survival rates as high as 65% with chemoradiation.

Cisplatin has been examined as a replacement for MMC in the Radiation Therapy Oncology Group (RTOG) and United Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial (ACT) II trials in an attempt to decrease hematologic toxicity; however, it demonstrated inferior outcomes, and therefore MMC remains standard of care. Other studies have investigated the addition of epidermal growth factor receptor inhibitors cetuximab or panitumumab to standard chemoradiation; however, these were associated with high levels of toxicity and poor outcomes. Radiation has also continued to be refined over the years, and current guidelines recommend the

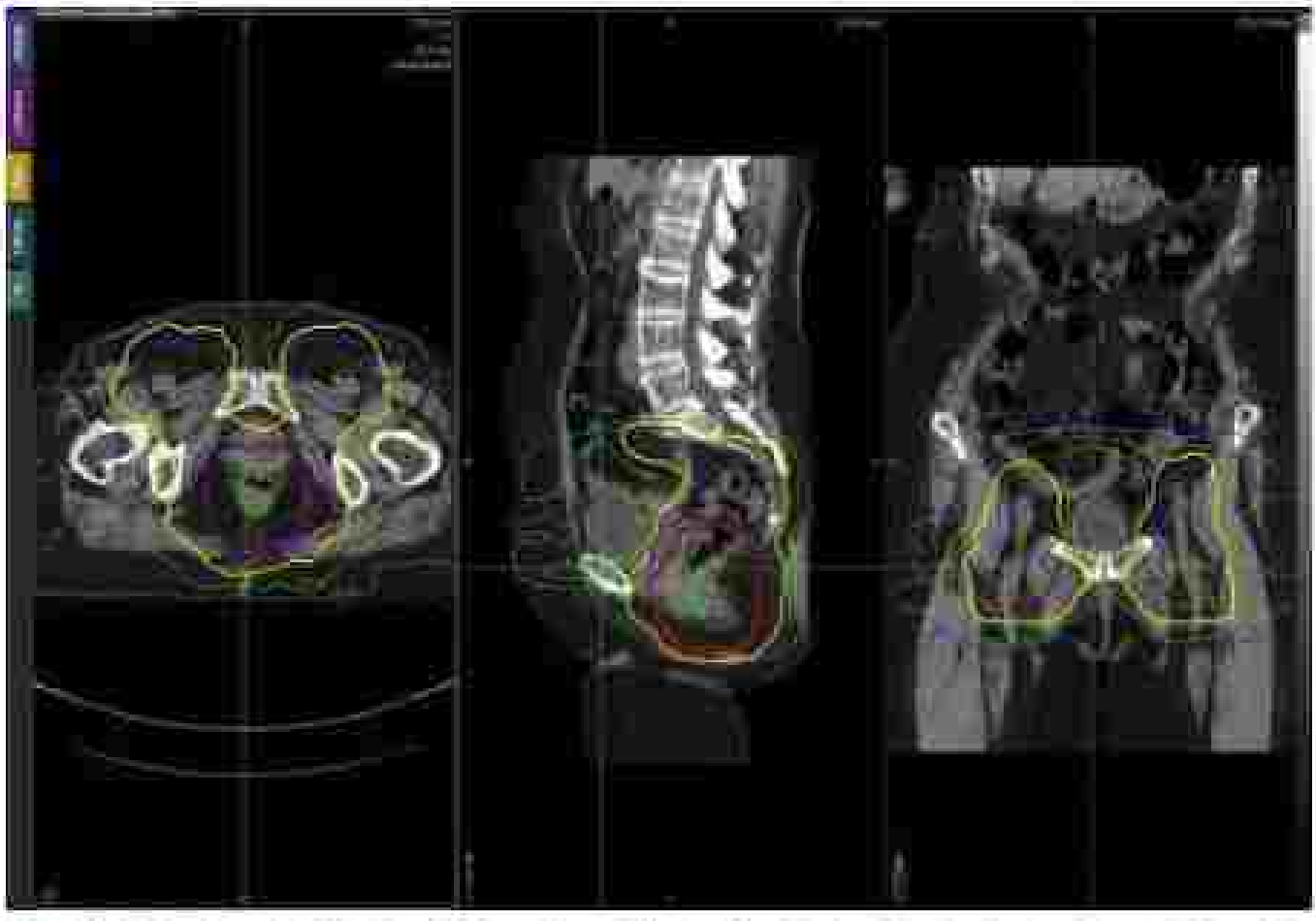

FIG. 4 Axial, sagittal, and coronal dose distributions of a planning computed tomography scan for anorectal intensity-modulated radiation therapy. Each colored line corresponds to a specific radiation dose. (Courtesy of Adam Kachnowski, Memphis, TN.)

use of intensity-modulated radiation therapy in order to spare adjacent organs and minimize toxicity. This technique breaks the radiation field into multiple beamlets of varying intensity administered in a three-dimensional fashion, allowing for increased precision, albeit at a higher up-front cost (Fig. 4). Application of this method also requires expertise and careful design to minimize reductions in local control, limiting its widespread use at all centers. Side effects of chemoradiation can be acute and/or chronic, and include gastrointestinal side effects (e.g., diarrhea, nausea, incontinence, and pain), urinary symptoms (e.g., frequency, incontinence, and dysuria), and sexual side effects (e.g., decreased libido, erectile dysfunction, and dyspareunia).

Role of Surgery

Anal SCC response to chemoradiation continues even beyond completion of treatment, and guidelines therefore recommend re-evaluation with visual exam and digital rectal exam (DRE) at 8 to 12 weeks after completion of chemoradiation. Patients are then classified into complete response, persistent disease, or progressive disease. In a subanalysis of the ACCUI trial comparing mitomycin versus cisplatin in 5-FU–based chemoradiation, 72% of patients without a complete response at 11 weeks achieved a complete response by 26 weeks. Persistent disease without evidence of progression can therefore be reassessed short term (4 weeks) for regression up to 6 months. Progressive or persistent disease beyond 6 months warrants repeat biopsy.

Surgery is typically reserved for local regional recurrence/persistence after chemoradiation, which has been reported to occur in 10% to 30% of patients. For patients recurring locally within the anal canal/perineum, salvage APR is the primary treatment, with a 5-year OS of 25% to 60% compared to a 5-year OS of 5% for patients who are not surgical candidates. Large recurrences, adjacent organ involvement, persistent disease, positive resection margins, and HIV positivity portend a worse prognosis. Many patients requiring salvage APR are predisposed to poor perineal healing due to prior chemoradiation and the need for wide margins and thus may benefit from reconstructive tissue flaps such as the vertical rectus abdominis myocutaneous (VRAM) flap or local myocutaneous flaps (e.g., gracilis, gluteal). Patients undergoing minimally invasive APR may preferentially undergo local myocutaneous flaps, as open approach VRAM flap harvest negates the benefits of a minimally invasive approach. There is growing interest in minimally invasive harvesting techniques for rectus abdominis flaps. It is generally recommended that patients presenting with isolated inguinal recurrence after chemoradiation undergo inguinal node dissection.

Posttreatment Surveillance

The NCCN guidelines recommend evaluation with physical exam, DRE, and anoscopy every 3 to 6 months for 5 years for patients with a complete response after chemoradiation. Additionally, patients with T3/T4 or N-positive disease on initial presentation or patients who received salvage APR should undergo CT chest, abdomen, and pelvis for the first 3 years.

Metastatic Disease

Ten to twenty percent of patients will present with metastatic disease, most commonly in the liver, lungs, lymph nodes, peritoneum, bones, and brain. Due to its rarity, there is a paucity of evidence supporting

the use of chemotherapy in this setting, however, the most common regimen is 5-FU and cisplatin. Most studies have demonstrated a response rate of approximately 60%, most of which are partial responses, and many patients experience disease progression within the first 12 months. Several small, retrospective studies have also examined carboplatin plus paclitaxel as a first line option with some durable responses. More recently, nivolumab and pembrolizumab, immunotherapy against the programmed cell death ligand receptor (PD-1), have been examined in phase I and II trials as second line therapy with response rates of 17% to 24%.

Perianal Cancer

Tumors at or within 5 cm distal to the anal margin (squamous mucocutaneous junction) are typically described as perianal cancers if they can be seen in their entirety with gentle traction placed on the buttocks. Traditionally, such lesions have been thought to behave similarly to skin cancers, however, they are staged in the same manner as anal canal cancers. National and international guidelines recommend WLE with 1 cm margins for T1N0, well differentiated perianal SCC, while more advanced perianal cancers are managed with definitive chemoradiation.

ADENOCARCINOMA

Most anal adenocarcinomas originate from the columnar epithelium in the upper anal canal or glandular cells of the ATZ and can be difficult to differentiate from low rectal adenocarcinomas. They can also originate from anal glands and chronic fistula tracts, which are typically defined as perianal adenocarcinomas. Patients can present with anal pain, discomfort, or abscess formation. Due to its rarity, treatment recommendations are based on small cohort studies and experiences with low rectal adenocarcinoma. Although WLE can be considered for T1 well differentiated tumors with no high risk features, T2 lesions and greater should generally be managed with neoadjuvant chemoradiation using a rectal adenocarcinoma protocol followed by APR and adjuvant chemotherapy.

PAGET'S DISEASE

Extramammary Paget's disease occurs where apocrine glands are found, including the perianal region. Diagnosis is typically delayed, as signs and symptoms are limited and can be mistaken for eczema or dermatitis. Skin biopsy is confirmatory, with histology revealing an intraepithelial adenocarcinoma characterized by large rounded vacuolated Paget cells. Paget's disease can be a primary lesion arising from the apocrine glands or as a synchronous or metachronous lesion from another site, with 33% to 86% of patients having previous or concurrent colorectal or genitourinary malignancy. It has therefore been suggested that patients undergo colonoscopy, evaluation as well. It is recommended that complete assessment of the anal margin with random mapping biopsies be performed to detect microscopic disease. This typically involves random biopsies taken at radial intervals beginning at the dentate line and around the anus in a clocklike fashion (Fig. 18).

The mainstay of treatment is WLE with a 1 cm margin. Frequently, the remaining defect is not amenable to primary closure and requires the use of myocutaneous or cutaneous flaps. Based on small series, recurrence rates after WLE have been reported to be 30% to 40%, with 5 year OS rates of 60% to 67%, suggesting that despite high local recurrence rates, Paget's disease does not tend to be systemically aggressive. If lesions are locally invasive or occur in conjunction with an anorectal adenocarcinoma, neoadjuvant chemoradiation followed by APR is the treatment of choice.

MELANOMA

Anal melanoma is rare and accounts for less than 2% of all melanomas. Patients typically present with bleeding, pain, or perianal mass, with pigmented lesions commonly mistaken for thrombosed hemorrhoids, while 30% are amelanotic. Prognosis is poor regardless of surgical approach with median survival reported to be less than 2 years. Retrospective studies have demonstrated the development of early distant metastases in most patients, therefore, where possible, preferred surgical treatment is typically WLE, with APR reserved for patients with extensive sphincter involvement, particularly bulky tumors or significant incontinence.

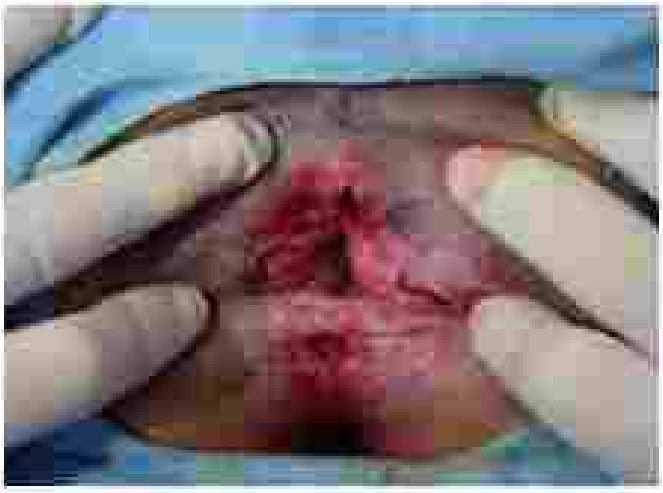

FIG. 18 Anal mapping. Four quadrant biopsies are obtained, starting at the dentate line, at the anal verge, and on the perianal skin. They are sent separately to the pathologist for permanent section.

NEUROENDOCRINE TUMORS AND MESENCHYMAL TUMORS

Neuroendocrine tumors arising from colorectal type mucosa or in the ATZ can occasionally arise in the anal canal, as well as mesenchymal tumors such as smooth muscle tumors or gastrointestinal stromal tumors. Typically, lesions are small and can be managed with local excision alone, with radical resection reserved for larger or locoregionally advanced tumors.

MALIGNANT LYMPHOMA

Although rare, Hodgkin's and non-Hodgkin's lymphomas have been reported in the anal canal, particularly in immunocompromised patients. These are typically high grade B cell lymphomas and are primarily treated with chemoradiation.

SUGGESTED READINGS

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PET Scanning in the Management of Colorectal Cancer

James Taylor, MBBChir, MPH, and Bashar Safar, MBBS

Fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) is a glucose analogue that carries a positron emitting isotope (¹⁸F). ¹⁸F-FDG is preferentially taken up by metabolically active cells; however, unlike glucose, FDG cannot be metabolized and therefore accumulates within cells. The subsequent emission of photons and the intensity of the positron emission tomography (PET) signal are proportional to the accumulation of FDG in cells; thus those that are more active, such as cancer cells, will have a greater signal intensity than surrounding tissue.

Cancer cells are not the only metabolically active cells with increased glucose uptake. Inflammatory tissue and even some benign lesions accumulate FDG, therefore resulting in low sensitivity and specificity when trying to differentiate between cancerous and non-cancerous tissue. In addition, slow growing tumors with low metabolic activity, such as mucinous carcinomas, will not have a high signal with FDG PET, thus limiting its clinical use.

The positron-emitting radioisotopes used in PET imaging have a short half-life and thus minimize the radiation absorbed by the patient. Tissue activity is measured at a fixed point and normalized to body surface area. This technique is called standardized uptake value (SUV).

The main limitation of PET is the lack of anatomic correlation; for this reason it is often integrated with a contrast-enhanced computed tomography (ceCT) scan to provide further anatomic information.

INCIDENTAL DETECTION OF COLORECTAL CANCER

Incidental ¹⁸F-FDG uptake within the gastrointestinal tract frequently represents malignant or premalignant lesions. The rate of detected colorectal incidental foci ranges from 1% to 9% of FDG-PET/CT scans done for other reasons, and subsequent colonoscopy detects cancer or polyps in more than 50% of these patients.

Kayser published a retrospective study of 9023 patients who underwent PET/CT over a 4-year period for a wide variety of reasons, including cancer and nononcologic workups. A total of 82 patients without a history of colonic disease had focal colonic FDG uptake and underwent colonoscopy. From these patients, 107 foci of colonic FDG uptake at PET/CT and 150 lesions at colonoscopy were detected. Among the 107 foci of FDG uptake, 63% corresponded to a lesion at colonoscopy (true positive), whereas 39% did not (false positive). Among the 158 lesions, 57% were not FDG avid (false negative). The authors subsequently concluded that subsequent colonoscopy should not be limited to the FDG-avid region of the colon, but that the entire colon should be investigated.

A further study by van Derzy and colleagues aimed to discover whether the SUV of incidental lesions could be used to differentiate between benign and malignant lesions, and thereby help to guide the urgency of colonoscopy. They found, in a study of 2318 patients, that maximum standardized uptake value (SUVmax) was significantly higher in malignant lesions; however, it was not possible to differentiate between benign lesions and adenomas. Thus any incidental finding on PET/CT within the colon should be investigated with a full colonoscopy, without delay.

TUMOR STAGING

Initial staging of the primary tumor is paramount in the workup of colorectal cancer (CRC) to determine the best treatment strategy. The decision to opt for early surgical intervention, versus neoadjuvant therapy, hinges on accurate staging. After a histologic diagnosis of CRC, CT scanning of the chest, abdomen, and pelvis should be done to rule out malignant disease. In rectal cancer, magnetic resonance imaging (MRI), transrectal ultrasonography (TRUS), or both are performed to provide local staging information. FDG PET/CT does not play a significant role in the initial clinical assessment of CRC, but it can be of value in patients with advanced disease (stage III and IV).

COLORECTAL CANCER

The role of FDG PET/CT in primary CRC is considered limited (Table 1). In 2013 Ogo and colleagues prospectively evaluated 64 patients with CRC, mostly nonmetastatic at initial diagnosis. In their series, PET/CT changed surgical management in only two (3.2%) patients (one had a liver metastasis, whereas one had a positive supraclavicular lymph node). The authors thus conclude that FDG PET/CT should not be routinely performed as part of the initial staging protocol.

Peterson and colleagues reviewed 67 patients in a retrospective analysis, all of whom had advanced CRC. They underwent FDG-PET/CT in addition to conventional CT staging, with changes in management occurring in 20 (30%) patients. The differences in findings between the two studies are likely attributed to the different patient populations.

A study by Engelman and colleagues aimed to compare the diagnostic accuracy of FDG PET/CT with conventional CT. The accuracy for tumor, nodal disease, and metastases by FDG-PET/CT were 82%, 66%, and 80%, respectively, compared with 77%, 69%, and 69% for conventional CT. The authors noted that FDG PET/CT was particularly helpful in discriminating and characterizing "indeterminate lung lesions" found on CT. They therefore concluded that FDG PET/CT found metastatic staging showed better specificity and higher accuracy than CT for unusual metastatic deposits. These results have been echoed in a recent publication by Lee and colleagues, who noted the increase in specificity and accuracy of FDG PET/CT compared with CT for detection of lymph node metastases.

A recent meta-analysis conducted by Ye and colleagues concluded that FDG PET/CT shows good performance in preoperative tumor detection rate, T staging and M staging in patients with CRC compared with CT alone. However, they highlight that the quality of prior studies is a limiting factor. FDG PET/CT should therefore be seen as a useful diagnostic tool for staging select patients with advanced disease, suspected distal metastases, or both; however, at this time it should not be part of the initial staging workup in the majority of patients with CRC.

RECTAL CANCER

Preoperative staging for rectal cancer dictates the sequence of treatment modalities, and therefore staging accuracy is imperative. Depth of tumor penetration, the presence of lymph node metastases, adjacent organ involvement, and distant metastases, all play a role in staging rectal cancer. Treatment options based on stage range from local resection to radical surgery with either neoadjuvant or adjuvant chemoradiation therapy for more advanced lesions.

Accurate staging is traditionally accomplished using MRI, TRUS, or both to define the T and N stage and ceCT to evaluate and define the M stage. The literature is sparse regarding the use of FDG PET/CT to stage primary rectal cancer (Fig. 1).

In 2014, Ono and colleagues prospectively evaluated 97 patients diagnosed with primary rectal adenocarcinoma, who first underwent traditional ceCT, followed by FDG PET/CT. Most of the patients

TABLE 1 Effect of FDG-PET/CT on Changing Management in Patients with Newly Diagnosed Colorectal Cancer

Study	n	Study Design	Modality	Changes Resulting From PET Imaging
Park et al (2006)	100	Prospective	FDG-PET/CT	Change in management in 14%
Dowey et al (2008)	83	Prospective	FDG-PET/CT	Change in management in 8% Change in overall management in 12%
Ope et al (2013)	68	Prospective	FDG-PET/CT	Change in management in 3.2% Restaging in 71%
Llamas-Elvira et al (2007)	101	Prospective	FDG-PET	Change in therapy in 58% of unresectable patients Restaging in 13% Modified scope of surgery in 12%
Herbst et al (2004)	86	Prospective	FDG-PET	Change in management in 17% Change in disease stage in 39%
Petersen et al (2010)	67	Retrospective	FDG-PET/CT	Change in management in 30%
Ramaswamy et al (2014)	61	Prospective	FDG-PET/CT	Change in management in 26%
Lee et al (2014)	266	Retrospective	FDG-PET/CT	Change in management in 6.1% of stage III Change in management in 12.7% of stage IV

CE, Computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

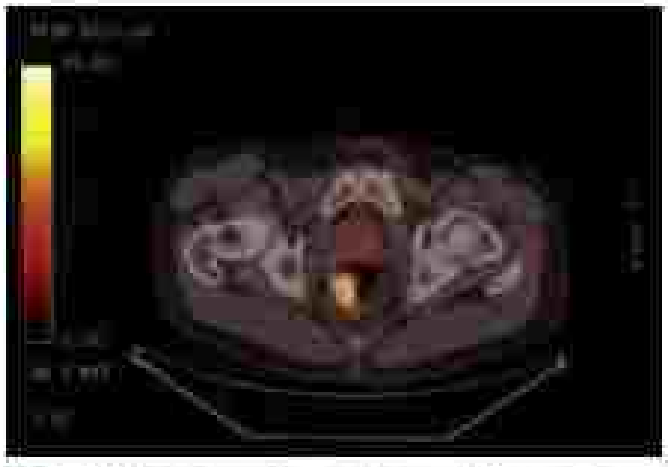

FIG. 1. Axial positron emission tomography-computed tomographic image identifying rectal tumor.

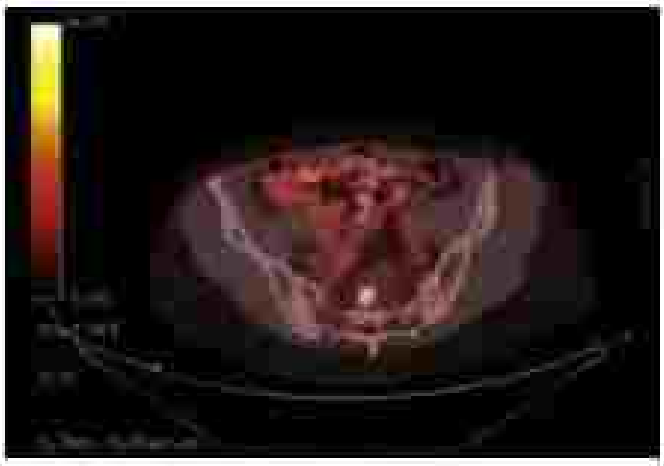

FIG. 2. Proximal jejunal mass identified on positron emission tomography-computed tomography.

were stage II or higher. CeCT and FDG-PET/CT were comparable in 62 (72%) patients; however, FDG-PET/CT provided additional data for 21 (24.4%, $P = .01$) of 97 patients. Specifically, FDG-PET/CT detected more distant metastases and lymph nodes (Fig. 2). In 14 patients (14.4%), the stage of the disease was changed, and there was a need to make adjustment to the patient's treatment strategy (n = 10) or operation type (n = 4).

The role of FDG-PET/CT in primary staging of rectal cancer remains to be fully elucidated. New techniques are being piloted, including the fusion of continuously moving table MRI and PET, which appear to improve lesion detection, especially in the case of recurrent lesions. At present, the recommendation is to reserve FDG-PET/CT for patients with advanced disease, to which the CT, MRI, or TRUS results are equivocal.

Liver Metastases

Liver metastases are present in 25% of patients at the time of initial diagnosis of CRC (Fig. 3). An additional 50% of patients will develop metastases during follow up. The liver is the most common site of hematogenous spread, and in 80% of cases this is the only organ involved. Resection of a liver metastasis is the only potential curative therapy at present, and 5 year overall survival (OS) is greater than 40% after this intervention. Predictors of early recurrence and a poor outcome include presence of extrahepatic disease, carcinoembryonic antigen (CEA) of more than 200 ng/mL, more than one tumor, size of a single tumor exceeding 5 cm, and a short disease free interval. These criteria are continuously changing, and the survival rates are improving.

Several anatomic factors should be considered before planning hepatic resection, especially the number of segments involved, proximity to major arteries, veins, and bile ducts, and the predicted volume of liver remnant that would be left after resection. The goal of liver surgery for metastatic disease is the removal of all metastatic lesions with negative margins, while preserving sufficient liver parenchyma. Often ceCT is used to evaluate the presence of metastases. Lesions are typically hypovascular during the portal venous phase. However, suboptimal accuracy has been reported for lesions less than 1cm in diameter, thus requiring a second imaging modality. MRI has a greater sensitivity compared with ceCT (95% vs 63%), especially

FIG. 3 Axial positron emission tomography-computed tomographic image showing a metastatic lesion in the left lobe of the liver.

for smaller lesions. MRI is considered the current gold standard for evaluating the liver when CRC metastases are detected by ceCT. The clinical benefit of FDG PET/CT in the assessment and surgical planning of liver metastases lies primarily in the detection of extrahepatic metastatic disease (Fig. 4), thus avoiding unnecessary laparotomies or palliative liver resections.

Several studies have investigated the value added of FDG PET/CT before liver resection on the surgical management of colorectal metastases. Moulton and colleagues randomized 404 patients with metastatic CRC (mCRC). Of the 404, 229 were randomly assigned to FDG PET/CT, whereas 134 patients were randomized to the control group of ceCT only. Of the 263 FDG PET/CT scans finally performed (seven patients dropped out of the trial), 111 provided new information; 62 were classified as negative (i.e., lesions seen on prior CT and considered malignant, but not identified on PET/CT), and 49 had abnormal or suspicious lesions as interpreted by the PET/CT reader. This resulted in a change in management in 23 patients (8%) in the FDG PET/CT group: 7 patients (2.7%) did not undergo laparotomy, 4 (1.5%) had more extensive surgery, 9 (3.4%) had additional organ surgery, and the abdominal cavity was opened, but the procedure was abandoned in 1 patient. Of note, OS was not impacted by the use of FDG PET/CT.

Huebner et al compared the rates of futile laparotomy among 188 patients who had preoperative PET/CT versus those not having PET/CT (20% and 45%, respectively). Again, despite the changes in the rate of laparotomy performance, OS and disease-free survival were not significantly affected between the FDG PET/CT group and conventional ceCT (61.3% and 35.5% vs 63.8% and 29.0%, respectively). Several other studies have found that FDG PET/CT offers potential benefit in selecting the appropriate candidates for resection; this information is summarized in Table 2.

Despite the potential benefits of FDG PET/CT in reducing futile surgical procedures, a recent study by Schulz and colleagues looked at the sensitivity and specificity of ceCT, FDG PET/CT and MRI for patients scheduled for resection of suspected CRC liver metastases. They found that for small sensitivity/specificity was 89%/81% for ceCT, 90%/87% for MRI, and 81%/99% for PET/CT. Thus they conclude that MRI should be used for detection of CRC liver metastases; however, they note that evolving techniques combining MRI and PET could potentially optimize the diagnostic performance.

Several recent studies have looked at the economic impact of adding FDG PET/CT to the workup for CRC with liver metastases. Wirring and colleagues noted in a randomized trial that the addition of FDG PET/CT to a conventional workup for potentially resectable CRC liver metastasis results in a reduction in futile laparotomies by 38%. When considering a follow-up period of 3 years and including all health care costs accumulated in this time, the addition of FDG PET/CT resulted in higher costs. However, the authors concluded in a cost-effectiveness analysis that the avoidance of unnecessary laparotomies justifies the expense. The economic benefits would be logistical, that is, improving hospital performance and quality of care because of more effective planning of operating room capacity and hospital resources. In conclusion, FDG PET/CT can improve the staging accuracy of patients with CRC liver metastases, particularly when extrahepatic disease is suspected.

FIG. 4 Sagittal positron emission tomography-computed tomographic image highlighting extensive fluorodeoxyglucose activity in the peritoneum, bowel, and diaphragm.

LUNG NODULES

The lungs are the most common extraabdominal site of metastases in CRC. The 5-year OS after resection of a lung metastasis can range between 24% and 67.8%, however, still only 4.1% of patients with synchronous pulmonary lesions are treated with surgical curative intent. Indeterminate lung lesions (ILL) are found in 4% to 42% of patients when staged with ceCT.

FDG-PET and FDG-PET/CT are well established staging modalities to assess ILL greater than 1 cm in diameter, with a sensitivity of 97% and specificity of 78%. A study by Yim et al retrospectively reviewed 106 pathologically proven ILL and showed that PET/CT had an accuracy of 81.2% in diagnosing malignancy, with a sensitivity of 86.7%, and specificity of 50%. They also noted that the likelihood of malignancy increased with SUVmax. The authors also elucidate that false-negative results can occur with small lesions, because of PET's limited spatial resolution, leading to considerable underestimation of the true anatomic or activity within the lesion.

Sim and colleagues prospectively analyzed 230 patients who underwent operation for CRC and were followed up for a median of 24 months. In 20% of them, an ILL was detected by preoperative ceCT. Patients with ILL had a FDG PET/CT performed at 3 months and a low dose ceCT performed at 6, 12, 18, and 24 months after surgery. Four patients (8.5%) had lung metastases identified at a median of 9 months after surgery, whereas two (4.3%) had other lung malignancies. In the patient population that had normal preoperative ceCT, 10 of the 180 (5.6%) developed lung metastases, detected at

TABLE 2. Management Changes by FDG-PET/CT of Patients with Colorectal Liver Metastases

Study	n	Design	Management Change (%)	Investigator Conclusions
Ruers (2006)	150	Prospective	39%	FDG PET/CT significantly reduces the number of futile laparotomies due to unsuspected extrahepatic disease.
Schmidt (2004)	36	Prospective	22%	Important additional information provided by FDG PET/CT in patient with presumed resectable CRC liver metastases.
Briggs (2011)	94	Retrospective	30%	FDG PET/CT improves staging accuracy, characterizes indeterminate lesions and helps assign patients to appropriate treatment.
McLarty (2012)	54	Retrospective	67%	FDG PET/CT profoundly affects management of patients with resectable CRC liver metastases.
Georgakopoulos (2013)	19	Prospective	37%	FDG PET/CT provides relevant information for patients with CRC liver metastases.
Chua (2007)	76	Retrospective	25%	FDG PET/CT performed better in detecting both colorectal and noncolorectal liver metastases and frequently altered patient management.
Moulton (2014)	404	Prospective	8%	FDG PET/CT compared with CT alone did not result in frequent change in surgical management.

CT, Computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

a median 16 months after surgery. This was significantly later than the patients with H.L. ($P = .001$). The authors concluded that, despite the relatively low number of H.L. that turn out to be malignant, it is advisable to use FDG PET/CT scan in the follow up to detect lung metastases as soon as possible to better the prognosis.

A recent study by Shimo and colleagues found significant correlation between OS and SUVmax values of patients with pulmonary metastases who underwent resection. The 5-year OS rates of patients with SUV max of 4.5 or greater and less than 4.5 were 51.6% and 74.0%, respectively. Thus they conclude that FDG PET/CT can play a role in estimating a patient's prognosis. FDG PET/CT can be used to detect and characterize H.L during primary staging of CRC and follow up of these lesions for detection, surgical management, and perhaps even provide counseling on prognosis.

ASSESSMENT OF TREATMENT RESPONSE

Patients with mCRC usually are treated on the location and extent of disease with systemic chemotherapy and monitored by CECT. On the basis of changes in cancer cell glucose metabolism, FDG-PET/CT is able to detect response to therapy during the early phases of treatment, before morphologic changes become evident.

Colorectal Cancer

Treatment effect during chemotherapy is measured by the Response Evaluation Criteria in Solid Tumors (RECIST), which looks at changes in the morphology or size of the lesion. The main limitation of RECIST is that a decrease in size does not necessarily translate into an improvement in prognosis, and it may take several weeks before changes in size become apparent. Patients often receive a full course of chemotherapy, with its associated toxicity and side effects, before a size change is detectable. This led to the development of the Positron Emission Tomography Response Criteria in Solid Tumors, whereby FDG PET/CT is used to measure a metabolic response to a tumor. Metabolic changes can occur before an anatomic change occurs, thus defining early response to treatment and potentially predicting histopathologic response and patient outcomes.

Reports on the correlation of patient outcomes with FDG PET/CT–based metabolic response after 1 to 2 months of chemotherapy are inconsistent, partially due to methodologic issues in multimodality assessment. Hyslop and colleagues assessed 54 patients with mCRC with FDG PET before treatment and after two cycles of irinotecan-based combination chemotherapy. They measured visual changes in tumor FDG uptake and also compared it to radiologic response on CECT after 4 and 8 cycles. Using the surrogate for tumor response of a change in SUV by more than 25% during treatment, as defined by the European Organization for Research and Treatment of Cancer guidelines, they found a strong correlation between metabolic response and objective response ($r = 0.52$, $P = .00001$), with a sensitivity of 77% and a specificity of 76%. However, in contrast to radiologic response, metabolic response did not reflect survival, indicating that factors additional to the immediate inhibition of tumor cell metabolism can influence long-term outcome. This contrasts the work of de Geus-Oei, which revealed that changes in tumor glucose metabolism were highly predictive for patient outcomes. Increased rates of death and progression were associated with worse response on FDG-PET.

Mertens and colleagues used FDG PET/CT to look at 38 mCRC patients with liver metastases before and after five cycles of second-line chemotherapy. SUVmax and standardized added metabolic activity (SAM) was correlated with morphologic response, as well as progression free (PFS) and OS. Seven of the original 38 patients underwent resection of their liver lesions, and strong correlation was seen between metabolic and morphologic response. Although there was no correlation with the baseline FDG PET/CT with PFS or OS, the follow up SUVmax and SAM were found to be prognostic factors. The median PFS and OS in the patient group with a high follow-up SUVmax were 10.4 months and 32 months, compared with 14.7 months PFS and a yet unreached median OS in the low follow up SUVmax group.

In conclusion, baseline parameters measured by FDG PET/CT do not correlate with prognosis in patients with mCRC, however, changes in metabolic activity before and after chemotherapy can help to predict treatment response and can be used as prognostic indicators. Several multicenter clinical trials are currently underway to further assess the prognostic potential of FDG PET/CT.

Rectal Cancer Response to Neoadjuvant Chemoradiation

Patients with locally advanced rectal cancer (LARC) are offered neoadjuvant chemoradiation (nCRT) as a standard of care, followed by radical surgery and adjuvant chemotherapy. Assessing the treatment response can be challenging, with MRI, rectal US, or EUS often unable to differentiate between fibrosis, necrosis, inflammatory tissue, or residual tumor foci. Studies have suggested that FDG PET/CT is a more accurate method of assessing treatment response.

Li and colleagues investigated the association between FDG PET/CT parameters, CEA and tumor response in LARC patients receiving nCRT. Of the 64 patients that were prospectively studied, 38 patients were identified as responders and 19 exhibited pathologic complete response (pCR). The response index of SUVmax (RI_SUVmax) was the most accurate measure of predicting responders, whereas the CEA post and change in CEA exhibited the greatest accuracy in predicting pCR. The authors concluded that FDG PET/CT is an accurate tool for predicting tumor response to nCRT in LARC. These results were further echoed by Koo and coauthors, who looked at 107 patients with LARC who underwent nCRT with FDG PET/CT and to predict pCR. They found that a pCR occurred in 22 patients (21.4%) and showed that post nCRT SUVmax and change in the SUVmax (ΔSUVmax) were significant predictors of pCR. They also highlighted that low SUVmax (<2.5) after nCRT and a high ΔSUVmax (>62.5%) were associated with increased OS.

Recent studies have focused on detecting early response after 1 to 2 weeks of therapy, to either modify therapy or to spear unnecessary morbidity of radiation therapy. Cascini and colleagues performed a baseline FDG PET, with further scans at 12 days after initiation and at completion. They were able to correctly identify responders by decrease in SUVmean (mean value of SUV, decrease >22%, accuracy 100%) and SUVmax (decrease >42%, accuracy 94%). Ianson and colleagues also confirmed these findings, showing a significant reduction in SUVmax was detectable after the first week of therapy.

A meta-analysis performed by Mullenix and colleagues looked at 10 studies, with a total of 200 patients, to evaluate the value of FDG PET/CT to detect early response of patients with LARC receiving nCRT. FDG PET/CT was found to have a sensitivity and specificity of 79% and 78%, respectively.

Patients who achieve a pCR after nCRT have a better disease-free survival (DFS) and OS compared with partial responders and nonresponders. As such, a watch and wait approach can be adopted, with robust surveillance and early detection of regrowths allowing for a high rate of successful salvage surgery. FDG PET/CT has been suggested to form part of the surveillance algorithm. Perez and colleagues prospectively monitored 98 patients who underwent FDG PET/CT at baseline and after 6 weeks and 12 weeks after completion of neoadjuvant treatment before clinical assessment. Sixteen patients (16%) had a pCR and were managed without surgery. FDG PET/CT was used during a strict follow-up program; however, the authors found that at 6 weeks the scan was able to detect less than 50% of true complete responders.

The use of FDG PET/CT in the management of LARC continues to evolve; however, as of yet there is no definitive consensus. It has the potential to detect early responders, predict survival, and aid in the determination of pCR to guide nonoperative intervention.

DETECTION OF RECURRENCE

Local and systemic recurrence after CRC surgery occurs in up to 30% of patients in the first 2 years. Early detection allows for higher resectability and better survival, with 5-year survival rates of 30% to 40% in selected patients with single organ metastatic disease. The most common sites for recurrence are liver locally—especially for rectal cancer—and lung.

Postoperative surveillance protocols based on the site and stage of the original cancer include clinic visits with history and physical examination, CEA levels, endoscopy (sigmoidoscopy or colonoscopy), and CT scanning for 5 years after surgical resection. Intensive follow-up to ensure the detection of recurrences does not always diminish mortality rates, thus the optimal monitoring strategy remains in doubt.

Several studies have shown that FDG PET is sensitive and specific in detecting recurrence in CRC patients, thus affecting management. This remains the most common use of FDG PET in data, particularly in patients who have had potentially curative resection of liver or lung metastases. However, the clinical value and overall efficacy of FDG PET/CT in surveillance are not yet established. A recent open-label multicenter trial conducted by Subhani and colleagues enrolled patients in remission of CRC (stage II perforated, stage III, or stage IV) after curative surgery. One hundred twenty patients were in the intervention arm of 6-monthly FDG PET/CT for 3 years, whereas 119 patients in the control arm underwent usual monitoring alone (3-monthly physical and tumor marker assay, 6-monthly liver ultrasonography and chest radiography, and 6-monthly whole-body ceCT). The trial found that the failure rate (unresectable recurrence or death) was not significantly different between the intervention and control arms (29.2% and 33.7%). Multivariate analysis also showed no difference. The median time to diagnosis of unresectable recurrence (months) was significantly shorter in the intervention group (7 [range, 3–30] vs 14.5 [range, 7.5–27], $P = .016$); however, the mean cost per patient was significantly higher in the intervention group. The authors concluded that, when FDG PET/CT is added every 6 months, increased costs are seen without decreasing treatment failure rates in patients in remission of CRC. Also, neither OS nor DFS was better in the intervention arm.

Several other studies have found improved survival with intensified follow-up; however, the components of monitoring vary considerably, so that no definitive conclusions can be drawn. A Cochrane review of 15 studies including 5403 participants with stage II or III CRC—despite variability in settings and follow-up intensity—showed more salvage surgery with curative intent in patients in the group undergoing intensified follow-up. However, a meta-analysis from Verga and colleagues of 16 randomized controlled trials, including 11 with survival data, revealed that intensified monitoring was not associated with better survival. So, although FDG PET/CT appears to detect recurrence at an earlier time point, doing so does not appear to impact survival but does incur a financial burden.

Detection of Recurrence in Patients with Elevated Carcinoembryonic Antigen

CEA is produced by the columnar and goblet cells of the colon, as well as colonic cancer cells, and has a half-life of 5 to 11 days. Serial determination of plasma CEA concentrations is widely used in the postoperative surveillance of CRC; however, clinicians face a major challenge when the CEA is elevated but no evident relapse can be localized. CEA can also be elevated in smokers, patients with inflammatory bowel disease, or other epithelial tumors, resulting in 60% to 70% sensitivity and 80% specificity in the diagnosis of recurrent CRC. Studies have demonstrated a median lead time of 9 months between serum CEA elevation and detection of recurrent disease. Furthermore, normal CEA levels do not exclude tumor recurrence, and an increased CEA does not provide information of the location of the recurrence. Thus imaging is required to confirm and localize recurrence, and in current clinical practice ceCT is the modality of choice. However, it is often difficult to differentiate between pelvic recurrence and postoperative fibrosis.

To discover the value of FDG PET or FDG PET/CT in the detection of recurrent CRC in patients with elevated CEA, Liu and colleagues conducted a systematic review and meta-analysis of the literature to 2013. A total of 510 patients from 11 studies (10 retrospective) were included. The authors showed that both FDG PET and FDG PET/CT performed well with a high sensitivity (90.3% and 94.8%, respectively for FDG PET and FDG PET/CT) and specificity

(80% and 77.2%, respectively), with equally impressive accuracy (89% and 92.3%, respectively). In addition, FDG PET or FDG PET/CT detected 20% of patients with CEA elevation resulting from other causes.

Vallam and colleagues demonstrated a correlation between the degree of CEA elevation and the likelihood of recurrence of CRC. They retrospectively analyzed all PET/CT scans performed for elevated CEA during surveillance after complete resection of primary tumor followed by adjuvant therapy. In their sample of 104 patients with elevated CEA, 62 patients (59.6%) were found to have recurrent disease. At CEA levels less than 5, 5.1 to 10, 10.1 to 15, 15.1 to 50, and greater than 50 ng/mL, disease recurred in 10%, 43%, 70%, 94%, and 100% of patients, respectively. Sensitivity and specificity of PET/CT to were 92.7% and 95.2%, respectively, thus indicating that PET/CT is a valuable tool to detect recurrence.

When comparing standard ceCT imaging with FDG PET/CT, the latter appears to be superior in detecting recurrence in patients with elevated CEA. This was confirmed by Ozkan and colleagues in a retrospective study that included 69 patients, showing a sensitivity and specificity of 97% and 61% for FDG PET/CT, compared with 73% and 61% for ceCT.

Detection of Recurrence in Patients With Normal Carcinoembryonic Antigen

Several studies have looked at the utility of FDG PET/CT to detect recurrence in patients with normal CEA levels. Sanli and colleagues retrospectively reviewed 236 patients with recurrence, of which 118 had a normal CEA. The sensitivity and specificity of detecting recurrence were 100% and 84%, respectively, whereas in those with elevated CEA the sensitivity was 97.1%, and specificity was 84.6%. The investigators therefore concluded that, regardless of the CEA levels, FDG PET/CT can successfully detect recurrence.

These results have been supported by several other studies, including the work of Zhang and colleagues, who compared ceCT to FDG PET/CT in patients with different CEA concentrations. FDG PET/CT had a sensitivity, specificity, and accuracy of 95.2%, 82.6%, and 92.3%, respectively, whereas ceCT showed values of 80.7%, 73.9%, and 93%. The sensitivity and accuracy were significantly higher for FDG PET/CT compared with ceCT, and no statistical difference was found between patients with normal and increased CEA levels. Thus, even when CEA levels are not elevated, clinical, endoscopic, or conventional suspicion of recurrence should be evaluated with FGD PET/CT.

CONCLUSIONS

The use of FDG PET and FDG PET/CT in the evaluation of CRC continues to evolve. Although the use of PET for initial staging appears to be limited and not cost effective, it is evident from the data presented in this chapter that PET can play an important role at several key stages in a patient's journey through CRC treatment. In patients with suspected recurrent disease and in patients with liver metastases who might not be amenable to surgery, PET has been shown to have a distinct advantage compared with conventional imaging. In addition, PET can help to determine response to neoadjuvant therapy, especially in the case of rectal cancer, and can help to guide prognosis.

Despite these findings, the database for PET remains largely retrospective, with few prospective studies or clinical trials contributing to the field. More randomized controlled trials would add greater weight to the evidence presented in this chapter.

Suggested Readings

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Neoadjuvant and Adjuvant Therapy for Colorectal Cancer

Ron G. Landmann, MD, and Alexandra W. Elias, MD

Colon and rectal cancer, or colorectal cancer (CRC), is a common disease in the United States with an estimated 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer in 2018. The lifetime risk of developing CRC is approximately 1 in 22 (4.49%) for men and 1 in 24 (4.15%) for women. Although the mortality and incidence rates have been declining over the last few decades, CRC remains the third leading cause of cancer-related deaths among both men and women in the United States, with an estimated 50,630 cancer-related deaths in 2018. The decline in both incidence and mortality is likely due to several factors, such as cancer prevention, improved screening, and potentially curative therapies. There are currently more than 1 million CRC survivors in the United States.

For early stage CRC (stages I through III), surgical resection remains the basis of curative treatment. Recurrence, particularly distant recurrence, despite appropriate surgical resection is common and thought to be due to micrometastatic disease that is not readily detectable by current methods. For this reason, neoadjuvant and adjuvant therapies are often utilized to target micrometastases with the goal of complete eradication and prolonged survival. The challenge lies in determining which patients will benefit from additional therapy beyond surgical resection. The decision to add neoadjuvant or adjuvant therapy is based in large part on risk calculators, which take into consideration not only clinical tumor stage, but also patient-specific data, clinicopathologic features, such as lymphovascular invasion, and molecular profiling, such as microsatellite instability (MSI) status, KRAS, NRAS, and BRAF mutations. Surgical, adjuvant, and neoadjuvant therapeutic approaches to CRC are different for colon versus rectal cancer and are discussed separately in this chapter (Fig. 1).

STAGING

Formal CRC staging is essential to risk stratification for guiding clinicians' treatment decisions for individual patients. Guidelines from the National Comprehensive Cancer Network (NCCN) for preoperative workup of newly diagnosed CRC should include the following: colonoscopy (plus consideration of rigid proctoscopy for rectal cancer) with biopsy and pathology review; complete blood counts; chemistry profile, and carcinoembryonic antigen (CEA) serum level; computed tomographic (CT) scan of chest, abdomen, and pelvis for colon

(80% and 77.2%, respectively), with equally impressive accuracy (90% and 92.3%, respectively). In addition, FDG PET or FDG PET/CT detected 20% of patients with CEA elevation resulting from other cancers.

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Detection of Recurrence in Patients With Normal Carcinoembryonic Antigen

Several studies have looked at the utility of FDG PET/CT to detect recurrence in patients with normal CEA levels. Sanli and colleagues retrospectively reviewed 236 patients with recurrence, of which 118 had a normal CEA. The sensitivity and specificity of detecting recurrence were 100% and 84%, respectively, whereas in those with elevated CEA the sensitivity was 97.1%, and specificity was 84.6%. The investigators therefore concluded that, regardless of the CEA levels, FDG PET/CT can successfully detect recurrence.

These results have been supported by several other studies, including the work of Zhang and colleagues, who compared ceCT to FDG PET/CT in patients with different CEA concentrations. FDG PET/CT had a sensitivity, specificity, and accuracy of 95.2%, 82.6%, and 92.3%, respectively, whereas ceCT showed values of 80.7%, 73.9%, and 93%. The sensitivity and accuracy were significantly higher for FDG PET/CT compared with ceCT, and no statistical difference was found between patients with normal and increased CEA levels. Thus, even when CEA levels are not elevated, clinical, endoscopic, or conventional suspicion of recurrence should be evaluated with FGD PET/CT.

CONCLUSIONS

The use of FDG PET and FDG PET/CT in the evaluation of CRC continues to evolve. Although the use of PET for initial staging appears to be limited and not cost effective, it is evident from the data presented in this chapter that PET can play an important role at several key stages in a patient's journey through CRC treatment. In patients with suspected recurrent disease and in patients with liver metastases who might not be amenable to surgery, PET has been shown to have a distinct advantage compared with conventional imaging. In addition, PET can help to determine response to neoadjuvant therapy, especially in the case of rectal cancer, and can help to guide prognosis.

Despite these findings, the databank for PET remains largely retrospective, with few prospective studies or clinical trials contributing to the field. More randomized controlled trials would add greater weight to the evidence presented in this chapter.

Suggested Readings

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Sobhani I, Itti E, Luciani A, et al. Colorectal cancer (CRC) monitoring by 6-monthly 18FDG-PET/CT: an open-label multicentre randomised trial. *Ann Oncol*. 2018;29:931-937.

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Neoadjuvant and Adjuvant Therapy for Colorectal Cancer

Ron G. Landmann, MD, and Alexandra W. Elias, MD

Colon and rectal cancer, or colorectal cancer (CRC), is a common disease in the United States with an estimated 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer in 2018. The lifetime risk of developing CRC is approximately 1 in 22 (4.49%) for men and 1 in 24 (4.15%) for women. Although the mortality and incidence rates have been declining over the last few decades, CRC remains the third leading cause of cancer-related deaths among both men and women in the United States, with an estimated 50,630 cancer-related deaths in 2018. The decline in both incidence and mortality is likely due to several factors, such as cancer prevention, improved screening, and potentially curative therapies. There are currently more than 1 million CRC survivors in the United States.

For early stage CRC (stages I through III), surgical resection remains the basis of curative treatment. Recurrence, particularly distant recurrence, despite appropriate surgical resection is common and thought to be due to micrometastatic disease that is not readily detectable by current methods. For this reason, neoadjuvant and adjuvant therapies are often utilized to target micrometastases with the goal of complete eradication and prolonged survival. The challenge lies in determining which patients will benefit from additional therapy beyond surgical resection. The decision to add neoadjuvant or adjuvant therapy is based in large part on risk calculators, which take into consideration not only clinical tumor stage, but also patient-specific data, clinicopathologic features, such as lymphovascular invasion, and molecular profiling, such as microsatellite instability (MSI) status, KRAS, NRAS, and BRAF mutations. Surgical, adjuvant, and neoadjuvant therapeutic approaches to CRC are different for colon versus rectal cancer and are discussed separately in this chapter (Fig. 1).

STAGING

Formal CRC staging is essential to risk stratification for guiding clinicians' treatment decisions for individual patients. Guidelines from the National Comprehensive Cancer Network (NCCN) for preoperative workup of newly diagnosed CRC should include the following: colonoscopy (plus consideration of rigid proctoscopy for rectal cancer) with biopsy and pathology review; complete blood counts; chemistry profile, and carcinoembryonic antigen (CEA) serum level; computed tomographic (CT) scan of chest, abdomen, and pelvis for colon

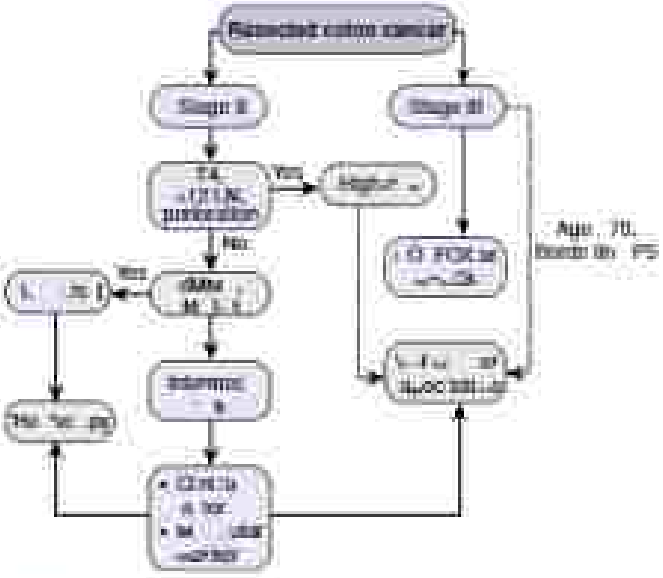

FIG. 1 Algorithm for use of adjuvant treatment for colorectal cancer. 5-FU/LV, 5-fluorouracil and leucovorin; *5-FU*, 5-fluorouracil; *cetuximab*, CM, lymph nodes; *dMMR*, deficient mismatch repair; *MSI-H*, microsatellite instability high; *PS*, performance status; *XELOX*, capecitabine and oxaliplatin.

cancer versus CT chest with magnetic resonance imaging (MRI) of the abdomen and pelvis with contrast for rectal cancer. Endorectal ultrasound for rectal cancer is no longer indicated unless a patient has contraindications to MRI, such as an incompatible pacemaker. One of the reasons preoperative staging is particularly important in rectal cancer is because it determines whether patients receive neoadjuvant radiation therapy (RT), with the goal of down staging. Positron emission tomography is not recommended (NCCN Guidelines, 2018).

CRC is staged based on the TNM staging system (T, primary tumor; N, regional lymph nodes; M, distant metastasis) adopted by the American Joint Committee on Cancer (AJCC; Table 1). In the most recent version of the *AJCC Cancer Staging Manual* (8th edition, 2016), several modifications were made to assist clinicians with prognostication, including the additional subdivision of M1c, which details peritoneal carcinomatosis as a poor prognostic factor; clarification in how tumor deposits in lymph nodes are defined; reintroduction of the "C" and "V" elements to further identify lymphatic and vessel invasion; and the identification of MSI status, KRAS, NRAS, and BRAF mutation as additional prognostic and predictive factors. This is discussed further in later sections. The importance of accurate staging is reflected in Fig. 2, which outlines the predicted 5-year survival rates.

RESECTED COLON CANCER

Adjuvant Therapy for Colon Cancer

Stage II Colon Cancer

For stage III colon cancer, the addition of adjuvant fluorouracil-containing chemotherapy regimens has demonstrated a significant survival benefit and has been established as the standard of care since a systematic review in 1988; however, the use of adjuvant chemotherapy in stage II colon cancer is controversial. Trials for adjuvant chemotherapy in stage II disease have not shown a clear benefit, although some studies have shown small increases in disease free survival (DFS), particularly in patients with high risk disease. Because most patients with III resections of stage II disease have a good predicted 5-year survival rate (see Fig. 2), an excellent benefit from adjuvant therapy would be needed to demonstrate improved overall outcomes. Additionally, stage IIC patients have a poorer overall survival (OS) at 5 years compared with stage IIIA patients; thus there may be a subset of patients who would derive improved long-term outcomes with adjuvant chemotherapy. Although randomized trials have failed to demonstrate a statistically significant improvement in OS with adjuvant chemotherapy for patients with stage II cancer, the number of patients with high risk stage II disease in these studies is likely inadequate to demonstrate benefit. For this reason, the American College of Clinical Oncology states the risks and benefits of adjuvant chemotherapy should be discussed with patients, and individualized treatment plans should be constructed.

There are three AJCC approved web-based prognostic tools which can be used to help counsel patients. To predict recurrence and survival, these tools take into consideration such factors as age, sex, race, body mass index, performance status, T category, tumor differentiation/grade, number of regional lymph nodes evaluated, number of positive regional lymph nodes, and tumor location. In addition, gene assays such as Oncotype DX Colon and Colaprint, as well as circulating DNA profiles, can help predict recurrence and response to therapy; however, they should be used with caution, as prospective trials have not demonstrated that these tests can determine which patients benefit from adjuvant chemotherapy.

High risk features for which a clinician may be more inclined to offer adjuvant therapy to a patient with stage II colon cancer include having inadequate lymph node sampling (<12 nodes in the surgical specimen), T4 stage, perforation/obstruction, poorly differentiated histology (except with microsatellite instability high [MSI-H] or mismatch repair deficiency [dMMR] as discussed later in this chapter), lymphovascular or perineural invasion, indeterminate/positive margins, high preoperative CEA levels, or mutations in KRAS/NRAS/BRAF, or loss of heterozygosity at chromosome 18q, 17p, or 8p. Additional research is ongoing to identify further genetic features that can be used to guide therapy.

Although many large studies have failed to show significant improvements with adjuvant chemotherapy in stage II disease in unselected patients, most of these studies have not separately analyzed patients with the aforementioned high risk features. For patients who are low risk or average risk, NCCN recommends discussion of observation versus clinical trial versus 6 months of adjuvant 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine, whereas for patients who are high risk, NCCN recommends discussion of clinical trial versus standard adjuvant regimens for stage III disease, including infusional 5-FU/LV and oxaliplatin (FOLFOX), capecitabine-oxaliplatin (CapeOx), infusional 5-FU/LV and oxaliplatin (FLOX), or 5-FU/LV versus capecitabine without oxaliplatin.

Tumors with a dMMR or MSI-H phenotype (approximately 20% of tumors) have an excellent prognosis in early stage disease but should not receive adjuvant 5-FU due to high rates of resistance. Pembrolizumab (PD-1 immunotherapy drug) was granted accelerated approval by the Food and Drug Administration for MSI-H dMMR tumors in 2017, after a study of 149 patients with metastatic or unresectable solid tumors (90 of whom had CRC) had a response rate of 34.2% with sustained response at 6 months in 78% of responders.

Several studies (Table 2) have helped guide current recommendations. A 2011 analysis of SEER (Surveillance, Epidemiology, and End Results) data, which included 24,047 patients with stage II cancer, of whom 25% had one or more poor prognostic features and 38% received chemotherapy, did not demonstrate a survival advantage with adjuvant therapy regardless of presence of risk factors. The study did, however, demonstrate benefit for stage III disease.

The United Kingdom QUASAR (Quick And Simple And Reliable) trial demonstrated that patients with stage II colon cancer who are not selected based on risk have a 3% benefit in 3-year DFS and OS with bolus 5-FU/LV (± levamisole) as adjuvant chemotherapy.

The Intergroup Analysis was a meta-analysis with multiheart, six analysis adjusted for T stage, histologic grade, and nodal status, designed to evaluate the benefit of adjuvant 5-FU based chemotherapy, which demonstrated a statistically significant improvement in 5-year DFS favoring chemotherapy (72% vs 72%), without a statistically significant difference in OS (81% vs 76%).

The International Multicenter Pooled Analysis of Colon Cancer Trials (IMPACT) was a meta analyses that assessed the benefit of adjuvant fluoropyrimidine based chemotherapy to patients with resected stage II colon cancer, which did not support the use of 5-FU/LV to all patients with stage II colon cancer.

The Multicenter International Study of Oxaliplatin/5-FU/LV in Adjuvant Treatment of Colon Cancer (MOSAIC) showed the addition of oxaliplatin affected a small survival benefit for stage II patients with high risk features, but there was no overall improvement in outcome with FOLFOX.

The Ontario group analysis compared 5-FU/LV versus observation for stage II colon cancer by analyzing 37 trials and 11 meta-analyses, and determined chemotherapy was associated with a small but significant absolute improvement in DFS (5% to 10%) without a statistically significant difference in OS (risk ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.02; P = .07).

Additional key trials are summarized in Table 2. A meta analysis of chemotherapy by portal vein infusion has also shown a benefit to DFS and OS for stage II patients, however results have been difficult to reproduce.

TABLE 1 TNM Criteria and Staging of Colorectal Cancer

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intraepithelial carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissue
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

Definition of Regional Lymph Nodes (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: • subserosa • mesentery • or nonperitonealized pericolic, or perirectal mesenteral tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis by imaging, etc., no evidence of tumor in distant sites or organs (this category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Continued

TABLE 1 TNM Criteria and Staging of Colorectal Cancer—cont'd

AJCC Prognostic Stage Groups			
When T is...	And N is...	And M is...	T for the stage group is...
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1–N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

From Amin M, Edge S, Greene F, et al. (Eds.). AJCC Cancer Staging Manual. Vol. 8. New York: Springer; 2017.

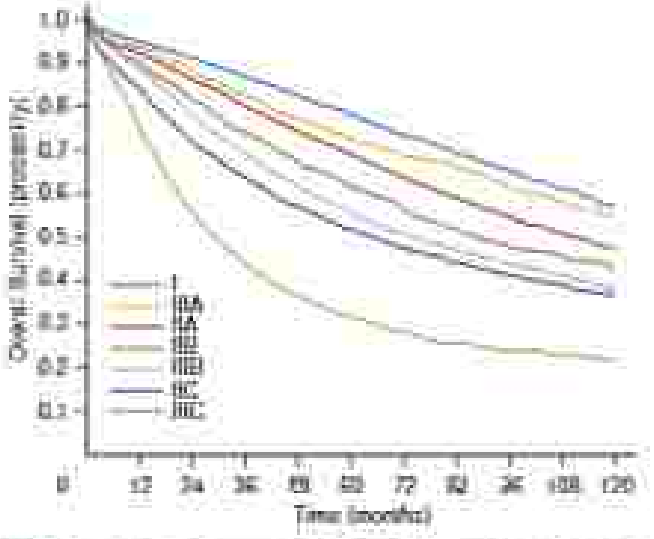

FIG. 1 American Joint Committee on Cancer 7th edition overall survival by stage.

Stage III Colon Cancer

In stage III colon cancer, adjuvant chemotherapy has been the standard of care since 1990, with several large randomized clinical trials showing benefits in both OS and DFS (Table 3). The addition of adjuvant chemotherapy to surgical resection in patients with stage III colon cancer leads to an approximately 30% reduction in recurrence and 22% to 32% reduction in mortality.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 was conducted between November 1977 and February 1983. It randomly assigned 1156 patients to semisynchronous 5-FU (MOF) versus observation, and was the first trial to demonstrate 5-year OS benefit for adjuvant therapy in colon cancer.

Unfortunately, both the MOF regimen and adjuvant 5-FU plus levamisole regimen, a regimen with benefit demonstrated by the North Central Cancer Treatment Group (NCCTG) trial, had unacceptable side effects.

The NSABP C-03 trial, along with other smaller studies, demonstrated inferiority of MOF to 5-FU/LV regimens. Other studies examined method of delivery, and although continuous infusional 5-FU did not demonstrate superiority over bolus 5-FU in first trials, it was shown to have a more favorable side effect profile. Subsequently, oral fluoropyrimidine (capecitabine), which is metabolized to fluorouracil was demonstrated to be noninferior to 5-FU/LV.

The benefit of the addition of FOLFOX was demonstrated by the MOSAIC trial (n = 2246), in which the 5-year DFS was significantly higher (73% vs 67%, hazard ratio [HR], 0.8), although febrile neutropenia, peripheral neuropathy, and grade 3 to 4 diarrhea were also more common. The benefit for patients with stage III disease was significantly higher than for those with stage II disease, as discussed in the previous section.

Additional trials examined different 5-FU/LV + oxaliplatin regimens. The NSABP U-07 trial utilized FLOX (weekly bolus 5-FU/LV + oxaliplatin), which was more effective than nonoxaliplatin regimens, but more toxic than FOLFOX. XELOX has also been shown to be inferior to FOLFOX in the setting of metastatic disease.

When capecitabine was combined with oxaliplatin (XELOX or CapeOx) and compared to bolus 5-FU/LV, XELOX demonstrated significantly improved DFS (HR for DFS, 0.80; 95% CI, 0.69 to 0.93) after a median follow-up of 7.6 months.

Irinotecan is another drug that was studied as an additive to 5-FU/LV; however it failed to demonstrate a benefit in resected stage III

TABLE 2 Clinical Trials Informing Current Recommendations for Adjuvant Therapy

Trial	Stage (% Patients)	Regimen	Disease-Free Survival (%)	*P* Value; HR (95% CI)	Overall Survival (%)	*P* Value; HR (95% CI)
X-ACT (N = 1987)	III	Mayo	3-year: 63.8	.525; 0.87 (0.75–1.02)	N/A	N/A
		Capo	3-year: 64.6			
MOSAIC (N = 2246)	II/III (40/60)	FA/5FU2	—	<.001; 0.77 (0.65–0.90)	6-year: 76.0	.0660 (0.75–1.00)
		FOLFOX	—		6-year: 78.5	
	II	FA/5FU2	—	.82 (0.60–1.13)	6-year: 86.8	.9061 (0.75–1.61)
		FOLFOX	—		6-year: 86.9	
	III	FA/5FU2	—	.25 (0.62–0.89)	6-year: 68.7	.023 (0.65–0.97)
		FOLFOX	—		6-year: 72.9	
NSABP C-07 (N = 2407)	II/III (29/71)	RP	3-year: 71.6	<.004 (0.67–0.93)	6-year: 77.5	.86 (0.72–1.01)
		FLEX	3-year: 76.5		6-year: 78.3	
XELOXA (N = 1886)	III	RP/Mayo	3-year: 67.0	.0045 (0.68–0.93)	N/A	N/A
		XELOX	3-year: 71.0		N/A	
QUASAR (N = 3239)	II	5-FU/LV + levamisole vs observation	RR risk of recurrence 0.78	.001	5-year: 3%–4% absolute benefit; RR of death, 0.82	.008
Intergroup Analysis (N = 3382)	II/III	LV- or levamisole-modulated 5-FU	76%	.049	83%	.115
		Surgery only	72%		76%	
IMPACT I (N = 1493)	II/III (56/44)	5-FU and folinic acid	5-year: 79%		5-year: 88%	
		Surgery only	5-year: 76%		5-year: 80%	
IMPACT 2 (N = 1016)	II (2340)	Surgery plus 5-FU and leucovorin	5-year: 76%	1.18–3.83	5-year: 82%	
		Surgery only	5-year: 73%		5-year: 80%	
Intergroup Trial INT 0089 (N = 3239)	High-risk II/III (28/80)	5-FU with LV and/or levamisole vs surgery only			5-year: 55%–72%	
SEER 2011 (N = 43,932)	II/III (58/42)	Any adjuvant chemotherapy (20% of patients with stage II; 57% of patients with stage III) vs surgery only			5-year: Stage III: 44% Stage II: no poor prognostic features: 69%; any poor prognostic features: 57%	5-year: Stage III: HR, 0.64 (0.60–0.67) Stage II: no poor prognostic features: HR, 1.02 (0.84–1.25); any poor prognostic features: HR, 1.03 (0.94–1.13)

5-FU, 5-fluorouracil; Capo, capecitabine; CI, confidence interval; FOLFOX, bolus 5-FU/LV plus oxaliplatin; FOLFOX4, bolus/infusional 5-FU/LV plus oxaliplatin; HR, hazard ratio; IMPACT, International Multicenter Pooled Analysis of Colon Cancer Trials; LV, leucovorin; MOSAIC, bolus/infusional 5-FU/LV regimen; Mayo, Mayo Clinic bolus 5-FU/LV regimen; MOSAIC, Multicenter International Study of Oxaliplatin/5-FU/LV in Adjuvant Treatment of Colon Cancer; NA, not available; NSABP, National Surgical Adjuvant Breast and Bowel Project; QUASAR, Quick And Simple And Reliable; RR, Roswell Park bolus 5-FU/LV regimen; RR, relative risk; SEER, Surveillance, Epidemiology and End Results; X-ACT, Xeloda in Adjuvant Colon Cancer Therapy; XELOX, capecitabine plus oxaliplatin; XELOXA, Roche Study NO.ML18048; XELOX + Oxaliplatin.

TABLE 3 Randomized Prospective Clinical Trials Comparing Adjuvant Treatment

Trial	Stages Included	Regimens	No. of Patients	Disease-Free Survival	*P* Value	Overall Survival	*P* Value
NSABP C-01	II, III	No adjuvant therapy	344		5-year = .32		5-year = .85
		MOF	379				
		BCC	383				
NSABP C-02	All stages	No adjuvant therapy	661	44%	4-year = .02	73%	4-year = .07
		Portal vein infusion of 5-FU	577	74%		81%	
INT-0035	III	No adjuvant therapy	315	<40%	3-year = .0001	47%	3-year = .0007
		Levamisole	310	<40%		49%	
		5-FU plus levamisole	304	>40%		68%	
NCCTG and Mayo Clinic	II, III	No adjuvant therapy	155		3-year:		3-year:
		Levamisole	130		= .05		= .12
		5-FU plus levamisole	136		= .003		= .09
NSABP C-03	II, III	MOF	524	68%	3-year = .0004	77%	5-year = .003
		5-FU/LV	523	73%		84%	
NSABP C-04	II, III	5-FU/LV	680	5-year: 62%		5-year: 78%	
		5-FU plus levamisole	681	60%		72%	
		5-FU/LV plus levamisole	686	59%		75%	
NSABP C-05	II, III	5-FU/LV	1088	69%	4-year = .34	80%	4-year = .41
		5-FU/LV plus α interferon	1088	70%		81%	
INT-0089	II, III	5-FU/LV Mayo Clinic	908	62	5-year = .05	66	5-year = .05
		5-FU/LV Roswell Park	910	58		66	
		5-FU plus levamisole for 6 months	892	55		60	
		5-FU plus levamisole for 12 months	780	49		58	

From Gen C, Pfister DG. Adjuvant Systemic Therapy in Stage II and III Colon Cancer. 2014. UpToDate. https://www.uptodate.com/contents/colorectal-cancer-beyond-pathogenesis-to-treatment/adjuvant-systemic-therapy-in-stage-ii-and-iii-colon-cancer

5-FU, 5-fluorouracil; BCC, bacillus Calmette-Guérin; INT, National Cancer Institute–sponsored cancer clinical trials; INTERGROUP, cooperative groups; IV, intravenous; MOF, semustine, vincristine, 5-FU; MOSTC, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project.

disease. CALGB 89803 was a randomized prospective trial that compared bolus 5-FU/LV with or without irinotecan. The group treated with the addition of irinotecan experienced significantly more side effects without demonstrating a survival benefit.

Although targeted agents such as bevacizumab and cetuximab have demonstrated a benefit in OS for metastatic disease, benefits in DFS or OS have not been demonstrated when used as adjuvant therapy for stage III disease. Panitumumab may be considered for MSI-H 4MMF disease, as discussed in the prior section.

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration analyzed a randomized trials of 6 versus 3 months of oxaliplatin-based adjuvant therapy. Results suggested that 6 months of therapy remains the standard of care for high risk cancers; however, in light of the small difference in DFS (absolute difference 0.9% at 3 years) but significantly lower rates of oxaliplatin neuropathy, shorter duration of therapy may be considered for low risk disease (T1–T3, N1).

The current recommendation for adjuvant therapy for stage III colon cancer is 4 to 6 months of an oxaliplatin containing regimen such as FOLFOX or XELOX. For patients with significant comorbidities, peripheral neuropathy, or age greater than 70 years, 6 months of infusional 5-FU/LV or capecitabine without oxaliplatin can be considered. Unlike rectal cancer adjuvant regimens, radiotherapy is generally not indicated for colon cancer.

As new biomarkers and predictors of recurrence/prognosis are discovered, and as more antineoplastic agents are developed, treatment guidelines will continue to be updated, likely leading to more highly individualized cancer therapy algorithms.

NEOADJUVANT AND ADJUVANT THERAPY FOR RECTAL CANCER

Although rectal cancer has similar pathogenesis and molecular phenotypes to colon cancer, local recurrence rates in rectal cancer are significantly higher than in colon cancer. This discrepancy may be secondary to both differences in tumor factors, such as differences in vasculature and lymphatic drainage patterns associated with the anatomic location, and surgical factors, such as completeness of excision of mesorectum and extent of lymphadenectomy.

As many as 10% of patients with T1–T2 rectal cancer, 15% to 20% of patients with T3N0 rectal cancer, and 45% to 65% of patients with node positive T3–T4 rectal cancer will experience local recurrence with standard resection without neoadjuvant or adjuvant therapy. These rates can be decreased with total mesorectal excision (TME) to 10% in stage II and 17% with stage III. Local recurrence rates can be further decreased with chemoradiotherapy.

This emphasizes the importance of appropriate resection (i.e., TME) in conjunction with neoadjuvant and/or adjuvant therapy for reducing the risk of local recurrence and its associated morbidity (pain, bleeding, obstruction, abscess, fistulas) in addition to controlling distant metastasis.

Adjuvant Therapy

Although neoadjuvant therapy is now the standard of care (as discussed in the next section), initial rectal cancer studies attempting to reduce local recurrence focused on adjuvant pelvic RT with or without chemosensitization. Currently, indications for consideration of surgical resection without neoadjuvant therapy include proximal cT1N0 tumors for which RT may not be recommended after TME, or a tumor with borderline cT2 versus cT3 status on preoperative imaging.

One of the main trials which established combined chemoradiation as a key to therapy was the Gastrointestinal Tumor Study Group trial, in which 227 patients were randomly assigned to observation, postoperative RT alone, chemotherapy alone, or postoperative RT with concurrent chemotherapy. In this trial, recurrence rates were significantly reduced with combined chemoradiotherapy (33%) versus observation (59%), chemotherapy alone (66%), or radiotherapy alone (48%). OS was longer for combined chemoradiotherapy as well, although it did not reach statistical significance.

Two widely utilized adjuvant chemoradiotherapy regimens were 2 months of chemotherapy, 6 weeks of concomitant chemoradiation (5-FU/LV or capecitabine for radiosensitization and radiation with 5 daily fractions of 1.8 Gy per week up to a total of 45 Gy), followed by 2 additional months of chemotherapy versus 4 months of chemotherapy followed by 6 weeks of concomitant chemoradiation.

Neoadjuvant Therapy

Neoadjuvant therapy with 5-FU as a radiosensitizer was established as standard of care for stage II and III rectal cancer after a large randomized trial (The German Rectal Cancer Trial) was published, which compared continuous infusion 5-FU plus radiation after TME versus before TME for T3–T4 or node positive rectal cancer. This study demonstrated a reduction in local recurrence (13% vs 6% at 5 years) and toxicity (both acute and chronic) with a higher rate of sphincter preservation ($P = .006$) for neoadjuvant therapy.

The only definitive indication for neoadjuvant therapy is a T3–T4 tumor, but relative indications include clinically evident node-positive disease, distal rectal tumors, and evidence of mesorectal fascial invasion on preoperative imaging.

Currently, the majority of United States cancer centers utilize a combined modality approach to neoadjuvant therapy with radiosensitizing chemotherapy (5-FU/LV or capecitabine) and concurrent radiotherapy (50.4 Gy total radiation dose over the course of 5 to 6 weeks), known as 50.4/5FU/CMT, followed by surgical resection 5 to 8 weeks after completion of chemoradiotherapy. Although still controversial, the majority of patients also receive adjuvant chemotherapy similar to adjuvant therapy for resected colon cancer (e.g., 6 months of FOLFOX, 5-FU/capecitabine, or FLOX).

Although both adjuvant and neoadjuvant combined modality chemoradiation can cause acute (e.g., grade 3–4 diarrhea, proctitis, cystitis, bone marrow suppression) and long-term complications (e.g., sexual dysfunction, sacral fractures), neoadjuvant therapy seems to be better tolerated without creating additional perioperative morbidity/mortality risks. Additional benefits of neoadjuvant as opposed to adjuvant chemoradiation include increased rates of sphincter preservation, decreased local recurrence, and lower rates of anastomotic strictures and chronic enteritis.

Owing to the apparent benefits of neoadjuvant therapy, studies began analyzing the advantages of total neoadjuvant therapy (TNT; preoperative systemic chemotherapy in combination with chemoradiation) compared with the traditional approach of preoperative chemoradiation and postoperative adjuvant chemotherapy in patients with locally advanced (T3/4 or node positive) rectal cancer. In one retrospective cohort analysis, in which 308 patients treated with TNT were compared with 328 patients treated with neoadjuvant chemoradiation with planned adjuvant chemotherapy, patients in the TNT cohort received greater percentages of the planned systemic chemotherapy, had higher rates of complete pathologic response (in patients who underwent surgery) and sustained clinical response (in patients who did not undergo surgery) (36% for TNT vs 21%), and were more likely to have temporary ileostomy reversed within 15 weeks of proctectomy. This study supported NCCN guidelines that categorize TNT as a viable treatment strategy for rectal cancer, but long-term follow-up is still needed to determine whether TNT leads to improved OS. Additionally, researchers proposed that given its high CR rate, TNT may facilitate nonoperative treatment strategies aimed at organ preservation.

Given patients whose tumors respond to chemotherapy and radiation are more likely to be cured than those whose tumors do not, controversy exists as to whether surgery is necessary in patients with pathologic complete response to neoadjuvant therapy, or whether watchful waiting is a reasonable option. One small study demonstrated 40 of 53 patients who had a complete clinical response after 6 weeks of chemoradiation (determined by CT/MRI 6 weeks after treatment with no metastases and complete tumor regression with negative tumor site biopsies), who underwent observation had only a 13.5% rate of local recurrence at 4 years (95% CI, 3.9% to 24.3%). Authors of the study concluded watchful waiting after high dose chemoradiotherapy without TME may not compromise outcomes in selected patients. Additional large studies, including a phase II randomized trial that opened for accrual in January 2006, evaluating 3-year DFS in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy and TME or nonoperative management, are ongoing to further assess the viability of a watchful waiting approach.

Because of the undesirable side effects from radiation, several small studies have also assessed the use of neoadjuvant chemotherapy with the selective use of radiotherapy and demonstrated promising results. In one such study, 30 of 32 patients had good clinical response after 6 cycles of FOLFOX + bevacizumab and went on to TME without chemoradiation; at 4 years, local recurrence rate was 0 and DFS was 84% (95% CI, 67% to 94%). Currently, a large phase III randomized prospective trial (PROSPECT N0398) is ongoing to assess chemotherapy alone versus chemotherapy plus RT in treating patients with locally advanced rectal cancer (T2N1, T3N0, T3N1) undergoing surgery. Primary outcome measures include R0 resection rate, DFS, and time to local recurrence. Secondary outcome measures include rate of pathologic complete response, OS, adverse event profiles, and rates of receiving preoperative or postoperative 5FU/CMT. Event monitoring of patients will continue up to 8 years post-randomization.

Endorectal brachytherapy/high dose rate brachytherapy (HDR) are alternative methods of delivering radiation that are being investigated. Endorectal brachytherapy is ideal for patients with mid-distal rectal cancers not involving the anal sphincters and lymphadenopathy confined to the mesorectum, as it is able to deliver higher doses of radiation to the tumor and mesorectum with less chronic toxicity. Typically, this treatment is delivered once a week for a total of 5 weeks, with concurrent capecitabine (oral 5-FU) chemotherapy. Currently, some centers advocate for use of HDR for patients with locally persistent or recurrent disease after chemoradiation who decline to undergo or are unfit for abdominal resection. In addition, a phase I dose escalation study is underway to evaluate the safety of endorectal brachytherapy with concurrent capecitabine or 5-FU in the management of locally recurrent/residual rectal cancer in patients who have received pelvic external beam radiation with or without chemotherapy.

Just as in colon cancer, there is clear heterogeneity in tumor responses to treatment despite being of the same stage. Therefore studies seeking to identify molecular profiles and biomarkers that are better able to predict which patients will benefit from specific therapies are ongoing.

SURVEILLANCE

Despite the ever-evolving therapies for CRC, distant and local recurrence rates can be as high as 40%, with the majority of recurrences occurring in the first 2 years after completion of initial definitive therapy. Early identification of recurrence or new primary tumors may allow for potentially curative therapy (surgical resection or systemic therapy) and improved outcomes. For this reason, appropriate aggressive surveillance is imperative. Although there are subtle differences among professional organizations, most guidelines are generally in line with the NCCN guidelines, 2018.

For patients with stage I colon or rectal cancer, recommended surveillance is colonoscopy 1 year after resection, with subsequent colonoscopies dependent on findings (as detailed later in this section). For patients with rectal cancer who underwent transanal local excision only, the addition of proctoscopy with endoscopic ultrasound scan or MRI with contrast is recommended every 3 to 6 months for the first 2 years, then every 6 months until year 5.

For patients with stages II through IV colon or rectal cancer, surveillance recommendation is history and physical examination with serum CEA (only if patient is a candidate for further intervention) every 3 to 6 months for 2 years, then every 6 months until year 5; colonoscopy within 1 year of resection (within 3 to 6 months if not completed preoperatively) and subsequent colonoscopies dependent on findings (as detailed later in this section); and CT chest, abdomen, and pelvis, with frequency dependent on stage at diagnosis: for stage II or III, perform every 6 to 12 months for 5 years versus for stage IV, perform every 3 to 6 months for 2 years, then every 6 to 12 months until year 5. Positron emission tomography/CT is not indicated for routine surveillance.

For screening colonoscopies following resection, if there is no advanced adenoma, repeat colonoscopy in 3 years, then every 5 years; if an advanced adenoma is present, repeat colonoscopy in 1 year.

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Management of Colon Polyps

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The adenoma to carcinoma progression is well established. Colonic screening programs to remove adenomas have been shown to decrease the incidence of adenocarcinoma. The great majority of colon polyps are smaller than 0.5 cm and are readily removed endoscopically using either a cold biopsy forceps or a snare. Sessile polyps smaller than 2 cm and larger pedunculated polyps can usually be removed with a hot snare; for sessile polyps, a saline lift before snare application is advised. Larger sessile polyps pose difficulties and challenges in regard to endoscopic treatment. This chapter concerns the management of these larger sessile polyps.

There are few areas of medicine where the treatment of a condition in first world countries varies as widely as for large sessile benign polyps of the colon. Large polyp management is also an area in which there is a great deal of innovation occurring that has the potential to notably facilitate the removal of these lesions. In Japan and much of the Far East, these lesions are routinely removed via the technically challenging endoscopic submucosal dissection (ESD) technique. This technique permits en bloc removal of the mucosal lesion with a margin of normal mucosa as well as much of the submucosa beneath the polyp. Of note, there is also a growing body of data that suggests that en bloc removal of a superficial invasive cancer (<1000 µm invasion) via ESD constitutes definitive treatment. En bloc removal allows for a more thorough pathologic evaluation and margin assessment. Our position is that ESD is superior to en bloc resection, to the gold standard endoscopic polypectomy method for large flat polyps.

Endoscopic mucosal resection (EMR), which is most commonly used in the United States, removes most large polyps in a piecemeal manner with a snare. By repetitively applying the snare, large polyps can be removed. Critically important to both ESD and EMR methods is the establishment of a "lift" by injecting saline or other solution into the submucosal layer beneath the lesion to increase the thickness of the bowel wall, which decreases the risk of perforation.

In the West, particularly the United States, where the penetration of ESD methods has been limited, the vast majority of these lesions (about 28,000 cases per year) are dealt with via segmental colorectal resection with its attendant morbidity and mortality (approximately 1.5%, 420 patients/y). In contrast, the mortality associated with ESD is about 1 in 10,000 cases. Also, the cost of ESD is a fraction of that of a segmental colectomy. In the United States, there is a considerable effort underway in both the gastroenterology and colorectal surgery fields to teach and popularize ESD and advanced polyp removal methods. These efforts coincide with the introduction of a number of innovative devices designed to facilitate en bloc removal (e.g., snare cautery devices, improved needle knives) as well as the release of better lift solutions. The goal is to avoid colectomy (notably higher costs, morbidity, and mortality) for benign colon polyps and for SM1 superficially invasive colon cancers. It is a very interesting time in this field.

CHALLENGE OF LARGE FLAT POLYPS

The problem posed by large flat benign lesions is that the bowel wall is thin and there is a considerable risk of perforation when an attempt is made to remove these polyps with a standard snare, which simply burns through the encircled and snare-entrapped tissue. For these reasons, EMR methods were developed and introduced. As mentioned, central to advanced colon polyp removal methods is the creation of a mucosal lift, which increases the thickness of the submucosal layer of the bowel wall by injection of saline or another solution. A perforation is far less likely when a snare or needle knife is used at the mucosal surface of a lifted area because the deep muscle and serosa are a good distance away. EMR permits piecemeal removal of large polyps with repeated application of a snare to a "lifted" area. Although large polyps can be removed via EMR only, a limited pathologic evaluation can be carried out because the pathologist receives disarticulated pieces of the polyp that do not permit lateral margin assessment. Largely in response to this issue, ESD methods were developed and introduced in Japan and have become the gold standard for the treatment of large sessile benign polyps.

Unlike snare polypectomy and EMR, with ESD the polyp is "surgically excised" with a needle knife by progressively scoring, in segments, the mucosal surface around the lesion and then dividing the submucosal attachments below the lesion. Ideally, an en bloc excision is achieved. When performing ESD, to cut the tissue the endoscopist must move the scope tip with a hot needle knife extended in a coordinated and controlled manner. This is in contrast to snare polypectomy or cold biopsy, which is done with the scope tip held stationary while the forceps or snare is pushed out of or pulled into the scope. Learning to finely control the moving scope tip is a challenging task. A training strategy and much practice are needed to acquire these skills.

MUCOSAL LIFT

The mucosal lift increases the thickness of the submucosal layer of the bowel wall. The lift is established via sclerotherapy needle or needle-less high-pressure injection device. The sclerotherapy needle (either 23 or 25 gauge) method is most commonly used. There are two drawbacks to this method. First, it is difficult to puncture the mucosa because it has a relatively "loose" surface layer that slides away from the needle; a hard push is most always needed to breech the mucosa and, invariably, the needle tip ends up deep in the wall (muscularis propria or submucosa layer) or transmural. Because of the deep starting position of the sclerotherapy needle, it is possible to expand the submucosal or muscularis propria space, which will not facilitate submucosal dissection. Care must be taken to ensure a superficial submucosal lift is made and not a deep wall lift. To decrease the chances of generating a deep wall lift, position the scope tip such that the scope is as close to and as tangential to the polyp bearing side of the bowel wall as possible to ensure that the sclerotherapy needle enters the wall at a minimal angle. This increases the chances of keeping the needle in the submucosal layer. A more acute angle of entry is likely to put the needle tip deeper in the wall. The second downside to the sclerotherapy needle method is that each needle puncture leaves a mucosal defect through which lift fluid can leak out. The alternative to the sclerotherapy needle approach is needleless high-pressure injection.

To generate a lift without puncturing the mucosa, the blunt tip of the needleless high-pressure injection tubing is advanced and positioned so that it touches the mucosal surface at a 90 degree angle. Next, a lift is established by pumping the saline or other lift solution through the tubing either by hand (gun-like device similar to through the channel endoscopic balloon dilating devices) or electric foot controlled pump. Because there is no actual puncture of the mucosal surface, this method is not likely to result in a deep

wall lift (expansion of the muscularis propria or submucosal layer). Also, because the hole made in the mucosal surface is very small, there is little or no leakage of lift solution. Of note, the electric pump can be paired with an ESD capable electrosurgical generator such that a hollow needle knife can be used. This knife pumps saline into the submucosa via the central hollow channel either above or at the same time the needle knife is activated, thus, "debulking" the lift as the knife is used.

A variety of different solutions have been used to lift the mucosa, including normal saline (+ epinephrine), sodium hyaluronate, albumin, 10% glucose, glycerol, hypromellose (ophthalmic solution, Akorn Company), and Viscoat (Alcon Pharmaceuticals). Usually, methylene blue or other dye is added to the solution to facilitate identification of the submucosal layer. The duration of the lift is a key attribute; the longer the duration, the better. A number of studies have compared the various solutions; however, the parameters and solutions considered varied widely and thus there is no clear consensus regarding the best lift solution. Hyaluronate solutions have been widely used in Japan but are not commercially available in the United States. Several new lifting solutions are currently in development.

Unfortunately, incising the mucosa and dividing the submucosal fibers promotes leakage of lift solution from the wall and decreases lift duration. Periodically, the lift needs to be reestablished with additional bowel wall injections. It gets more difficult to regenerate the lift as the resection progresses because the submucosal plane is widely exposed. Maintaining a substantial lift is critical to ESD and EMR.

BASIC EMR

The use of a lift agent after establishment of a mucosal lift to remove a polyp constitutes an EMR. In expert hands, the en bloc resection rate with EMR methods is between 33% and 57%. Most often, full removal requires multiple applications of the snare, which means that the lesion is removed piecemeal. The lift decreases the chances of perforation. A variety of snares available: large or small, flexible or stiff, and round or hexagonal in shape. Some EMR proponents do not routinely establish a mucosal lift before snare application. This approach is hard to defend; the addition of the lift facilitates the safe performance of the polypectomy. The snared tissue is retrieved via suctioning through the scope into a trap, pulling larger fragments out of the anus after applying suction, a basket net, or a wire basket. Endoscopic clips can be used to bring together the mucosal edges of small and moderate-sized mucosal defects after EMR. The EMR perforation rate in two decent-sized studies was 0% to 1.2%. The polyp recurrence rate is between 14% and 21%. The rate of bleeding complications ranges from 3.1% to 11.3%.

ESD

ESD is performed with a needle knife that consists of an insulated sheath containing a wire or other metal tip that can be advanced several millimeters from the sheath's edge. The knife is connected to a specialized electrosurgical generator that can generate a variety of different currents to either mark or incise the mucosa or cut the submucosal fibers. A plastic hollow dissection cap is attached to the endoscope tip so that cap dissection can be performed, if desired. The endoscopist must be able to finely control the moving scope tip with the knife protruding to cut tissue. The patient should be positioned so that the polyp is in the "up" position; this allows gravity to retract the partly detached polyp downward. At times, considerable torque needs to be applied to the scope shaft to obtain the desired orientation between the scope and the polyp. The steps involved with ESD are the following: (1) initial marking of the outlines of the planned excision with a series of superficial mucosal spot burns, (2) incising 15% to 20% of the mucosal circumference, (3) cutting the submucosal fibers beneath the polyp adjacent to the incised mucosa, (4) inserting the scope tip with plastic cap affixed to allow cap dissection (optional), (5) scoring of additional mucosal margins and then dividing adjacent submucosal fibers, and (6) repeating these steps until the polyp has been excised and fully detached (Fig. 1). Depending on the size of the polyp and the technique of the endoscopist, cap dissection may be used during the case. Cap dissection refers to inserting the scope tip (with cap in place) into the submucosal layer and pushing forward, which stretches the submucosal fibers and "presents" them to the needle knife (Fig. 2).

When ESD is used, the en bloc resection rate is 84% to 92%, rate of bleeding complications is 1.5% to 3.7%, perforation rate is 2% to 10%, and recurrence rate is 0% to 2% in expert hands.

HANDLING OF THE POLYPECTOMY WOUND

Some polypectomy wounds lend themselves to closure with through-the-channel endoscopic clips that draw the mucosal edges together. Larger "bear claw" type clips can also be applied. There is an endoscopic suturing device that is affixed to the scope tip that can be used to close partial or full thickness colon wall defects; this innovative tool, however, has a notable learning curve. Provided the muscularis propria is intact and the bowel wall is healthy, it is reasonable to leave the mucosal defect open. If ESD/EMR is done in the operating room setting and the patient has consented, a perforation can be closed or the bowel wall mitigated laparoscopically after the endoscopic polypectomy has been finished (see the following section).

OPERATING ROOM SETTING FOR ESD AND LAPAROSCOPIC EVALUATION POSTPOLYPECTOMY

Incorporating ESD into one's practice is a challenge. The necessary skill set needs to be acquired (see the "Training" section) and a general resection strategy chosen (e.g., proximal to distal, distal to proximal). One approach, which we use, is to perform these cases in the operating room with the understanding that if a colonic ESD is completed, a laparoscopic evaluation will be done immediately after (under the same anesthesia) to assess the integrity of the bowel wall and, if necessary, suture repair or imbricate the bowel wall. In the case that endoscopic removal of the polyp was judged not feasible or failed, an immediate laparoscopic segmental colectomy would be performed. Of course, the patient needs to have signed a very broad consent and fully understand that the endoscopic polypectomy, even if successful, will be followed by a laparoscopy. Only carbon dioxide gas should be used for colonic insufflation via the colonoscope since it is fully absorbed within 15 minutes, thus permitting laparoscopy under the same anesthesia.

The surgical endoscopist needs to be willing to use a combination of ESD and EMR methods early on to destroy the lesion. Although en bloc resection is the goal, a colectomy can be avoided via EMR. In some instances, the polyp turns out to best dealt with via EMR (large, partly pedunculated purely sessile lesions or smaller lesions that do not warrant ESD). Regardless of whether an ESD or EMR is carried out, a follow-up colonoscopy 3 to 6 months later is advised to check the site for a persistent or recurrent polyp.

NEW TECHNOLOGY

This is an exciting time because a number of new devices and instruments designed to facilitate endoscopic polypectomy are being introduced and assessed. Two new devices allow the

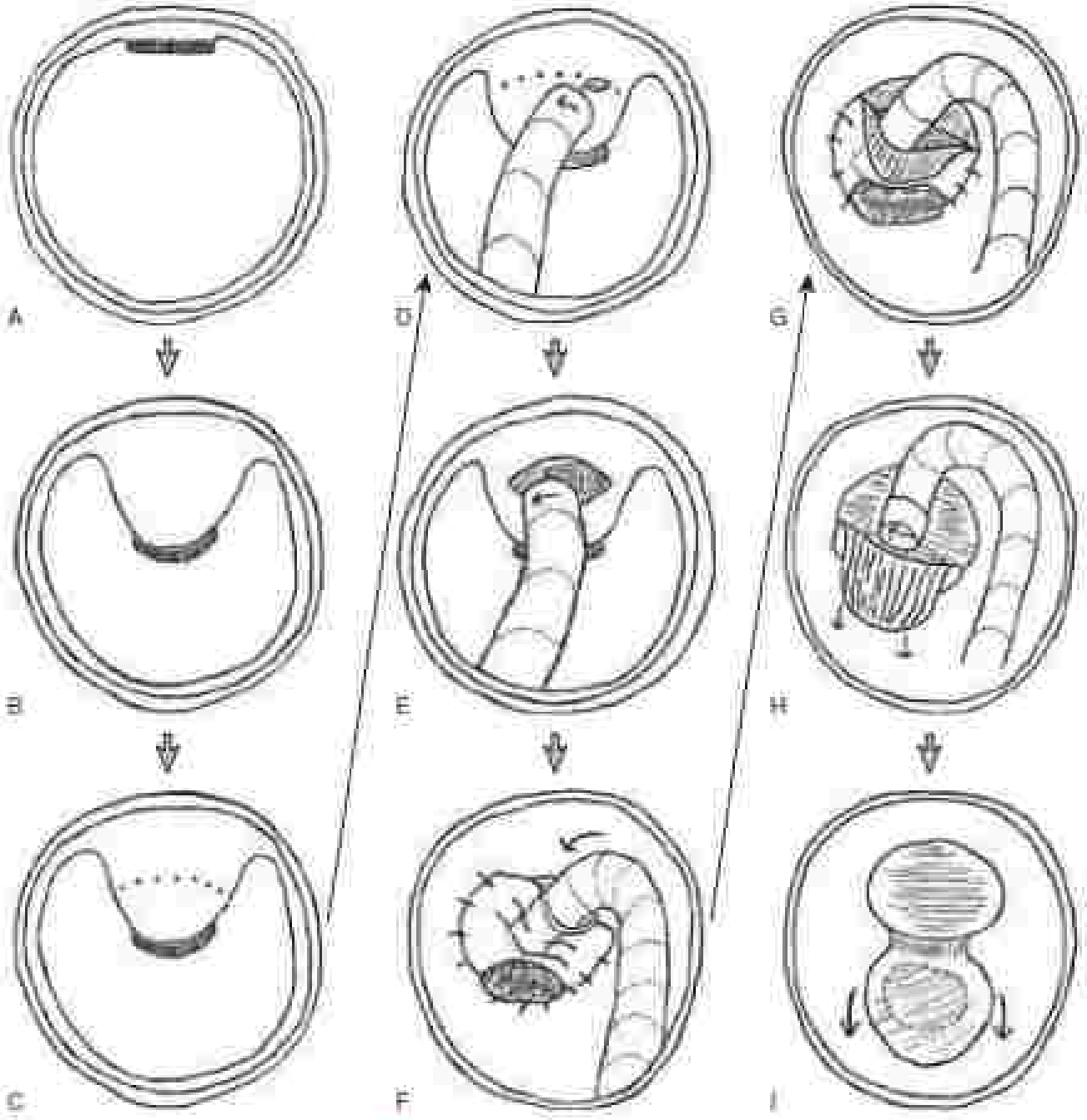

FIG. 1 (A–I) Endoscopic submucosal dissection.

endoscopist to establish a therapeutic work zone in the polyp-bearing segment. Presently, both are mainly being used and assessed for left-sided polyps. The colonoscope is passed through both flexures before insertion into the patient. The Cuscuff device (Cuscuff Corporation) has two separate collapsed balloons that are part of the cuffrube located close to the scope tip. When the scope is at the level of the polyp and the scope oriented tangential to the polyp, the balloon closest to the scope tip is advanced into the colon until it is well proximal to the polyp, at which point it is inflated. Next, the second, more distal, balloon, situated along the scope shaft close to the tip, is also inflated. This locks the colonoscope in position and creates a zone maintained by the balloons as well as by the insufflated carbon dioxide or air. This device frees the surgeon from having to maintain the torque on the scope shaft, which facilitates the ESD or EMR.

The Boston Scientific device (for sigmoid or rectal lesions only) is a series of plastic tube struts and plastic flat, which, when extended beyond the scope tip create a "therapeutic zone" that supports about two-thirds of the colon circumference to the area surrounding the lesion (the polyp sits in the open part of the colon wall). When deployed, a stable working space is created. Two instrument channels run along the outside of the device through which hollow tubes can be placed that have a 30- or 45-degree angled distal end. Tissue graspers can be inserted through these tubes. The angled end of the cuffrube directs

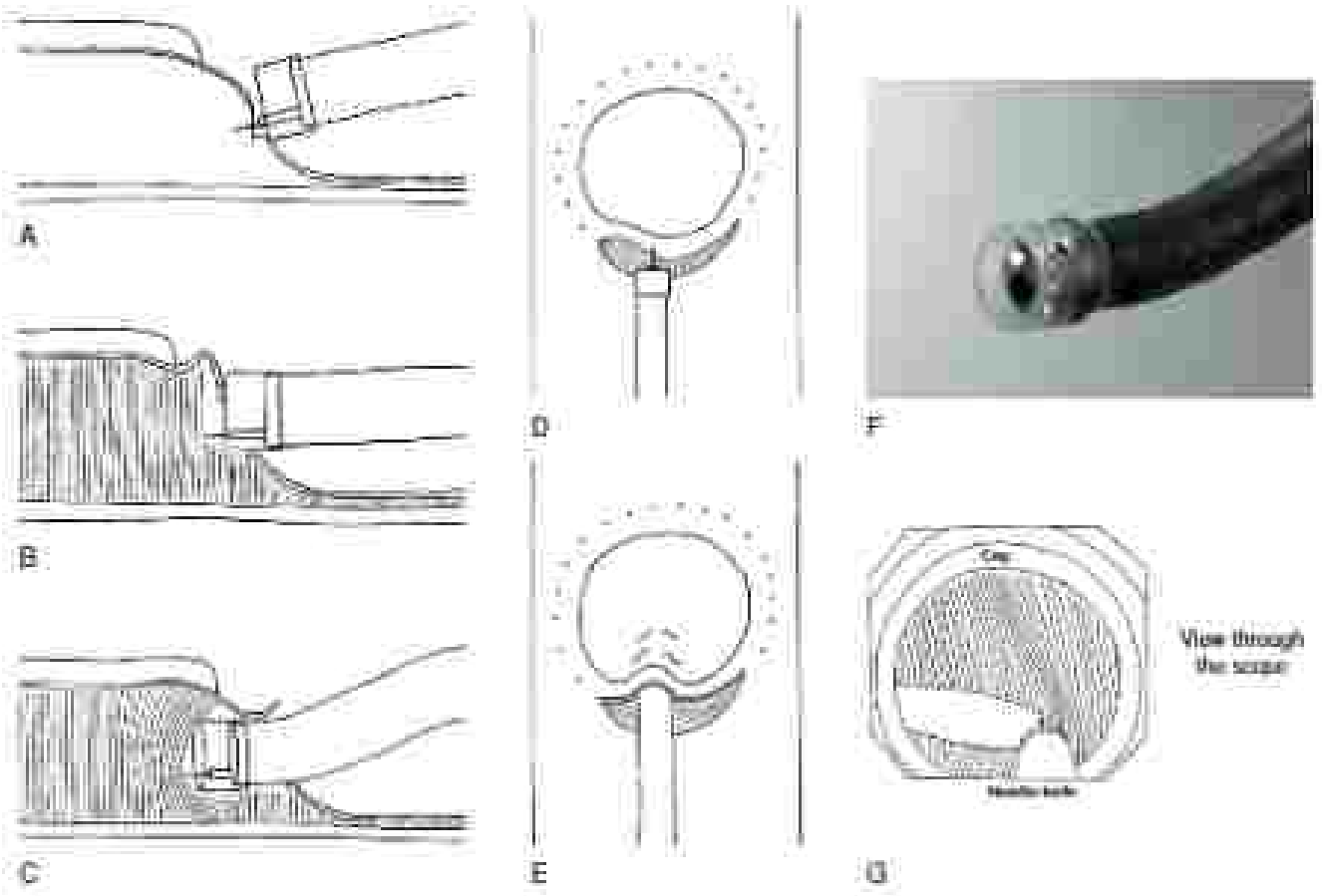

FIG. 2 (A–G) Cap dissection.

the grasper toward the polyp sitting at the bottom of the field. The best polypectomy strategy using this device has yet to be determined, however, after the snaress has been twisted around the polyp, the cut mucosal edge is grasped and then lifted by tensioning the grasper eversely. This provides traction that greatly facilitates detachment of the polyp using a needle knife placed through the colonoscope's instrument channel.

A second-generation Lasso-it device with external cutting channels is soon to be released. Conceptually, a grasper and tissue cutting device can be passed through the channels and finely controlled such that the polypectomy can be performed using the colonoscope as a camera only. Tissue cutting does via one of the external channels while the polyp edge is retracted by the grasper1. There are other new treatment platforms being introduced including several robotic approaches.

Several new lifting solutions are also soon to be released that have the potential to facilitate ESD and EMR. A variety of unique and novel needle knives are also in development by a number of companies that facilitate safe tissue cutting and ESD type polypectomy.

COSTS AND NEED FOR CPT PROCEDURE CODES

ESD and EMR are quite expensive from the viewpoint of disposable needle knives, special lift solutions, sclerotherapy catheter or high-pressure insufflation device, or flush net or wire basket. These new polypectomy facilitating tools and devices will add considerably to the cost of the procedure; in the case of the therapeutic tissue cutting devices, this could be several thousands of dollars. Presently, in the United States, there is no CPT code for ESD; therefore, physicians performing ESD must use the existing codes or bill the procedure under the "unlisted code" category, which is time consuming and does not ensure fair payment to either the institution or the physician. Presently, the performance of ESD or complex EMR are money losing endeavors for both the institution and the physician. The great majority of existing polypectomy codes refer to simple snare removal (15- to 20-minute procedure) and not a several-hour long ESD or EMR. There is a new EMR code, but in the opinion of advanced endoscopists and administrators, it does not fairly reimburse for complex polypectomies. It is critical, therefore, that new codes be developed to cover the costs of the instruments as well the time investment on the part of the endoscopist. For this to happen, patients, gastroenterologists, surgeons, and industry must work together to lobby Congress and the appropriate federal agencies for new fair codes. In the absence of new codes, it will be difficult to popularize these important advanced endoscopic techniques that allow patients to avoid a considerably more costly and morbid segmental colectomy.

TRAINING

The endoscopic skill set necessary for ESD is not easily come by. The ability to finely control and direct the moving scope tip with an active, extended cutting device requires hours of practice and training. "Surgically" detaching a polyp in the submucosal plane with only

gravity as retractor is a challenging and frustrating job. New training approaches are needed.

To teach scope tip control, an inanimate model that uses a bell-low plastic tube with a window cutout can be used. A piece of paper with line figures can be placed in the window and a modified echinotherapy catheter "gun" that is passed through the scope instrument channel used to trace the line figures. Saline with methylene blue or other dye serves as the "ink." Actual ESD procedures can be carried out on pieces of pig stomach with an overlying Rowy pad cut that are placed over the tube's window cutout. Excised but intact bovine colon and rectum (3–4 feet long) can also be used to perform ESD. The bovine model is more realistic since it requires insufflation of the bowel (proximal end sealed with large clip and rip tie placed around the anus); this model is more versatile since the position of the "polyp" target and the shape of the colon is be varied. We believe that by performing 30 to 40 full ESD cases using the porcine and bovine models, surgeon trainees will be able to start a clinical program, perhaps doing the lower outlined above (operating room setting with goal being ESD/EMR with fluoroscopy backup).

One could argue that, with the advent of new tools and platforms that it is not necessary to learn ESD methods. For the foreseeable future, however, even with the new tools, successful en bloc polypectomy requires a submucosal lift and the ability to navigate and work with a needle knife in the submucosal space. Thus, fine motor control of the moving scope tip is still required. These training approaches will teach these skills and, hopefully, prepare the next generation of endoscopists to perform these endoscopic sparing procedures.

SUMMARY

It is now possible to remove the great majority of large sessile adenomas endoscopically. These lesions can be removed via EMR; however, ESD methods are the gold standard because they permit en bloc resection which allows for pathologic determination of both the horizontal and vertical margins. En bloc resection and detailed pathologic evaluation, in turn, have led to the realization that for superficial invasive cancers (SM1, <1000 μm depth of invasion) segmental colectomy is not necessary. ESD utilization rates around the world are steadily increasing and new tools are being introduced that will considerably simplify the removal of these lesions. New procedural codes that take into account the complexity of these procedures as well as the increased cost of the required disposable tools are needed. Where advanced endoscopic polypectomy methods have been widely embraced and implemented the rate of colectomy for benign lesions should dramatically decrease from the current level of 28,000 cases/y in the United States. The next 10 years will see much movement in this area.

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MANAGEMENT OF PERITONEAL SURFACE MALIGNANCIES

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Peritoneal surface malignancies (PSMs) describe a heterogeneous collection of histopathology affecting the peritoneal lining of the abdominopelvic cavity. They encompass primary malignancies, such as diffuse malignant peritoneal mesothelioma or primary peritoneal carcinoma, as well as peritoneal metastases from gastrointestinal, gynecologic, and uncommon etiologies. Traditionally, the diagnosis of a PSM portended a poor prognosis with limited role for surgical intervention, and its diagnosis still may elicit substantial nihilism from clinicians. However, certain histopathologic subtypes in select patients have now been shown to be amenable to surgical debulking with significant impact on overall survival (Table 1). Cytoreductive surgery (CRS), which entails macroscopic tumor removal and commonly multivisceral resection, is often combined with hyperthermic intraperitoneal chemotherapy (HIPEC) to maximize therapeutic benefit. This chapter focuses on the approach to the management of PSM arising secondary to peritoneal mesothelioma, appendiceal adenocarcinoma, and colorectal malignancies.

APPENDICEAL NEOPLASMS

Epidemiology and Classification

The true incidence of epithelial appendiceal cancers is unknown but is thought to be about 8 to 10 million per year, with primary malignant tumors of the appendix being incidentally discovered in about 1% of appendectomy specimens. Primary cancers may have mucinous or nonmucinous (colorectal type) histology, and either can contain a signet ring cell component. Appendiceal neoplasms with mucinous histology may give rise to the clinical entity known as *pseudomyxoma peritonei* (PMP), which is a condition characterized by mucinous ascites and peritoneal implants. Because of the rarity of appendiceal neoplasms and their unique biologic behavior, terminology and classification can be a source of confusion and debate. In 1995, Ronnett et al. described and classified peritoneal metastases resulting from PMP into three distinct groups: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous adenocarcinosis (PMCA), and an intermediate group (PMCA I). A subsequent retrospective multiinstitutional review of 2298 patients with PMP of appendiceal origin has since validated the prognostic value of this histopathologic classification in predicting overall survival. Multiple terms have been applied to primary appendiceal neoplasms of mucinous histology as well. The 2010 World Health Organization recognized three categories of primary appendiceal neoplasms: mucinous adenoma, low grade appendiceal mucinous neoplasm, and mucinous adenocarcinoma. The 2016 Peritoneal Surface Oncology Group International Consensus developed a classification to correctly describe both the primary lesion and peritoneal disease. It also further classified noncarcinoid epithelial neoplasms of the appendix itself and added a new term, high grade appendiceal mucinous neoplasm for lesions with the low grade architectural features of low grade appendiceal mucinous neoplasm but with high grade cytologic features (Box 1). Finally, to further delineate the nomenclature to describe PMP and retained Ronnett et al.'s terminology of DPAM and PMCA (Table 2).

Clinical Manifestations

Clinical symptoms on presentation can be vague and nonspecific. The most common symptom in both men and women is increasing abdominal girth. Patients often complain of weight loss despite increasing abdominal girth, fatigue, bloating, pain, and constipation. The diagnosis is sometimes made incidentally after initial presentation for acute appendicitis with perforation. Men may also present with inguinal or umbilical hernias, whereas women may often present with a pelvic mass. It is not an uncommon scenario for a woman to be treated initially by a gynecologic oncologist for a pelvic mass presumed to be ovarian cancer, only to be determined at the time of surgical exploration that there is an appendiceal primary. In some patients, ascites may have been detected on axial imaging triggering an initial workup for cirrhosis before a diagnosis is made. Since it is not uncommon for patients often arrive to the surgeon's office by a circuitous route

Diagnostic Tests and Preoperative Workup

Patients who present with appendiceal neoplasms should be staged with axial imaging. Computed tomography of the chest, abdomen, and pelvis is commonly obtained for staging purposes, but delayed gadolinium enhanced magnetic resonance imaging has been used in some institutions with reportedly increased accuracy for staging and selection for surgical intervention. The role for positron emission tomography is limited as the mucinous content of tumors often dilutes the metabolic signal. In addition to routine laboratory tests of complete metabolic panel, complete blood count, and coagulation panel, tumor markers consisting of CEA, CA 19-9, and CA 125 should be obtained. Although none of these tumor markers are specific for appendiceal malignancies, in about 50% to 70% cases, at least one marker may be elevated, allowing for postoperative surveillance. A colonoscopy should be performed if one has not been performed, however, results are frequently negative for any detectable intraluminal malignancy. It is also our routine practice to have the slides reviewed by a pathologist with expertise in gastrointestinal malignancies if this was not done previously; we have observed a diagnostic discordance of approximately 30%. In patients who do not have an established diagnosis in the setting of radiographic findings of peritoneal disease and/or ascites, a diagnostic paracentesis or image guided biopsy (fine needle aspiration or core biopsy) may be performed, although it is not uncommon for these tests to be nondiagnostic. In the absence of a diagnosis, we have found diagnostic laparoscopy to be extremely valuable as a means to obtain tissue and to stage the extent of disease. At laparoscopy, ascites should be aspirated and biopsies of the peritoneum or omentum should be performed. Laparoscopic trocars may be placed midline to facilitate easy excision of port sites if needed at the time of cytoreduction. Laparoscopy provides additional information on tumor burden and the potential for complete gross cytoreduction. Extensive involvement of the serosal surfaces of the bowel may preclude a complete cytoreduction, and the patient may then be rapidly referred to medical oncology for consideration of systemic chemotherapy.

Patient Selection for Surgery

Patients who have peritoneal metastases without evidence of extraperitoneal metastases from appendiceal cancer with a disease burden amenable to complete cytoreduction (resection of all gross disease) are potential candidates for CRS with HIPEC. Disease location that often precludes a complete cytoreduction include the serosal surfaces of the small bowel or encasement of the porta hepatis. Those with high grade histology (PMCA/high grade mucinous carcinoma peritonei) and disease unresectable by imaging are initially treated with systemic chemotherapy to better assess disease biology and determine surgical candidacy because patients who progress on systemic chemotherapy are much less likely to benefit from CRS/HIPEC

TABLE 1 Histopathologic Subtypes Amenable to Cytoreductive Surgery

Origin	Histopathologic Subtype
Primary disease of peritoneum	Diffuse malignant peritoneal mesothelioma Gynecologic: Primary peritoneal carcinoma
Metastatic disease of peritoneum	Gastrointestinal: Appendiceal mucinous neoplasms and adenocarcinoma Colorectal cancer Gynecologic: Epithelial ovarian cancer Fallopian tube cancer Borderline mucinous ovarian tumor Sarcoma: Desmoplastic small round cell tumor Other: Urachal adenocarcinoma Mucinous adenocarcinoma of unknown origin

The outstanding survival observed in the PSOGI 2016 study following complete cytoreductive surgery clearly suggests that surgical excision of isolated peritoneal metastases from colorectal cancer should be adopted as a standard of care, whereas the addition of hyperthermic intraperitoneal chemotherapy deserves further study, particularly in patients with intermediate disease burden.

BOX 1 PSOGI 2016 Classification of Noncarcinoid Appendiceal Epithelial Neoplasms

Tubular, tubulovillous or villous adenoma, low- or high-grade dysplasia
Serrated polyp with or without dysplasia (low or high grade)
Low-grade appendiceal mucinous neoplasm
High-grade appendiceal mucinous neoplasm
Mucinous adenocarcinoma, well, moderately or poorly differentiated
Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
(Mucinous) signet ring cell carcinoma
Adenocarcinoma, well, moderately, or poorly differentiated

PSOGI, Peritoneal Surface Oncology Group International.

Those with low-grade histology (LAMN/low-grade mucinous carcinoma peritonei) who are not candidates for complete cytoreduction because of disease burden but who have surgically manageable symptomatic disease (i.e., obstructive symptoms) may be treated with palliative debulking without HIPEC (Fig. 1).

COLORECTAL CANCER

The care of patients with stage IV colorectal cancer (CRC) has evolved significantly over the past several decades. Advances in multiagent systemic therapy have increased median survivals from 12 months in the 5-FU alone era to approximately 30 months in the current age. Unfortunately, the majority of studies contain very few patients with peritoneal metastases. Data from multiple phase III studies revealed poorer outcomes for patients with peritoneal metastases treated with systemic therapy than for those patients with visceral metastatic disease. During this time, the practice of surgical resection of patients with isolated hepatic metastatic disease was broadened to include patients with (1) larger burdens of liver involvement, (2) isolated lung metastases, (3) liver and lung metastases, and (4) other isolated sites of metastatic disease. There is now an abundance of retrospective and an increasing amount of prospective data demonstrating that, in selected patients, surgical resection of all visible peritoneal metastases often combined with regional hyperthermic chemotherapy can result in long-term survival and cure for patients with CRC, not generally achievable with systemic therapy alone.

TABLE 2 Classifications of Pseudomyxoma Peritonei

Ronnett et al. 1995 Classification	WHO 2010 Classification	PSOGI 2016 Classification
DPAM PMCA I	Low-grade appendiceal mucinous neoplasm	Acellular mucin Low-grade mucinous carcinoma peritonei or DPAM
PMCA	Invasive mucinous adenocarcinoma	High-grade mucinous carcinoma peritonei or PMCA High-grade mucinous carcinoma peritonei with signet ring cells or PMCA I

DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous adenocarcinoma; PMCA I, peritoneal mucinous adenocarcinoma intermediate.

Epidemiology

Among patients with CRC, the peritoneum is a common site of metastatic disease both at diagnosis (10%–15%) and at the time of relapse (35%–50%). Retrospective series vary but suggest that in 2.5% to 55% of CRC patients, the peritoneum will be the only site of metastatic disease. Risk factors for peritoneal metastases include mucinous histology, T4 cancer, and perforation, either spontaneous or iatrogenic.

Clinical Manifestations

As in the case of other histologies, peritoneal metastases secondary to CRC may present with ascites manifest as increasing intra-abdominal girth, pain, or small bowel obstruction. However, just as often, synchronous peritoneal disease may be asymptomatic and detected at the time of primary surgery. For patients with metachronous disease, it is most common to identify peritoneal metastases during surveillance given the intensity of imaging use in current practice.

Preoperative Workup

Patient selection for CRS HIPEC is always critical, but even more so for high-grade malignancies such as CRC. The principal goals of the workup are to (1) ensure that the peritoneal surfaces are the only site of metastatic disease, (2) determine the potential for complete cytoreduction, and (3) determine the patient's medical fitness for the procedure.

Preoperative evaluation should consist of a complete history and physical examination, with attention to any signs of inherited cancer susceptibility. Axial imaging (computed tomography or magnetic resonance imaging) of the chest/abdomen and pelvis are essential. In reality, we have observed most patients referred to our practice have had positron emission tomography imaging as well, though it is unclear as to its value as a routine study. We do believe positron emission tomography has clear value in the setting of equivocal findings on axial imaging. Routine preoperative bloodwork should include CEA at initial diagnosis or if it has been elevated previously. We suggest a full colonoscopy if it has not been performed within the past 2 years.

For the majority of patients, we have used diagnostic laparoscopy as a staging tool for several reasons. Axial imaging has poor sensitivity for the detection of peritoneal metastases; therefore, determining the potential for complete cytoreduction is challenging based on axial imaging alone. In our hands, diagnostic laparoscopy has an 83% positive predictive value to determine the potential for a complete cytoreduction. We find it extremely valuable in the informed consent process as well because it allows a much more accurate discussion regarding the planned procedure, its potential morbidities, and the anticipated length of stay. Obtaining photographs of the extent of disease also allows patients and families to better understand the disease process and the rationale for recommending or not recommending CRS/HIPEC.

Patient Selection for Surgery

Patient selection for CRS and HIPEC in metastatic CRC is even more stringent than for appendiceal neoplasms. Unlike mucinous appendiceal cancer, which frequently exhibits peritoneal only metastasis, CRC has a greater propensity for nodal and extraperitoneal metastasis. Also, unlike appendiceal primary neoplasms, patients with peritoneal metastatic CRC are less likely to benefit from incomplete debulking, including CC-1 cytoreduction.

We believe that patients with CRC with even limited resectable peritoneal disease at the time of synchronous presentation/diagnosis are best treated with neoadjuvant systemic therapy to select out those who have rapid disease progression and to assess response, before embarking on CRS. Patients with extraabdominal disease in the

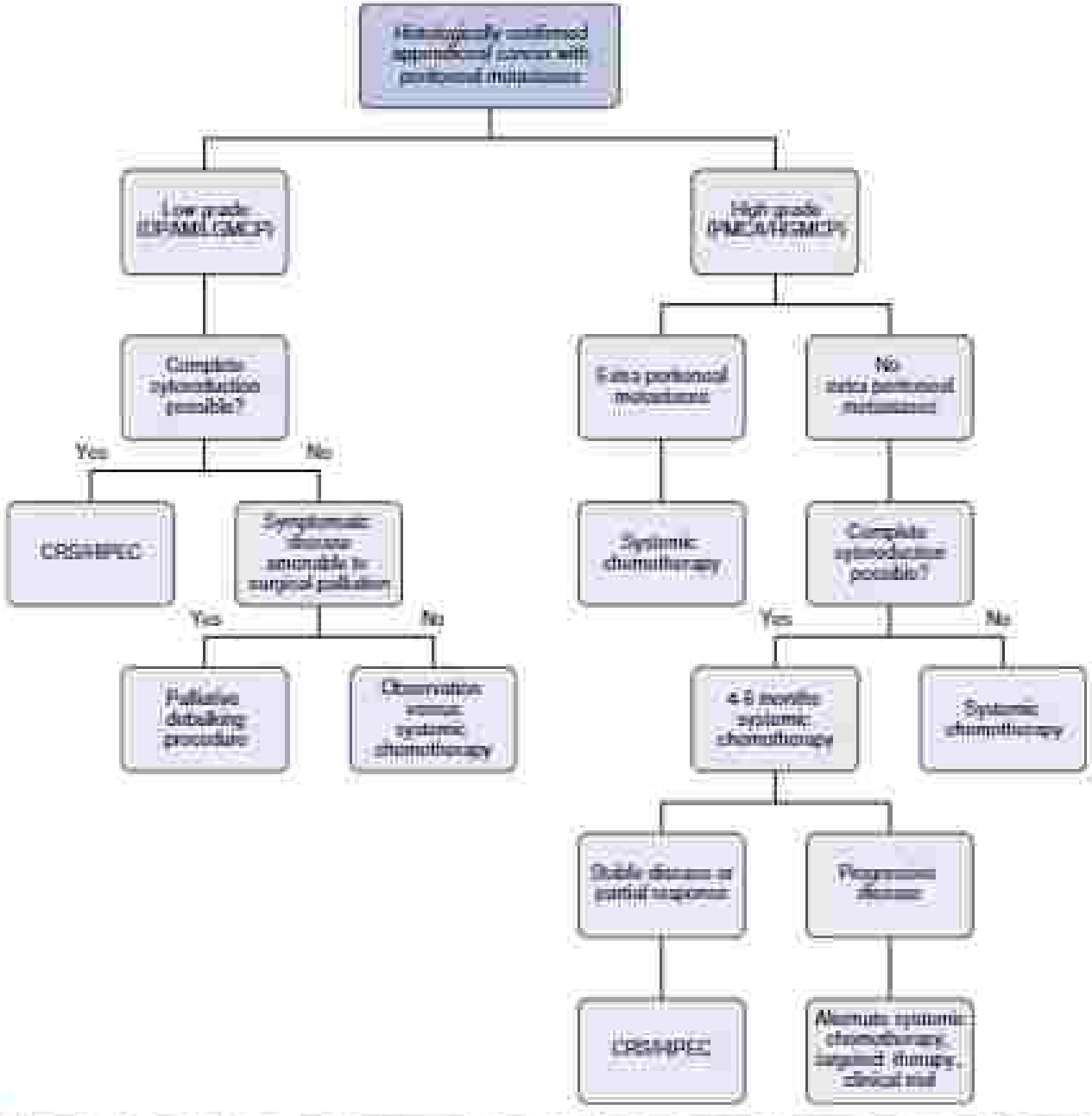


FIG. 1. University of California San Diego algorithm for management of patients with peritoneal metastasis from appendiceal neoplasms. CRS, cytoreductive surgery; CRSM, disseminated peritoneal adenomucinosis; HGMCP, high-grade appendiceal mucinous neoplasm; HIPEC, hyperthermic intraperitoneal chemotherapy; LGMCP, low-grade appendiceal mucinous neoplasm; PMCA, peritoneal mucinous adenocarcinoma.

peritoneum detected on surveillance imaging after previous curative-intent treatment for a primary CRC need careful staging, ideally with laparoscopy. Patients with metachronous peritoneal disease felt to be potential candidates for CRS should be discussed in a multidisciplinary tumor board setting to decide on an optimal sequence of therapy because they are likely to require further systemic treatment as well. Those who are fit for surgery have a limited peritoneal disease burden, and those who have had a long disease-free interval (>6 years) since their primary treatment may be considered to go straight to CRS, which may include HIPEC. More often though, patients develop peritoneal recurrence in the first few years after their primary treatment, and so upfront systemic therapy followed by CRS in those with responsive or stable disease is usually the best approach.

Patients presenting with synchronous or metachronous peritoneal metastases with symptoms, such as small bowel obstruction, have a worse prognosis and are less likely to benefit from CRS with HIPEC. As mentioned previously, the majority of patients with peritoneal metastases from CRC have at least one site of extraperitoneal disease as well, most commonly parenchymal liver and/or lung metastases. Although extraperitoneal disease has been shown to be a poor prognostic factor in some series, it is not an absolute contraindication to CRS with HIPEC in younger, fit patients who have had stable disease on systemic therapy and whose disease is amenable to complete resection. Table 3 summarizes relative and absolute contraindications to CRS with HIPEC that we use in practice our institution. In addition to the Peritoneal Cancer Index (PCI), scored on a scale from 0 to 39 (Fig. 2), the peritoneal surface disease severity score and, more recently, the colorectal peritoneal metastasis prognostic surgical score are prognostic nomograms that aim to guide patient selection for CRS and HIPEC. Both take PCI into account but also consider other clinical variables, and both have been validated in peritoneal metastatic CRC with reasonably good model performance.

TABLE 3 Relative and Absolute Contraindications to CRS With HIPEC in Patients With Peritoneal Metastatic CRC

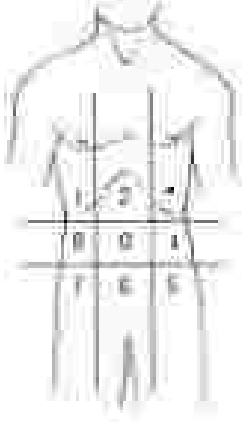
Absolute Contraindications	Relative Contraindications
Poor performance status/frailty	Short disease-free interval (if metachronous)
Disease not amenable to complete (CC-0) cytoreduction	PCI >20
Disease progression on systemic therapy	Serosa positive
Malignant small bowel obstruction	

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, Peritoneal Cancer Index.

PERITONEAL MESOTHELIOMA

Epidemiology, Classification, Clinical Manifestations, and Surgical Selection

Malignant peritoneal mesothelioma (MPM) is a rare, aggressive primary malignancy of the peritoneum. It comprises 10% to 15% of all mesotheliomas, and the annual incidence in the United States of MPM is approximately 400 cases. Asbestos exposure is the most well-characterized risk factor for mesothelioma, although the attributable risk of asbestos for MPM is only 25% to 50%. Other potential risk factors for MPM include prior radiation therapy, maternal fiber exposure, chronic peritonitis, and germline BRCA 1–associated protein (BAP 1) gene mutation. Histologic subtypes of MPM include epithelioid, which is the most common and least aggressive subtype; sarcomatoid, which is the most aggressive subtype; and biphasic, which has histologic and behavioral features of epithelioid and sarcomatoid. Patients with MPM often present similarly to other patients with PSM, with vague symptoms of abdominal distension, pain, and early satiety. Imaging findings are often subtle and include ascites and omental and/or mesenteric fatty infiltration. Diagnosis is obtained histologically, by percutaneous biopsy of a large omental/abdominal mass (if present), by laparoscopic biopsy, or by biopsy obtained during surgery for another indication when MPM is discovered incidentally. The natural history of MPM is aggressive; without treatment, median survival is approximately 6 months. Median survival of MPM with systemic chemotherapy alone is approximately 16 months. Patients with MPM are considered for surgical therapy with CRS/HIPEC if their disease burden is amenable to resection of all or nearly all (CC-0 or CC-1) visible disease, and they are suitable to for such extensive



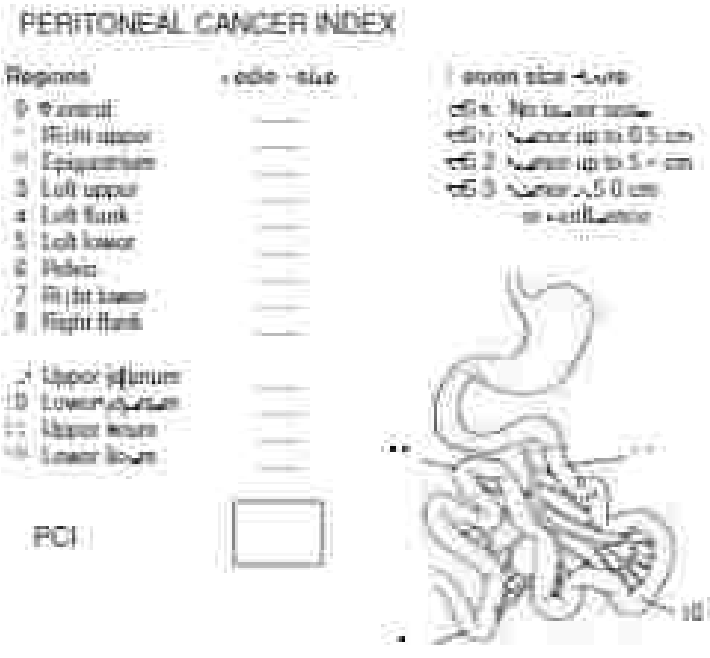


FIG. 2 The Peritoneal Cancer Index allows a quantitative assessment of the extent of peritoneal metastatic disease. The abdomen is divided into 13 quadrants and the small bowel into 4 distinct regions. Each is assigned a score of 0 to 3 based on the size of the metastatic lesions, if present, before cytoreductive surgery. (From Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH, ed. Peritoneal Carcinomatosis: Principles of Management. Boston: Kluwer Academic Publishers; 1996:359–374.)

surgery. We often use laparoscopy to determine if a complete cytoreduction can be performed because imaging generally underestimates the extent of disease in MPM. Preoperative chemotherapy with platinum-based regimens and pemetrexed are given to patients with disease burdens of borderline potential for complete cytoreduction.

INTRAOPERATIVE MANAGEMENT AND TECHNIQUE

The primary goal of CRS is to resect all visible peritoneal metastases. HIPEC involves perfusion of the peritoneal cavity with heated cytotoxic chemotherapy with the goal of eradicating residual microscopic disease, with a putative tissue penetration of 2 to 5 mm. Administration of the cytotoxic agent directly into the abdominal cavity takes advantage of the peritoneal plasma barrier and therefore allows for the delivery of a higher local concentration and less systemic toxicity than is possible via the intravenous route. Moreover, hyperthermia is toxic to malignant cells and can provide additive or synergistic benefit when combined with cytotoxic chemotherapy.

Patients typically undergo a mechanical bowel preparation with oral antibiotics prior to surgery. Because CRS with HIPEC procedures are often long, we prefer supine positioning whenever possible. If proctectomy is required, it usually involves the upper rectum at or above the peritoneal reflection (except in cases of rectal primary tumors) so very low rectal anastomoses are not usually required. We prefer a reverse end-to-end anastomosis technique in which the anvil of the circular stapler is placed in the rectal stump with a purse-string suture and the stapler is passed through a colotomy or enterotomy on the bowel on the proximal side of the anastomosis. This allows for the procedure to be performed without prolonged low lithotomy positioning and eliminates crossing staple lines during completion of the anastomosis. We routinely administer prophylactic subcutaneous heparin preoperatively as well as prophylactic antibiotics. Communication with the anesthesia team is important during CRS with HIPEC so that adequate urine output is maintained throughout and core body temperature is carefully monitored. Cooling blankets or ice packs applied to the patient's head and neck areas are sometimes required during the HIPEC portion of the procedure. An epidural catheter is preferred for postoperative pain control.

The procedure is begun with a complete evaluation of the extent of peritoneal metastases, generally via a full midline incision, to determine if a complete cytoreduction can be achieved. This exploration may require extensive adhesiolysis of benign or malignant adhesions from prior surgery or peritoneal metastases. A precytoreduction PCI is assessed, followed by complete cytoreductive surgery with resection of all visible peritoneal tumor if possible. Note that although a PCI score provides information about the amount of tumor burden, it does not necessarily convey if the patient is amenable to a complete cytoreduction. For example, a patient with low grade histology and a PCI score of 39 may be amenable to complete cytoreduction, whereas a patient with high grade histology and PCI score of 18 may not. A complete, systematic inspection of the peritoneal cavity is critical, including the bilateral diaphragm surfaces, the lesser sac, the porta hepatis, and the small bowel and its mesentery, and the pelvis. Particular areas that warrant careful inspection include the falciform ligament where it inserts into the liver parenchyma, the fold of peritoneum that makes up the ligament of Treitz, the pelvic cul-de-sac, and the base of the bladder. These are sites where small deposits of disease can be easily missed. We recommend complete running of the small bowel from the ligament of Treitz to the ileocecal valve or prior colonic anastomosis with assessment of all areas that might need resection prior to performing any resection. This allows for planning ahead to minimize the length of bowel to be resected. Generally, lesions without serosal invasion can be removed sharply with sweeping of resultant serosal defects. Full thickness/invasive lesions require either excision with primary repair or formal segmental resection. Both sides of the mesentery also need to be fully inspected. Very small (<2–3 mm) mesenteric implants or confluent areas of miliary deposits may be amenable to thermal ablation with an argon beam coagulator or other similar device. Extensive small bowel disease not amenable to resection with sufficient remnant or nodal disease involving the root of the mesentery are contraindications to complete cytoreduction.

Complete cytoreduction generally requires a greater amount of time, selective peritonectomy of diseased parietal peritoneum, and visceral resections as indicated for organs invaded by or with densely adherent, soft peritoneal tumor nodules. The parietal peritoneum on the surface of the diaphragm, particularly on the right side, is a common site of involvement. For complete diaphragm stripping, the liver must be mobilized away from the diaphragm by taking down the triangular ligament. The peritoneum is then carefully stripped. If a hole is made in the diaphragm during the dissection, a chest tube is recommended as reactive pleural effusions and residual pneumothorax is common.

If HIPEC is used, we begin once all visible disease has been removed and the patient is hemodynamically stable with adequate (1 mL/kg per hour) urine output. Although either an open or a closed perfusion technique may be used, we use a closed technique because it reduces chemotherapy exposure to the operating team. It is undertaken by inserting inflow and outflow cannulas along with thermistor probes for temperature monitoring and with temporary skin closure around the cannulas (Fig. 3). Using a hyperthermia perfusion pump, between 3 and 4 L of warmed perfusate (typically, lactated Ringer's) is instilled. Once adequate abdominal distention is achieved based on intraoperative assessment of the peritoneal cavity volume, the perfusate is then circulated at a flow rate of 1 L/min and heated using the perfusion pump, with a goal intraperitoneal temperature of 42°C to 43°C. When the target temperature is reached, the chemotherapy is infused into the perfusion circuit and the abdomen is manually agitated for the entirety of the chemoperfusion. For appendix and CRC's, mitomycin C or cisplatin are the two most common agents used, and cisplatin with or without gemcitabine is used for mesothelioma. The chemoperfusion is undertaken for 30 to 120 minutes (90 minutes at our institution). At the end of the chemoperfusion, additional perfusate is then added to the perfusion circuit and the residual chemotherapy is flushed out of the abdomen.

The abdomen is then reopened for reexploration, gastrointestinal reconstruction, and drain placement. We have a low threshold for placement of a decompressive Stamm gastrostomy tube (G tube). This is because postoperative ileus is common following CRS with HIPEC, and because patients are at risk for recurrent disease in the peritoneum and reaccumulation of ascites and/or ascites in the

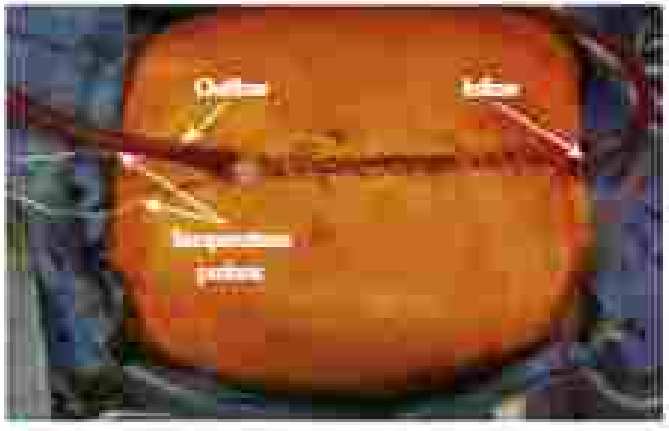


FIG. 3. Intraoperative image demonstrating the closed perfusion technique for hyperthermic intraperitoneal chemoperfusion. Inflow and outflow cannulas enter and exit the patient's abdomen after the skin is temporarily closed. Temperature probes monitor the intraperitoneal temperature consistently with a target of 42°C to 43°C.

future. Even once the initial tube has been removed, the stomach remains sutured to the anterior abdominal wall to facilitate easy tube replacement should the patient develop recurrence and require gastric decompression in the future. We also typically leave at least one surgical drain near any high-risk anastomoses. The fascia is then definitively closed. A completeness of cytoreduction score is assigned at the end of the case (Table 4).

MANAGEMENT OF INCIDENTALLY NOTED PERITONEAL METASTASES

One of the most taxing situations for many surgeons is determining management of patients with peritoneal metastases secondary to colorectal or appendiceal neoplasms noted at elective colectomy or at the time of appendicectomy (now most often laparoscopic appendectomy). When colorectal metastases are noted during elective colectomy for cancer, the proper management depends on several factors: (1) the extent of the disease and concomitantly, the ability of the surgeon to thoroughly assess this, and (2) whether the planned resection is purely elective or whether the patient has a component of obstruction, bleeding, or evidence of perforation. In all cases, biopsy of the peritoneal disease is critical because it is the accurate documentation of the extent of disease, as best can be determined. Most important, it is critical for the operating surgeon to assess and document the presence of visceral metastases, and the extent of disease involving the serosal surfaces of bowel and mesentery. If the operation is purely elective, then biopsy and documentation alone, without resection of the primary cancer is probably optimal because it will allow the patient to rapidly recover and go on to systemic chemotherapy and possible CRS at a later date as indicated. If the cancer is complicated by obstruction, perforation, or bleeding, then in addition to biopsy and documentation, colon resection should be performed in a conservative manner. In the rare circumstance in which peritoneal metastases are extremely limited (i.e., a single focus of disease to the omentum), it is reasonable for the surgeon to perform a colectomy and excision of all gross disease, ensuring that a complete exploration of the abdomen is possible.

In the setting of peritoneal metastases noted at laparoscopic appendicectomy, the appendicectomy may be completed if it is straightforward, but again, the most important aspects of the procedure are biopsy of the peritoneal metastatic disease and documentation of the status of the remainder of the abdomen.

POSTOPERATIVE MANAGEMENT

Patients are generally admitted to the intensive care unit postoperatively for the first 24 to 48 hours. Patients are initially allowed sips of water and ice chips with the decompressive G-tube open to gravity drainage. Ambulation and incentive spirometry are encouraged on the first postoperative day. We generally advance patients to a liquid diet as long as they are not reporting nausea and are not distended. The G-tube is kept open to gravity until there is flatus or a bowel movement. We then begin interval clamping of the G-tube with 1 hour clamped and 3 hours open for a day, then progressively clamp for longer periods until continuous clamping is tolerated. Once the patient is tolerating continuous clamping, we advance them to a soft or low residue diet. The G-tube may be removed before discharge depending on the length of stay, or more often in the clinic within 2 weeks of discharge. Patients are given prophylactic low molecular weight heparin during the entire postoperative hospital stay and for 2 weeks following discharge.

TABLE 4 Completeness of Cytoreduction Score

Score	Residual Disease
CC-0	No gross visible disease
CC-1	Tumor nodules <2.5 mm
CC-2	Tumor nodules between 2.5 and 2.5 cm
CC-3	Tumor nodules >2.5 cm

SURGICAL OUTCOMES

Recent large series from high volume CRS/HIPEC centers report postoperative mortality rates of 1% to 3%. Major postoperative morbidity occurs in 15% to 35% of patients from major CRS/HIPEC centers. The most common causes of surgical morbidity of Clavien Grade 3 or higher include (Table 5) include enteric leak or fistula (in 5%–10%), intraabdominal abscess (in 10%–15%), venous thromboembolism (in 5%–15%), as well as other less common major complications, including pleural effusion, pneumonia, renal failure, and wound dehiscence. Other less severe, but more common complications include prolonged ileus (in 10%); superficial wound infection (in 10%–20%), and neutropenia (in up to 10%, depending on the HIPEC agent used). Long term risks include ventral hernia formation and adhesive bowel obstruction, which have a more uncertain incidence.

Appendiceal Neoplasms

Oncologic outcomes after CRS/HIPEC for appendiceal cancers vary greatly depending on histology. Median progression free survival after CRS/HIPEC for low grade appendiceal mucinous neoplasms with peritoneal dissemination (DPAM/low grade mucinous carcinoma peritonei) is 3 to 5 years from the largest published series and the median overall survival ranges from 10 to 15 years. Patients with high grade appendiceal mucinous tumors with peritoneal metastases (PMCA with or without signet ring cells) have a 12- to 18-month median progression free survival and a 24-month median overall survival. Risk factors for recurrence and disease related mortality among patients after CRS/HIPEC for appendiceal cancer include histologic grade, completeness of cytoreduction (with higher rates of progression and mortality with more residual disease after cytoreduction), and lymph node status.

CRC

Oncologic outcomes following CRS with HIPEC for colon cancers have been evaluated in both randomized, prospective clinical trials and in large retrospective series. Median overall survival for patients who undergo complete cytoreduction in modern series is approximately 20 to 40 months. Median recurrence free survival ranges from 11 to 14 months. Five-year overall survival rates are on the order of 15% to 25%.

TABLE 5 Potential Complications of CRS/HIPEC

Complication	Rate (%)
Death	1–3
Enteric leak or fistula	5–10
Deep/organ space surgical site infection	10–15
Venous thromboembolism	5–15
Prolonged ileus	10
Superficial surgical site infection	10–20
Neutropenia	10

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

As of this writing, the results of the PROPHECY-3 study were reported in abstract form. This study randomized 265 patients with isolated peritoneal metastasis from CRC who had undergone a complete or near complete cytoreduction (residual tumor nodules <2 mm) to receive HIPEC with oxaliplatin and intraoperative systemic 5-FU/folinic acid versus CRS alone. At a median follow up of 63.8 months, the median survival was 41.2 months in the new HIPEC arm and 41.7 months in the HIPEC arm. The median relapse free survival was 14.1 months in the new HIPEC arm and 13.1 months in the HIPEC arm (hazard ratio, 0.90), whereas the 1 year relapse-free survival rates were 56.1% in the new HIPEC arm and 59% in the HIPEC arm. Interestingly, a subgroup analysis did find a significant improvement in survival (hazard ratio, 0.40) favoring the HIPEC arm for patients with a PCI of 11 to 15, whereas no difference was observed for patients with either low or high burdens of disease. The particular HIPEC regimen of a 30 minute perfusion with oxaliplatin, popular in Europe has not been used extensively in the United States, where mitomycin C for 90 minutes has been the preferred regimen.

MPM

The median survival after CRS+HIPEC for MPM is 4 to 5 years based on retrospective series. The best predictors of outcome after CRS+HIPEC are (1) histologic subtype, with patients with epithelioid subtype having much more favorable survival than those with biphasic or sarcomatoid subtypes; and (2) completeness of cytoreduction, with patients undergoing CC-0 cytoreduction demonstrating the most favorable outcomes (96 month median survival vs 47 months for CC-1, 48 months for CC-2, and 12 months for CC-3).

CONCLUSIONS

Although the low incidence of the disease has precluded conduct of randomized trials, the role of CRS with HIPEC in the treatment of appendiceal neoplasms and peritoneal neoinclusions has been well established via a large number of single and multiinstitutional studies. Future efforts are underway to better understand molecular aberrations in these neoplasms and to identify or develop novel agents for intraperitoneal administration.

Suggested Readings

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Appendicitis

Mark L. Kovler, MD, and David J. Mackam, MD, PhD

Appendicitis represents one of the most common causes of an acute surgical abdomen worldwide, and in the United States alone, more than 300,000 appendectomies are performed each year. The lifetime risk of developing appendicitis is greater than 12%, and the global burden of disease appears to be rising. Despite centuries of experience with the diagnosis and treatment of appendicitis, a clear understanding of its pathogenesis remains lacking. In general terms, the development of appendicitis is thought to arise from an obstruction of the appendiceal lumen, resulting in impaired blood flow and bacterial infection. The conceptual approach to the management of appendicitis should be one of the most straightforward tasks in all of surgery and requires removal of the inflamed appendix, administration of antibiotics directed toward the subsequent bacterial infection, and careful dietary advancement. That said, various factors have altered the traditional management of appendicitis, including the widespread implementation of minimally invasive approaches, a greater understanding of the role of percutaneous drainage for perforated appendicitis, a recognition that chronic appendicitis is a condition amenable to appendectomy, and most recently, various reports indicating the success of patients with appendicitis after treatment nonoperatively.

Anatomy of the Appendix

The appendix is a hollow viscus with a blind ending tip and a base located at the confluence of the three taenia coli of the cecum. Knowledge of its location at the confluence of these muscular, easily identifiable bands is critical because these bands provide confirmation of the base of the appendix during appendectomy and help ensure that the entire appendix is removed. The tip of the appendix can vary in location, which may contribute in part to the challenges associated with establishing a diagnosis of acute appendicitis (Fig. 1). The appendix may be positioned adjacent to the ileocecal valve, retrocecal or pelvic, and these different locations often result in diverse presenting signs and symptoms. Pain may be difficult to localize when the appendix is retrocecal or when the tip is oriented toward the center of the abdomen. The blood supply is from the appendicular artery, a terminal branch of the ileocolic artery that traverses the mesoappendix.

Pathophysiology of Acute Appendicitis

Acute appendicitis is thought to result from a fairly well described sequence of pathologic events, although there is actually little definitive proof that these events mediate the onset of appendicitis in all patients, and even less proof that appendicitis is the same disease in all patients. It is well accepted that obstruction of the appendiceal lumen leads to appendiceal distention, resulting in bacterial overgrowth and venous congestion. The ongoing obstruction can then progress

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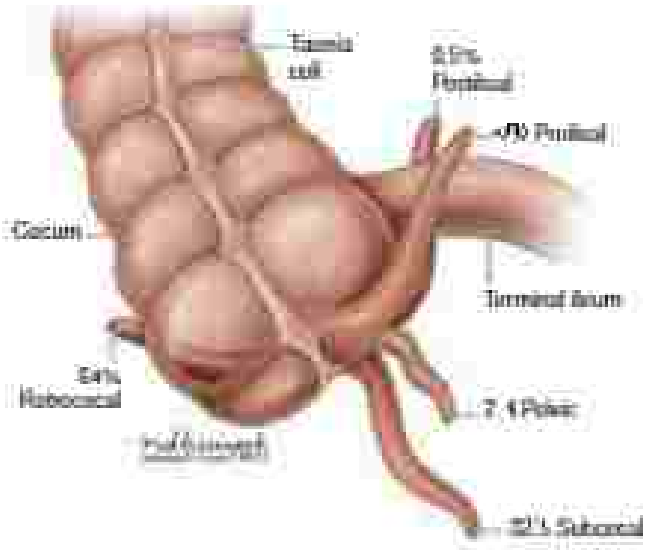

FIG. 1 Variations in the position of the vermiform appendix.

TABLE 1 Clinical Signs and Symptoms of Acute Appendicitis

History	Onset of vague abdominal discomfort, cramping, nausea, progressing to right lower quadrant pain, with associated anorexia, vomiting, and general malaise
Physical examination	Right lower quadrant tenderness, voluntary and involuntary guarding, fever, tachycardia, occasionally palpable mass
Laboratory examination	Typically leukocytosis, normal urinalysis, negative pregnancy testing
Diagnostic imaging	Distended fluid filled appendix with surrounding inflammation, perforation, abscess, fecalith

is ischemia and necrosis. The inciting luminal obstruction may be secondary to a fecalith in the appendiceal orifice (appendicolith), although a fecalith is actually seen in only 15% to 30% of cases, which raises questions about the validity of this pathophysiologic framework. A more precise understanding of appendicitis may be limited by the lack of adequate animal models to gain specific insights into its pathogenesis and by the fact that the disease is readily cured with simple removal of the appendix in so many cases. A greater understanding of the role of nonoperative management of appendicitis may shed light on the pathogenesis of this disease while also providing greater insight into how best to care for patients.

CLINICAL PRESENTATION AND DIAGNOSIS

History, Physical Examination, and Blood Work

The classic presentation of acute appendicitis is an otherwise healthy individual who complains of the vague onset of diffuse, periumbilical abdominal discomfort, which progresses to cramping, and nausea, and becomes localized to the right lower quadrant pain (Table 1). Although these symptoms strongly point to the diagnosis of appendicitis, they occur with such precision in only approximately half of patients. The physical examination reveals fever, tachycardia, and an ill-appearing patient. Abdominal findings typically include right lower quadrant tenderness, which is most intense at McBurney's point, which is the point one third of the distance from the right anterior superior iliac spine to the umbilicus. Although rebound tenderness may be present, eliciting this sign adds little to the diagnosis and causes pain, and is both nonspecific and inaccurate. Additional physical examination maneuvers that elicit localized peritoneal inflammation in acute appendicitis include Rovsing's sign, when palpation in the left lower quadrant increases pain in the right lower quadrant; obturator sign, when pain on internal rotation of the right hip indicates a pelvic appendix; and psoas sign, when pain is produced with extension at the right hip in order to reveal the presence of a retrocecal appendix. Table 2 summarizes the operating characteristics of these maneuvers in the literature and indicates that some of these maneuvers has very high sensitivity.

TABLE 2 Clinical Examination Operating Characteristics for Diagnosis of Acute Appendicitis

	Sensitivity (%)	Specificity (%)
Rovsing's sign	22–68	58–96
Obturator sign	21–34	79–96
Psoas sign	16–39	90–95

Despite a classic history and physical examination, the differential diagnosis for patients remains broad and includes ovarian pathology, urinary tract, trauma, musculoskeletal pain, Meckel's diverticulum, and inflammatory bowel disease, among others. Ancillary laboratory studies and imaging can assist in the diagnosis of acute appendicitis and decrease negative appendectomy rates.

Various blood tests may add to the diagnostic accuracy of acute appendicitis, including the white blood cell count and measurement of C-reactive protein. The white blood cell count is commonly elevated in acute appendicitis. In 2003, Andersson published a large meta-analysis of more than 3000 patients that showed that a white blood cell (WBC) count higher than 10,000 cells/mm³ had a sensitivity of 83% and specificity of 67% for acute appendicitis. Wang et al. validated the utility of WBC counts in children, demonstrating the high negative predictive value of a low or normal WBC count in the pediatric population (negative predictive value 89%–96% depending on age). Therefore, a WBC level elevated beyond 10,000 raises the suspicion for acute appendicitis, whereas a broader differential should be considered in patients with a normal WBC level. A normal urinalysis and negative pregnancy test are also consistent with acute appendicitis. Elevated C-reactive protein has been shown to be a strong predictor of acute appendicitis in young children, especially when its value is 10 or greater.

Diagnostic Imaging

The role of diagnostic imaging is to both ascertain a diagnosis of acute appendicitis preoperatively and to plan a safe resection while excluding the possibility of other intraabdominal or retroperitoneal diagnoses. The choice of a particular radiographic study is based on patient age, body habitus, and risks of radiation exposure. In the adult population, computed tomography (CT) is the most widely used study, although Applegate et al. note in a large meta-analysis that magnetic resonance imaging (MRI) may be gaining in popularity. A CT can be obtained rapidly, is relatively inexpensive, and can provide the diagnosis with sensitivity and specificity of near 100%. Two large meta-analyses by Terasawa et al. and van Randen et al. demonstrated the accuracy of CT scan for diagnosis of acute appendicitis and the ability of CT scan to detect an alternative diagnosis when appendicitis was not present. Colitis, diverticulitis, small bowel obstruction, inflammatory bowel disease, gynecologic pathology, and omental infarction

were identified on CT scans, which had been obtained for suspected acute appendicitis. Additional retrospective data suggest the use of CT scan in evaluation of appendicitis is associated with a reduction in both negative appendectomy rate and cost of care. Therefore, the American College of Radiology continues to recommend CT scan as appropriate for the initial evaluation of suspected acute appendicitis in nonpregnant adults. In children, both the National Cancer Institute and the American Pediatric Surgical Association recommend the use of nonionizing radiation where possible. Similar recommendations are in place for pregnant women. Chandy et al. report the largest series of almost 3000 ultrasound examinations to evaluate acute appendicitis in children, with a diagnostic accuracy of 92.5% and sensitivity and specificity of 97.1% and 94.8%, respectively. When ultrasound is equivocal, the literature supports cross-sectional imaging in the form of MRI. When CT scanning is performed in children, low dose radiation techniques should be used. Both a systematic review by Aly et al. and a prospective randomized controlled trial by the Low Dose CT for the Diagnosis of Appendicitis in Adolescents and Young Adults Trial demonstrate that low dose CT is not inferior to standard dose CT in the diagnosis of acute appendicitis.

MANAGEMENT OF ACUTE APPENDICITIS

The management of children with appendicitis follows surgical principals of resuscitation, antibiotics, and prompt operative intervention. Resuscitation occurs with intravenous crystalloid, and antibiotics with broad gram negative coverage should be initiated. The results of a 2005 Cochrane systematic review by Andersen et al. emphasized the consensus that all patients with acute appendicitis should receive preoperative antibiotics because they decrease the rate of wound infection and abscess. Kumar Mittinus et al. showed a cephalosporin and metronidazole combination led to the greatest reduction in infections compared with piperacillin-tazobactam and metronidazole-ciprofloxacin in a randomized controlled trial. Preoperative antibiotic choice at our institution is ceftriaxone and metronidazole. In cases of nonperforated acute appendicitis, the current approach is to perform an appendectomy. If the diagnosis is certain and the patient has been prepared for surgery, there is no advantage to delaying surgical treatment, and appendectomy should be performed promptly. However, there is now high level evidence that suggests a short in-hospital delay is not associated with an increased rate of perforated appendicitis or postoperative complications. In the most comprehensive prospective study to date, Bhangu et al. showed that the odds ratio of complicated appendicitis was not significantly increased when appendectomy was delayed between 12 and 24 hours after presentation. More extensive delays should be avoided. In cases in which the symptoms are longer than 4 to 5 days in duration, or preoperative imaging reveals the presence of an abscess, patients should be managed with percutaneous abscess drainage, antibiotics, pain management, and considered for interval appendectomy at 6 to 8 weeks to allow for the inflammatory process to subside as is described in the following section.

Laparoscopic Appendectomy

Laparoscopic appendectomy has emerged as the gold standard approach to appendectomy because it results in faster recovery, lower rates of wound infection, decreased pain, and improved cosmesis compared with open appendectomy. Sixty seven studies comparing laparoscopic and open appendectomy are summarized in Sauerland et al.'s 2010 Cochrane review, which favors the minimally invasive approach. Although the primary open approach through a McBurney's muscle splitting incision is still described, most open appendectomies are performed as a conversion from a laparoscopic approach through a low midline laparotomy. The most common reasons for conversion from laparoscopic to open appendectomy include dense adhesions and difficulty with removing the appendix secondary to perforation.

Details of the Operation

The patient is positioned on the operating table supine with the left arm tucked for ease of laparoscopy from the left side (Fig. 2). Patients are encouraged to void immediately before surgery, and in most cases a Foley catheter can be avoided. Laparoscopic access is gained through an umbilical port placed using either an open Hasson or Veress needle technique. After insufflation and under direct visualization, two 5-mm working ports are placed in the left lower quadrant and suprapubic positions. Many surgeons avoid the suprapubic port to decrease bladder injury risk and place an umbilical port as well as two ports on the patient's left side, spaced as far apart as possible. In cases of severe inflammation of the appendix, or in the presence of significant ileus resulting in distention of the intestinal contents, a fourth port may be placed for retraction purposes; this can be most helpful if placed in the central or left upper abdomen. Placing the patient in Trendelenburg

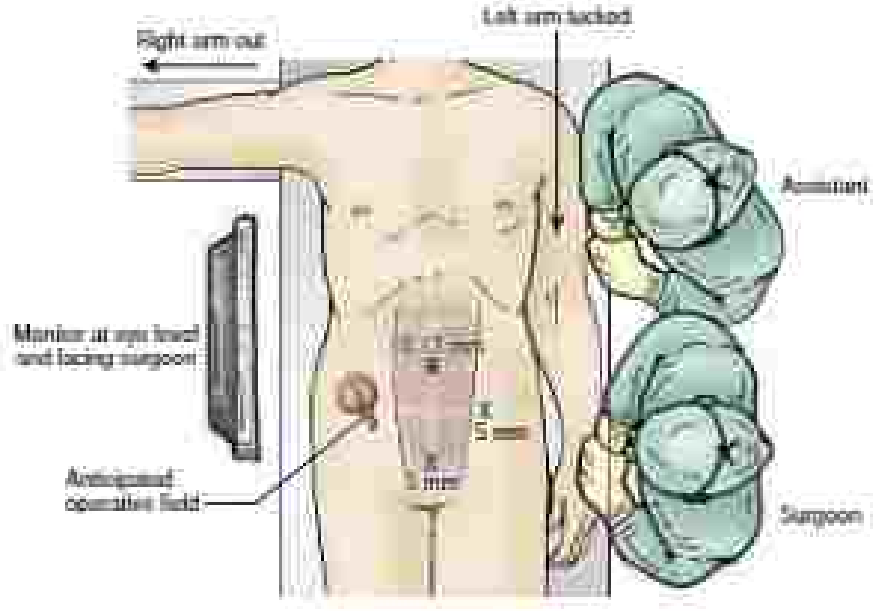

FIG. 2 Operating room, patient positioning, and port placement for laparoscopic appendectomy in pediatric patients. The right arm may also be easily tucked and smaller ports may be utilized.

position with the left side down increases exposure. When a normal-appearing appendix is found at laparoscopy for suspected appendicitis, it should be removed to decrease future diagnostic uncertainty. The base of the appendix is exposed at the convergence of the taenia coli of the cecum. Careful blunt and sharp dissection is carried out to identify the tip of the appendix, which is grasped and elevated toward the anterior abdominal wall. This can be quite challenging in the case of severe inflammation. It may be helpful to mobilize the cecum and the ascending colon, especially in the case of an inflamed retrocecal appendix. A tunnel is then created bluntly at the base of the appendix, and the mesoappendix is divided with an endoscopic vascular stapler, leaving the uninflamed base of the appendix exposed. In children, we have used hook electrocautery to divide the mesoappendix instead of a stapler. An endoscopic gastrointestinal stapler is then placed across the base of the appendix and fired, and the specimen is placed in an endoscopic bag and removed through the initial umbilical port site (Fig. 3). It is critical to ensure that the entire appendix is removed, which is accomplished by careful attention to the presence of the base at the confluence of the taenia coli.

When obviously murky fluid is encountered, it should be aspirated completely. In the presence of an abscess, the cavity should be aspirated. Data from prospective randomized trials by Irish Peter et al. and Akkersdijk and Tuma show no benefit of moderate peritoneal irrigation with normal saline. Other reports have shown irrigation may actually increase postoperative intra-abdominal abscess formation.

Postoperatively, most patients advance to a regular diet within 1 day and are discharged the day following surgery. In properly selected patients who meet discharge criteria in the postanesthesia recovery unit, outpatient appendectomy can be considered. Fraser et al. performed outpatient appendectomy in more than 80% of cases, with low morbidity (7%), low readmission (1%), and high patient satisfaction (89% preference for outpatient management). No postoperative antibiotics are indicated for nonperforated acute appendicitis. In a randomized controlled trial of 268 patients, the rate of postoperative infectious complications was not significantly different between groups who received 1 dose of perioperative antibiotics, 3 doses of antibiotics, or 5 days of perioperative antibiotics (6.7%, 6.8%, and 3.6% respectively).

Risks of laparoscopic appendectomy include surgical site infection, bleeding, bowel injury, prolonged postoperative ileus, incisional hernia, and bowel obstruction. Although morbidity is quite rare and the risk of complications in simple appendicitis is low, postoperative morbidity can be expected more frequently after surgery for perforated appendicitis. After laparoscopic appendectomy for perforated appendicitis, median length of stay is 3.7 days vs 1.86 for simple appendicitis. Almost 10% of patients with perforated appendicitis will develop an intra-abdominal abscess after surgery, which can usually be treated with percutaneous drainage.

Management of Perforated (Complicated) Appendicitis

Perforation is confirmed in up to 20% of appendicitis at presentation. Some of these patients will have diffuse peritonitis, and others will have a well-formed periappendiceal abscess. The presence of a perforated appendix on preoperative imaging does not preclude up front surgery, and perforation is detected at laparoscopy in nearly half of all cases when perforation is not suspected, although a more difficult operation should be anticipated. The management of patients with perforated appendicitis is therefore dictated by the clinical presentation and illness severity. In patients with generalized peritonitis or septic shock, patients should be resuscitated and undergo immediate appendectomy, and the initial approach should still be laparoscopic. By contrast, patients with complicated appendicitis with phlegmon or abscess formation can be considered for treatment by antibiotics and radiographically guided percutaneous drainage. As shown in a meta-analysis of more than 1500 patients by Swallis et al., immediate appendectomy in this group is associated with higher incidence of bowel obstruction, prolonged ileus, intra-abdominal abscess, surgical site infection, and need for reoperation. Another meta-analysis of 61 studies by Andersson and Petrosil found similar results and showed that nonsurgical treatment was successful in 93% of cases. In contrast, some surgeons advocate for up-front appendectomy and Mentula et al. found operative abscess drainage to be feasible, safe, and associated with fewer readmissions and additional interventions. Because more than 10% of patients in that study required conversion to open surgery, bowel resection, and incomplete appendectomy, antibiotics and percutaneous drainage remains the recommended treatment. Empiric intravenous antibiotics follow preoperative recommendations for broad gram-negative coverage, and conversion to oral antibiotics occurs when a regular diet is tolerated. Antibiotic choice may be narrowed based on operative cultures. If source control is successfully achieved by radiographically guided percutaneous drain placement, antibiotics should be continued for four days only.

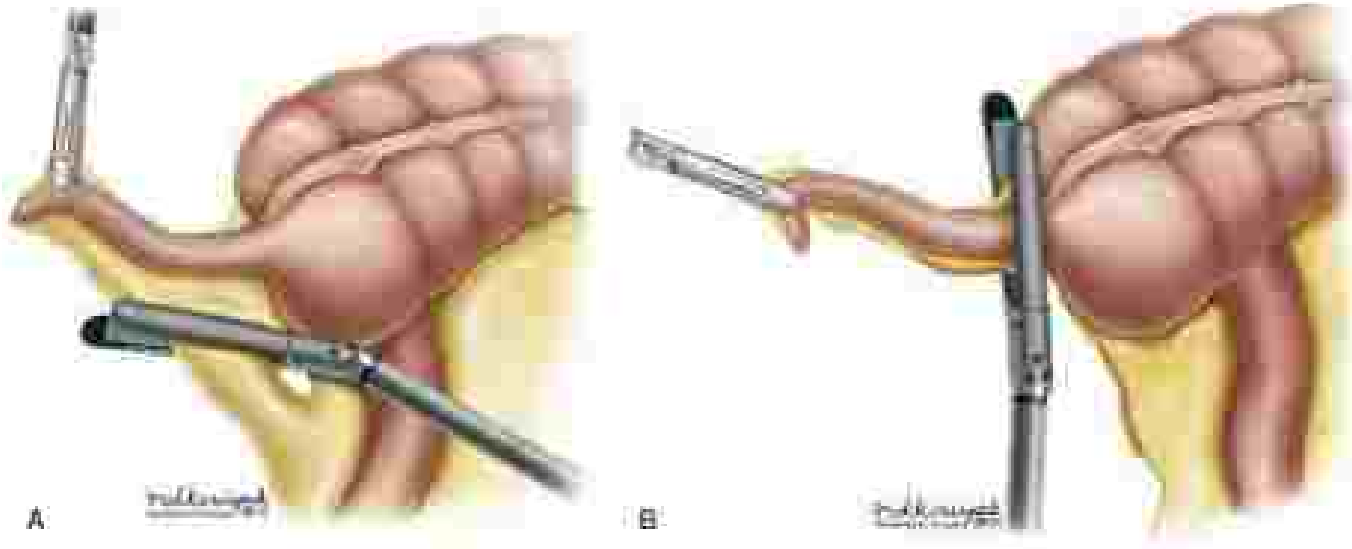

FIG. 3 (A) A window is created through the mesoappendix adjacent to the base of the appendix, and the mesoappendix is divided with a vascular stapler. (B) The base of the appendix is stapled and divided using an endoscopic gastrointestinal stapler.

as dictated by the SIS Multicenter Study of Duration of Antibiotics for Intraabdominal Infection trial. However, if there is no drainable collection and if source control cannot be achieved completely, a longer course of antibiotics (7 days) is warranted. If patients fail to improve clinically with antibiotics and drainage, operative intervention may be indicated.

CURRENT CONTROVERSIES AND SPECIAL PATIENT SITUATIONS

Nonoperative Management of Acute Appendicitis

Although appendectomy remains the treatment of choice for acute appendicitis, several randomized trials have compared appendectomy with a nonoperative approach that involves treatment with antibiotics alone. Results show that up to 37% of patients do end up requiring appendectomy within the first year after antibiotic treatment. Additionally, in a 5-year follow-up of the Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis randomized controlled trial published in 2018, 64% of patients who were randomized to antibiotics alone underwent appendectomy between 1 and 5 years after diagnosis. Sakran et al compiled the highest quality meta-analysis of five randomized controlled trials of nonoperative management of acute appendicitis. They found treatment efficacy at 1 year was only 63.8% in nonoperative treatment versus 93% in patients who underwent appendectomy. Additionally, they found no advantage to nonoperative management with regard to length of hospital stay, duration of pain, and time off work. An important limitation is that all studies excluded immunocompromised and pregnant patients.

Interval Appendectomy

Interval appendectomy is considered in patients who have undergone initial nonoperative management of perforated appendicitis. Removal of the appendix is considered safe after 6 weeks or so, by which time the acute inflammatory process will have settled down. Those who advocate for performing an interval appendectomy state its role in eliminating recurrence while also excluding underlying appendiceal malignancy, whereas others caution that most patients will never develop appendicitis after an initial perforation, perhaps because the appendiceal lumen has become obliterated. For these reasons, interval appendectomy is not universally recommended, although patients 40 years and older should undergo interval CT scan and colonoscopy to rule out malignancy. In children, the 2017 multicenter randomized Children's Interval Appendectomy trial found that up to 23% of children randomized to "active observation" had an appendectomy within 1 year of initial occurrence, and the morbidity of interval appendectomy was low at 6% (half that of the reported morbidity in adults). Interval appendectomy is thus generally offered to children.

Appendicitis in Pregnancy

Acute appendicitis is the most common nonobstetric indication for surgery during pregnancy and affects 1 in 500 to 2000 pregnancies. The concern here is the development of both fetal and maternal morbidity, which is influenced by the severity of the underlying inflammatory process, the risk of surgery, the danger of performing a negative exploration, and the risks of anesthesia. Fetal loss is 1.5% in nonperforated appendicitis but rises to 36% in complicated appendicitis. A multidisciplinary approach with early anesthesia and obstetric consultation should be standard. In pregnant patients, appendectomy is highly recommended over a nonoperative approach, and laparoscopic appendectomy should be offered as the initial approach in all trimesters of pregnancy. A recent large meta-analysis shows potential advantages to laparoscopic appendectomy in pregnancy, despite prior low-level evidence that indicated it was associated with increased fetal loss and early delivery. General laparoscopic principles in pregnancy apply for appendectomy. Hasson's technique is preferred for access, pneumoperitoneal pressures should be minimized, and dependent positioning may alleviate hemodynamic derangements. Special consideration to the cephalad position of the appendix throughout pregnancy should be noted and necessitates adjusted port placement.

Appendicitis in Infants and Small Children

Acute appendicitis in infants and small children may raise additional diagnostic challenges, especially in the infant and toddler age ranges, in which high rates of perforation are seen and contributes to increased morbidity. Several studies reveal that children younger than 5 years represent approximately 17% of cases of pediatric appendicitis. Within this cohort, as age decreases, perforation rates increase: more than 80% of patients younger than 3 years present with perforated appendicitis. Presentation is often delayed, with average time from onset of symptoms to emergency department arrival of 1.6 days. Presenting complaints are more commonly fever (85%), vomiting (47%–56%), and diarrhea (13%–43%). The differential diagnosis for these symptoms includes more common ailments such as primary respiratory disease, intussusception, and gastroenteritis. Early pediatric surgical involvement is crucial to reduce rates of complicated appendicitis in infants and small children.

Incidental Appendectomy

Incidental appendectomy is the resection of the appendix accompanying a separate operation without overt or definitive evidence of appendicitis. The rationale for incidental appendectomy is to eliminate the risk of appendicitis in the future or in the setting of diagnostic uncertainty. The risks of incidental appendectomy include an increased risk of infection and potential loss of the appendix for subsequent gastrointestinal or urogenital reconstruction. Incidental appendectomy should therefore be strictly avoided in patients at risk for bowel and bladder incontinence, specifically those with choanal malformations, exstrophy, anorectal malformations, neurologic conditions including ventriculoperitoneal shunts for hydrocephalus, chronic constipation, and Hirschsprung's disease because the appendix may be used as part of the reconstruction. In general, incidental appendectomy should be reserved for cases in which future appendicitis will pose a particular diagnostic dilemma or future appendectomy is predicted to be unusually challenging.

Chronic Appendicitis

Various authors have described a subgroup of patients who present with chronic lower abdominal pain that is relieved by performing appendectomy. These patients have often been worked up for other known gastrointestinal conditions, most notably inflammatory bowel disease, and often have evidence on CT or MRI showing a dilated appendix or an appendicolith. In these patients, blood work is universally normal, and there are no particular aggravating or relieving factors linked with the lower abdominal pain. Although performing an appendectomy can be curative in selected patients, those patients who do not have chronic appendicitis will not benefit, and so patient selection is very important. Van Rossem et al report their series of successfully treating 10 patients with chronic right lower quadrant pain with elective appendectomy. In their strict selection process, patients underwent preoperative imaging and colonoscopy to rule out inflammatory bowel disease and malignancy. Only patients with typical localized pain were offered surgery, and the pain was often described as persistent and progressive. None of the patients in their cohort suffered infectious complications, and 8 of 10 specimens showed evidence of inflammation. Similarly, in a randomized controlled trial of 42 patients evaluating laparoscopic appendectomy for chronic right lower quadrant pain, Reumers et al found that removing the appendix was more likely to result in pain relief than not. Inclusion criteria in Reumers et al's study included at least 3 months of persistent right lower quadrant pain. Patients with chronic back

pain, previous abdominal surgery, inflammatory bowel disorder, and gynecologic disease were excluded. In summary, chronic right lower quadrant pain without evidence of acute inflammation may warrant elective appendectomy in selected patients.

SUMMARY AND FUTURE DIRECTIONS

Management of appendicitis remains one of the hallmarks of a well-qualified abdominal surgeon. That said, the diagnosis can be extremely challenging, in part because of the variable anatomic location of the appendix and significant uncertainty regarding the underlying pathogenesis of the disease. Although patients who undergo prompt appendectomy can be cured successfully, those who present after a prolonged duration of symptoms can have significant morbidity resulting from untreated abdominal sepsis. For these reasons, appendicitis remains a major cause of death in underresourced environments. In otherwise stable patients, controversy exists regarding the very need for appendectomy, given that many patients will be successfully treated with antibiotics alone. Future research will therefore continue to optimize our ability to more accurately ascertain the diagnosis of appendicitis and will more successfully predict the clinical course of patients treated with operative versus nonoperative approaches.

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MANAGEMENT OF HEMORRHOIDS

Izi Okukhare, MD, and Robert Arnaja, MD, FACS, FRCS, FASCRS

The term *hemorrhoid* is used to describe abnormally large or symptomatic, dilated vascular cushions in the anal canal or anal verge (Fig. 1). The normal human anal canal has specialized vascular cushions that contribute to approximately 20% of the normal anal resting pressure. These vascular cushions contain submucosal blood vessels, connective tissue, and smooth muscle. Hemorrhoids are typically located in the left lateral, right posterior, and right anterior regions of the anal canal. The presence of these vascular cushions is critical to the maintenance of normal fecal continence during times of increased anal tone and increased abdominal pressure. Internal hemorrhoids are located proximal to the dentate line and covered with anoderm, whereas external hemorrhoids are located distal to the dentate line and are covered with skin. Internal hemorrhoids are classified based on the degree of prolapse.

ETIOLOGY AND SYMPTOMS

Hemorrhoids are typically caused by increased intraabdominal pressure resulting from constipation or diarrhea. Other causes of hemorrhoids include pregnancy, chronic obstructive pulmonary disorder, and hepatic dysfunction resulting in increased portal venous pressure. The increase in pressure results in abnormal dilation of the internal hemorrhoidal venous plexus and subsequent distention of the arteriovenous anastomosis and prolapse of the engorged hemorrhoidal tissue. Obtaining a complete history before the anorectal examination is crucial to identify the cause of the hemorrhoid.

Symptoms of hemorrhoids range from mild to severe and, in some rare cases, can result in life-threatening hemorrhagic shock as a result of massive rectal bleeding. Approximately 10 million people in the United States suffer from hemorrhoidal symptoms. More than 50% of patients with hemorrhoidal disease are older than 50 years. In the United States, the reported prevalence of symptomatic hemorrhoidal disease is 4.4%, with approximately 10 million people affected.

Hemorrhoidal symptoms include rectal bleeding, anal bulge, pruritus, anal pain, mucus discharge, itching, and difficulty with daily hygiene.

As a cautionary note, most patients with other anorectal maladies may present with complaints of hemorrhoids. It is crucial to evaluate for other causes of rectal bleeding such as anal fissure, rectal prolapse, and pruritus, and anorectal cancer resulting from similar presenting symptoms. Hemorrhoidal bleeding is typically described as bright red and some with bowel movement with little or no transmas. The extent of prolapse should be documented clearly to avoid misdiagnosis. A family history of colorectal cancer should be documented as well. A thorough examination of the anorectal area, including an anoscopy or proctoscopy when appropriate, should be performed in the clinical setting. Patients with atypical symptoms such as symptoms of a bowel obstruction or abdominal pain should be referred for colonoscopy as well to avoid delay of the appropriate diagnosis.

The most common symptom of internal hemorrhoidal disease is painless bleeding; however, other symptoms such as swelling, prolapse, hygiene problems, fecal incontinence, pruritus, and anal pain can also be present. Bleeding because of hemorrhoidal disease is typically bright red in color from the distal location and the arteriovenous source of bleeding. Patients also report bleeding during bowel movements with squirting of blood into the toilet during straining. Melanotic stools or blood mixed in the stool is typically indicative of a more proximal bleeding source requiring endoscopic evaluation. Prolapse of internal hemorrhoids below the dentate line may lead to compromise of the anal sphincter tone resting pressure, resulting in fecal incontinence and anal pruritus. Documentation of the presence of incontinence as well as anal sphincter tone before any surgical intervention is vital to defend against any frivolous litigation after surgical intervention if incontinence persists.

External hemorrhoids, on the other hand, typically cause severe rectal pain and discomfort when acutely thrombosed or ulcerated (Fig. 2). The pain from thrombosed hemorrhoids is quite different from that of an anal fissure. The pain from thrombosed external hemorrhoid typically subsides in 48 to 72 hours, whereas the pain from anal fissure is cyclical in nature and worsens with bowel movements. It lasts for 30 minutes to 1 hour after bowel movements. Patients describe the pain from a fissure as "passing shards of glass"; in contrast, acute pain from incarcerated ulcerated internal and external hemorrhoids usually progressively worsens and could lead to perianal sepsis. Anorectal examination of patients with severe anorectal pain can be quite challenging in the absence of sedation in the office or clinical setting due to the degree of discomfort associated with an anorectal examination. For such patients, stringent examination

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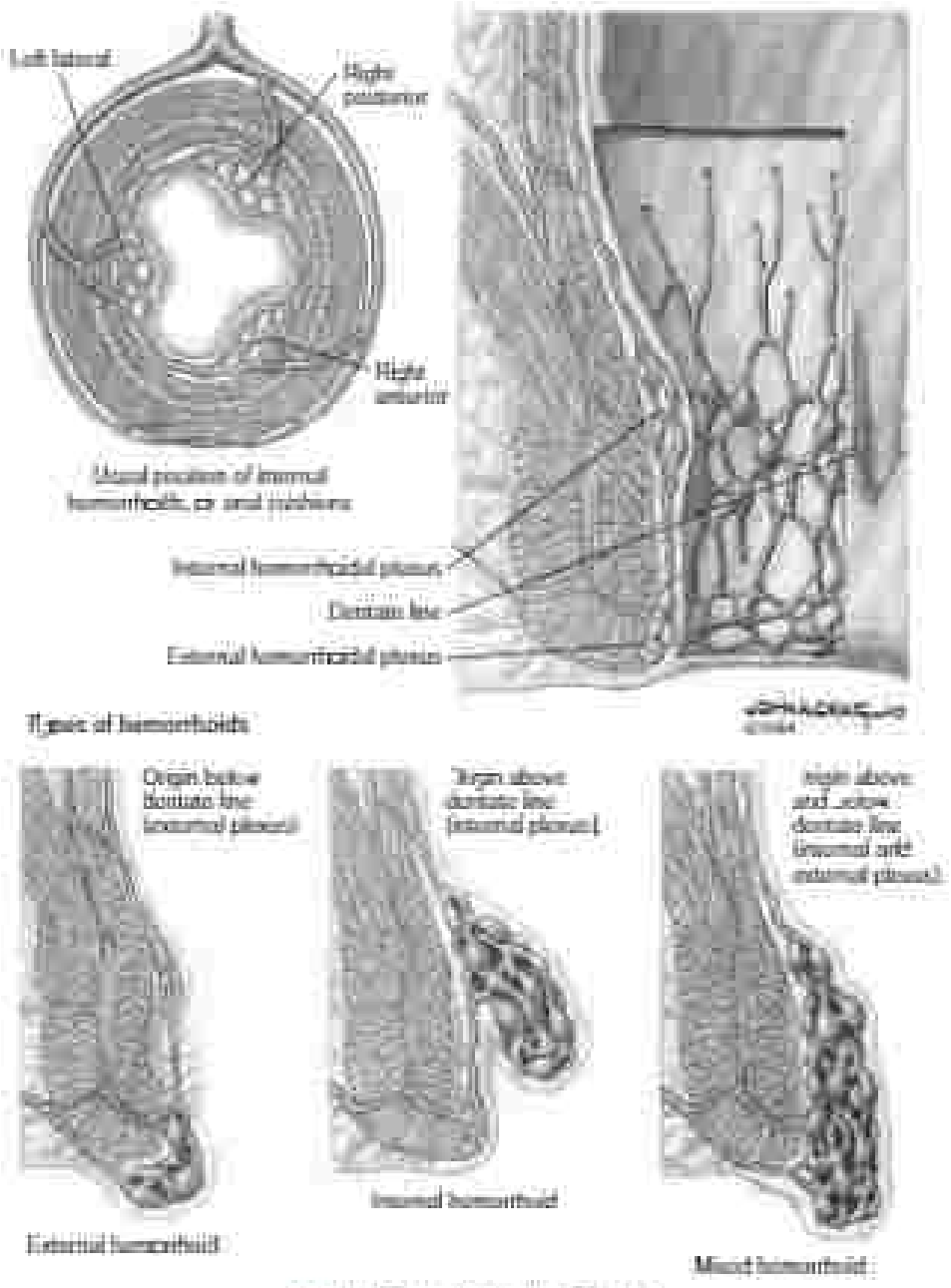


FIG. 1 Location and types of hemorrhoids.

under anesthesia with immediate treatment of the anorectal malady may be the best option for management.

CLASSIFICATION

The classification system for hemorrhoidal disease applies only to internal hemorrhoids. Internal hemorrhoids are managed based on the classification. Grades I and II can be managed nonoperatively, whereas grades III and IV often require surgical management.

Internal Hemorrhoid Classification

Grade I: Small bulge into the anal canal, no prolapse, may bleed.
Grade II: Prolapse reduces spontaneously, may have bleeding, burning or itching.
Grade III: Prolapse must be manually reduced, bleeding, itching, and mucoid drainage.
Grade IV: Prolapse not amenable to manual reduction, pain, bleeding, mucoid drainage, and may have secondary thrombosis.

TREATMENT OF HEMORRHOIDS

Medical Management

Treatment for hemorrhoidal disease typically begins with lifestyle modification as a first line therapy for most patients. Patient should be placed on fiber supplementation, increased water intake, and physical activity. Patient should be encouraged to drink at least eight glasses of water a day, except for patients with congestive heart failure. An attempt to reduce the amount of time spent while having bowel movements should be emphasized. Reading or using electronic devices while having a bowel movement should be discouraged because this prolongs the duration of straining with bowel movement, resulting in concomitant increase in the anorectal pressure from prolonged squatting.

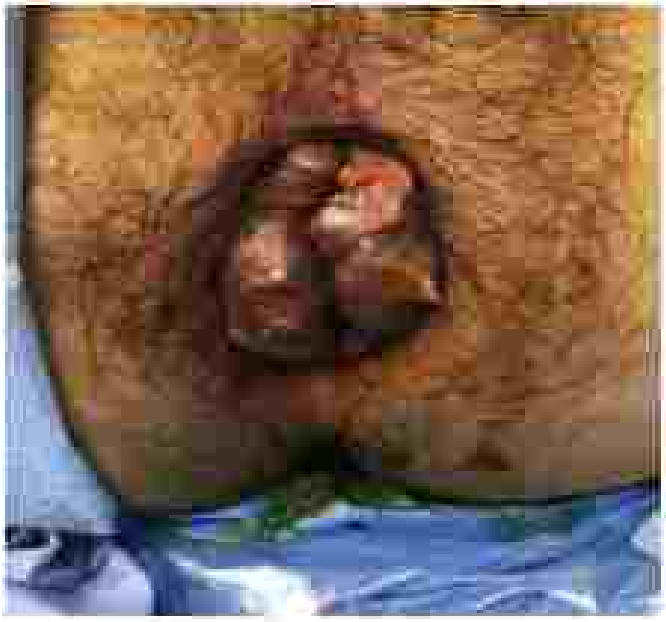


FIG. 2 Prolapsed external and internal hemorrhoids.

A large systemic review showed that conservative therapy in patients with grade I internal hemorrhoids was sufficient enough to decrease symptomatic bleeding and prolapse. The recommended optimal medical therapy for symptomatic grades I and II hemorrhoidal disease includes warm sitz baths two to three times daily, fiber supplementation up to 24 g daily, increased water intake, and regular laxative use. Topical hemorrhoidal creams available over the counter have not been shown to consistently reduce symptoms or treat the underlying disease. After failure of medical therapy for grades I and II hemorrhoidal disease, rubber band ligation, sclerotherapy, or infrared coagulation can be used to treat patients in the office without requiring general anesthesia.

Most patients self medicate with over the counter products before seeking treatment from an experienced physician. Over the counter products include ointments, creams, suppositories, foams, and wipes. Most products contain either a single or combination of several agents including a protectant and an active ingredient. These agents either provide temporary relief from pain, itching, burning, and lubrication. Some products contain local anesthetics such as benzocaine, lidocaine, and pramoxine. Some other active agents include vasoconstricting substances such as epinephrine, phenylephrine, or ephedrine. Barrier products include dimethicone hydrous gel, cocoa butter, mineral oil, zinc oxide, starch, and petrolatum. Corticosteroids can be used as well, which provide antiinflammatory relief. Prolonged use of these products may result in thinning of the perianal skin or exacerbation of symptoms if used incorrectly for more than 4 weeks.

Rubber Band Ligation

Rubber band ligation is the most common office procedure used to treat symptomatic internal hemorrhoids (Fig. 3). It is efficacious for grade I to III hemorrhoids and does not require local anesthetics. Patients are typically placed in the jackknife position or a left lateral decubitus (Sims position). We prefer the latter position because it provides excellent exposure and is more comfortable for patients with all body types.

After careful visual examination of the perineum and anal verge, a digital rectal examination is performed before anoscopy to evaluate for any other anorectal lesions present in addition to the hemorrhoids. It is crucial to ensure that the patient does not have a full thickness rectal prolapse because placing a rubber band on prolapsed rectum will result in a solitary rectal ulcer and further bleeding. The rubber band is typically placed 2 cm above the dentate line to avoid somatic pain (Fig. 3), although suction rubber band ligator is available, this device requires the use of a pneumatic suction device. Sensation above the dentate line is tested with McGivney hemorrhoidal forceps before application of one or two rubber bands per hemorrhoidal tissue. Banding several hemorrhoids at the same sitting increases the risk of complications such as pain, fever, bleeding, thrombosis of adjacent hemorrhoidal tissue, urinary retention, and perineal sepsis. If the patient has extreme pain after placement of a rubber band, immediate removal of the rubber band is recommended using either a No. 11 blade or a suture hook. Avoidance of blood thinners for at least 7 days reduces the risk of postbanding bleed. The use of narcotics or oral antibiotics is not necessary after hemorrhoid band placement. Delayed symptoms such as fever, pelvic sepsis, and urinary retention should be addressed immediately because they may represent early signs of perineal sepsis.

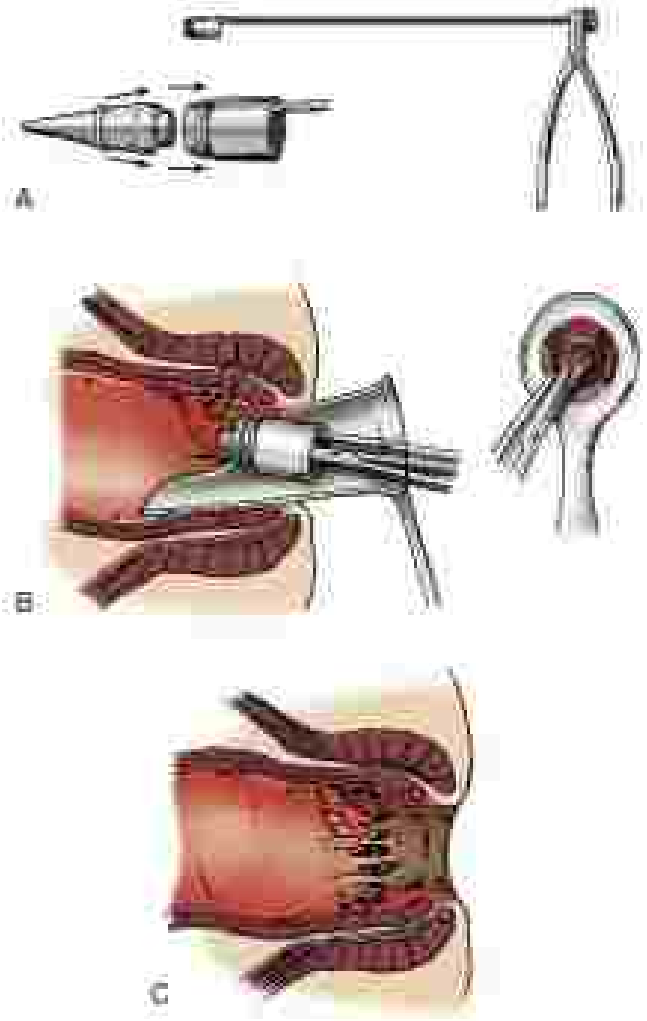


FIG. 3 Rubber band ligation of internal hemorrhoids. (A) Rubber band placed onto banding gun. (B) Hemorrhoid is grasped 2 cm above the dentate line and the band advanced over the hemorrhoid. (C) Band in correct position after ligation.

Sclerotherapy

Sclerotherapy is less commonly used for management of hemorrhoidal disease. A sclerosing agent is injected directly into the hemorrhoids, resulting in scarring, fibrosis, and fixation of the hemorrhoidal tissue. Agents typically used include hypertonic saline solution or 5% phenol

solution. The sclerosing agent is injected using a long 25-gauge needle just above the dentate line into the submucosa of the hemorrhoid. Approximately 2 to 3 mL of the sclerosing agent is injected without the aid of anesthesia. Side effects of this procedure include bleeding, injection site pain, ulceration, and sloughing of the mucosa with subsequent abscess or perirectal sepsis. Repetitive sclerotherapy can result in scarring, anal stricture, or anal fistula. Symptoms of fever, urinary retention, perineal drainage, and worsening pain should necessitate a repeat visit to the office and examination under general anesthesia if needed.

Other Office-Based Procedures (Infrared Coagulation)

Infrared photocoagulation, bipolar diathermy, and direct current electrical therapy are other office based procedures used less commonly than ligation (Fig. 4). The technique uses infrared energy to generate heat, resulting in protein coagulation and inflammatory response in the hemorrhoidal bed. The end effect is scarring and fixation of the hemorrhoid. A tungsten halogen lamp is used to generate the infrared radiation (IRC 2100, Redfield Corporation). Application of this device will yield a 4 mm^3 focus of coagulation with a 2.5-mm deep ulcer.

The HET bipolar system (Covidien) can also be used in the clinical setting without anesthesia. Using a bipolar clamp, the hemorrhoidal bundles are grasped and cauterized. This technique is used for grades I and II hemorrhoidal disease. The complications and postoperative care are very similar to that for sclerotherapy and infrared coagulation.

OPERATIVE TREATMENT

Operative hemorrhoidectomy is indicated for patients who do not respond to nonoperative management and office based procedures. It is also reserved for mixed hemorrhoids with internal and external components or grade III to IV internal hemorrhoids with bleeding. Preoperative history and physical examination as well as careful counseling about the risks, benefits, and expected results after the surgical procedure are crucial to ensuring patient satisfaction. A meticulous documentation of preoperative anal sphincter tone and presence or absence of incontinence is crucial to the defense against frivolous lawsuits in the face of the most dreaded long-term complication of incontinence after hemorrhoidectomy.

Approximately 5% to 10% of patients with hemorrhoids require hemorrhoidectomy compared with the large number of patients with hemorrhoidal symptoms. Excisional hemorrhoidectomy remains the gold standard because of the low risk of complications and its efficacy profile. The notorious postoperative pain can be ameliorated by using a standardized pain management protocol in the perioperative period. Incorporation of nonnarcotic analgesics, constipation, or diarrhea reducing regimen as well as long-acting local anesthetic remains the cornerstone of postoperative pain management after hemorrhoidectomy. The excisional hemorrhoidectomy technique can be divided into three major types discussed in the following section.

Ferguson's Hemorrhoidectomy

Ferguson's hemorrhoidectomy (closed) was first described in 1971 and is the most commonly performed hemorrhoidal procedure in United States (Fig. 5). Enemas are given before the procedure to clean out the distal rectum, and the patient is typically placed in the lithotomy position in stirrups or in the prone jackknife position with the buttocks taped apart. The patient is then given either general or regional anesthesia in conjunction with local anesthetic. We prefer to give a bilateral pudendal nerve block with long-acting local anesthetics as well as injecting the base of the hemorrhoidal bundle during the procedure. The perineal and anorectal examination with an anoscope are performed first to evaluate for any other anorectal abnormalities. The hemorrhoidal bundle is grasped using forceps and a Kelly clamp is placed at the base of the hemorrhoidal column, with care taken to avoid involvement of the internal and external anal sphincters. A ligation of the vascular pedicle of the hemorrhoidal bundle was performed at the apex of the clamp using an absorbable suture either consisting of Vicryl or chromic on a tapered needle. The hemorrhoidal bundle is then excised from the sphincter complex using either fine tip scissors or a bipolar sealing device such as the Harmonic or LigaSure device. Multiple studies have shown that the Harmonic Ace has reduced postoperative pain, bleeding, and results in a significantly faster operation than monopolar diathermy. Although the increased cost of this device is a limiting factor, the use of a bipolar sealing device should be considered in cases of complicated prolapsed thrombosed hemorrhoids and in patients receiving anticoagulation therapy. The resultant hemorrhoidal bed is then closed in a running locking fashion using absorbable sutures to reduce hemorrhage and to enhance rapid healing of the defect. We prefer to perform this procedure with the patient under general anesthesia in the lithotomy position with stirrups. A small opening is typically left distally to minimize stenosis and facilitate anal drainage of any retained fluid in the hemorrhoidal bed, reducing the risk of perirectal sepsis.

Milligan-Morgan Hemorrhoidectomy

This open technique is the most commonly used in the United Kingdom. It follows the technique described by Milligan and Morgan in 1937. The technique is identical to Ferguson's technique except that, after the apex of the hemorrhoidal bundle is suture ligated, the

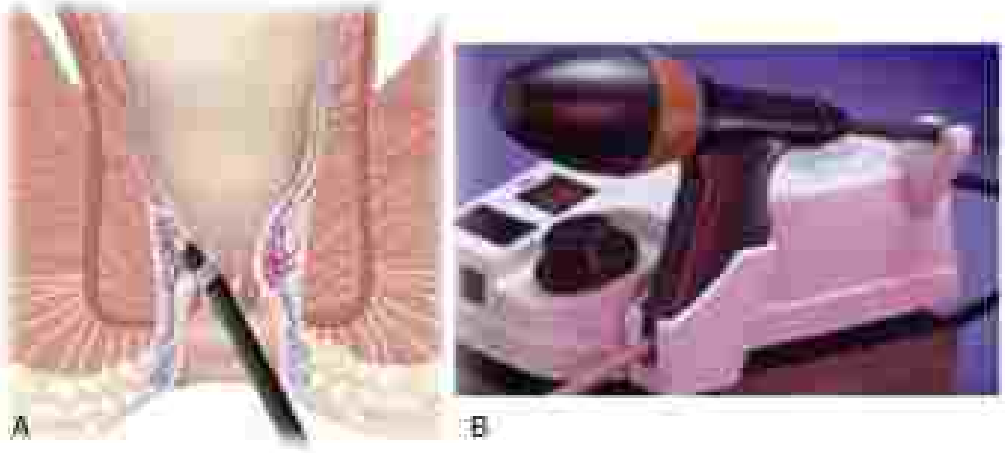


FIG. 4 Infrared coagulation of internal hemorrhoids. (A) Applicator is applied to the apex of the hemorrhoid. (B) IRC 2100 device (Redfield Corporation).

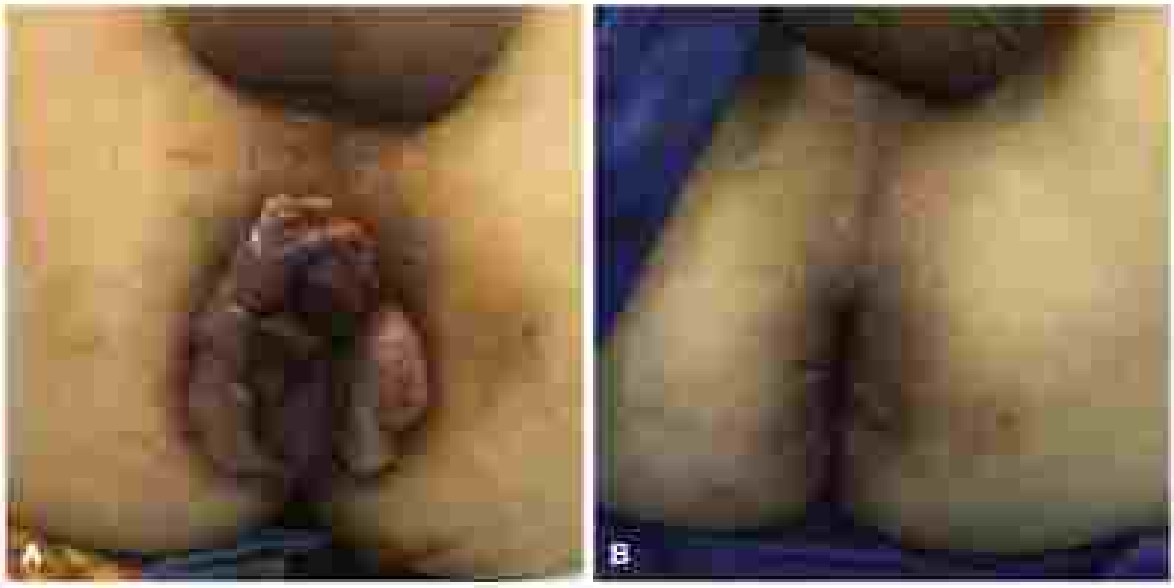
hemorrhoidal bundle is amputated and the defect is left open to granulate. The advantage of this technique includes reduced operative time and decreased pain; however, it typically presents with longer healing time compared with the closed technique. Multiple modifications of the excisional hemorrhoidal technique is available including hemorrhoidectomy, which involves suture ligation of the hemorrhoidal bundle without any removal of the hemorrhoidal tissue and can be used when necessary to prevent removal of excessive anal tissue and anal stenosis.

Circumferential Technique

The circumferential technique, also known as the whitehead hemorrhoidectomy, involves circumferential excision of the internal hemorrhoids as well as redundant mucosa just proximal to the dentate line. This technique is more commonly performed in the United Kingdom with low utilization in the United States. The drawback of this technique is the significant mucosal ectropium, also known as whitehead deformity, and high rates of anal stenosis and incontinence. This technique may have a utility in patients with significant circumferential mucosal prolapse in addition to symptomatic hemorrhoidal disease.

Transanal Hemorrhoidal Dearterialization

Doppler-guided hemorrhoidal artery ligation is a newer technique that involves using a transanal hemorrhoidal Doppler for targeted



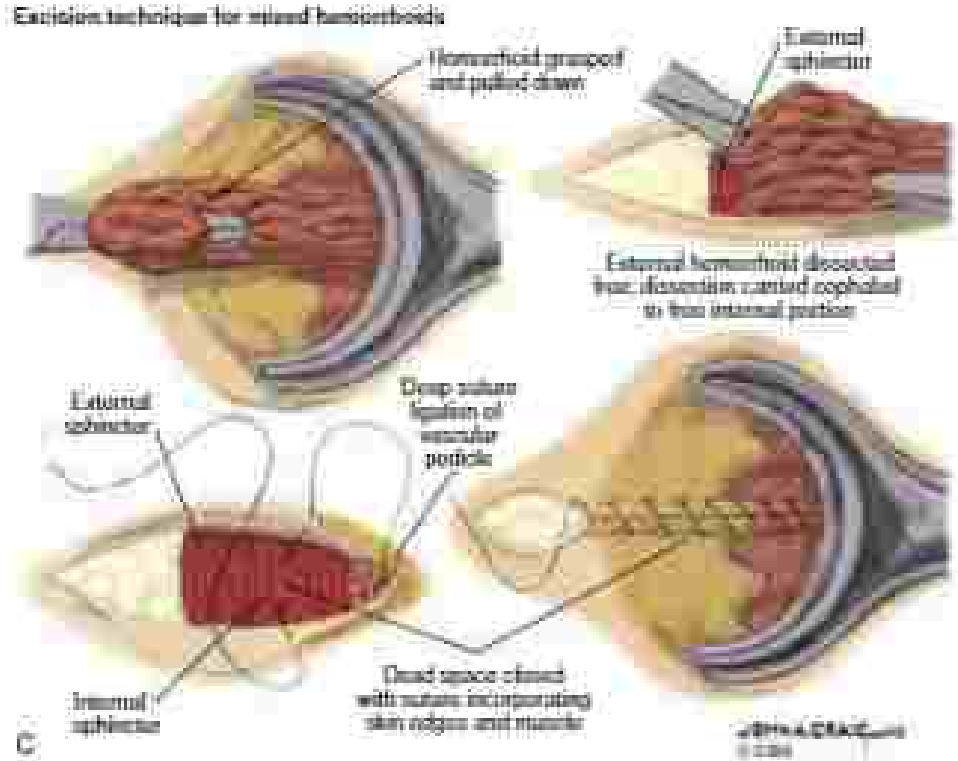


FIG. 5 (A) Before and (B) after excisional hemorrhoidectomy. (C) Ferguson's hemorrhoidectomy.

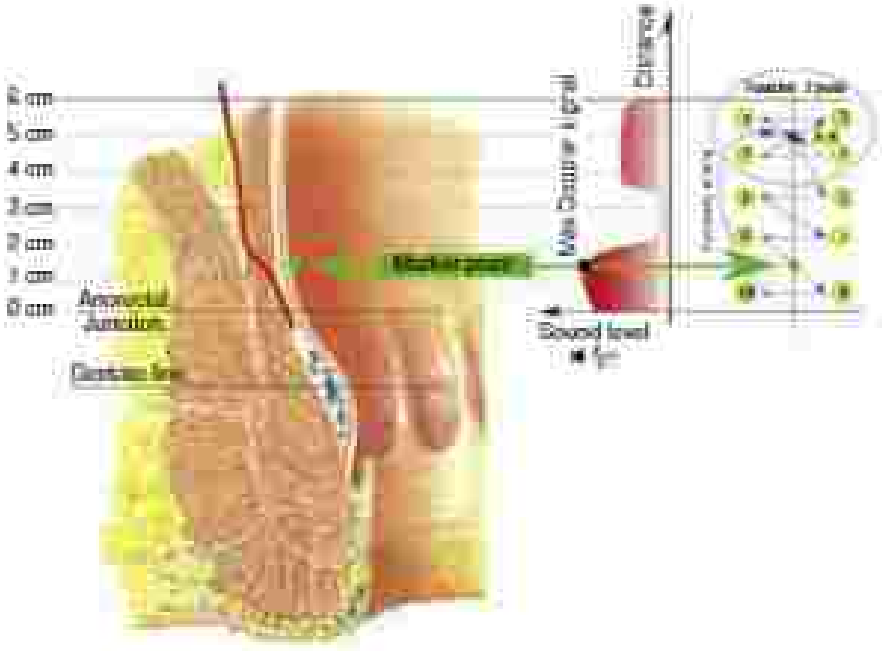


FIG. 6 Schematic of transanal hemorrhoidal dearterialization and mucopexy. Marker points denote the location of the best Doppler signal for hemorrhoidal ligation. A 2-suture is placed at the location for ligation above. For higher grade hemorrhoids, mucopexy with running sutures is performed starting proximally and encompassing the ligation point, pulling the redundant mucosa up into the rectum (right side of image). [From Kaur C, et al. Doppler guided ligation of hemorrhoidal arteries with mucopexy: a novel approach for the treatment. Ann Surg. 2004;239(5):616.]

hemorrhoidal dearterialization (Fig. 6). Doppler guidance is used to isolate hemorrhoidal arteries for ligation. This technique is typically used for grade II to III internal hemorrhoids. There is less pain and shorter operative time with this procedure. The anesthesia and patient position are similar to that of other hemorrhoidal techniques. Several targeted figure of 8 stitches are placed to ligate the hemorrhoidal vascular bundles. Four or more sutures are typically placed at a single setting. In addition, for high grade hemorrhoids such as grade III to IV hemorrhoids, mucopexy is performed; this is known as mucopexy repair. The combination of the transanal hemorrhoidal dearterialization and mucosal repair procedures in a prospective single blinded study showed a 12 month prolapse recurrence rate of 11%.

Stapled Hemorrhoidopexy EEA Stapler

Stapled hemorrhoidopexy, the procedure for prolapsing hemorrhoids first described by Longo in 1998, is typically reserved for complicated hemorrhoids with mixed internal and external components as well as grade III to IV circumferential hemorrhoids. It was developed to reduce anal pain associated with excisional hemorrhoidectomy. This technique involves the use of a specialized 33 mm end to end anastomotic circular stapler that removes mucosa and submucosa proximal to the hemorrhoids, resulting in a devascularized segment of hemorrhoidal tissue (Fig. 7). The hemorrhoidal tissue is not removed and there are no wounds below the dentate line. As a result, postoperative pain is reduced significantly compared with excisional hemorrhoidectomy. The drawback of stapled hemorrhoidectomy is that it does not adequately address any external hemorrhoidal tissue. The complication rates from stapled hemorrhoidectomy are similar to excisional hemorrhoidectomy; however, the technique has serious additional complications such as perineal sepsis, rectovaginal fistula, rectal ureteral fistulas, rectal perforations, and anal stenosis, which are often very difficult to treat. The stapled hemorrhoidectomy is performed under anesthesia. The hemorrhoidal kit contains an anal dilator, clear plastic anoscope and operating anoscope, and stapler. The anal dilator is inserted first and, circumferentially, a submucosal purse string suture using permanent suture is placed 3 to 4 cm proximal to the dentate line. The partial thickness purse string sutures are placed with care taken to not involve the vaginal wall, seminal vesicles, or the prostate anteriorly. After placement of the purse string suture, the purse string is tied around the anvil of the stapler and the stapler is fired with complete closure. The result is a specimen that contains the mucosa and submucosa of the distal rectum.

Special Situations and Other Considerations

Immunocompromised Patients

Management of hemorrhoids in this cohort of patients can be a challenge for the treating physician. Immunocompromised patients should be managed conservatively because of risk of perineal sepsis and poor wound healing after hemorrhoidectomy. Delayed and failed wound healing has been associated with AIDS. In a study by Moremadi et al., 50% of AIDS patients had incomplete healing 30 weeks after hemorrhoidectomy. For bleeding internal hemorrhoids, when absolutely necessary, sclerotherapy was described as the safer option compared to either rubber band ligation or hemorrhoidectomy.

Portal Hypertension and Hemorrhoids

Portal hypertension is another condition that can result in rectal bleeding and hemorrhoids because of the distal collateral between the inferior hemorrhoidal vein and the systemic venous drainage system. The treating physician should maintain a high index of suspicion with these patients. Rectal varices are common in patients with portal hypertension. One report showed rectal varices were found in up to 78% of patients with portal hypertension. The diagnosis of portal hypertension leading to rectal bleeding is made based on history and physical examination. Nonetheless, a flexible sigmoidoscopy, colonoscopy, and endoscopic ultrasound have been described as useful adjuncts to obtaining the correct diagnosis. Rectal varices on endoscopy are visualized as blue tinted submucosal elevations located in the rectum with direct communication with the portal venous system. Hemorrhoidal bleeding in portal hypertension should be treated conservatively. Rubber band ligation is contraindicated because of the risk of delayed bleeding. Sclerotherapy, if available, is the next treatment of choice when conservative management fails. Sclerotherapy, suture ligation of the bleeding hemorrhoidal vessel, or a stapled hemorrhoidopexy is reserved as the next line of therapy after optimal medical therapy to reduce portal pressure and transjugular intrahepatic portosystemic shunt procedure. In addition to the aforementioned armamentarium, embolization of the bleeding rectal varices has been described.

Pregnancy

The complex changes in the human physiology during pregnancy can aggravate preexisting hemorrhoids or cause new ones. Patients typically present with symptoms ranging from mild to severe. During pregnancy, hemorrhoidal symptoms worsen because of increased

FIG. 1 (A) EEA hemorrhoid and prolapse stapler with DST Series technology. (B) Stapled hemorrhoidopexy technique. Left, Purse-string sutures applied 4 cm above the dentate line. Middle, Stapler advanced into rectum and excision held on the suture. Right, Staple line after completion of procedure. (Courtesy Medtronic, Copyright 2014.)

pelvic pressure resulting from the fetus, increased blood volume, decreased venous return, constipation, and labor related straining. The prevalence of symptomatic hemorrhoid during pregnancy is between 25% and 35%. It is most common in the third trimester. Symptoms are self limiting for the most part and resolve after delivery, rarely needing intervention. Treatment is conservative unless there is strangulated gangrenous, or extensively thrombosed hemorrhoids. In one study, only 2% of pregnant women with strangulated hemorrhoids required emergent hemorrhoidectomy. This was necessary to reduce the incidence of narcotic use and premature labor.

SUMMARY

Hemorrhoidal disease is quite a common complaint in the adult population because of increased constipation and a low fiber diet. A complete history and physical examination involving a digital rectal examination and anoscopy are crucial to exclude other differential diagnoses such as anal fissure, condyloma, and pruritus, rectal prolapse, and anal cancer. Conservative management and dietary changes in addition to stool softer, laxatives, and fiber supplementation remain the mainstay of treatment for stage I to II hemorrhoidal disease. However, after failure of medical therapy and other procedures for recurrent stage III to IV hemorrhoidal disease, excisional hemorrhoidectomy can be recommended after careful counseling to provided about the risk and benefits of the procedure to adequately tailor and manage expectations. Caution should be exercised when dealing with patients in special situations to reduce the likelihood of unrest and complications.

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Diagnosis, Treatment, and Surgical Management of Fissures-in-Ano

Daniel Martin, DO, Marco Ferrara, MD, and Mark K. Sullivan, MD, FACS, FASCRS

Anal pain is a common complaint for patients seeking medical consultation. Although the differential is varied, one of the primary causes are anal fissures. An anal fissure is a longitudinal tear along the sensitive epithelium of the distal anal canal. Often, patients will recall the sentinel event as severe sharp pain during and after defecation. This often leads to fear of subsequent bowel movements. Blood can be apparent on toilet paper or seen in a streak like minimal on stool. Spasms that persist for several hours after a bowel movement are not uncommon.

Although 90% of fissures are located in the posterior midline, up to 25% of fissures in females are found in the anterior midline. Fissures that veer away from the midline should prompt suspicion for other disease processes such as Crohn's disease, anal carcinoma, tuberculosis, syphilis, human immunodeficiency virus, and human papillomavirus. An acute fissure will have the appearance of a simple tear in the anoderm and is defined by symptoms of less than 6 to 8 weeks in duration. Chronic fissures are distinct with their typical hallmark physical examination findings of a distal sentinel pile, a proximal hypertrophied anal papilla, and an exposed internal anal sphincter (IAS) muscle.

The etiology for this disease is uncertain. Although classically described after passage of a large, hard stool, fissures can also be caused by anal trauma and chronic diarrhea. An elevated resting IAS tone has been demonstrated on manometric studies in patients with anal fissures, although it is uncertain if this is a cause or effect of the fissure. The anorectal angle tends to place the greatest mechanical stress in the posterior midline. Paired with the fact that this area has relatively poor perfusion and is susceptible to ischemia, this helps account for the majority of fissures occurring in this location.

Examination of a fissure can be difficult particularly if it is acute as the area can be very sensitive. Gentle skin retraction of the buttocks will often reveal the fissure (Fig. 1).

Once the fissure is confirmed, further examination of the anal canal with fingers or instrumentation is typically not required because the patient will likely not tolerate any invasive examination. If the diagnosis of a fissure is not apparent, an examination under anesthesia may be required for further evaluation to look for other diagnoses. Atypical fissures with suspicious characteristic findings such as lateral appearing, multiple locations, nonhealing, or painless warrant further evaluation and possible biopsies or cultures.

TREATMENT

Nonoperative Management

For patients who present with acute anal fissures, conservative therapy with examination should be the first line of therapy. Fiber supplementation, stool softeners, and sitz baths twice daily, with or without the addition of topical antiinflammatory creams or anesthetics will heal approximately 50% of fissures. A goal of 25 to 30 g of fiber daily for men and 20 to 25 g for women should be an. Adequate hydration with at least eight glasses of water daily is also essential. Fiber and sitz baths are effective in providing symptomatic relief in the first weeks of a developed fissure as well long term healing and recurrences (Jensen, 1986). Sitz baths or heat of any source can help alleviate spasms. A detachable shower head can also be used to apply warm water to the affected area when a bath tub is inconvenient or unavailable.

Although conservative management is quite effective for acute fissures, only approximately 25% of chronic fissures heal with the aforementioned management. Nonoperative management focuses on the hypertonicity of the IAS and ways to induced relaxation of the sphincter. Nitroglycerin and diltiazem are the most common topical solutions. Botulinum toxin (Botox) injections are an alternative to the topical solutions that promote IAS relaxation.

Topical nitroglycerin in the form of 0.2% glyceryl trinitrate (GTN) has a marked effect on healing chronic anal fissures. A recent study by Nelson and colleagues (2012) showed healing rates of 48.9% vs 35.5% in the placebo group. Recurrences at long term follow up were greater than 31% to 47% with a high noncompliance rate resulting from the side effect of headaches. Both diltiazem and nifedipine, either oral or topical, also produce similar relaxation of the IAS compared to GTN. The topical form of diltiazem seems to have the greatest effect on sphincter relaxation with added benefit of fewer side effects, particularly headaches, compared with GTN. The healing rates of fissures are similar to GTN. Rectiv (0.4% nitroglycerin) is an enteral ointment that received US Food and Drug Administration approval in 2011. It is applied twice daily for 6 to 8 weeks with a healing rate of 77% at 24 weeks (Perez-Legaz et al., 2012). Diltiazem and nifedipine, although commonly prescribed, are not US Food and Drug Administration approved for treatment of fissures and require compounding pharmacies to make a topical solution from oral formulations.

Botulinum toxin injections relax the sphincter by inhibiting the release of acetylcholine at the neuromuscular junction. The effects of the injection can produce relaxation for up to 2 to 4 months. Injections can be done in an outpatient setting depending on the patient's tolerance levels. Application dosages as well as location varies per practice with no uniform recommendations. Botox injections were found to be more effective than GTN in terms of healing and side effects, but lateral internal sphincterotomy for healing refractory fissures was 97.3% compared with 60% in the Botox group (Arroyo et al., 2004). A more recent randomized controlled trial comparing Botox injection in conjunction with topical diltiazem to have a 1 year healing rate of 65% compared with 98% with lateral internal anal sphincterotomy (Gandhiraker et al., 2015). Botox may be more beneficial for patients in which continence maybe an issue after surgery.

Operative Management

Sphincterotomy, or partial division of the internal anal sphincter, has been the mainstay therapy for failed medical management and leads to fissure healing in 88% to 100% of patients. The lateral internal sphincterotomy can be performed in an open or closed technique. The posterior midline is avoided because of the high rates of keyhole deformities that can lead to fecal incontinence and soiling. The open technique involves making a small radial incision over the intersphincteric groove, dissecting and separating the internal sphincter muscle away from the anoderm, and partially dividing the muscle. Care is taken not to divide the sphincter completely because this increases the rate of incontinence. The closed technique is performed by inserting the scalpel blade, classically a No. 11 blade, aligned with the intersphincteric groove, turning the blade medial and dividing the muscle without open exposure of the IAS.

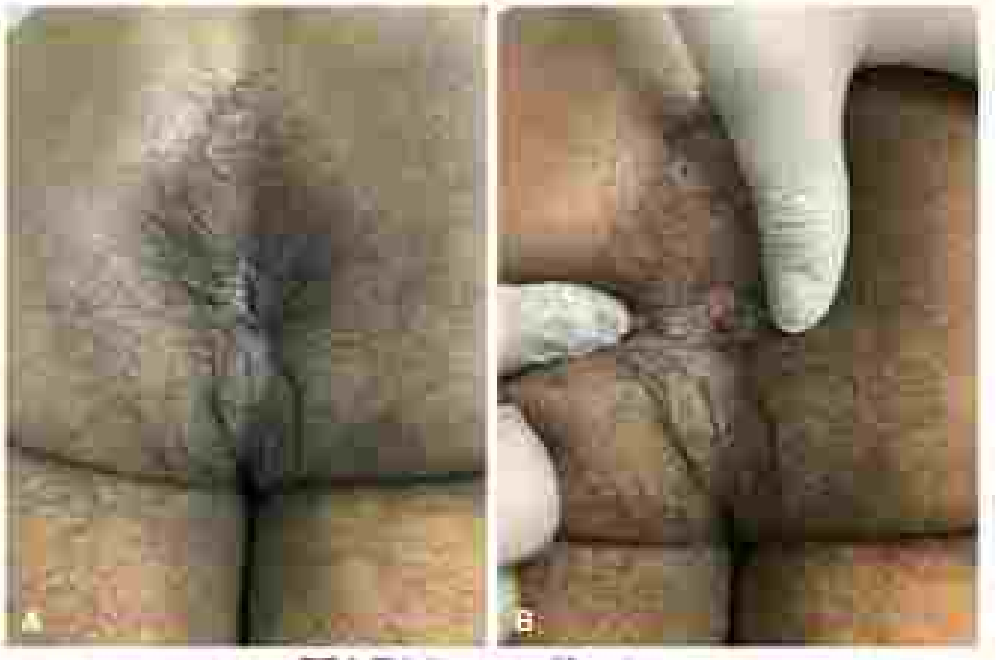

FIG. 1 Clinical appearance of fissure-in-ano.

Incontinence is the main complication with lateral internal sphincterotomy. Up to 30% of patients can experience some form of temporary incontinence to stool, gas, or soiling (Nelson et al., 2011). When comparing the open against the closed technique for rate of incontinence and treatment failure, there was no significant statistical difference; however, the length of sphincterotomy did increase the risk for incontinence.

Fistulectomy can be included in the sphincterotomy. This involves unroofing the fissure tract, removing the hypertrophied anal papilla, and removing the external sentinel tag. Proponents for including fistulectomy state it may promote faster healing of the fissure. Fistulectomies can also be accompanied with advancement flaps. This is particularly useful when there is a risk of anal stenosis, low pressure in the sphincter, or a hypotonic anus (Kimberly et al., 2002).

SPECIAL CONSIDERATIONS

Atypical Fissures

A detailed history and physical examination can often elucidate the cause of a fissure. Even so, fissures located away from the midline should raise an index of suspicion for other disease processes. Biopsies and/or cultures may help establish a diagnosis. Fissures affect approximately one-third of Crohn's disease patients and should be suspected when a fissure presents with atypical appearances. Crohn's disease can be associated with deep ulcerations, abscesses, and fistulas. The dictum is to intervene only when necessary with fissures caused by Crohn's disease. These patients benefit from a multifaceted approach and, with appropriate medical management, can have good success rates for healing (Draught et al., 2001).

CONCLUSION

Anal fissures are a very common cause for anal pain and can often be treated successfully with conservative measures. A combination of fiber, stool softeners, and sitz baths can alleviate symptoms while awaiting more invasive procedures. Chronic fissures will likely require sphincter relaxing agents to facilitate healing. Surgery remains the most effective treatment; however, sphincterotomy does carry a risk for potential lifelong incontinence. Following a step-wise progression to fissures is paramount when treating fissures, and the clinician should always be wary of alternative diagnoses masquerading as fissures.

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Management of Anorectal Abscess and Fistula

Kyle G. Cologne, MD, and Sean J. Langenfeld, MD

Approximately 100,000 patients in the United States seek care for anorectal sepsis each year. The peak age of presentation is between 20 and 40 years; males are twice as likely as females to have the condition. Cryptoglandular disease accounts for the vast majority of cases, followed by inflammatory bowel disease. Up to 50% of patients treated for an acute anorectal abscess will develop a fistula in ano, which requires further surgical treatment.

Management of anal abscess and fistula includes four basic principles: (1) control the septic process (drain the pus); (2) define the involved anatomy; (3) treat the underlying process without compromising sphincter function; and (4) minimize recurrence risk. Although most presentations are straightforward, complex and recurrent fistulas challenge even the most experienced surgeon. It is crucial for anyone managing this disease to understand the anorectal anatomy, particularly with respect to the anorectal nerve and muscle function. It is also important to treat patients in the context of their comorbid conditions (e.g., Crohn's disease) and apply the appropriate surgical technique. Improper management with unusual areas of undrained infection (e.g., the deep perianal space) can lead to unwanted sequelae such as chronic discomfort, impaired defecatory function, incontinence, or potentially life-threatening sepsis.

ANORECTAL ABSCESS

Cause and Classification

The anal glands empty into the rectum at the level of 10 to 15 crypts of Morgagni located circumferentially at the dentate line. If this drainage becomes blocked, pressure builds in the septic source grows and propagates along paths of least resistance within or through the potential space between the internal and external sphincter muscles (the intersphincteric space). Infection grows to fill one of several potential pathways of suppurative extension. These anatomic spaces of anorectal sepsis are intersphincteric, submucosal, perianal, ischiorectal, perianal (subdivided into superficial and deep by the anococcygeal ligament), and supralevator (Fig. 1).

The intersphincteric abscess, located at the site of the anal glands, tracks cranioscaudally between the sphincter layers. A submucosal abscess represents the least extensive suppurative process, located just beneath the mucosa above the dentate line. These often grow to other types of left untreated. Perianal abscesses descend through the intersphincteric space to the subcutaneous tissue around the anus and below the sphincter complex. The submucosal abscess involves a vast amount of fat in the submucosal fossa, and infection has extended either laterally via the intersphincteric space or caudally from above the external sphincter (supralevator discussed later). The vast ischiorectal fossa is a fat-filled space that encircles the external sphincter caudal to the levators and medial to the ischial tuberosities. The perianal space is located posteriorly between the levators (cranially) and the external sphincter (caudally); this space is subdivided by the anococcygeal ligament into superficial and deep spaces. Infections in the deep space are often missed because the physician must pop through this ligament to access the space during drainage procedures. The perianal space (which exists in the midline) may be solely involved, or infection may extend laterally into the ischiorectal fossa, forming the so-called horseshoe abscess. Supralevator abscesses, located above the levators as the name implies, are caused by either cranial extension of cryptoglandular sepsis or by caudal extension of an intraabdominal process, such as diverticular disease, that perforates through the peritoneum. Recent evidence suggests either of these causes are rare, with most series reporting less than 10% of overall abscesses.

Understanding the anatomic spaces of anorectal sepsis is key to deciphering the patient's presentation and planning the appropriate intervention. One attains one of the basic principles of sepsis management because complete drainage reduces subsequent complications such as systemic sepsis, recurrence, fecal incontinence, and complex fistula formation. Although the cryptoglandular etiology is believed to be responsible for the majority of anorectal abscesses, it is crucial to identify contributing conditions or alternate causes such as those displayed in Box 1, particularly if the method of presentation is atypical (multiple involved areas, edematous skin tags, red flag symptoms). The impact of these factors and causes on the nature of the disease and treatment strategy is discussed later in the chapter.

Presentation and Diagnosis

Anal pain independent of defecation is the most common complaint, which distinguishes this from anal fissure. Swelling and fever are often present. Associated symptoms and medical history suggestive of inflammatory bowel disease or immunocompromised states also should be gathered (history of rectal bleeding, diarrhea, or cramps abdominal pain). On anorectal examination, an indurated bulge with fluctuance and cellulitis near the anal verge is indicative of perianal abscess. Intersphincteric abscesses are unique in their lack of external findings but cause exquisite tenderness on attempted digital rectal examination. Ischiorectal abscesses typically have findings of induration, tenderness, and fluctuance a few centimeters away from the anal verge, but do not have the same degree of tenderness on digital rectal examination seen with intersphincteric infections.

Abscesses limited to the perianal space may have localized tenderness posterior to the anal verge, but without apparent induration or fluctuance. Bimanual examination (digital rectal examination while pinching the area next to the coccyx) will reveal the area of induration or fluctuance between the fingers. Supralevator abscesses may have no anorectal findings unless there is downward extension into another space; however, digital rectal examination may reveal findings above the puborectalis muscle sling. In this case, further evaluation with pelvic imaging should be considered to exclude their presence. Rectoscopy, proctoscopy, or flexible sigmoidoscopy can be performed to evaluate the rectal mucosa for signs of inflammatory bowel disease, but often is not tolerated and should not be pursued. Patients who cannot tolerate a digital examination should undergo an examination under anesthesia (EUA).

The majority of patients with a suggestive history and characteristic examination findings can be managed with bedside drainage or operative evaluation and treatment, particularly if the area of infection is readily visible on examination. Additional imaging, however, is useful in some acute situations. A computed tomography (CT) scan is helpful in patients with associated abdominal symptoms or findings, or with clinical suspicion of a supralevator abscess. A pelvic CT scan should not be relied on to exclude drainable anorectal infection because pendulous is often present in the absence of definitive CT findings, and bedside examination is generally more reliable. Untreated anorectal infection can lead to severe systemic infection and destruction of the anal sphincter complex itself or the nerve supply to it, resulting in varying degrees of fecal incontinence. Transanal ultrasound and magnetic resonance imaging (MRI) are not generally available or tolerated in the acute setting of an anorectal abscess. Both, however, are useful adjuncts in delineating another of the principles of management: the anatomy of complex, multiple, or recurrent fistula in ano.

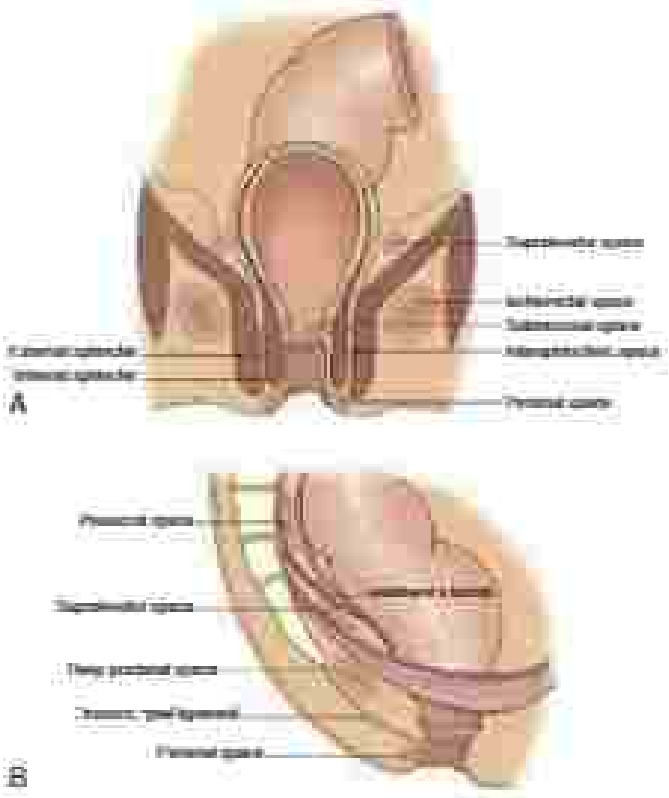

FIG. 1 Anal sepsis and fistula. Classification of anorectal abscesses by location. (A) Coronal view. (B) Sagittal view. (From Ko CJ, Lee SW, Mutinelli C. Surgery of the Alimentary Tract. 8th ed. Philadelphia: Saunders; 2013.)

BOX 1 Cause of Anorectal Abscess

- Cryptoglandular
- Iatrogenic (colorectal or genitourinary surgery)
- Perineal trauma
- Radiation injury
- Inflammatory bowel disease
- Acquired immunodeficiency syndrome
- Invasive fungal infection
- Hidradenitis suppurativa
- Pilonidal sinus
- Anal fissure
- Osteomyelitis
- Foreign body
- Malignancy (carcinoma, adenocarcinoma, hematologic malignancy)

Data from Hicks DC, et al, eds. The ASCRS Textbook of Colon and Rectal Surgery. 2nd ed. New York: Springer-Verlag; 2011.

Operative Evaluation and Drainage

Surgical drainage remains the definitive treatment of anorectal abscesses. Bedside drainage in the left lateral decubitus (or Sims) position under local anesthesia using 1% lidocaine with dilute epinephrine often is well tolerated for perianal abscesses and small submucosal abscesses. If there is concern for patient intolerance, bedside drainage can be accompanied by light sedation when available (e.g., within the emergency department) when additional healthcare providers and a monitored setting are available.

After infiltrating the area with local anesthetic, the surgeon makes a radially oriented semilunar or cruciate incision over the abscess. A critical point of this procedure is the incision should be oriented over the side of the abscess closest to the anal verge without transgression into the sphincter complex. This is done so that the subsequent fistula (which forms up to 50% of the time) is more likely to have a simple, short tract that is easier to manage. A common mistake is to drain the area over the maximum site of fluctuance or farthest away from the anal verge, which can make the subsequent fistula longer and much more difficult to treat. A hemostat or blunt probe is used to explore the wound and ensure no pockets of undrained infection remain. Usually, the outermost wall of the abscess cavity is thick and well defined and can be used as a guide. If a thinner wall is encountered, or if bimanual examination reveals additional areas of cavernous extension, these should be entered. However, care should be taken not to spread or digitally break down all fibrous tissue within the abscess because this often represents nerves, which are oriented in a radial pattern spreading outward from the anal verge. Destruction of these can result in anorectal muscle dysfunction.

A segment of skin (either an ellipse or cruciate with corners excised) at least 1 cm in size is excised to prevent premature closure of the skin. The cavity is irrigated and dry gauze is applied externally with the expectation of ongoing drainage. Dense packing is unnecessary in most cases and may only serve to damage the internal sphincters. Hemostasis can be obtained with direct pressure, cautery, the probe, silver nitrate, and the use of hibiclens with epinephrine.

Large abscesses (>5 cm), and those that must be approached externally (e.g., intersphincteric, horseshoe, and deep perianal space infections) are most appropriately done in the operating room under monitored anesthesia care or general anesthesia. The anorectal region is best exposed with the patient in the prone jack-knife position and the buttocks taped widely apart, but high lithotomy is often adequate, particularly in multiple comorbidity patients or those with a difficult airway. A headlamp or other source of good lighting is recommended. Commonly used instruments are: Hill-Ferguson, Fansler, or Pratt bivalve retractors; fistula probes and curettes; and angiocath needles with dilute hydrogen peroxide. The perianal region is inspected, noting any induration, fluctuance, or dermatologic abnormalities. A digital rectal examination is performed followed by anoscopy, looking for internal bulging or other abnormality including sphincter defects, fissures, and mucosal abnormalities. Biopsies should be performed on ulcerations, suspicious nodules, or part and lesions to exclude neoplasia. Biopsies and/or culture should be performed on recurrent abscess or fistula tracts as well to diagnose underlying inflammatory bowel disease, infections (such as tuberculosis or actinomycosis), or the rare malignancy. If the site of purulence is not obvious or deep to the skin surface, an 18-gauge needle can be used as a finder to aspirate in suspected areas. Culture data are rarely required but may be insightful in patients with recurrent infections, a history of methicillin-resistant *Staphylococcus aureus*, or patients with unaltering HIV infection in whom atypical microbes may be present.

For large ischiorectal abscess, multiloculated counterincisions can establish adequate drainage rather than a large incision that needs excising healthy tissue and prolongs healing unnecessarily. Digital examination while probing the cavity is prudent to ensure that there is no extension into the perianal space or the contralateral fossa. Packing is usually not necessary and impractical for the patient to exchange. An alternate means of drainage uses a stab incision overlying the abscess, as close to the anal verge as possible, and the insertion of a 10F to 16F malecot catheter into the cavity. The catheter is secured with an anchoring suture and left in place for a week, with regular flushing. After a week, the majority of the infection should be drained and removal leaves in place a skin tract that will allow for ongoing drainage of any residual infection. These catheters can be left in for prolonged periods in cases of large or recurrent infections.

Drainage of a perianal space abscess deserves special note because it is often a source of missed or undrained infection. A radial incision is made from the posterior anal verge toward the coccyx. Subcutaneous tissue is divided and the underlying fibers of the anococcygeal

ligament are divided in a craniocaudal direction to access the perianal space. This is a fibrous ligament and often takes a bit of force to pop through. Often, the procedure up to this point has not resulted in a lot of pus, despite preoperative imaging or palpable fluctuant disease. Once the deep space is unroofed, pus usually flows freely. If a horseshoe abscess is present, the deep space is probed laterally, where elliptical counterincisions over the involved ischiorectal fossa can be created. Penrose drains can be looped between incisions to maintain patency. Alternatively, if small, these lateral extensions can be drained with small rubber catheters cutting out from the midline posterior incision. Rarely, an anterior horseshoe can exist. If an underlying fistula to the distalmost line is noted, a seton is placed to prevent recurrent sepsis (Fig. 2). A later (staged) procedure to address the fistula can be planned.

Intersphincteric abscesses are addressed minimally. The mucosa overlying the bulging/fluctuant area within the anal canal is divided with electrocautery. The underlying internal sphincter muscle, with circumferential transversely oriented muscle fibers, is thus exposed. A hemostat is passed through the internal sphincter into the suppurative intersphincteric space and advanced cephalad. The internal sphincter is divided over the hemostat with electrocautery. Because the external sphincter is not manipulated or divided, this generally does not compromise fecal continence, but patients should be informed of that small risk as part of informed consent. An alternative but less common method involves a stab incision at the anal verge to the intersphincteric groove and insertion of a small rubber catheter into the affected intersphincteric space. The catheter is secured to the anal verge and either removed outright or tracked out slowly as intervals after sepsis has resolved.

The source of a supralevator abscess determines its treatment. Descending abdominal or pelvic sources typically are addressed with imaging guided percutaneous drainage. More complex or severe intraabdominal disease may warrant transabdominal surgery or even fecal diversion to prevent ongoing sepsis. Ascending cryptoglandular infections travel via one of two routes: either through the intersphincteric space within the bowel or through the foramen from the ischiorectal fossa (outside of the bowel wall). This is a critical difference, as the goal of treatment is to prevent formation of a complex fistula. The intersphincteric source is treated with transanal drainage through the rectal wall; an (incorrect) surgical drainage through the perineal skin and ischiorectal fossa creates an iatrogenic suprasphincteric fistula. Conversely, the supralevator abscess with an ischiorectal source should be drained via the perineal skin incision via the ischiorectal fossa. In this second scenario, transrectal drainage would be inappropriate and also create an extrasphincteric fistula (Fig. 1). Even though supralevator abscesses are rare, this is the reason imaging may help delineate the source and trajectory, which subsequently may dramatically alter the treatment approach.

Anorectal abscesses are rarely appropriate for percutaneous drainage by the interventional radiologist. Although this may temporarily eliminate the need for urgent surgery, the route of catheter drainage, which crosses the levators, can increase the complexity of the underlying fistula when present. Even if sepsis is temporarily resolved, the patient is now left with a supralevator component to the fistula, which is much more difficult to resolve for the surgeon. The only possible exception to this is for supralevator abscesses originating from an abdominal source.

Antibiotics and the Immunocompromised Patient

Most patients do not require antibiotic therapy after effective incision and drainage. In certain populations, however, antibiotics are warranted because drainage alone may not resolve the systemic inflammatory response syndrome or septic response of sepsis thereof. Patients with large areas of cellulitis, signs of systemic sepsis or shock, prosthetic heart valves, or various immunocompromised states

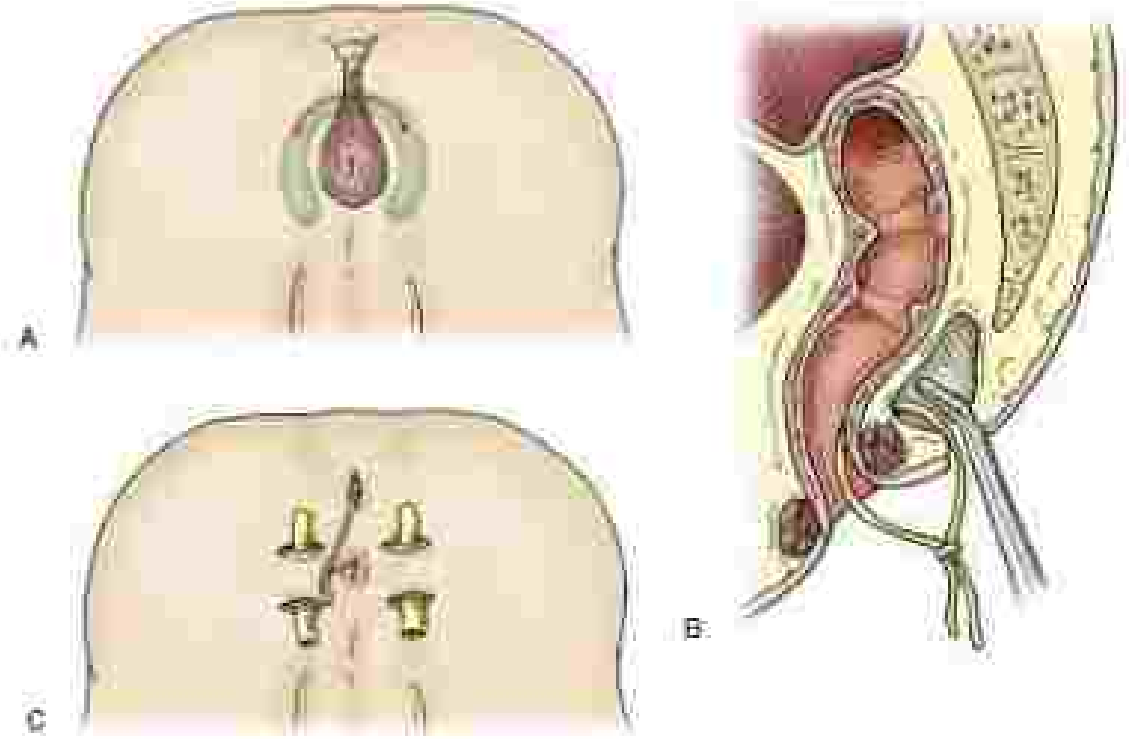

FIG. 2 (A) Horseshoe abscess shows that the deep perianal space is a window to the ischiorectal fossa bilaterally (arrows). (B) The deep perianal space is drained through a radial incision in the posterior midline. A clamp is placed in the perianal space to ensure adequate drainage. If an internal opening is identified, a seton is placed through the fistula tract, incorporating the posterior sphincter. (C) Counterincisions drain the ischiorectal fossa. Placement of Penrose drains through the cruciate incisions adequate drainage of the abscess cavities without significant soft-tissue loss. (Courtesy Cleveland Clinic, OH.)

warrant prolonged oral or parenteral antibiotics. Immunocompromised patient groups include those with diabetes mellitus, chronic corticosteroid use, AIDS, a history of bone marrow transplant, or active cytotoxic chemotherapy.

In contrast to all other patients with anorectal infection, profoundly neutropenic patients often are not addressed with surgery but are treated with antibiotics alone. Patients with absolute neutrophil counts below 500 per cubic millimeter often do not mount enough of an immune response to develop suppuration. Even with operative drainage, there is minimal pus encountered; therefore, patients with low absolute neutrophil counts and without fluctuance do not have a target for surgical drainage. Instead, prolonged, broad-spectrum antibiotics are recommended. The degree and duration of neutropenia is directly correlated with the incidence and prognosis of anorectal infection in this population. In addition, efforts to correct the neutropenia by holding chemotherapy and using pharmacologic neutrophil growth factors are employed. As the neutrophil count rises, these patients must be monitored closely because they can subsequently develop a suppurative response and require reimaging or EUS with aspiration if a drainable source develops. Progressive sepsis, obvious fluctuance, or expanding soft tissue infection is an indication for surgical evaluation, drainage, or debridement.

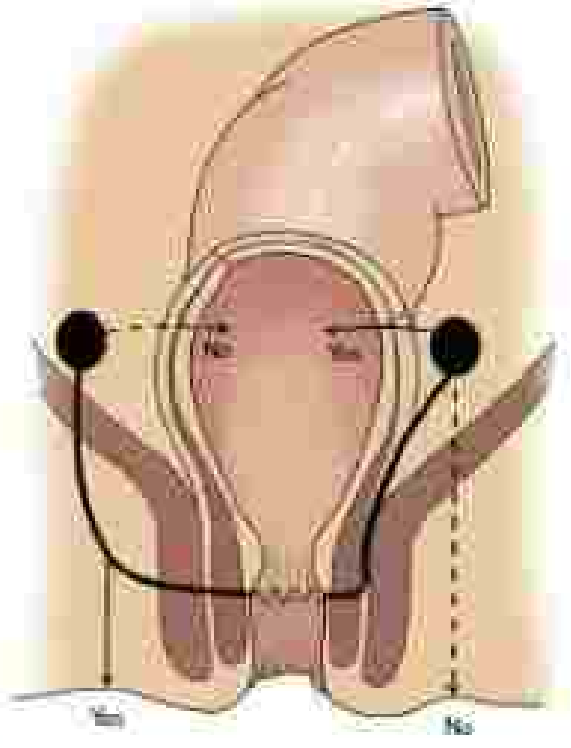

FIG 3 Drainage of a supralevator abscess (see text). On the right, the supralevator abscess is associated with a transsphincteric fistula and passage through the ischiorectal fossa; often there are associated findings of an ischiorectal abscess. This abscess is drained via the skin and ischiorectal fossa; anorectal drainage would be inappropriate because it would result in an extrasphincteric fistula. On the left, the supralevator abscess is associated with an intersphincteric fistula and should be drained transanally; drainage across the ischiorectal fossa would create a supralevator fistula. Supralevator abscesses also may be addressed via computed tomography–guided percutaneous drainage (alone or in combination with transanal transsphincteric approaches), particularly when they are due to downward extension of an intraabdominal process such as diverticulitis. (From Ky C, et al: Vital Atlas: Surgery of the Alimentary Tract, vol 7. Philadelphia: Saunders; 2007.)

Primary Fistulotomy

Fistulotomy at the time of incision and drainage of the initial anorectal abscess was once a controversial issue. Proponents argued that the presence of sepsis aided in defining the fistula tract, leaving open the tract would reduce recurrence. With increased data, however, it appears that primary or "prophylactic" fistulotomy submits a majority of patients who would never have recurrent or developed a fistula to sphincterotomy and the accompanying risks of fecal incontinence.

Primary fistulotomy should thus be considered only in the most straightforward of superficial or low transsphincteric fistulas where the fistula tract is obviously present. As a cautionary note, using fistula probes to explore abscesses can be dangerous, and care must be taken to avoid creating false passages and/or iatrogenic internal openings within the inflamed field. Such probing may not only result in persistence of the fistula but may also make subsequent fistula repair much more difficult. Primary fistulotomy is contraindicated in the elderly and in women (particularly those with previous or planned future childbirth) with anterior fistulas, as the muscle is quite thin in this area. Furthermore, it should not be done in patients with baseline fecal incontinence, Crohn's disease, AIDS, and high transsphincteric fistulas.

Necrotizing Perianal Skin Infection

Necrotizing perianal skin infections are destructive, life-threatening soft tissue infections that must be differentiated quickly from the more common anorectal abscess as the initial presentation because immediate surgical debridement offers the only chance at survival. Rapid development of severe anorectal pain that is out of proportion to physical examination is the classic harbinger of a necrotizing infection. Risk factors include diabetes, chronic renal disease, obesity, smoking, and underlying neurologic disease (such as dementia or spinal cord injury) that prevents early detection or communication of symptoms and previous anorectal infections. Tender, irregular red, violaceous, or black macules and blisters in the perianal region are early signs of this dangerous process. These types of infections may be associated with crepitus, induration, or gangrene. Septic shock and electrolyte disturbances may develop. Any anorectal infection in the presence of these severe systemic manifestations should be immediately explored in the operating room and given broad-spectrum intravenous antibiotics. Radical debridement of all nonviable tissue is necessary.

Patients will require supportive management in the intensive care setting and empiric coverage for potential flora while awaiting culture results. Multidisciplinary evaluation may also be required, depending on involvement and viability of the sphincter complex and urogenital organs. After initial debridement, if infection persists, consider transfer to a tertiary center with hyperbaric oxygen capability, which limits the growth of anaerobic and other forms of bacteria and boosts the effects of antibiotics and the immune system. The need for fecal diversion is debated but should be considered only in the subacute setting after hemodynamic stability is well established and when soft tissue wounds would be compromised by ongoing fecal spillage.

FISTULA-IN-ANO

Cause and Classification

The cryptoglandular theory suggests that the acute suppurative process of anorectal sepsis originates at 1 of 8 to 10 anal glands located at the dentate line. These glands, whose ducts penetrate the internal sphincter for varying distances into the intersphincteric space, can become blocked, thereby allowing bacteria to cause infection, which propagates along the path of least resistance out away from the blocked internal opening of the duct into the perirectal space. This process continues until an abscess forms and the growing pressure is relieved by surgical or spontaneous drainage. If the tract created by

this process seals closed. No further sequelae are noted, however, if the tract persists, an epithelialized fistula results. Although the cryptoglandular etiology is responsible for the vast majority of fistulas, Box 1 presents other causes of chronic inflammation, fistula formation, and epithelialization to the anorectum.

Fistulas are classified by their route between an internal opening in the anal canal and an external opening on the perianal skin. In 1976, Parks and colleagues published this classification system that is the most commonly used description. Fig. 4 depicts the four Parks classes of fistulas. Another type of fistula not included in this classification scheme is the superficial (or subcutaneous) fistula, which, as the name implies, does not involve the sphincter complex at all. This can be a result of scarring after recurrent infections and surgery, or another process, such as hidradenitis. Another possibility is primary, tiny skin bridging of a fissure.

Fistulas are categorized further as simple or complex. A complex fistula has features that increase the risk of recurrence and/or incontinence after intervention, either by its own anatomy or by patient factors. Table 1 defines features of complex fistulas, which include everything except subcutaneous, intersphincteric, and low transsphincteric trajectories.

Presentation and Diagnosis

Patients often have a history of an abscess that either drains spontaneously or requires surgical intervention, although the initial infection may be small and asymptomatic. Patients often have initial healing and a varying time (weeks, months, or even years) without symptoms. When a persistent tract exists, fecal material will continue to pass through the internal opening, and so patients will experience either (1) ongoing drainage through the external opening or (2) recurrent abscess as the external opening closes, blocking the exit of purulent and fecaloid material.

Because of this, patients describe intermittent anal pain, pruritus or drainage that is mucoid, bloody, purulent, or even fecaloid. Occasionally, blood per rectum occurs because of friable granulation tissue at the internal opening. Another common feature is cyclic discomfort and swelling resulting from pressure built up within the fistula tract that is relieved after spontaneous drainage.

Patients should be queried regarding gastrointestinal symptoms suggestive of inflammatory bowel disease (e.g., bloody diarrhea, crampy abdominal pain) and their current level of fecal continence. A history of anal surgery, anal infections, radiation, trauma, obstetric trauma, and systemic disease including inflammatory bowel disease,

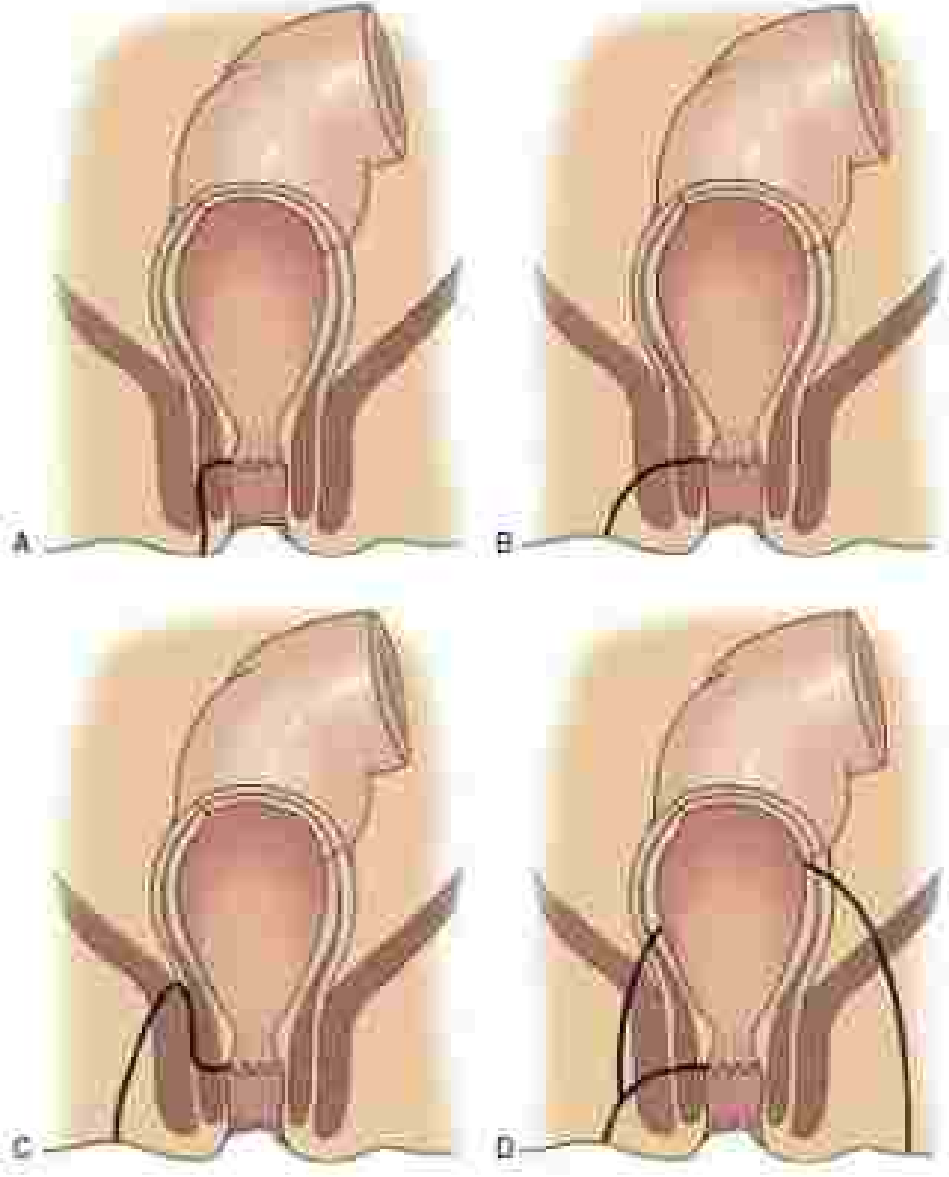

FIG. 4 Classification of anal fistula. (A) Intersphincteric: the tract remains in the intersphincteric plane. (B) Transsphincteric: the fistula tract passes from the intersphincteric plane through the external sphincter muscle. C, uncomplicated. (C) Suprasphincteric: there is an upward extension of the fistula tract in the intersphincteric plane. The tract then passes above the level of the puborectalis muscle and continues downward through the anterior/oral tract to the perianal area. (D) Extrasphincteric: there is a tract that passes from the skin of the perineum through the ischiorectal fossa and the levator muscles before entering the rectal wall. The fistula may be a consequence of an extension of a transsphincteric fistula or secondary to trauma, anorectal disease, or pelvic inflammation. (Modified from Ho D, et al. Management of Anorectal Fistulas. In: Management of Gastrointestinal Disorders. 2007.)

hematologic malignancy, or immunosuppression should be ruled because these characteristics create a high risk for nonhealing or worsening incontinence. On examination, the external opening is generally easily identifiable as an inflamed pyogenic granuloma with an associated palpable cord may adjacent to this that suggests the path of the tract. However, the external opening may be much more subtle and even closed in periods of inactivity. A fistula can usually be seen with a careful search. The internal opening occasionally can be palpated on digital rectal examination as a nodule or pit, usually at the level of the dentate line or cryptoglandular origin. Goodsall's rule states that fistulas with an external opening posterior to a transverse line across the anus drain via a curving approach to a posterior midline internal opening, whereas those with an external opening anterior to this line have short, straight (or radial) courses to the associated internal opening. This is not always accurate (particularly in females with anterior fistulas) and careful attention should be made to delineate the direction and length of any suspected fistula. Anoscopy, when tolerated, can assist in visualizing the internal opening as well as assess whether a distal proctitis is present. Further endoscopy can be considered in a patient with symptoms supportive of inflammatory bowel disease.

Surgical Treatment

There are four principles of fistula surgery: control the septic process, define the involved anatomy, treat the underlying process without compromising sphincter function, and minimize recurrence risk. Maintaining these principles is critical at each step of treatment.

1. *Control of Sepsis*

For many patients with complex fistulas or an abscess fistula at the time of operative treatment of an anorectal sepsis, a conservative, staged approach with the initial placement of a seton is most appropriate. It allows multiple future options without compromising sphincter integrity.

For a patient treated initially with a seton, a primary fistulotomy as a second stage procedure can be considered when the internal opening is less than 3 mm wide and the tract is simple, narrow, and without an associated abscess cavity. Ongoing sepsis, as evidenced by pus, cellulitis, induration, or a persistent cavity, prevents healing and closure of the tract and efforts to improve drainage (such as widening the external opening) before definitive procedure should be considered. Simple closure the fistula tract itself will likely fail, so excision or laying open of the tract is preferred, with healing by secondary intention. Complex fistulas with persistent sepsis should be assumed to harbor an undrained source of infection. Search for a high blind or circular tract. If additional treatable sources of the persistent sepsis cannot be identified or sepsis continues despite these approaches, imaging is warranted.

2. *Define Fistula Anatomy*

The anatomy of a fistula includes the internal and external openings, the course of the intervening tract(s), and the presence of any blind tracts or sinuses. Fistula anatomy can be estimated by office examination but is definitively established only by EUA. Most often, the patient can be consented for a definitive procedure, with the caveat that if a complex fistula or other unexpected findings are discovered at the time of EUA, a staged procedure may be required to preserve sphincter function. The patient is placed in prone jack-knife with the buttocks taped widely apart. It is also acceptable to use the left lateral decubitus or high lithotomy positions. When anatomy is in question, prone jack-knife may allow slightly better exposure.

The perianal region is inspected, identifying evident external openings, suspicious lesions, or scars. Digital rectal examination is performed to assess for undrained sepsis and location of the internal opening. Anoscopy is used to identify the internal opening as well as note any signs of proctitis or malignancy. A fistula probe is inserted into the external opening and gently advanced toward the anticipated internal opening with subtle redirection as resistance dictates. The fistula tract easily should accept the probe without the sensation of tissue destruction. Dilute hydrogen peroxide injected into the external opening via an angiocatheter can help identify an elusive internal opening. A false tract must not be created because it will only complicate the disease and neglect the primary tract. Once cannulated, the type of fistula is established by determining its relationship to the internal and external sphincter complex, the location, and presence of multiple fistulas or blind tracts. The percentage of sphincter complex caudal to the tract is determined by palpating the apex of the sphincter complex in relation to the probe. Low transsphincteric fistulas are defined as those with less than 30% of the external sphincter involved.

There are several troubleshooting tips to know. If the tract cannot be cannulated fully, the tract may be curved. A Kocher clamp can be used to attempt to straighten the tract. Alternatively, a partial fistulectomy or fistulotomy can be performed to follow the path of the fistula from the external opening toward the anal verge until it cannot be identified further or a draining catheter left in the external opening only. If the internal opening cannot be identified easily, the surgeon should not persist to find or make one. The internal opening may have temporarily sealed off or there may be other reasons why it is not identifiable at the time of surgery. In this circumstance, drain the infection, and re-evaluate things later. Although this approach may be associated with a higher recurrence risk, it avoids the critical mistake of making an iatrogenic internal opening at a false location. In this scenario, the identifiable portion of the fistula tract is curetted and the operation is terminated. Adjunctive imaging is performed after 3 to 6 weeks to allow for inflammation related to surgery to subside and hopefully better identify the fistula anatomy.

When a fistula is recurrent, thought to be complex, or if anatomy cannot be identified by EUA, imaging such as transanal ultrasound with contrast injection and MRI are the principal modalities applied. Both have high accuracy rates with high concordance to subsequent surgical exploration findings. Transanal (particularly three-dimensional) endosonography can also successfully predict the amount of sphincter that would be divided if primary fistulotomy is performed, as well as identify undrained sepsis, complex anatomy, and high blind tracts (Fig. 2). MRI has been shown to alter surgical approach in some cases and decrease recurrence rates, and it appears to be superior at identifying suprasphincteric or extrasphincteric tracts. CT scan lacks adequate resolution to identify fistula tracts and their relationship to the sphincters and lesions with comparable accuracy, but is highly sensitive and specific for acute abscess detection. Fistulography, in which contrast is injected into the external opening and the fistula course is traced with fluoroscopy, is rarely performed now with superior cross-sectional imaging.

TABLE 1 Features of Complex Fistulas

Anatomy	Comorbid Condition
Multiple fistulas	Compromised local continence
Suprasphincteric fistulas	Inflammatory bowel disease
Extrasphincteric fistulas	Refractory diarrhea
Associated high blind tract(s)	Anterior fistulas in women
High transsphincteric fistulas (> 30% of anal sphincter length)	Immunodeficiency or compromised wound healing History of regional radiation History of obstetric trauma Elderly patients Prior anorectal surgery

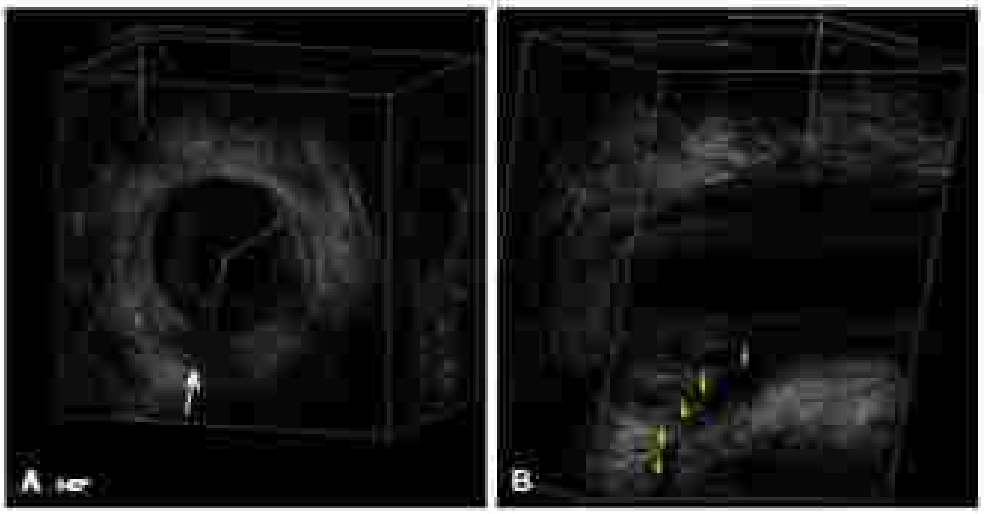

FIG. 3 Ultrasound of right posterior transsphincteric fistula. (A) Coronal view revealing a 140-degree internal sphincter defect on the left side from a previous hemorrhoidectomy. The hypoechoic ventral opening of a right transsphincteric fistula is noted by the arrow. Given the size of the internal sphincter defect, even the fistula tract, a ligation of the transsphincteric fistula tract procedure may not be feasible. (B) Angled sagittal view showing the hypoechoic transsphincteric fistula. Note the internal opening (arrow) nears half the length of the hyperechoic external sphincter; therefore, a fistulotomy would not be appropriate. (*Courtesy Amir Rezvani, Detroit, MI.*)

TABLE 2 Management Strategy by Fistula Classification

Type of Fistula	Fistulotomy	Seton*	LIFT	Advancement Flap	Fibrin Glue	Collagen Plug	Address Intersphincteral or Pelvic Sepsis
Superficial/intersphincteric	X						
Low transphincteric	X	X	X	X	X	X	
High transphincteric		X	X	X	X	X	
Suprasphincteric		X		X		X	X
Extrasphincteric						X	X

*Seton placement can be a first stage or definitive treatment option.
LIFT, Ligation of intersphincteric fistula tract.

3. Assess and Preserve Anal Sphincter Function

Although a controlled anal fistula with or without a seton can cause discomfort and problems with personal hygiene, fecal incontinence is far more disruptive to a patient's quality of life. For that reason, preservation of continence is always a priority when choosing the proper management or surgical strategy. Division of the internal sphincter usually is well tolerated without much effect on continence rates, particularly in men. Similarly, division of distal one third of the external sphincter is considered "safe" in healthy male individuals and can be considered posteriorly in females without preexisting sphincter dysfunction. The degree of sphincterotomy tolerated without affecting continence is patient dependent, and thus careful assessment and documentation of preoperative anatomy and continence rates are critical to the decision making process. Prior anorectal surgery, trauma, or childbirth as well as associated conditions that may cause diarrhea (such as colitis) or inhibit healing may increase the risk of incontinence. Women in particular are vulnerable to incontinence because of their shorter sphincter complex (or high pressure zone) and anatomic and neurologic injury to the pelvic floor sustained during childbirth (particularly when combined with normal muscle attenuation associated with aging). Great care should also be taken in patients with active inflammatory bowel disease involving the anorectum and rectovaginal fistulas because they often heal poorly and have recurrent or metachronous fistula disease. Sphincter preserving techniques are preferred in these patient populations. Table 2 provides a guide in choosing the proper surgical technique based on these and other factors.

4. Minimize Recurrence Risk

Complex fistulas are a frustrating chronic process because they are prone to recurrence despite meticulous surgical technique. Although primary fistulotomy has the lowest recurrence risk, it also is associated with the highest risk of incontinence because of inherent disruption to the sphincter complex. All other sphincter surgical procedures, although they preserve the muscular anatomy, are associated with much higher recurrence risk. This must be considered in an informed consent discussion with the patient. Although no definitive procedure has proven superiority, a surgeon's experience with any one of these described procedures may be the most important factor because reported outcomes vary widely.

Fistulotomy

Fistulotomy can be done at the time of abscess presentation, at the time of initial fistula presentation, or as a second stage procedure in appropriately selected patients. Regardless of timing, a fistulotomy is appropriate only in low risk patients with a superficial, intersphincteric, or low transphincteric fistula. Once the anatomy of the fistula is determined, the tract is cannulated and the tissue overlying the probe is divided with electrocautery. The epithelial lining of the tract

itself to fulguration with a cautic or electrocautery to remove debris and granulation tissue. The wound then heals by secondary intention. Objectively, this approach converts the fistula (or tunnel) into a valley or ditch.

For larger wounds, wound healing can be accelerated by marsupialization of the wound, which also can prevent premature epithelialization of the wound edges before the deeper areas heal (thereby creating a subcutaneous fistula). The skin or subcutaneous edges of the incision are sewn to the base of the wound with absorbable suture. Success rates are generally more than 90%, but also have the highest rates of some degree of fecal incontinence, up to 40% in some series. Hence fistulotomy is not appropriate (in most instances) for high or complex fistulas.

Seton

Two types of setons that can be used. A loose, noncutting seton allows for ongoing drainage of sepsis and prevents abscess, reformation, and shrinkage of the abscess cavity and of the fistula tract, often in preparation for a second stage procedure. The seton itself can be a thin Silastic band, vessel loop, or nonabsorbable suture (such as silk). In general, vessel loops cause less adjacent inflammation than braided sutures, and so the setons goal must be considered when choosing the material. The material is threaded through the tract and secured to a loop or omega shape so itself with several interrupted silk sutures. The noncutting (draining) setons should not be tight at the level of the skin. A hemostat should fit easily between the skin and loop without tension. The second stage procedure, either fistulotomy or a sphincter preserving operation, usually is performed 6 to 10 weeks later, though sometimes with larger or more complex fistulas, a waiting period of 3 to 4 months is advised. Setons used in this fashion for complex fistulas have success rates from 42% to 100%, depending on patient factors and the choice of the secondary procedure. For some Crohn's or other high-risk patients, draining setons can be the definitive procedure: it is left in place for prolonged periods (years) to prevent recurrent sepsis without the intention to perform a second stage procedure because of the likelihood of failure or iatrogenic incontinence. In this case, the setons are typically exchanged for a newer one when they become worn or extremely soiled (typically about once per year).

A cutting seton can be placed with the intention of slowly tightening it over time, so it pulls the fistula tract closer to the skin level under tension. In doing so, it cuts through the tissue forming a fibrous scar in the deeper layers, in theory maintaining the integrity of the sphincter complex. Cutting setons are typically tightened every 4 to 6 weeks. A critical extra step in placing these setons is the skin surface must be incised at the time of placement because it is extremely painful if placed on intact epithelium. Draining setons can be converted to cutting setons. It must be noted that cutting setons are associated with very high reported rates of fecal incontinence, and the practice has fallen out of favor in many institutions. However, it still may have a role to select cases at intermediate risk because the healing rates are relatively high and approach those of fistulotomy.

Ligation of Intersphincteric Fistula Tract

Ligation of the intersphincteric fistula tract (LIFT) procedure is a relatively new sphincter preserving technique first described in 2007. This is performed most often as a second stage procedure for a transsphincteric fistula after a mature tract has developed with or without aid of a draining seton.

With the patient in the prone jack-knife position with the buttocks taped widely apart, the fistula tract is cannulated with a probe. The external opening is widened to allow for drainage (Fig. 6). A 1- to 2-cm curvilinear incision is made with electrocautery over the palpated intersphincteric groove, and dissection is carried down to the location of the fistula tract (containing a probe for easier identification). A Lonnear retractor (Cooper Surgical) deployed along the anoderm edges provides excellent exposure. The intersphincteric plane is developed bluntly with a fine tipped hemostat. The fistula tract is isolated circumferentially with care to avoid disrupting it. The probe is removed and the two ends of the intersphincteric tract visualized within the intersphincteric incision are suture ligated with 3-0 absorbable suture. The tract is divided sharply with a scalpel. The external opening is injected with hydrogen peroxide. If there is a persistent leak, the intersphincteric opening of the external sphincter is oversewn until there is no longer a leak. Some authors test the internal opening with peroxide as well to ensure proper closure of the proximal portion of the tract. The anoderm is reapproximated with a running absorbable suture. Very high fistula tracts, or those that track long distances within the intersphincteric space may be difficult to properly isolate in the intersphincteric plane and are not good candidates for this approach.

Results of the LIFT procedure are highly varied and include several of the technical variations described previously as well as the addition of biologic mesh to the intersphincteric space. Primary healing rates vary between 47% and 95%. The impact on incontinence is not universally reported, but generally low. Success rates are comparable to those seen with endorectal advancement flap and quite superior to rates seen with glue or plugs. Tract length longer than 3 cm, prior anal fistula surgery, and obesity has been associated with LIFT failure. An interesting phenomenon is that when failure occurs, it sometimes does so at the level of the intersphincteric incision, thereby converting what was a more complex fistula into a simple, intersphincteric fistula. This phenomenon occurs if the external component of the fistula heals, but the internal opening persists. Some authors describe a subsequent primary fistulotomy to allow complete resolution of the problem.

Endorectal Advancement Flap

The endorectal advancement flap is also used as a second-stage procedure for high fistula tracts, suprasphincteric tracts, and low tracts in high-risk patients with healthy rectal mucosa (Table 1).

For lesions below the dentate line, fistulotomy or a dermal advancement flap is preferred to prevent the creation of a mucosal ectropion that can form if the rectal mucosa is brought down to the level of the anal verge. This can cause ongoing mucous drainage, pruritus, and other complaints. Patients may undergo a preoperative bowel preparation. The prone jack-knife position is preferred for most fistulas, although lithotomy position often is used to address posterior midline internal opening locations. The seton is removed and the internal opening serves to mark the apex of the flap as depicted in Fig. 7. Beginning at the internal opening, a flap is created by distal to proximal dissection with precise electrocautery, including mucosa, submucosa, and a few fibers of the internal sphincter (partial thickness). To ensure adequate perfusion, it is crucial that the base (proximal end) of the flap is wide, at least two to three times the width of the apex. Care should also be taken to prevent excessive handling of the flap, which can result in hematoma formation and tissue compromise. The internal opening itself is a good point of handling to create the necessary tension/countertension because this will subsequently be discarded. The trapezoidal shaped flap is typically 2 to 4 cm long to allow for tension free closure caudal to the level of the original internal opening. The fistula tract is debrided with a curette and the external opening is widened to allow for drainage. Absorbable suture is used to close the internal opening. Some test the integrity of the closure is tested with injection of hydrogen peroxide at the external opening, although this step can be omitted if closure is deemed adequate. The tip of the flap with the internal opening is amputated, and the flap is gently pulled distally over the natural internal opening at the level of the dentate line. Interrupted absorbable sutures are used to reapproximate the mucosal edges of the flap.

Success rates are also widely variable, with reported rates between 36.6% and 90.5%, with rates of 60% to 87% specifically for cryptoglandular disease. Factors including obesity, history of radiation, prior attempts at repair, smoking, and inflammatory bowel disease

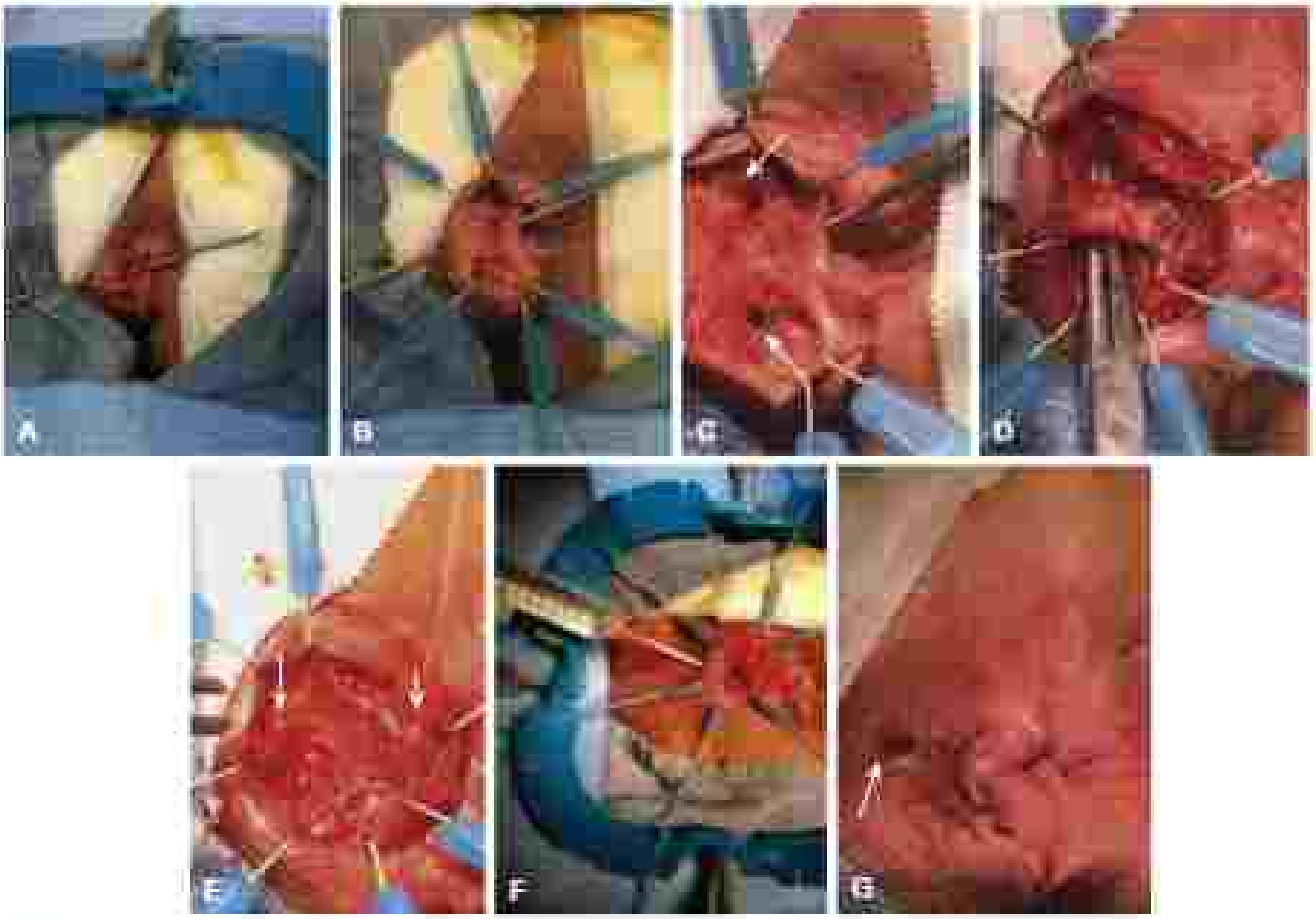

FIG. 6 (A) The fistula tract is considered. (B) A curvilinear incision is made overlying or slightly distal to the anocutaneous groove. A Lone Star retractor (Cooper Surgical) is helpful for exposure. (C) The anocutaneous pilot is developed on either side of the tract (arrows). (D) Chromic sutures ensnare the tract until it is excised. The probe is removed. (E) Dissection and ligation of fistula tract. The tract is extended with a Weitlaner (Weitlaner) tip and the tract is ligated at the border of the external anal sphincter (small arrow). If a long tract is present, it can be excised and the tract near the external anal sphincter is either ligated or imbricated with Vicryl suture (large arrow). (F) The repair is tested by injecting hydrogen peroxide into the internal and external openings. The ligated ends can also be probed to loosen sutures. If there is a leak, the fistula opening is further debrided. (G) The external opening (arrow) is slightly enlarged and the distal aspect of the tract is debrided with a curette. (Courtesy Jeffrey J. Hebrink, MD.)

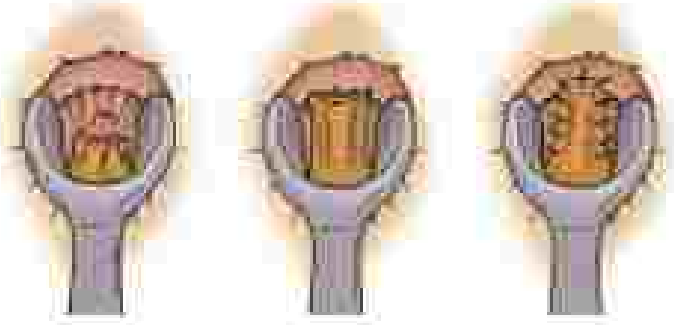

FIG. 7 Mucosal (Rowing) advancement flap. A longitudinal incision is made over the ischiorectal area to the anal canal. Proximal mucosal and anal mucosa are then undermined through a transverse incision starting at the proximal end of a previously made longitudinal incision. The flap is then sutured to the distal edge of internal anal sphincter, leaving open the most distal aspect of the wound. (From Ellsmere J, Hebrink JJ, Rosen KG, et al. New and old operations for anal fistula. Am J Surg. 2003;186:312.)

have been found to predict failure. Although the sphincter muscle is not divided, worsening of bowel continence has been reported in up to 30% of patients treated with this procedure.

Fibrin Sealant and Collagen Plug

Synthetic and biologic materials were promising new additions to the armamentarium of fistula treatment in the past 20 years. Their general principle is obliteration of the internal opening and fistula tract. Their primary benefit is a minimal risk profile because they do not involve any sphincter manipulation (and thus pose no risk to continence), are easily repeated in the case of recurrence, and do not preclude subsequent surgical management. However, low reported success rates (as low as 14%) have largely resulted in abandonment of their use. Furthermore, many insurance companies will not cover the cost of these expensive products because of low success rates.

Suggested Readings

Snyder LD, West S, Kaiser AM. Modified Hanley procedure for management of complex horseshoe fistulae. Dis Colon Rectum 2009;52(8):1451–5.

Sultan AH, Monga AK. Management of complex anal fistulae. Clin Colon Rectal Surg 2004;29(1):40–8.

Han JG, Wang ZJ, Zhang Y, et al. Curative of incomplete high fistula tract by ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug procedure in patients with transsphincteric anal fistula: early results of a multicenter prospective randomized trial. Ann Surg 2014;260(4):657–62.

Isaacs AH, Hesketh A, Keighley MR. Surgical intervention for perianal fistula. Cochrane Database Syst Rev 2010;(1):CD006318.

Ritchie RDL, Tucker DC, Biddle IP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis 2009;11(6):564–571.

Steele SR, Kumar R, Feingold DL, Rafferty JL, Buie WD. Standards practice task force of the American Society of Colon and Rectal Surgeons. Practice parameters for the management of perianal abscess and fistula-in-ano. Dis Colon Rectum. 2011;54(12):1549–1474.

Anorectal Stricture

Ruiqian Zhu, BS, and Yusuf Nassori, MD, FACS, FASCRS

Anal stenosis is the narrowing of the anal canal resulting from lesions, infections or inflammatory process, or the development of rigid connective tissue in place of pliable anal canal mucosa and muscles. Often, anal stenosis results in impaired bowel function and painful bowel movements. Stenosis can occur anywhere along the anal canal and, in rare cases, even involve the entire length. Because the primary focus of this chapter is the management of anatomic anal stenosis, physiologic/nonanatomic causes of anal canal narrowing, such as levator spasm and dyssynergic defecation, are not discussed. Anatomic anal stenosis may be congenital or result from secondary causes that can be iatrogenic, inflammatory, or neoplastic (Box 1). The most common cause of anal stenosis is anorectal surgery, in particular, hemorrhoidectomy. During the procedure, the excessive removal of anoderm and anorectal mucosa from the anal canal and suture/staple line dehiscence can result in scarring and the formation of chronic stricture. Therefore, the best approach to anal stenosis is prevention through the conservation of anoderm and avoidance of excessive circumferential excision and damage to the sphincter musculature during surgery. This chapter discusses the diagnosis, categorization, and nonoperative and operative treatment of anal stenosis.

DIAGNOSIS AND EXAMINATION

Symptoms of anal stenosis include constipation, obstipation, painful bowel movements, bleeding, and narrow caliber stools. Seepage and soiling may also occur as a result of sphincter damage or overflow incontinence. In an attempt to relieve symptoms, patients may resort to laxatives or digital manipulation, which can exacerbate the condition by causing more structural damage, spasm, and worsening anorectal physiology. Visual examination of the anal canal and perianal skin or digital rectal examination can confirm a diagnosis and identify the cause in most cases. By parting the gluteal folds, narrowing of the anal canal and circumferential scar formation may be observed. In addition, lesions such as anal condyloma or other infections or inflammatory conditions may be seen or present. For patients experiencing severe pain or anxiety, examination under anesthesia may be necessary. Under anesthesia, the full length of the anal canal can be evaluated, cultures and biopsies obtained, and functional and anatomic stenosis differentiated. If anal stricture is associated with fistulas or neoplasms, pelvic imaging in the form of magnetic resonance imaging can be informative. Magnetic resonance imaging of the pelvis can help delineate the extent and anatomy of related fistulae including secondary branches, and reveal extent of neoplastic involvement of surrounding tissues and organs.

CLASSIFICATION

Anorectal strictures can be classified by severity and extent of involvement of the anal canal. The categories described by Eberman and Thomas offer a comprehensive and clear description of different types of strictures.

Severity classification is as follows:

- Mild: anal canal can be examined by a lubricated index finger or medium (10F) Fergusson retractor
- Moderate: forceful dilation is necessary for the insertion of index finger or medium (10F) Fergusson retractor
- Severe: forceful dilation is required for the insertion of little finger or small (8F) Fergusson retractor

Involvement of the anal canal is described as:

- Low: more than 0.5 cm distal to the dentate line
- Middle: 0.5 cm distal and proximal to the dentate line
- High: more than 0.5 cm proximal to the dentate line

NONOPERATIVE MANAGEMENT

Stenoses that are infectious, inflammatory, or neoplastic in origin are best managed by treatment of the underlying disease (e.g., antibiotics, antivirals, biopsication, excision, or radiation). Stenoses of all severity can be managed with stool softeners, fiber supplements, and daily digital or mechanical anal dilation. Mechanical dilations can be particularly useful for patients with Crohn's disease because surgical treatment poses significant infectious complications. Generally, the first dilation is performed under anesthesia digitally or with dilators, such as Hegar dilators. For subsequent dilations, patients may self dilate with a digit or small dilator. Some patients may require multiple dilations under anesthesia. Practitioners may inject local corticosteroids following dilation to reduce stricturing scar formation. Although some patients respond well, manual dilations pose the risk of further fibrosis, worsening stenosis, and fecal incontinence as a result of damage to anal sphincter complex.

OPERATIVE MANAGEMENT

For moderate to severe stenosis, the solution to excised and perianal skin or rectal mucosa is brought in to reconstitute tissue inside the anal canal using various flap techniques. Flaps can be organized into three different categories: advancement, island, and rotational (Figs. 1 through 7). Comparison of the efficacy of different flap techniques is limited because prospective studies are difficult to conduct; therefore, technique should be selected based on the location, severity, extent of the stricture, and the surgeon's expertise. The condition of the rectal mucosa should be considered and endorectal mucosal advancement flaps avoided in patients with history of radiation therapy or Crohn's proctitis. In general, surgeons should familiarize themselves with two or three different types of flaps to appropriately tailor to most anal strictures. Procedural or technique-oriented textbooks and video clips can also provide a more in-depth insight into individual techniques.

ADVANCEMENT FLAPS

Advancement flaps have one free end that can be directly pulled into the defect. Because the survival of the flap depends on maximized

Suggested Readings

Brandler LRT, Wexner S, Kaiser AM. Modified Hanley procedure for management of complex hidradenitis fistulae. Dis Colon Rectum. 2009;52(8):1411–5.

Sathiyan G, Gallagher AG. Management of complex anal fistulae. Clin Colon Rectal Surg. 2014;27(1):O–40.

Han JG, Wang ZJ, Zhang Y, et al. Lateral sphincterotomy, fistula tract ligation of the sphincteric fistula tract plus a biosynthetic anal fistula plug procedure in patients with transsphincteric anal fistula: early results of a multicenter prospective randomized trial. Ann Surg. 2014;260(4):657–62.

Isseroff RR, Benkaith S, Knigsley MB. Surgical intervention for perianal hidradenitis suppurativa. Cochrane Database Syst Rev. 2010;(12):CD006318.

Ritchie RDH, Buckley BM, Biddle DP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis. 2009;11(6):564–571.

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ADVANCEMENT FLAPS

Advancement flaps have one free end that can be directly pulled into the defect. Because the survival of the flap depends on maximized

blood supply to the leading edge, the distal tip and highest tension suture areas to prone to ischemic necrosis.

Mucosal Advancements Flap

Mucosal advancement flaps are appropriate for midlevel and upper anal stenosis. This technique, also used to treat anal fistulas, is the primary technique that uses outward advancement of rectal mucosa. First, the scarred tissue is excised and a rectal mucosal flap created with a transverse incision at the dentate line. The flap usually involves

BOX 1 Classification of Anal Stenosis

Iatrogenic
Hemorrhoidectomy
Fistulectomy
Fissurectomy
Trans anal mass excision
Low anterior resection with coloanal anastomosis
Intersphincteric resection
Ileal pouch–anal anastomosis
Sphincteroplasty
Gracilis transposition
Excision of perianal skin tumor

Inflammatory
Crohn's disease
Anal fistula
Hidradenitis suppurativa
Tuberculosis
Schistosomiasis
Actinomycosis
Lymphogranuloma venereum
Acquired granuloma
Herpes simplex
Toxic epidermal necrolysis

Neoplastic
Condyloma acuminata
Bowen's disease
Paget's disease
Anal squamous cell carcinoma
Rectal adenocarcinoma

Miscellaneous
Radiation therapy
Perineal/anorectal trauma
Hot water enemas
Mucosal anti-inflammatory suppositories
Chronic laxative abuse
Chronic diarrhea

the mucosal and submucosal layers and small portion of underlying sphincter muscle complex. The tissue is then advanced past the excision area while maintaining blood supply through submucosal vascular plexuses. Last, the flap is sutured at the distal edge of the internal sphincter near the anal verge. Distal overextension of the flap or suture to the anal verge may cause ectropion, the outward turning of the anal mucosa into the anodermal junction or perianal skin.

V-Y Flap

V-Y advancement flaps are best suited for low stenosis and should not be used for strictures situated above the dentate line. The V-Y flap is example of an advancement flap that involves toward advancement of anoderm. First, a Y-shaped incision is made with the excision of the scar tissue constituting the vertical stroke of the Y. Then, a V-shaped flap (corresponding to the lip of the Y) with vascularized fatty subdermal tissue is made with the wide base facing away from the dentate line. Finally, the narrow tip of the V-shaped flap is sutured to the dentate line to form the final Y shape.

ISLAND FLAPS

Advancement transfer flaps are suitable for long strictures because they reduce the risk of tissue necrosis. Flaps are incised to the depth of the subcutaneous fat and the pedicle maintained to ensure the viability of the tissue island. The flaps should be loose enough to pull into the anal canal without tension. Flaps can be performed unilaterally or bilaterally based on the amount of tissue necessary to cover the excision area.

V-Y Flap

The V-Y flap is suitable for low, severe strictures. Following excision of the scar, a V-shaped incision with the wide base facing the dentate line is performed to form an isolated island of tissue that is slid over the excised area. The donor site is closed as a straight line.

Diamond Rhomboid Flap

Diamond flaps are suited for moderate to severe long strictures. Following the excision of the fibrous tissue, a diamond-shaped flap is created from healthy anoderm and pulled into the anal canal. The flap is then aligned with the defect and sutured to the edges. Finally, the original donor site is closed as a straight line.

House Flap

Because of its length, the house flap is capable of covering the entire length of anal canal and is suitable for long strictures or strictures above the dentate line. The fibrous tissue is excised, followed by the creation of a house-shaped flap in anoderm. The "roof" of the house faces away from the dentate line and the length of the "walls" matches the lengths of the scar tissue excision. The base of the house is sutured to the proximal end of the excision area.

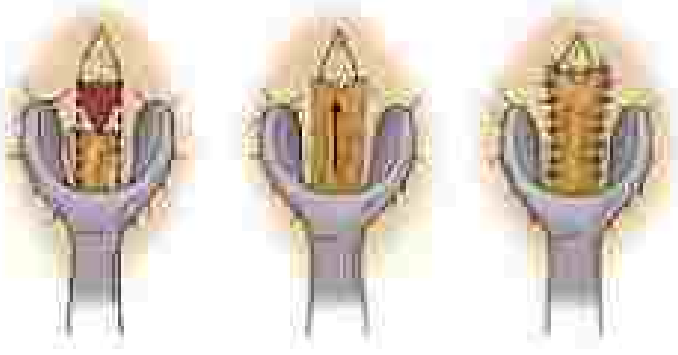

FIG. 1 Mucosal advancement flap. [From Hardiman JW. Mucosal advancement flaps. In: Beck DE, Wexner SD, editors. Fundamentals of Anorectal Surgery. 3rd ed. London: Saunders; 2006.]

U Flap

As with diamond and house flaps, U flaps are suitable for moderate to severe stricture. U flaps begin with a U-shaped incision distal to the scar tissue excision. The resulting oval flap of tissue is pulled down to the anal canal to cover the excision area. Although the flap is anatomically in place, the donor site is left open and is commonly left to granulate.

[illegible] FLAP

Extensive stenosis where a large amount of skin is necessary for coverage can be approached with the V rotational flap. A rotational flap optimally maintains tension and maintains blood supply. After the excision of scarred tissue, bilateral full-thickness diagonal flaps are made based on the pedicle arising from the anterior limit of the base of the V. The length should be as great as the length of the flaps are then rotated to an anatomical position. However, rotational flap techniques are generally used over V rotation as the latter are more complex and result in longer hospital stays.

POSTOPERATIVE CARE

Single and limited excisions can be performed in the outpatient setting. For more extensive procedures, hospital admission may be necessary. During the initial 2 to 3 weeks following surgery, patients should be placed on a short-stay regimen and must adhere to strict measures of wound management that decrease the flap risk of the postoperative complications such as contamination and infection. Sitz baths with dilute saline or mild soaps are encouraged over standard toilet paper. Such should be used for severe or hemorrhoidal patients. Additionally, it is recommended for patients to apply ice over areas of incision for the first 24 hours to reduce inflammation and swelling. Ice daily to the buttocks to alleviate associated spasm and discomfort. Patients should avoid excessive wiping after bowel movements and shower as an alternative to maintain hygiene. Potential complications include infection, suture line dehiscence, flap necrosis, incontinence, and exuberant granulation tissue development in open donor sites. Patients should be instructed to report excessive pain, diminish evacuations, ongoing bleeding, urinary retention, fever, or chills.

OUTCOMES

Outcomes of flap procedures in the literature are variable and difficult to assess because they are mostly retrospective reports of small patient series with variable follow-up times. The following discussion of a few noteworthy studies provides a brief overview. In their review of literature from 1972 to 2008, Brisinda et al. compiled retrospective data and case series to report outcomes of various flaps with a minimum follow-up of 3 months. With the exception of the V-Y flap, all flaps discussed in this chapter were reported to have a 90% or greater healing rate. Since the Brisinda review, Farid and colleagues conducted a prospective study randomizing 60 patients to either house diamond, or V-Y flap. Despite longer operative times, house flaps, when compared with diamond and V-Y flaps, had the lowest recurrence rate (3% vs 20% and 13%, respectively), lowest complication rate (13% vs 53% and 40%, respectively) and greatest anal caliber at 1-year follow-up. The house flap was also associated with greatest quality of life improvement and patient satisfaction. More recently, Boone et al. published their data on nine anal stenosis patients treated with the diamond flap. During the mean follow-up, all patients reported significant improvement in their symptoms and were able to pass bowel movement without difficulty.

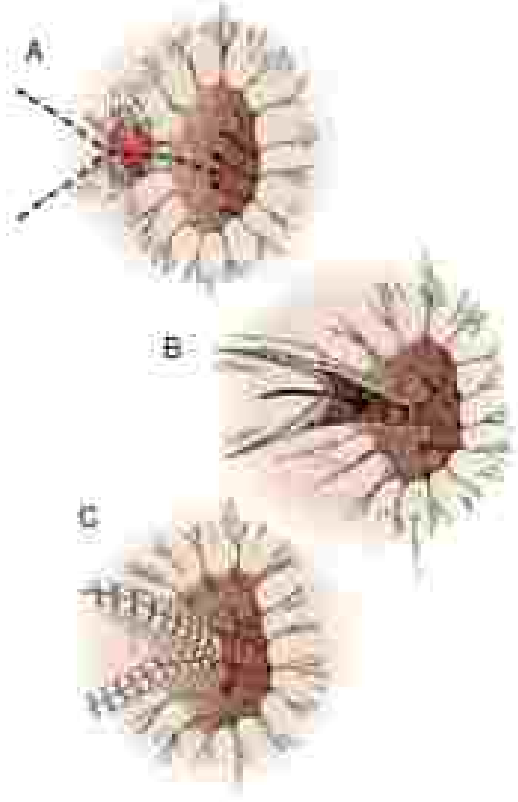

FIG. 2 (A–C) V-Y advancement flap [illegible]

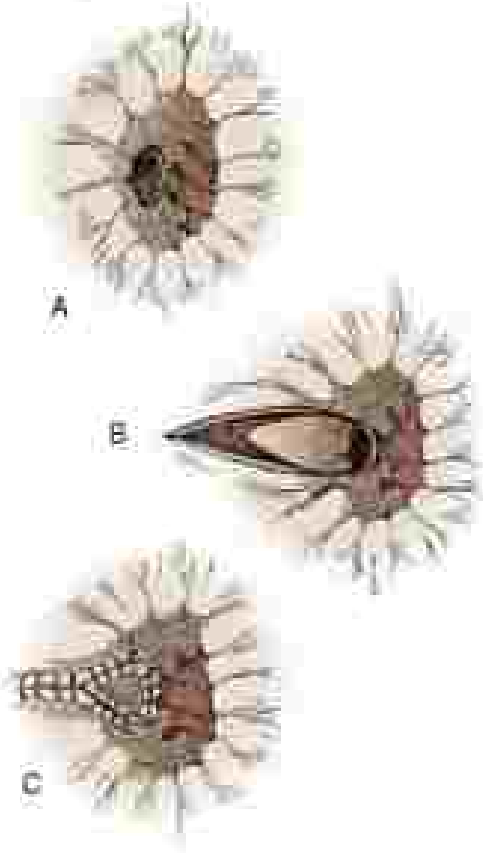

FIG. 3 (A–C) V-Y flap [illegible]

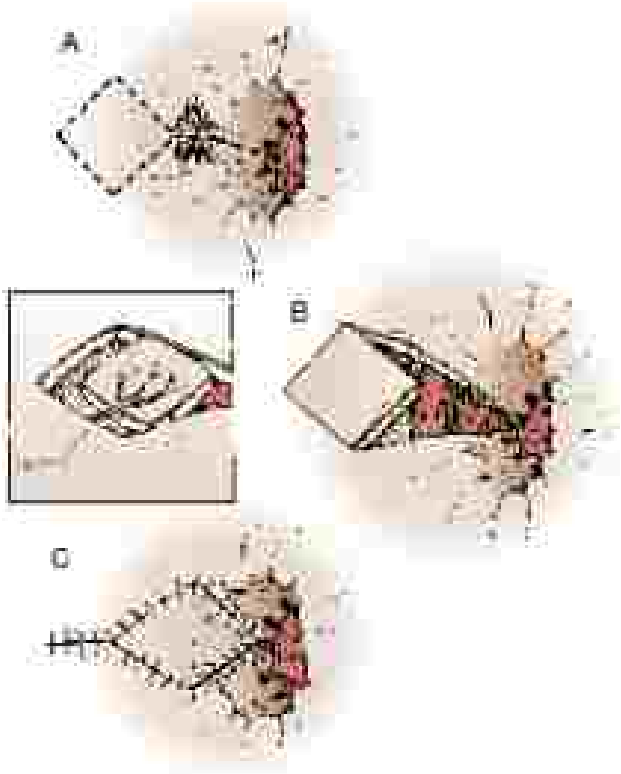

FIG. 4 (A–C) **Diamond flap.** [From Hollinger JW [book in use] and [title omitted], in Kirk DN, Wheeler M [editor, title omitted] on [name omitted] surgery, vol 2 [series location, 1988].]

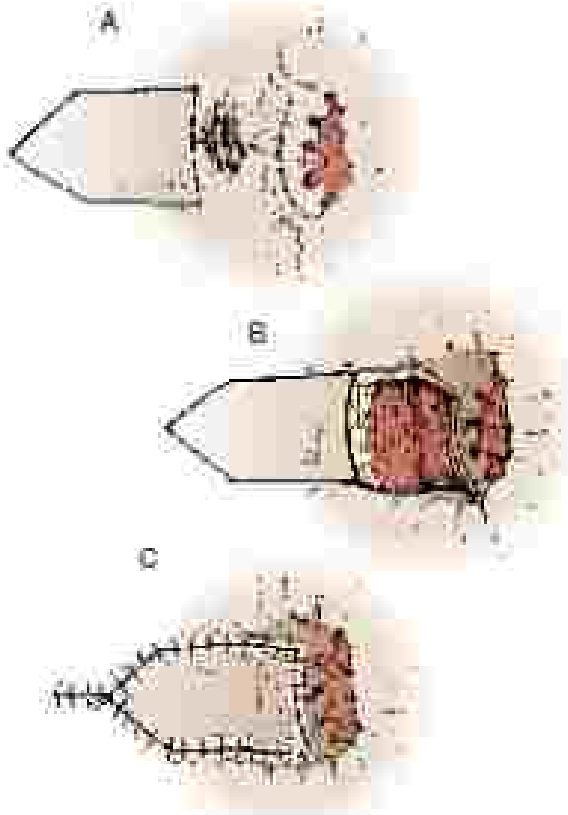

FIG. 5 (A–C) **Hexagon flap.** [In a like manner to [book in use] and [title omitted], in Kirk DN, Wheeler M [editor, title omitted] on [name omitted] surgery, vol 2 [series location, 1988].]

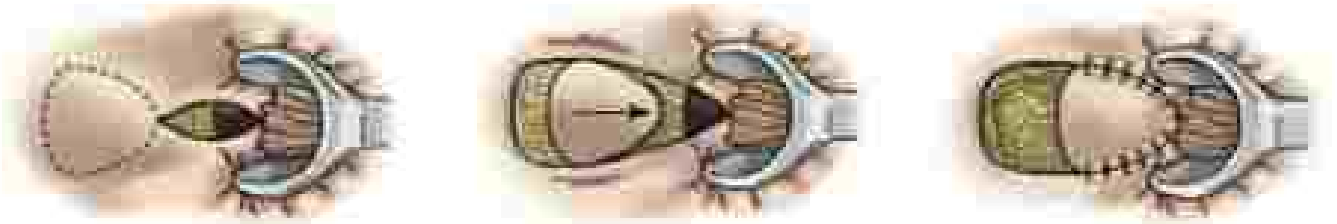

FIG. 6 (...) flap. [From Hollinger JW [book in use] and [title omitted], in Kirk DN, Wheeler M [editor, title omitted] on [name omitted] surgery, vol 2 [series location, 1988].]

FIG. 7 **Rhomboid flap.** [From Hollinger JW [book in use] and [title omitted], in Kirk DN, Wheeler M [editor, title omitted] on [name omitted] surgery, vol 2 [series location, 1988].]

SUMMARY

Anal stenosis is the narrowing of the anal canal and is most commonly associated with scarring after anorectal surgery. While nonoperative methods fail to provide adequate symptom relief, surgical treatment has been shown to be effective and provide good outcomes. While various flap techniques are available to address different types and severities of strictures, preventative measures to reduce iatrogenic injury during anorectal procedures should be emphasized.

SUGGESTED READINGS

[illegible]

[illegible]

[illegible]

MANAGEMENT OF PRURITUS ANI

Nathalie Massilla, MD, and Jean R. Cl[illegible]

Pruritus ani is a skin condition characterized by itching or a burning sensation of the perianal region. The causes are multifactorial, and patients typically present after attempting home remedies and over-the-counter medications, compounded by embarrassment to discuss these symptoms with healthcare professionals. Undoubtedly, pruritus ani is an unpleasant sensation that can greatly affect the quality of life of affected patients. The estimated incidence in the general population is up to 5%, with a male:female ratio of 4:1. Patients are often diagnosed in the fourth to sixth decades of life, with a slow progression of symptoms that worsen, particularly at night and in warm weather, because of excessive moisture of the perianal area. Pruritus ani can be localized or diffusely involve the perianal skin, and can be classified into primary or idiopathic cases, or secondary to certain disorders. Multiple conditions have been implicated in the etiology of pruritus ani, perianal soiling being the most common cause.

PATHOPHYSIOLOGY AND ETIOLOGY

The differential diagnosis of pruritus ani is composed of a long list of conditions that can be grouped into infectious, inflammatory, and neoplastic. Primary or idiopathic pruritus ani accounts for more than one-half of cases (Shelley, 1959), and although a variety of factors have been implicated in the pathophysiology (anatomic, dietary, hygienic, psychogenic, local irritants, and medications), fecal contamination and local skin irritation seem to be the common promoting factors. This phenomenon occurs by the activation of unmyelinated C fibers in the epidermis and subdermis; however, the neurophysiologic mechanisms behind the symptoms are much more complex. Unexpectedly, scratching can temporarily alleviate the itching sensation, but is thought to produce inadequate feedback to inhibit further symptoms (pruritoceptive itching). Avoiding scratching is key in the interruption of the vicious cycle of skin trauma, which is an additional stimulus for itching.

A number of foods have been associated with the production of perianal itching and are commonly excluded from the diet as part of the initial management. These prurigenic foods include coffee, colas, citrus fruits, chocolate, tea, energy drinks, alcoholic beverages, tomato, and spicy foods. They act as irritants of the perianal skin, and have also been implicated in altering bowel habits, stool consistency, and facilitating seepage. A detailed history and physical examination are critical in narrowing the diagnosis because in many cases both primary and secondary etiologies can be found. Secondary pruritus should be considered in cases in which an identifiable cause is found. The etiologies in this group are very broad and can be classified into five categories: infectious, dermatologic, systemic disease, benign and malignant anorectal diseases, and miscellaneous (Box 1).

Infectious

Among the infectious agents, sexually transmitted diseases are common causes of anal pruritus, particularly in patients practicing anoreceptive intercourse. The most common pathogens are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum*. Genital herpes infections, molluscum contagiosum, and condyloma acuminatum (human papillomavirus infection) are also encountered (Fig. 1). *Shigella* lesions are typically painful ulcers with associated perianal burning sensation that after rupture can leave superficial skin ulcerations (Fig. 2). Symptoms usually resolve after appropriate treatment. Pinworm infection is the most common cause of perianal dermatitis in children, whereas *Candida albicans* is frequently implicated in refractory dermatitis in adults. *Streptococcus pyogenes* is usually the causative agent of erysipelas, a superficial infection of the intertriginous skin often seen in warm weather. Fungal infections account for 10% to 15% of secondary anal pruritus, with *Candida albicans* being the most common fungi identified. Parasitic perianal infections are rare, but common parasites identified include *Ancylostoma duodenale* or *Necator americanus* (hookworm), *Strongyloides stercoralis*, and pediculosis pubis. Nocturnal and postdefecation pruritus ani in children is a characteristic symptom of pinworm infection.

Dermatologic

A wide variety of conditions have been associated with pruritus ani; therefore, a detailed history and physical examination are crucial. Perianal eczema is the most common dermatologic condition responsible for anal pruritus. Frequently, it originates as contact dermatitis to hygiene products or medications used to treat other anorectal conditions, such as over-the-counter hemorrhoidal ointments, deodorants, scented wipes or toilet paper, or soaps. Inquiry about anal hygiene habits and products used must be part of the history. These patients are more likely to have a history of other atopic conditions including asthma. Atopic dermatitis is another common cause of pruritus ani, with an estimated frequency of 1.4% to 2.8% of the population. Psoriasis is another skin problem associated with perianal pruritus, and although not as common, reports in the literature vary from 3% to 50%. Other less common dermatologic conditions that cause pruritus ani include seborrheic dermatitis, lichen planus, lichen sclerosus, and

SUMMARY

Anal stenosis is the narrowing of the anal canal and is most commonly associated with scarring after anorectal surgery. When nonoperative methods fail to provide adequate symptom relief, surgical treatment has been shown to be effective and provide good outcomes. While various flap techniques are available to address different types and severities of strictures, preventative measures to reduce iatrogenic injury during anorectal procedures should be emphasized.

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MANAGEMENT OF PRURITUS ANI

Nathalie Massella, MD, and Jose R. Cintron, MD

Pruritus ani is a skin condition characterized by itching or a burning sensation of the perianal region. Most cases are multifactorial, and patients typically present after attempting home remedies and over-the-counter medications, compounded by embarrassment to discuss these symptoms with healthcare professionals. Undoubtedly, pruritus ani is an unpleasant sensation that can greatly affect the quality of life of affected patients. The estimated incidence in the general population is up to 5%, with a male/female ratio of 4:1. Patients are often diagnosed in the fourth to sixth decades of life, with a slow progression of symptoms that worsen, particularly at night and in warm weather, because of excessive moisture of the perianal area. Pruritus ani can be localized or diffusely involve the perianal skin, and can be classified into primary or idiopathic cases, or secondary to certain disorders. Multiple conditions have been implicated in the etiology of pruritus ani, perianal eczema being the most common cause.

PATHOPHYSIOLOGY AND ETIOLOGY

The differential diagnosis of pruritus ani is composed of a long list of conditions that can be grouped into infectious, inflammatory, and neoplastic. Primary or idiopathic pruritus ani accounts for more than one half of cases (50%–90%), and although a variety of factors have been implicated in the pathophysiology (anatomic, dietary, hygienic, psychogenic, local irritants, and medications), fecal contamination and local skin irritation seem to be the common promoting factors. The phenomenon occurs by the activation of unmyelinated C fibers in the epidermis and subdermis; however, the neurophysiologic mechanisms behind the symptoms are much more complex. Consequently, scratching can temporarily alleviate the itching sensation, but is thought to produce inadequate feedback to inhibit further symptoms (pruritus-scratch-itching). Avoiding scratching is key in the interruption of the vicious cycle of skin trauma, which is an additional stimulus for itching.

A number of foods have been associated with the production of perianal itching and are commonly excluded from the diet as part of the initial management. These pruritogenic foods include coffee, colas, citrus fruits, chocolate, tea, energy drinks, alcoholic beverages, tomato, and spicy foods. They act as irritants of the perianal skin, and have also been implicated in altering bowel habits, stool consistency, and facilitating seepage. A detailed history and physical examination are critical in narrowing the diagnosis because in many cases both primary and secondary etiologies can be found. Secondary pruritus should be considered in cases in which an identifiable cause is found. The etiologies in this group are very broad and can be classified into five categories: infectious, dermatologic, systemic disease, benign and malignant anorectal diseases, and miscellaneous (Box 1).

Infectious

Among the infectious agents, sexually transmitted diseases are common causes of anal pruritus, particularly in patients practicing anoreceptive intercourse. The most common pathogens are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum*, but herpes infections, molluscum contagiosum, and condyloma acuminatum (human papillomavirus infection) are also encountered (Fig. 1). Herpetic lesions are typically painful vesicles with associated perianal burning sensation that after rupture can leave superficial skin ulcerations (Fig. 2). Symptoms usually resolve after appropriate treatment. β Hemolytic streptococci is the most common cause of perianal dermatitis in children, whereas *Staphylococcus aureus* is frequently implicated in refractory dermatitis in adults. *Corynebacterium minutissimum* is the causative agent of erythrasma, a superficial infection of the intertriginous skin often seen in warm weather. Fungal infections account for 10% to 15% of secondary anal pruritus, with *Candida albicans* being the most common fungi identified. Parasitic perianal infections are rare, but common parasites identified include *Enterobius vermicularis* (pinworm), *Sarcoptes scabiei* (scabies), and pediculosis pubis. Nocturnal anal pruritus are in children is a characteristic symptom of pinworm infection.

Dermatologic

A wide variety of conditions have been associated with pruritus ani; therefore, a detailed history and physical examination are crucial. Perianal eczema is the most common dermatologic condition responsible for anal pruritus. Frequently, it originates as contact dermatitis to hygiene products or medications used to treat other anorectal conditions, such as over-the-counter hemorrhoid ointments, deodorants, scented wipes or toilet paper, so soaps. Inquiry about anal hygiene habits and products used must be part of the history. These patients are more likely to have a history of other atopic conditions including asthma. Atopic dermatitis is another common cause of pruritus ani, with an estimated frequency of 15% to 20% of the population. Psoriasis is another skin problem associated with perianal pruritus, and although not as common, reports in the literature vary from 1% to 30%. Other less common dermatologic conditions that cause pruritus ani include seborrheic dermatitis, lichen planus, lichen sclerosus, and

BOX 1 Secondary Pruritus: Causes

Infectious

Bacterial
Fungal
Viral
Parasitic

Dermatologic

Psoriasis
Lichen planus, lichen simplex chronicus, lichen sclerosus
Contact dermatitis
Atopic dermatitis
Perianal psoriasis

Systemic disease

Diabetes mellitus
Leukemia, lymphoma, polycythemia vera
Liver disease (hyperbilirubinemia)
Chronic renal failure
Thyroid disorders (hyperthyroidism)

Anorectal Disease

Bowel
Hemorrhoids (internal and external)
Rectal prolapse (mucosal and full thickness)
Fissure
Fistula in ano
Diverticulitis
Secreting villous tumors
Fecal soiling and incontinence
Skin tags
Perianal Crohn's disease
Hidradenitis suppurativa

Malignant

Anal canal and anal margin cancer
Rectal cancer
Bowenoid disease
Perianal Paget's disease

Miscellaneous

Radiation-induced dermatitis
Vaginal discharge
Urinary incontinence

FIG. 1 Perianal condyloma acuminatum.

FIG. 2 Perianal herpes virus infection.

lichen simplex chronicus. A high index of suspicion is necessary for an adequate diagnosis and treatment.

Systemic Disease

Multiple systemic diseases have been associated with pruritus ani. Although the underlying triggering mechanisms are not known, treating the primary problem appears to alleviate the symptoms. Diabetes mellitus is one of the common diseases associated with anal pruritus, followed by liver disease (cholestasis), leukemia, lymphoma, chronic renal failure, uremic pruritus, pellagra, iron deficiency anemia, vitamin A and ^{1} deficiency, and hyperthyroidism.

Anorectal Disease

Pruritus ani is commonly found in patients with numerous benign anorectal conditions such as external and internal hemorrhoids (Fig. 3), anal fissures and fistulas (Fig. 4), hidradenitis suppurativa, perianal Crohn's disease, anal skin tags, and pilonidal disease. Symptoms can be caused by the disease itself or from local skin irritation associated with fecal soiling, prolapsing tissue, mucus discharge, and chronic drainage. Perianal disease commonly interferes with local hygiene, leading to skin irritation from residual fecal material. Management of the perianal condition is necessary and may improve symptoms, as it has been seen to patients with hemorrhoids after rubber band ligation or hemorrhoidectomy.

Malignant anorectal processes can also provoke pruritus ani and should be considered and ruled out when appropriate. Among these diseases are anal canal and anal margin cancer (Fig. 5), low rectal cancer, Bowenoid disease, or perianal squamous cell carcinoma in situ (i.e., ^{4}), and Paget's disease or cutaneous adenocarcinoma in situ. In patients with premalignant perianal lesions such as anal intraepithelial neoplasia caused by human papilloma virus infection, pruritus ani can be caused by the anal condyloma itself rather than the presence of dysplasia. The most common extramammary area affected by Paget's disease is the perianal region, occurring more frequently in white women in the sixth decade of life. In these cases, further evaluation of the gastrointestinal, urinary, and gynecologic systems is warranted, attributable to the high incidence of associated malignancy (33%–36%).

Miscellaneous

Radiation-induced perianal dermatitis is an undesired side effect of cancer treatments. Multiple grading systems have been used to grade skin damage from radiation. Regardless of the stage of dermatitis,

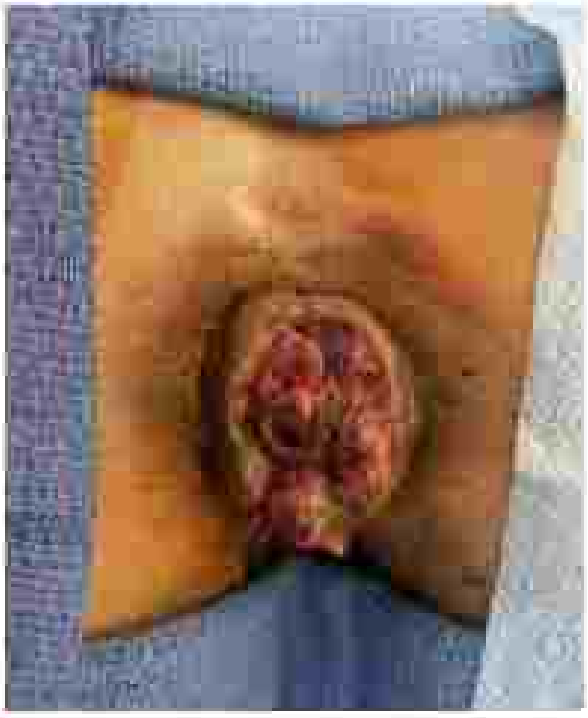

FIG. 3 Perianal mucosal hemorrhoid [illegible]

FIG. 5 Squamous cell carcinoma of anal margin.

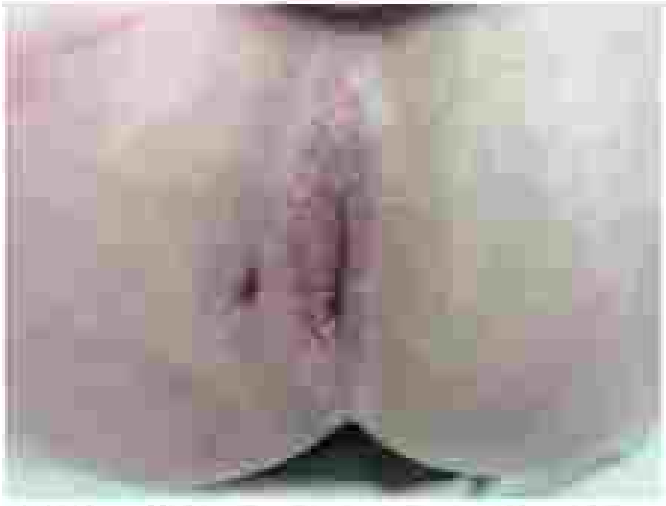

FIG. 4 Anorectal fistula with perianal dermatitis resulting from chronic drainage. [illegible]

FIG. 6 Hidradenitis suppurativa.

from dry desquamation to breakdown and ulceration of the skin; a large number of patients experience anal pruritus. Excessive moisture of the perianal skin from urinary incontinence or vaginal discharge is also associated with skin irritation and consequent pruritus ani.

EVALUATION AND DIAGNOSIS

Clinical History

Because a specialist often sees patients with pruritus ani after other treatments have failed, establishing a diagnosis can be challenging and frustrating. A detailed clinical history including presenting and associated symptoms, disease progression, comorbidities, allergies, and medications is warranted. Specifics about diet, sexual contact, bowel habits, hygiene products and behaviors, and prior use of local agents should be part of the initial clinical encounter. History of atopy, urogenital disorders or surgeries, and sexually transmitted diseases, among others, can aid narrowing the differential diagnoses.

Physical Examination

Inspection of the perianal area, perineum, and genitalia should be the first step of the physical examination. The examiner should look for erythema, fibrosis, ulcerations, maceration of the skin, residual

TABLE 1 Washington Hospital Staging Criteria

	Physical Findings
Stage 0	Normal-appearing perianal skin
Stage I	Erythematous and inflamed perianal skin
Stage II	White, lichenified perianal skin
Stage III	Lichenified skin with coarse ridges and ulceration

local material, drainage, and scratch marks. If creams or ointments have been applied, they must be gently cleansed to expose the area for proper evaluation. Frequently, no obvious abnormality is found on the initial evaluation. A digital anorectal examination followed by anoscopy should be performed to rule out anal canal conditions.

The Washington criteria, developed at the Washington Hospital Center, are commonly used to classify the severity of the pruritus ani based on clinical findings (Table 1). In patients with stage I disease, erythematous inflamed skin may be the only finding. In stage II, there is lichenified perianal skin as a result of excessive itching and scratching or rubbing of the skin, resulting in thick leathery appearing skin. In addition to these changes, stage III patients exhibit the presence of coarse ridges and ulceration of the affected skin. These staging criteria should be documented during clinic encounters because it is useful for follow up and evaluation of the response to treatment.

Microbiology testing should be performed based on index of suspicion and clinical findings. To avoid misleading results, appropriate sample collection and specimen manipulation is essential. For example, when feasible, drainage or secretions should be aspirated with a syringe and placed in a sterile container, and viral cultures should be kept on ice for transportation. In patients with diarrhea, bacterial stool cultures as well as ova and parasites testing must be considered.

When considered appropriate, a more extensive endoscopic examination can be performed, including examination under anesthesia, flexible sigmoidoscopy, and colonoscopy with tissue sampling for biopsies and cultures. Nonhealing skin lesions despite appropriate treatment are indications for a biopsy to rule out malignancy.

MANAGEMENT

The initial goal of treatment of patients with pruritus ani should be directed to relief of symptoms, healing of impaired skin, and protection and prevention of additional damage. Once a causative agent is identified (e.g., allergen, local irritant), further contact with the perianal skin must be avoided. Ultimately, management treats or controls the underlying condition after making a diagnosis in cases of secondary pruritus.

Education and Lifestyle Modifications

Particularly important in the management of idiopathic pruritus, a set of general strategies and recommendations should be implemented on the initial consultation. These changes are intended to reestablish the integrity of the perianal skin and prevent further damage, when there is no underlying condition responsible for the symptoms. Patients should be instructed to avoid applying any home remedies, over the counter products, perfumed wipes, powders, lotions, or soaps. "mild cleaning of the perianal area with water and unscented hypoallergenic soaps, followed by total air-drying the area or by dabbing with toilet paper. Avoiding excess moisture of the perianal area is paramount. This can be achieved by placing a cotton ball or a makeup removal pad after cleaning, which will aid to keep the area dry. Patients should also avoid tight fitting underclothing and synthetic fabrics, especially in warm climates. Maintaining regular bowel habits is very important, by controlling stool consistency, which may reduce the chances of stool leakage and soiling. There is significant

BOX 1 Food Products That Contribute to Pruritus Ani Symptoms

Caffeine containing products
- Colas
- Coffee
- tea
- Energy drinks

Citrus fruits and vegetables
Carbonated beverages
Chocolate
Tomato
Beer
Spicy and acidic foods
Refined carbohydrates
Nuts

value in the dietary recommendations for patients affected by pruritus ani; the elimination of problematic foods from the diet has shown significant improvement of symptoms in up to 60% of patients after 2 weeks (Box 2).

Topical Agents

If there is persistent symptomatology after 2 weeks of uninterrupted treatment, special attention should be placed on excluding other etiologies of secondary pruritus. Only after infectious causes have been eliminated from the differential diagnosis should topical steroids be considered. Low potency topical steroids such as hydrocortisone 1% are used as first line treatment with good results, decreasing symptoms and improving the quality of life. Duration of therapy should not exceed 8 weeks because prolonged therapy or the use of potent steroids is associated with skin atrophy and worsening of anal pruritus. Substance P is a neuropeptide that triggers itching and burning pain; capsaicin decreases its levels, successfully treating the symptoms in up to 70% of patients when compared with placebo. Topical steroids and capsaicin should be applied in the morning after cleaning, and at night. After completion of therapy, this topical preparation should be replaced by a zinc oxide–based skin protectant such as Calmoseptine.

In rare cases of idiopathic pruritus ani, symptoms may persist and become intractable, despite all treatment strategies and after secondary causes have been excluded. For this small subset of patients, intradermal injection of methylene blue has been described with acceptable success. The alleged mechanism of symptomatic relief is thought to be destruction of nerve terminations in the perianal area. The technique description including concentration and combination of drugs varies slightly among reports. Full-thickness skin necrosis is a complication of this treatment.

SUMMARY

Pruritus ani is a common anorectal condition that can become debilitating and frustrating for patients who suffer from it. A detailed clinical history and physical examination are of utmost importance to establish a diagnosis. When secondary pruritus is identified, the treatment should be tailored to the underlying condition. Biopsies, cultures, and other special testing methods should be performed when appropriate. The majority of the cases improve with education and lifestyle modifications such as cleaning habits and removing offending agents.

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Surgical Management of Fecal Incontinence

Evgeny R. [illegible], MD, and Amir [illegible] M. Rafi [illegible], MD, FACS, FASCRS

Fecal incontinence is defined as the involuntary loss of fecal contents (feces, gas) through the anal canal and the inability to postpone an evacuation until socially convenient. For practical reasons, the definition only applies to individuals older than age 4 years who have reached mental and developmental capacity or who previously achieved continence. Fecal incontinence is not a diagnosis but a debilitating symptom that results from an imbalance in a complex pathway regulating fecal control.

Fecal incontinence is much more frequent than acknowledged and is underreported because of its negative stigma. Obtaining accurate rates of prevalence depends on the cohort and methodology but seems to range from 1.4% to 11.5% in the general population. The quality of life of affected individuals and involved caregivers is severely diminished. In the United States, patients residing in nursing facilities are disproportionally affected (18%), and incontinence is in fact one of the leading immediate causes for institutionalization. As such, it generates a substantial financial and logistical burden to health care and society. In absence of any perfect treatment, goal-oriented management is important and may not infrequently be tasked to the practicing general surgeon.

Normal fecal control depends on various factors. Under normal circumstances, the combination of factors should allow to store (ideally formed) stool for a prolonged period. A functional unitimity with a sufficient and adjustable rectal outlet resistance is crucial. An intact, properly innervated, and responsive anal sphincter complex and pelvic floor musculature (e.g., puborectalis sling) provide the dynamic sphincter tone at rest and on demand (squeeze), but the hemorrhoidal cushions add a fine tuning seal of the anal canal. Assessing the various components depends on a complex network of central and peripheral nervous system pathways which allow for both awareness of rectal distention and coordination of the pelvic floor muscles and sphincter complex for timely and complete evacuation. Other factors relevant for fecal control should not be overlooked; a proper stool consistency as well as the sufficiently spacious rectal reservoir with normal elasticity are equally important.

There are numerous conditions that negatively affect this complex balance at various points and ultimately contribute to fecal incontinence (Table 1). Functional incontinence may result when a normal anatomy is (1) disrupted by psychological and habit deconditioning or (2) overwhelmed/exhausted by diarrhea (e.g., from irritable bowel syndrome, inflammatory bowel disease, dietary intolerances, laxative abuse) or by constipation with fecal impaction and paradoxical diarrhea or overflow incontinence. Such causes are very common and must be investigated and explored during the evaluation. Morphologic alterations may affect the macrostructure (e.g., rectal prolapse, cloaca, fistulae), or represent more hidden sphincter defects or pudendal nerve injury. Sphincter damage, as endured from obstetrical or anorectal surgical trauma (e.g., hemorrhoidectomy, hemorrhoidectomy), may clinically remain compensated for a substantial period (years) before coping mechanisms start to fail and fecal incontinence develops decades later. For example, up to 35% of women after vaginal delivery are found to have a sphincter defect, however, the symptoms of fecal incontinence are often delayed until years later (e.g., onset of menopause), and the presence of a defect alone may not correlate with the incontinence symptoms.

DIAGNOSTIC EVALUATION AND WORKUP

Patients presenting with fecal incontinence require a respectful but thorough and methodological history and physical examination. The purpose of the interview is to translate the patient's genuine complaints into a detailed understanding of the type and extent of incontinence, awareness of incontinence episodes (urge vs passive incontinence), timing and frequency of symptoms, stool characteristics and habits, and other associated symptoms (e.g., prolapse, drainage, urinary or sexual dysfunction). A detailed obstetrical and surgical history is essential. Underlying disease processes such as diabetes, stroke, inflammatory bowel disease, malignancy, or specific medications may contribute to fecal incontinence and should be documented. The examination is not limited to defining the sphincter tone at rest and during squeezing and Valsalva maneuvers, but should evaluate for the presence of pelvic organ prolapse, masses, surrounding skin irritation, hemorrhoids, fissures, hemorrhoids, or perianal/rectovaginal fistulas. The perianal and rectal sensation are assessed, and the clinical integrity and function of the sphincter complex and accessory muscles determined on physical examination.

Various patient-reported scoring systems are used to quantify patients' degree of fecal incontinence in a standardized fashion. The Cleveland Clinic Fecal Incontinence Score (Wexner) is one of

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Surgical Management of Fecal Incontinence

Gregory K. Lee, MD, and Andreas M. Kaiser, MD, FACS, FASCRS

Fecal incontinence is defined as the involuntary loss of rectal contents (feces, gas) through the anal canal and the inability to postpone an evacuation until socially convenient. For practical reasons, the definition only applies to individuals older than age 4 years who have respective mental and developmental capacity or who previously achieved continence. Fecal incontinence is not a diagnosis but a debilitating symptom that results from an imbalance in a complex pathway regulating fecal control.

Fecal incontinence is much more frequent than acknowledged and is underreported because of its negative stigma. Obtaining accurate rates of prevalence depends on the cohort and methodology but seems to range from 1.4% to 11.5% in the general population. The quality of life of affected individuals and involved caregivers is severely diminished. In the United States, patients residing in nursing facilities are disproportionally affected (18%), and incontinence is in fact one of the leading immediate causes for institutionalization. As such, it generates a substantial financial and logistical burden to health care and society. In absence of any perfect treatment, goal-oriented management is important and may not infrequently be tasked to the practicing general surgeon.

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There are numerous conditions that negatively affect this complex balance at various points and ultimately contribute to fecal incontinence (Table 1). Functional incontinence may result when a normal anatomy is (1) disrupted by psychological and habit deconditioning or (2) overwhelmed/exhausted by diarrhea (e.g., from irritable bowel syndrome, inflammatory bowel disease, dietary intolerances, laxative abuse) or by constipation with fecal impaction and paradoxical diarrhea or overflow incontinence. Such causes are very common and must be investigated and explored during the evaluation. Morphologic alterations may affect the macroanatomy (e.g., rectal prolapse, cloaca, fistulae), or represent more hidden sphincter defects or pudendal nerve injury. Sphincter damage, as endured from obstetrical or anorectal surgical trauma (e.g., hemorrhoidectomy, hemorrhoidectomy), may clinically remain compensated for a substantial period (years) before coping mechanisms start to fail and fecal incontinence develops decades later. For example, up to 35% of women after vaginal delivery are found to have a sphincter defect, however, the symptoms of fecal incontinence are often delayed until years later (e.g., onset of menopause), and the presence of a defect alone may not correlate with the incontinence symptoms.

DIAGNOSTIC EVALUATION AND WORKUP

Patients presenting with fecal incontinence require a respectful but thorough and methodological history and physical examination. The purpose of the interview is to translate the patient's genuine complaints into a detailed understanding of the type and extent of incontinence, awareness of incontinence episodes (urge vs passive incontinence), timing and frequency of symptoms, stool characteristics and habits, and other associated symptoms (e.g., prolapse, drainage, urinary or sexual dysfunction). A detailed obstetrical and surgical history is essential. Underlying disease processes such as diabetes, stroke, inflammatory bowel disease, malignancy, or specific medications may contribute to fecal incontinence and should be documented. The examination is not limited to defining the sphincter tone at rest and during squeezing and Valsalva maneuvers, but should evaluate for the presence of pelvic organ prolapse, masses, surrounding skin irritation, hemorrhoids, fissures, hemorrhoids, or perianal/rectovaginal fistulas. The perianal and rectal sensation are assessed, and the clinical integrity and function of the sphincter complex and accessory muscles determined on physical examination.

Various patient-reported scoring systems are used to quantify patients' degree of fecal incontinence in a standardized fashion. The Cleveland Clinic Fecal Incontinence Score (Wexner) is one of

the most commonly used system which scores the frequency of 5 different parameters from 0 to 4 and sums it to an aggregate score of 0 (perfect control) to 20 (complete incontinence). Other scoring instruments have a different emphasis and may be used in lieu of or complementary to the Wexner score. Examples include the Fecal Incontinence Severity Index, Fecal Incontinence Quality of Life Score, and the St. Marks Incontinence Score. All scoring systems are limited by the subjectivity of the reporting, failure to include coping mechanisms, a lack of objective physiologic test data, and most importantly the inability to accurately predict outcomes.

Objective workup primarily focuses on assessing (1) the sphincter integrity and (2) the anorectal function. Endoanal ultrasound is considered the most sensitive means to evaluate the integrity of the sphincter complex (Fig. 1). The anorectal function (muscle strength and the reservoir function) is assessed through a combination of anal manometry, anorectal sensation, volume tolerance, and determination of rectal compliance. Conventional water-based manometry has increasingly been replaced by high-resolution manometry using an integrated probe that allows for three-dimensional analysis and visualization of pressure profiles. Pudendal nerve terminal motor latency and electromyography may be useful in select circumstances, but they are of very limited prognostic value. It should be noted that amphetamine testing is not helpful because it is commonly distorted in patients with a severe anatomical pathology such as a full-thickness rectal prolapse. It is recommended that the anatomy first be corrected before subjecting the patient to predictably unreliable assessment of the anorectal function.

Additional workup steps are optional and depend on the individual setting. Occasionally, particularly with predominant pelvic organ instability (organ descent/prolapse), a dynamic magnetic resonance imaging scan, and/or defecating proctogram may be useful to visualize the positional instability and the involved pelvic compartments. If necessary, based on findings or clinical suspicion, consider early multidisciplinary involvement by gynecology, urology, and/or neurology.

Patients who meet national screening guidelines or have concerning symptoms should undergo a full colonoscopy, otherwise, flexible sigmoidoscopy is adequate to evaluate for associated masses or inflammation. If tests reveal a specific disease such as cancer or inflammatory bowel disease, the primary focus lies in appropriate management of these conditions according to respective guidelines.

TABLE 1 Causes of Fecal Incontinence

Category	Details
Acquired structural abnormalities	Obstetric injury (vaginal delivery) Anorectal surgery (e.g., hemorrhoid, fistula, fissure) Rectal intussusception/prolapse Sphincter sparing bowel resection Trauma (e.g., pelvic fracture, anal impalement, and laceration)
Functional disorders	Chronic diarrhea Irritable bowel disease Inflammatory bowel disease Radiation proctitis Hypersecretory tumors Fecal impaction (paradoxical diarrhea) Physical disabilities Psychiatric disorder
Neurologic disorders	Pudendal neuropathy (radiation, diabetes, chemotherapy) Spinal surgery Multiple sclerosis Dementia Central nervous system disorder: stroke, trauma, tumor, infection Spina bifida
Congenital disorders	Imperforate anus Cloacal defect Spina bifida (myelomeningocele, meningocele)

NONOPERATIVE MANAGEMENT

Patient Self-Directed Measures

The initial management of fecal incontinence, regardless of etiology, should be nonoperative and begin with the patient to control symptoms and attempt to correct any modifiable factors contributing to the patient's presentation. The most pressing goals are to (1) optimize stool consistency, (2) slow down bowel motility, and (3) minimize the average stool load in the rectum, particularly before going to bed or leaving the security of the private home. Supportive measures

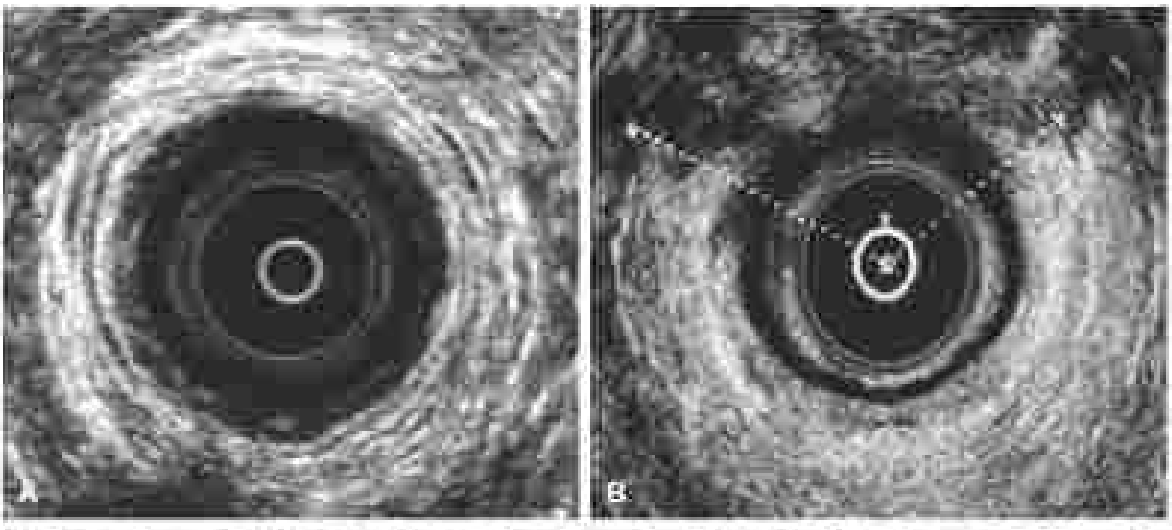


FIG. 1 Endoanal ultrasound imaging of the anal sphincter muscle. (A) Intact circumferential sphincter complex. (B) Approximately 110-degree anterior sphincter defect.

include perianal skin care to minimize irritation, which is a common complaint in incontinent patients and can progress to larger wounds and predispose patients to infection. Incontinence pads and barrier creams are useful adjuncts in this setting. A number of anal plugs have come to market over time, but most were either poorly tolerated or utterly ineffective in controlling fecal incontinence or skin complications.

The nonoperative therapy goal of optimizing stool consistency and decreasing the stool burden and the propulsive motility can be pursued by dietary and habit changes, as well as pharmacological and bowel management interventions. Dietary changes should focus on avoiding foods that promote urgency or diarrhea and on managing daily fluid intake. In individuals with a weak sphincter function, dietary fiber supplementation requires caution and may prove counterproductive because of increased stool volume or less desirable stool consistency. Pharmacologic interventions include antidiarrheal medications such as loperamide and diphenoxylate atropine. In patients with irritable bowel syndrome, tricyclic antidepressants such as amitriptyline or newer irritable bowel syndrome–specific drugs such as alosetron or ibrexadoline may be considered. A bowel management program starts with patient education about regularity and timing in relation to the gastrocolic reflex and further aims to eliminate misconceptions. In addition, scheduled tap water enemas may be a useful adjunct to reduce the stool load, particularly if antidiarrheal medications seem to aggravate constipation; enemas are a must in patients with fecal impaction and overflow incontinence.

Professional Nonoperative Intervention

Physical therapy and biofeedback training are common techniques that focus on strengthening and re-coordinating the pelvic floor and sphincter function in response to rectal distention. The approach is simple, noninvasive, and without any adverse side effects. A subjective benefit has been noted in 64% to 89% of the patients. However, an objective improvement compared with standard care is frequently impossible. The most significant effect from physical therapy and biofeedback training may be that the patients are tasked to take an active role in addressing their incontinence.

OPERATIVE MANAGEMENT

If conservative management in patients with fecal incontinence has been exhausted and failed to offer an acceptable quality of life, surgical options are explored. Depending on the nature and severity of the symptoms, the operative strategy has several levels of intervention (Table 2). Before focusing on incontinence-specific approaches, it is important to correct major anatomic abnormalities such as rectal or hemorrhoidal prolapse, rectovaginal/rectourinary and other fistulas, and chronic (or severe) keyhole deformities. Restoring a comparably normal anatomy itself has the potential to normalize much of the missing control function.

Regarding specific strategies, several options that involved different types of implants have unfortunately recently been taken off the market. Therefore, the remaining surgical strategies are limited to a sphincter repair, sacral nerve stimulation (SNS), or creation of a stoma. Fortunately, however, there are a few additional entries as well as new modalities that are in the research and development stage or early clinical implementation.

SPHINCTEROPLASTY

If there is a relevant defect in the sphincter complex from obstetric injury, anorectal surgeries, or trauma, a repair of the sphincter (sphincteroplasty) seems to be a rational and still probably the most frequently used approach. The goal is to reconstitute the circular configuration of the muscle around the anal canal. This will restore the high-pressure zone at rest and during squeezing (Fig. 2). Furthermore, the shortening of the muscle fibers during a contraction translates into a centripetal force that effectively narrows the anal canal.

Patient selection is important for the success of sphincteroplasty. Even in a defect size between 60 and 180 degrees, repair of smaller defects, isolated internal sphincter defects, or of multisegmental sphincter fragmentation is not typically beneficial. Furthermore, repeat sphincteroplasties or repair of very scarred muscles without identifiable contractility are not promising.

The data as for other anorectal procedures, the prone jackknife offers many advantages, but some surgeons prefer the lithotomy position. A transverse or curvilinear incision in the perineum midway between the anus and vagina (Fig. 3) provides access to the anterior defect to dissect down to the sphincter complex and associated scar tissue. Injuries to either the rectum or vaginal wall should be avoided under all circumstances because they may be complicated by formation of a fistula. The concept is to mobilize the scarred ends of the sphincter on either side as much as necessary to allow for an overlap but as little as possible to avoid denervation (pudendal nerves) or ischemia. If the sphincter muscle is absent in the middle and has been replaced by an unstructured scar, it is sometimes challenging to find the right level of dissection that continues into the true sphincter structures. Trimming the scar tissue is not desirable because it provides a much better anchor for the sutures than the native muscle tissue would. The scar tissue overlying the anterior defect is divided and subsequently overlapped (Fig. 3). A series of 2-0 absorbable mattress sutures are placed and subsequently tied. It is important to create an adequate length of a high-pressure zone. This may be supplemented by adding an anterior levatoroplasty. A sphincter repair without overlap but more end-to-end apposition may be considered in cases of acute sphincter disruptions if done at the time of the injury. A sphincter plication if there is no identifiable defect has proven ineffective.

Short-term results following anterior sphincteroplasty are generally favorable with rates of improved incontinence in the range of 75% to 80%. Because the effect of the original and reparative surgical trauma are undetermined, however, this response over time appears to deteriorate such that less than one half of patients remain fully continent at 5 to 10 years. Nonetheless, and not since the artificial

TABLE 2 Surgical Targets and Options

Goal	Options
Correction of complex pelvic deformities	Prolapse Repair, correction, or removal of: • Cloaca • Keyhole deformity • Rectovaginal fistula • Cloacogenic anomaly • Tumor
Sphincter repair	Overlapping sphincteroplasty
Enhancement of impaired sphincter function	Sacral nerve stimulation Radiofrequency energy administration (SECCA) Injection of bulking agents (e.g., NASHA/Dx, Solesta)
Sphincter replacement/support	Artificial bowel sphincter Implantation of magnetic anal sphincter (Torax) Levatoroplasty Implantation of cardiac (Dynamyo) Implantation of pelvic sling system
Diversion	Colostomy
Reduction of fecal load	Malone antegrade continence enema

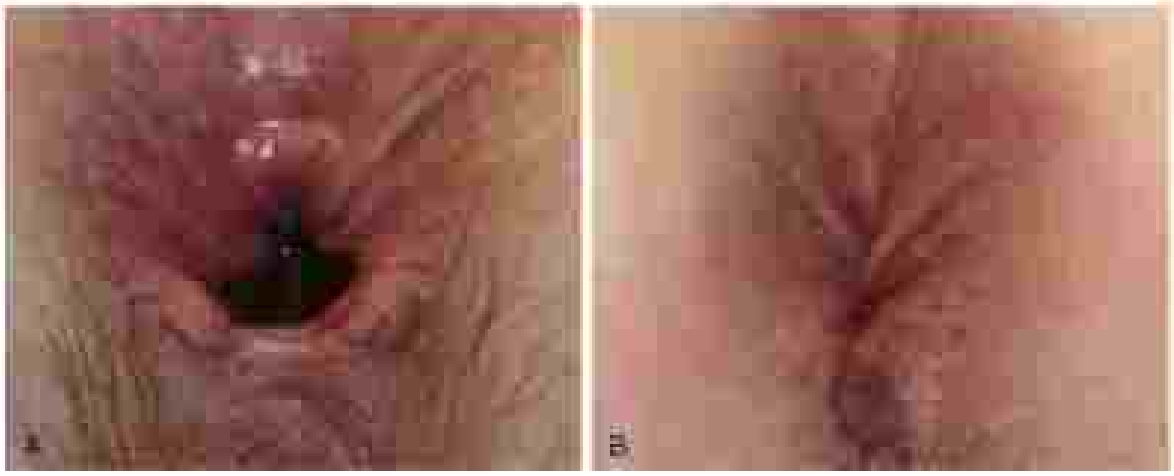


FIG. 2 Impact of overlapping sphincteroplasty on the external appearance of the anus. (A) Preoperative patulous anus. (B) Restored resting tone with closure of the anus.

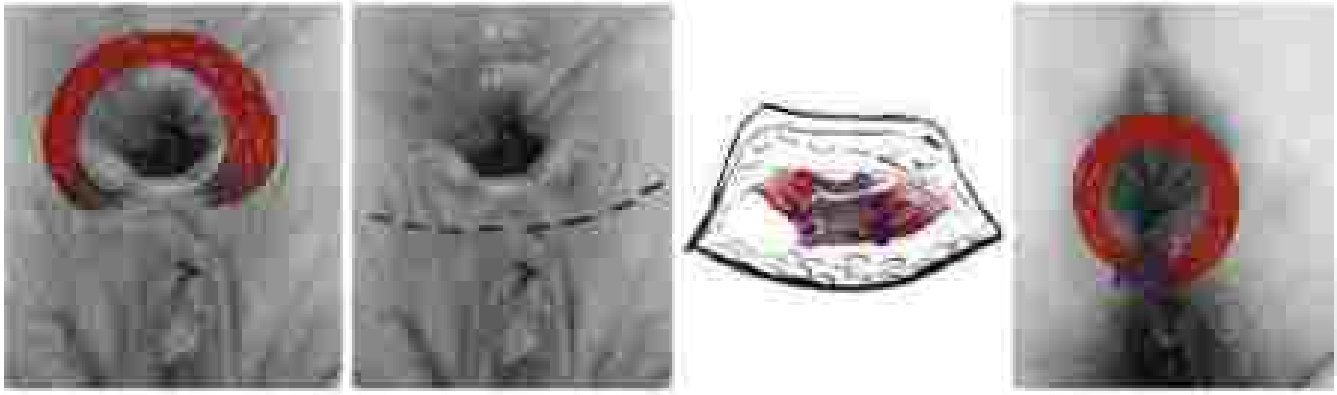


FIG. 3 Steps of overlapping sphincteroplasty.

sphincter implant options have been taken off the market, a substitute approach is not justified and should be avoided.

SNS

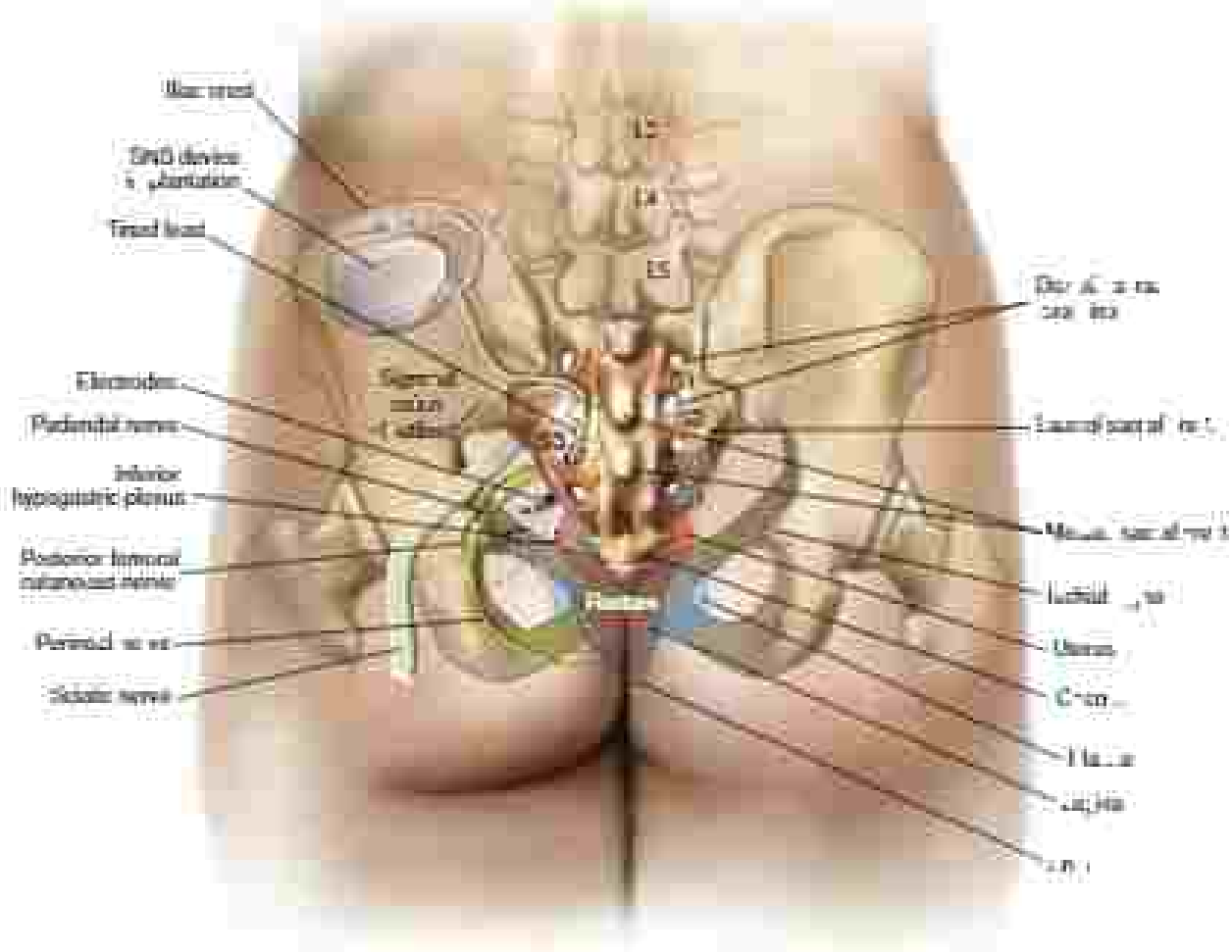
SNS has evolved into the treatment of choice for patients with fecal incontinence with very few exceptions. The treatment initially expanded after a benefit on bowel control was noted in patients treated with SNS for urinary incontinence. In 2011, it secured US Food and Drug Administration approval for use in patients with fecal incontinence. Although the exact mechanism of action remains unclear, SNS via direct, low voltage stimulation of the sacral nerve roots appears to simultaneously affect multiple levels of the complex neuromuscular pathway that controls fecal continence. The implantation is carried out in two stages, both in the outpatient setting. The first stage is considered a trial phase and involves the percutaneous placement of a wire with four leads into the S3 foramen (Fig. 4). Correct lead placement is confirmed by means of fluoroscopy (Fig. 5) and intraoperative test stimulation, which should result in a contraction of the pelvic floor musculature (Barlow's sign) and ipsilateral great toe flexion. These leads are then connected to an external stimulator. Symptoms are tracked over 2 weeks before and after the implantation. If the stimulation results in at least a 50% reduction in fecal incontinence episodes, it is considered a success, and the patient moves on to stage 2; otherwise, the temporary lead is removed. Stage 2 procedure involves the permanent implantation of the actual stimulator in the soft tissue of the buttocks just below the iliac crest (Fig. 6).

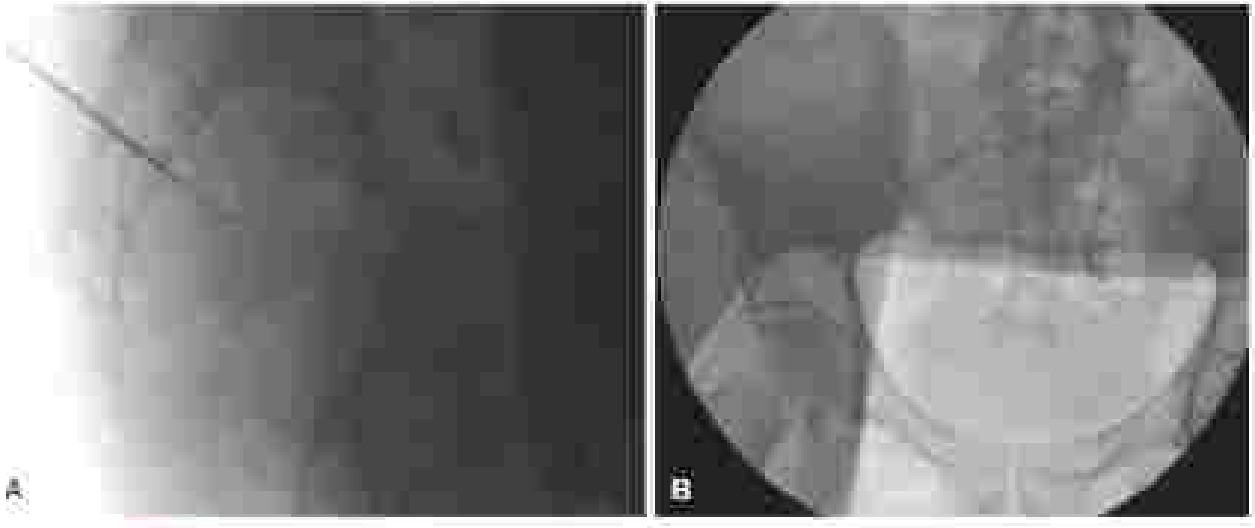
Studies have shown that definitive implantation was associated with a greater than 50% improvement in bowel incontinence episodes in 80% to 83% of patients and with nearly perfect control in 40% of the patients. Even in the long-term analysis, the success appeared to persist, but after 3 to 5 years, a battery change is needed. The method has a favorable safety profile, and complications (e.g., pain, infection, bleeding, paresthesia) are comparably rare.

The success of SNS has caused a major paradigm shift in the workup and treatment of patients with incontinence. It has become clear that no preoperative test, but only the trial lead placement, can predict treatment success. Therefore, the traditional recommendation to do anal physiology and pudendal nerve testing before any surgical intervention has lost regard. SNS is now indicated following failed nonoperative management of any incontinence regardless of whether there is a sphincter defect or pudendal neuropathy. Exceptions are limited to gross congenital or acquired anatomical alterations of the rectum and pelvic floor, local tissue infections, a predictable need for magnetic resonance imaging scans, or a failed test phase.

FECAL DIVERSION

Fecal diversion with the creation of a well-constructed diverting colostomy at a carefully selected site remains a more satisfying than acknowledged approach that gives the patient back predictability and health. Despite the negative stigma that many patients associate with stomas, most report minimal negative impact on quality of life, and approximately 80% would choose fecal diversion again. A thyroid colostomy, laparotomy loop or end stoma, is the preferred method. If


Electrodes
Pudendal nerve
Inferior hypogastric plexus
Perineal nerve
Sciatic nerve


A
B

there is a history of previous pelvic reactive surgeries, caution should be used to ensure the exact blood supply of the existing anatomy is well studied.

UNAVAILABLE OR UNCOMMON SURGICAL OPTIONS

It is rational to consider methods to increase the anorectal outlet resistance if the sphincter complex is weak and dysfunctional. Different approaches have been explored and obtained US Food and Drug Administration approval. They included, from most to less effective, the implantation of the artificial bowel sphincter (Acticon Neosphincter), the magnetic ring (Fenix), radiofrequency administration (Secca), or injection of bulking agents (e.g., NASHA/Dx) into the anal canal. Risks and effectiveness seemed to have a direct correlation. Options with a low risk profile had (despite statistical significance) very low clinical success rates (radiofrequency, bulking agents); the magnetic ring was associated with an intermediate risk profile and offered moderate clinical success; and the artificial bowel sphincter had a significant complication rate (infection, erosion), but was highly effective in patients who did not experience complications. Mostly for economic reasons though, the manufacturers took these options off the market, and their future remains uncertain.

Other options, such as a gracilioplasty or the Malone antegrade continence enema are rare options in adult patient populations and should be reserved for centers with experience.

FUTURE OPTIONS

Research centers around other types and delivery mechanisms to enhance the outlet resistance (e.g., placement of perianal self-expandable implants that are placed by means of an applicator gun [LiaoKeeper]). Definitely a cause for excitement is the stem cell research that has the goal to regenerate muscular tissue around the anus. There have already been early-stage reports and most recently presentations about three-dimensional bioprinters that are able to generate contractile tissue rings.

CONCLUSIONS

Fecal incontinence is frequent but, because of the stigma, underreported. It results from an imbalance or decompensation of the continence factors (anal sphincter complex, stool consistency, rectal reservoir function, neurologic function). Symptom severity should be quantified using one of several validated scoring systems. Objective evaluation tools include anorectal ultrasound and anorectal physiology testing but may lead to further imaging or a referral to associated specialties (urology, gynecology). There is no single technique that would guarantee perfect outcomes without any morbidities, and successful management needs to combine different approaches. Operative strategies are explored for patients with obvious structural deformities or significant fecal incontinence that is refractory to conservative management. Current options include sphincter repair, SNS, or creation of a stoma. Other options such as implants have despite efficacy been taken off the market.

Suggested Readings

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Rectovaginal Fistula

Mitchell A. Bornstein, MD, FACS, FASCRS, and Josef A. Shikhani, MD, FACS, FASCRS

Rectovaginal fistulas (RVFs) are abnormal communications between the anus or rectum and the vagina and can present a challenge for both the patient and the surgeon. Patients may present with stool per vagina resulting in frank incontinence, or gas or drainage per vagina. This condition can have extensive morbidity related to a negative impact on the patient's social, sexual, and overall quality of life and can be extremely disabling and associated with significant distress to affected women. Additionally, the morbidity and success of a repair is directly dependent on both the cause and the complexity of the fistula. Many surgical repair options exist for this disease; however, many patients fail multiple procedures before going to a tertiary care center. RVFs are uncommon in the general population but are seen frequently by colorectal surgeons.

The literature is made up of case series with small numbers of patients and the systematic reviews analyzing them. It is therefore difficult to advocate for one repair technique or directly compare the results between techniques.

With these limitations in mind, in this chapter we discuss the surgical management of RVF and propose a broad treatment algorithm based on current reported literature.

ETIOLOGY/CAUSES

RVFs are most commonly the result of obstetric injuries, cryptoglandular disease, or Crohn's disease. Other causes encountered are malignancy, radiation therapy, or complications following leaks from a colorectal, colonal, or ileal pouch anal anastomosis (Box 1).

Obstetric injury is the most common cause of RVF. Approximately 2% of all vaginal deliveries are associated with third- and fourth-degree perineal tears with 3% of these patients subsequently developing an RVF accounting for 0.1% to 0.3% of all vaginal deliveries. Fistulas arising from obstetric injury often are associated with anterior anal sphincter defects that lead to fecal incontinence in

there is a history of previous pelvic reactive surgeries, caution should be used to ensure the exact blood supply of the existing anatomy is well studied.

UNAVAILABLE OR UNCOMMON SURGICAL OPTIONS

It is rational to consider methods to increase the anorectal outlet resistance if the sphincter complex is weak and dysfunctional. Different approaches have been explored and obtained US Food and Drug Administration approval. They included, from most to less effective, the implantation of the artificial bowel sphincter (Acticon Neosphincter), the magnetic ring (Fenix), radiofrequency administration (Secca), or injection of bulking agents (e.g., NASHA/Dx) into the anal canal. Risks and effectiveness seemed to have a direct correlation. Options with a low risk profile had (despite statistical significance) very low clinical success rates (radiofrequency, bulking agents); the magnetic ring was associated with an intermediate risk profile and offered moderate clinical success; and the artificial bowel sphincter had a significant complication rate (infection, erosion), but was highly effective in patients who did not experience complications. Mostly for economic reasons though, the manufacturers took these options off the market, and their future remains uncertain.

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Fecal incontinence is frequent but, because of the stigma, underreported. It results from an imbalance or decompensation of the continence factors (anal sphincter complex, stool consistency, rectal reservoir function, neurologic function). Symptom severity should be quantified using one of several validated scoring systems. Objective evaluation tools include anorectal ultrasound and anorectal physiology testing but may lead to further imaging or a referral to associated specialties (urology, gynecology). There is no single technique that would guarantee perfect outcomes without any morbidities, and successful management needs to combine different approaches. Operative strategies are explored for patients with obvious structural deformities or significant fecal incontinence that is refractory to conservative management. Current options include sphincter repair, SNS, or creation of a stoma. Other options such as implants have despite efficacy been taken off the market.

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RECTOVAGINAL FISTULA

Mitchell A. Bornstein, MD, FACS, FASCRS, and Josef A. Shabahang, MD, FACS, FASCRS

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The literature is made up of case series with small numbers of patients and the systematic reviews analyzing them. It is therefore difficult to advocate for one repair technique or directly compare the results between techniques.

With these limitations in mind, in this chapter we discuss the surgical management of RVF and propose a broad treatment algorithm based on current reported literature.

ETIOLOGY/CAUSES

RVFs are most commonly the result of obstetric injuries, cryptoglandular disease, or Crohn's disease. Other causes encountered are malignancy, radiation therapy, or complications following leaks from a colorectal, colonal, or ileal pouch anal anastomosis (Box 1).

Obstetric injury is the most common cause of RVF. Approximately 2% of all vaginal deliveries are associated with third- and fourth-degree perineal tears with 3% of these patients subsequently developing an RVF accounting for 0.1% to 0.3% of all vaginal deliveries. Fistulas arising from obstetric injury often are associated with anterior anal sphincter defects that lead to fecal incontinence in

BOX 1 Cause of Rectovaginal Fistulas

Obstetric Injury

Episiotomy, third- and fourth-degree perineal lacerations

Inflammatory Bowel Disease

Crohn's disease

Iatrogenic

Anorectal surgery (hemorrhoidectomy)
Vaginal surgery (hysterectomy, sectocele repair)
Abdominal surgery (hysterectomy, low anterior resection, J pouch, procedure for prolapse and hemorrhoids)

Infectious

Cryptoglandular abscess, diverticulitis, tuberculosis

Neoplastic

Anal cancer, rectal cancer, vaginal cancer, cervical cancer

Radiation Induced

External beam radiation, brachytherapy

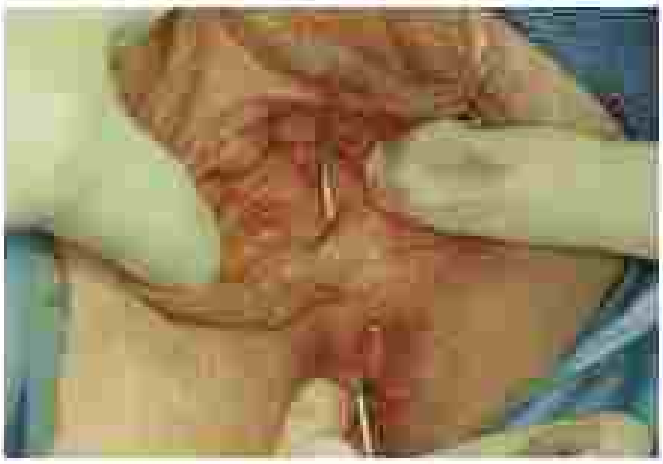

FIG. 1 Small rectovaginal fistula with intact perineum and anal sphincters. (From Kumar RR, Rectovaginal fistula and perineal injuries. In Wexner SD, Abcarian H, eds. Surgery and Interventional Tools. Surgery 4th ed. Philadelphia: Elsevier; 2015.)

varying severity. They typically become apparent around 1 to 2 weeks after delivery following the breakdown of a fourth-degree repair. Prolonged labor resulting in compression of the rectovaginal septum by the infant's head can lead to necrosis of the rectovaginal septum and cause an RVF that presents in a more delayed fashion. These generally occur cephalad to the pelvic floor and sphincter complex where the rectovaginal septum is thinnest. Traumatic injury from an instrumented delivery can also result in fistula formation and generally occurs in the thin portion of the rectovaginal septum.

Crohn's disease is the second most common cause of RVFs. Approximately 10% of women with Crohn's disease will develop an RVF, and they are more common in those who suffer from colonic Crohn's disease. RVFs associated with Crohn's disease have a high recurrence rate and often require multiple procedures before healing repair. They are variable in their presentation and location, are the result of transmural inflammation from the anorectum, and frequently associated with perianal sepsis, branching fistula tracts, as well as scarring and stricturing of the anorectum.

Cryptoglandular disease, commonly the cause of simple anorectal fistulas, can also cause RVFs. If an anteriorly located anal gland or its associated duct becomes occluded it may result in abscess formation within the rectovaginal septum and decompression into the vagina. If the communication fails to heal, an RVF results. These are generally located at the level of the dentate line on the rectal side and course through the anal sphincters to the low vagina or introitus.

CLINICAL INDICATIONS AND APPROACH TO DIAGNOSIS

In the initial evaluation and treatment of RVFs, underlying pathology such as cryptoglandular abscess, inflammatory bowel disease, or malignancy must be addressed first because procedures performed to eliminate the fistula in the setting of active disease or infection will often fail.

Symptoms may vary depending on the etiology, although generally the most common presenting symptoms are passage of stool or gas via the vagina, which often can be misinterpreted as fecal incontinence. In addition, patients may offer a history of recurrent urinary tract infections, dyspareunia, or vaginal discharge. History and physical examination are of paramount importance because details may affect the approach and method of repair.

History taking may be directed toward the patient's previous obstetric history, history of abdominal and anorectal operations, history of radiation treatment, and signs and symptoms of Crohn's disease or diverticulitis (which may help to differentiate from a colovaginal fistula).

On physical examination, an indurated fistula tract can often be identified on digital examination. Anoscopy or vaginal speculum examination may be used to visualize granulation tissue at the level of the fistula tract. Additionally, the condition of the perineal body and rectovaginal septum should be noted. Care should be taken to assess the quality and strength of the anal sphincters because the status of the sphincter complex plays an integral role in the choice of repair. Although large RVFs may be readily apparent on rectal examination, bimanual examination may be required to detect smaller fistulas. The location of the fistula relative to the sphincter muscles and pelvic floor should be determined as this can affect the type of repair chosen. Nevertheless, not all RVFs are identified on an initial clinical examination in the office. In these cases, an office-based tampon test can be undertaken. A tampon is placed in the vagina, and an enema of diluted methylene blue dye is given as an enema. The patient is asked to ambulate and later (i.e., after 20–30 minutes), the tampon is removed and inspected for evidence of blue dye. If dye is identified on the tampon, a fistula is highly suspected. If still not clinically apparent, an examination under anesthesia (EUA) is the best modality to define the fistula tract and plan surgical treatment. If the primary opening is identified, but with difficulty identifying the secondary opening, hydrogen peroxide or methylene blue can be used. A fistula probe can be placed into the fistula tract (Fig. 1).

Physical examination should also reveal any signs of continuing perianal sepsis, such as undrained abscesses or purulent perineal drainage and in many instances patients with Crohn's disease should also undergo an EUA as an initial step after clinical examination to identify the fistulous anatomy and evaluate for the degree of inflammation of the anus and rectum which may affect timing of surgery.

The necessary steps in preoperative evaluation are to (1) identify the fistula, (2) determine the cause, (3) evaluate the extent of the disease, and (4) identify surrounding injuries. The evaluation and management of simple or low rectovaginal (anovaginal) fistulas may differ from the approach to complex and high RVFs. Endoanal ultrasound (EUS) and magnetic resonance imaging are the most useful imaging studies to identify a fistula, with magnetic resonance imaging also having the advantage of identifying other disease within the pelvis. Both modalities may be enhanced by injecting hydrogen peroxide into the fistula tract. EUS is also useful in that it enables assessment of the anal sphincters. It should be performed routinely in patients with an RVF secondary to obstetric trauma as they may have associated sphincter damage. Anorectal manometry and pudendal nerve

terminal motor latency testing may be necessary if there is a history of an anal sphincter injury or presence of fecal incontinence because anal sphincter injury or pudendal nerve injuries can cause recurrent symptoms of fecal incontinence even after a successful fistula repair.

In cases of malignancy and inflammatory bowel disease, a complete evaluation of the small bowel or colon and rectum may be necessary to determine the extent of luminal stigmata. This workup may include small bowel series, endoscopy, computed tomography/magnetic resonance enterography, computed tomographic/magnetic resonance colonography, endoscopy, or contrast enema.

If a fistula is still not identified, alternate etiologies to explain the patient's symptoms should be considered, such as a colovaginal fistula rather than an RVF. Colovaginal fistulas from diverticulitis are a more common condition, and a contrast computed tomography scan of the abdomen and pelvis may demonstrate inflammation of the sigmoid colon directly overlying the vagina if this is the case. This would be more prevalent in patients that are postHysterectomy. However, very small or high RVFs may not be palpable on examination.

Classification

RVFs are often classified according to their relationship to the anal sphincter complex and are broadly classified as low RVFs and high RVFs. (high fistulas are defined as those above the sphincter complex and low fistulas are those at or below the level of the sphincters. these also are referred to as anovaginal. Trauma after vaginal delivery is almost always the cause of low fistulas, which often are associated with an associated sphincter injury. Alternatively, RVFs may be classified as simple or complex. Simple fistulas are located in the middle or lower portion of the rectovaginal septum, are less than 2.5 cm in diameter, and are caused by local trauma or infection. Commonly, complex fistulas are usually greater than 2.5 cm, located in the upper portion of the rectovaginal septum, or are secondary to causes other than trauma and infection, such as neoplastic, diverticular, effects of pelvic radiation, or inflammatory bowel disease.

Preoperative management

The extent of preoperative preparation is largely subjective but usually varies with the extent of the procedure planned for the repair. For simple repairs and local vaginal-based repairs, a phosphate enema on the morning of the procedure is adequate. For more extensive repairs, such as an overlapping sphincteroplasty or an interposition flap, and especially when fecal diversion is anticipated, or a bowel resection with a coloproctostomy or colorectal anastomosis, a full mechanical and antibiotic bowel preparation should be performed. Perioperative antibiotics and deep venous thrombosis prophylaxis are administered as per Surgical Care Improvement Project and institutional guidelines.

Surgical Management

In the initial evaluation and treatment of RVFs, underlying pathology such as cryptoglandular abscess, inflammatory bowel disease, or malignancy must be addressed and controlled first as procedures performed to eliminate a fistula in the setting of active disease or infection will often fail. The presence of active sepsis is an absolute contraindication to any attempt at surgical repair. Surgical drainage of any abscesses and resolution of sepsis is the first and most important step and a draining seton may be required to facilitate resolution of acute inflammation, edema, or infection associated with RVF infection so that the success of subsequent repair is more likely. Setons may also provide long-term symptomatic relief for patients who are poor candidates for definitive repair and may benefit patients with an active inflammatory or neoplastic process that requires other treatments before or as part of definitive repair of the fistula. Although there is no defined period of drainage before definitive repair, a seton should be left in place until the acute inflammation and any infection have resolved. This may last 3 to 6 months in some cases. In certain instances, when a seton and wound care are inadequate to control RVF associated symptoms, a diverting ostomy may be necessary.

The goal of treatment is to preserve continence while achieving healing of the fistula. Because the status of the sphincter complex plays an integral role in the choice of repair, assessment of anal sphincter function is another key step in the initial evaluation.

There are four general categories of surgical approaches to an RVF: transanal, transvaginal, transperineal, and transabdominal.

Transanal

Fistulotomy

A fistulotomy, by definition, is the laying open of the fistula tract, which may also be curetted or excised (Fig. 2). This often is performed as a two-stage procedure: first, a draining seton is placed and then removed after fistula tract maturation and fibrosis. The second stage involves cutting of the remaining tissue to lay open the tract. Although fistulotomy is the most successful surgery for managing perianal fistulas, it is in some cases contraindicated because it inevitably results in some degree of incontinence, either from the paucity of sphincteric muscle to suture internally or a resulting keyhole defect. The incontinence is often permanent. Therefore, although lay-open fistulotomy theoretically is indicated for superficial fistulas, it very rarely is used today. Epiproctotomy, which involves fistulotomy followed by subsequent sphincter repair, is discussed later.

Endorectal Advancement Flap

Endorectal advancement flap (ERAF), with or without sphincteroplasty, is a mainstay of treatment for most simple and low RVFs (Fig. 3). The procedure uses a partial-thickness flap of rectal wall to cover the defect in the rectovaginal septum and is typically performed in the prone jack-knife position, which offers excellent exposure of the anterior rectal wall. Both the anus and vagina are prepared, and the fistula is identified with a fistula probe or a previously placed seton. A Pratt bivalve anoscope is used to expose the anterior rectal wall and a U-shaped flap then is outlined with the base cephalad and twice the width of the apex. The U shape and 2:1 dimension ensure that there are no flap corners to become ischemic and the flap pedicle is adequate to ensure blood supply to the advancement or suture line. The flap is created 1 cm distal to the fistula and consists of the rectal mucosa, submucosa, and a portion of the underlying internal sphincter, including the fistula opening at the apex; this is raised in cephalad manner with the use of needle tip electrocautery. A sufficient length of flap should be mobilized 3 to 4 cm proximal to the fistula opening to ensure a tension-free closure after excision of the fistula. Injection of a dilute epinephrine solution facilitates dissection and minimizes blood loss.

After the flap is elevated, the fistula tract is curetted to remove all granulation tissue, and the defect in the remaining internal sphincter is closed by approximating the fibers of the muscle with simple interrupted absorbable sutures. The apex of the flap then is excised to remove the fistula opening, and the flap is advanced cephalad and sutured in to tension-free. The flap is sutured in place with 2-0 running rapid absorbable sutures to close the wound by first placing sutures at either end of the wound and then continually bisecting the wound with sutures until closed. The vaginal opening is left open to facilitate drainage. Postoperative care includes a high-fiber diet, laxatives to avoid fecal impaction, and sitz baths.

The ERAF offers the advantages of performing the repair from the high-pressure side of the fistula as well as sphincter preservation. Short-term success rates for rectal advancement flaps alone vary from 43% to 88% in the small series in the current literature with varying and often short follow-up. The primary downside of the ERAF is the need for dissection of otherwise healthy rectal wall and sphincter. Flap failure and ischemia may result in flap loss and a subsequent rectal defect that is much larger than the original opening. Rates of early (within 1 week) flap loss have been reported as high as 6% with

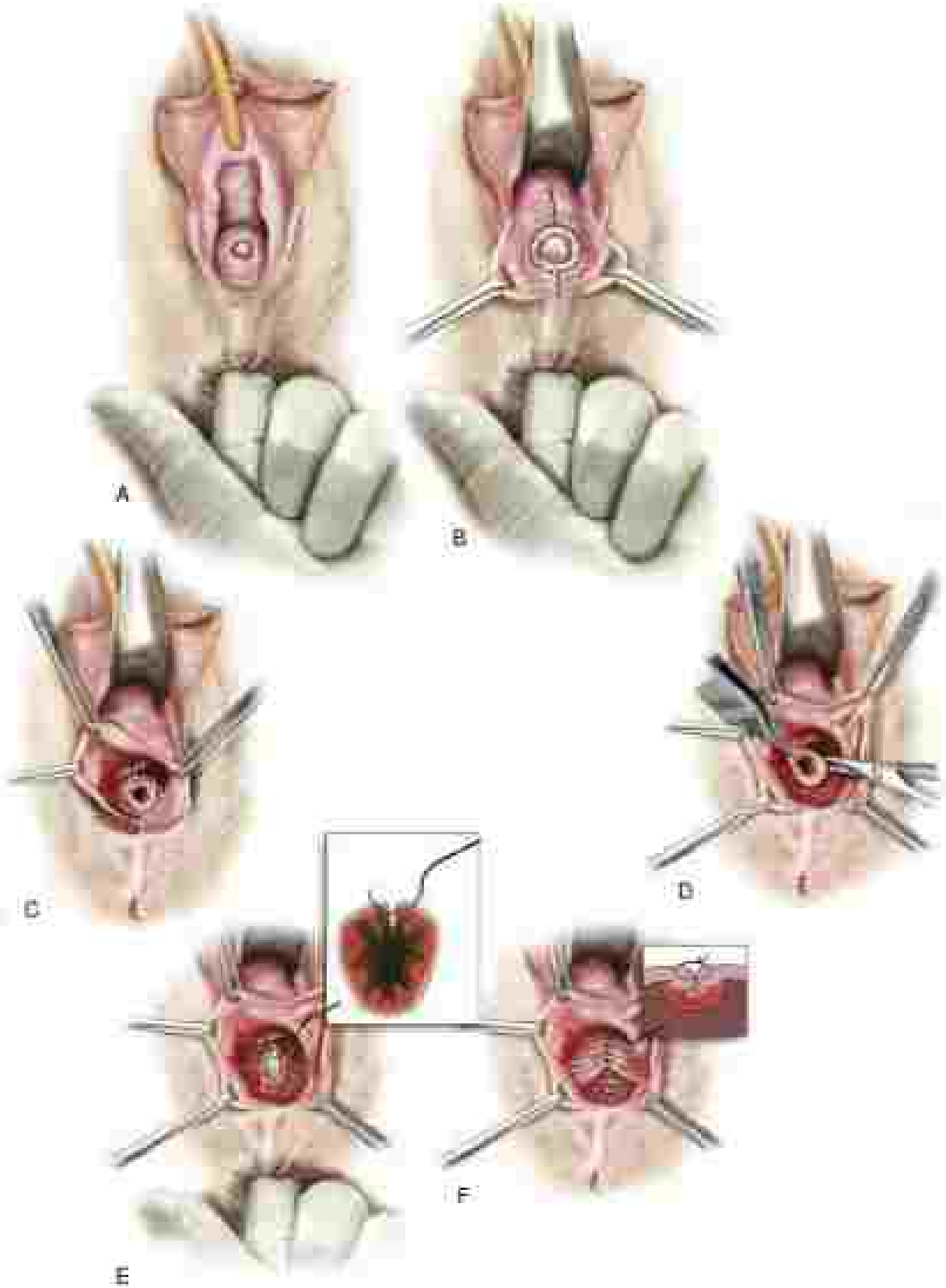

FIG. 3. Rectovaginal fistula repair in a patient with an intact perineum. (A) A rectovaginal fistula present in the midportion of the posterior vaginal wall. (B) The dashed line demonstrates the site of the posterior vaginal wall incision. (C) The vaginal wall is mobilized off the posterior rectal wall. (D) The fistulous tract is excised. The rectal wall is not back-cut from edges are reapproximated. (E) Perpendicular closure of the posterior rectal wall with decomposed, fine, indigent, absorbable sutures. (F) The second layer interposes the muscular portion of the wall of the rectum over the initial layer. The repair is completed by placing the rectovaginal tissue over the posterior vaginal wall. [Mark Klimek MM, Rectovaginal fistula and postanal pseudotract. In Walters and Klimek: Urogynecology and Reconstructive Pelvic Surgery. 4th ed. Philadelphia: Mosby; 2011.]

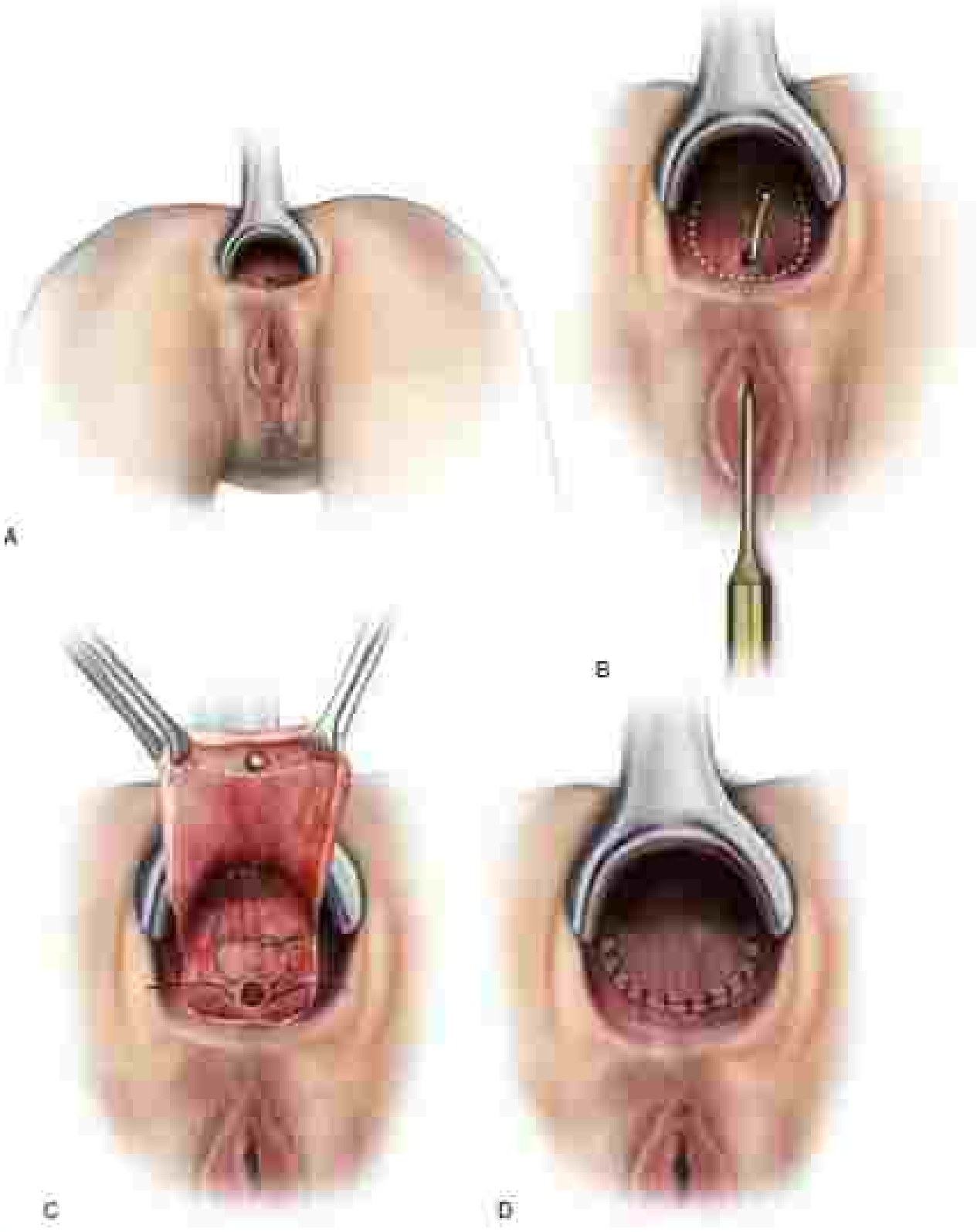

FIG. 3 Technique of endonasal advancement flap procedure. (A) The patient is placed in the prone position with the hips elevated in preparation for a low or mid-level rectovaginal fistula repair. (B) With the patient in the prone position, the anal speculum is placed posteriorly. The rectovaginal fistula is identified by placing a small probe from the anal into the vagina. The dissection line outlines the borders of the rectal mucosa used to develop the advancement flap. (C) The epithelium-lined fistula tract is excised, and the muscular wall of the rectum is reapproximated with absorbable sutures. The rectal advancement flap has been mobilized and is ready to be placed over the site of the fistula repair. (D) The flap is secured with interrupted absorbable sutures. (From Fleming MM, Birnbaugh K, Rodin DA, Gurland B. Endonasal flap and anterior sphincteroplasty for complex anterior fistula. Surgery. 2015;157(1).)

late flap breakdown rates ranging from 16% to 37%. Patients with fecal incontinence or a sphincter defect detected by EUS or an anal manometric defect who underwent sphincteroplasty had markedly higher (>80%) fistula healing rates than those who underwent flap alone (33%). The link between endorectal advancement flap failure and incontinence mandates a careful assessment of anal sphincter function and consideration of EUS before repair of RVFs. Additional factors that may be associated with failure of this technique may include Crohn's disease, complex fistula, and recurrent fistula. Although prior failed attempts at fistula repair are a risk factor for endorectal advancement flap failure, success with repeat flaps is possible, albeit lower, with success reported in 30% to 92% of patients. A diverting stoma has not been shown to improve the outcome of endorectal advancement flap for RVF but can be considered on an individual basis.

Some surgeons have described a technique of using a biologic graft as part of the procedure, whereby the endorectal flap was raised, and a 2 × 3 cm graft from porcine small intestine mucosa was placed in the rectovaginal space, and the flap sutured over the graft. They reported successful healing in 15 of 21 patients (71%).

Last, the use of an endorectal advancement flap for the treatment of low rectovaginal (anovaginal fistula) may potentially lead to bothersome anal mucus discharge. To prevent this, an alternative flap, created from the underarm and perineal skin (axillothoracic), instead of rectal mucosa, may be considered. This technique, combined with sphincteroplasty, was used by Chew and Rieger for seven patients with obstetrical low RVFs and resulted in healing in 100% of patients.

Fibrin Glue

At the time of EUS, the rectal and vaginal fistula tract openings are identified. The fistula tract then is curetted and fibrin adhesive is injected into the fistula tract until it exits the secondary opening. The goal of fibrin glue placement is to plug the fistula with material that allows fibrous tissue ingrowth and results in analogous fistula healing with no disruption of the surrounding structures or sphincters. However, experience with fibrin glue in RVFs has been very limited and plagued by disappointing results predominantly secondary to glue extrusion because of short fistula length.

Bioprosthesis

Two bioprosthetics have been used for RVFs: the bioprosthetic mesh (Surgisis mesh; Cook Surgical) and the RVF plug (Surgisis Doughnut Button; Cook Surgical). Both products are made from lyophilized porcine intestinal submucosa, which provides a matrix for ingrowth of connective tissue.

The bioprosthetic mesh is used as an interposition graft. The rectovaginal septum is dissected through a perineal incision, and the fistula is excised. After closure of the rectal and vaginal openings, the rehydrated mesh is placed between the rectum and vagina with an adequate overlap over the rectal and vaginal closures; it is sutured in position with interrupted absorbable sutures, with the mesh kept as taut as possible. The bioprosthetic mesh is useful when tissue grafts are not suitable options.

The bioprosthetic RVF plug is tapered at one end to facilitate insertion. A fistula probe is introduced from the vaginal to the rectal opening, and the tapered end of the plug is tied to the probe with a suture. The probe is then withdrawn, the plug is brought from the rectal to vaginal side, excess length on the plug is trimmed, and it is sutured in place with absorbable suture, which close the rectal mucosa over the plug. The vaginal side is left open. The short length of the fistula tract poses the same problem with the plug as with fibrin glue, which makes the plug suitable only for RVFs that are more than 1 cm in length. The experience with bioprosthetics in RVFs is very limited. Success rates of fistula closure by interposition techniques have been reported to be from 50% to 86% with short follow up. Complications are rare and generally benign and include primarily infection and plug extrusion.

Transvaginal Approach

Vaginal Advancement Flap

In a technique similar to the rectal advancement flap, a flap of vaginal mucosa is raised, and the fistula tract is excised. The rectal mucosa is closed separately, over which the defect in the rectovaginal septum is approximated with interrupted absorbable sutures. The apex of the flap then is trimmed to excise the fistula opening and is sutured into position to close the wound. The primary advantage of a vaginal flap is the use of healthy, pliable, and well-vascularized vaginal tissue, and proponents of a transvaginal repair emphasize the relative ease and better exposure gained through the vagina as compared to the anus. Nevertheless, the disadvantage remains that the repair is on the low-pressure side of the fistula. A vaginal flap is easier to mobilize than a rectal flap, therefore transvaginal repairs should involve closure of the rectum and not just of the vagina. A comparative analysis of 11 studies showed no statistically significant difference in the closure rates between a rectal and vaginal advancement flap closure in RVFs resulting from Crohn's disease. Therefore, especially when fibrotic rectitis disease is present in the anus or a transanal approach has failed, a transvaginal advancement flap is a viable option, although many of these patients may have fecal diversion as part of the treatment plan as well.

Transperineal Approach

Episiosphincteroplasty

Episiosphincteroplasty is a transperineal approach that may be used to repair obstetrical or cryptoglandular RVFs associated with extensive anal sphincter damage and associated fecal incontinence. This repair converts the fistula into a fourth degree perineal tear by dividing all the tissue between the rectum and vagina through the perineal body (Fig. 4). The rectum and vagina are separated from one another and the fistula tract divided. Ideally, some tissue, preferentially muscle, is interposed between the rectum and vagina. This may be done via levatoroplasty or sphincteroplasty. A layered closure then is performed to close the rectal mucosa, the rectal and vaginal muscular walls, and finally the vaginal mucosa. A rectal advancement flap can be added to the procedure. Success rates for this technique range from 70% to 80% in the literature with a reduction of preoperative fecal incontinence from 50% to 8% (Halverson, et al.).

Following repair, some authors advocate placement of a biologic graft to separate the vagina and rectum. Ellis described a transperineal repair with a graft made from porcine intestinal submucosa placed in the rectovaginal septum. He reported an 81% success rate (22 of 27).

The greatest disadvantage of this procedure is the creation of a full thickness defect in a previously uninjured part of the anal sphincter; therefore, a repair deficiency risks significant incontinence, which may not have been the case preoperatively. This procedure should be attempted only by experienced surgeons and in patients with documented existing sphincter defects with fecal incontinence. In experienced hands, healing rates superior to EAAF closure (97.7% vs 62.5%) have been reported with improved sexual function ($P = .04$) and decreased rates of fecal incontinence (improved in episiotomy group, unchanged in EAAF group, $P = .001$) when compared with EAAF.

Transperineal Ligation With a LIFT Procedure, Overlapping Sphincteroplasty

Simple transperineal ligation of the fistula tract can be undertaken with the ligation of the intersphincteric fistula tract procedure similar to a repair of a fistula in ano. A perineal incision is made over the intersphincteric groove and carried through the intersphincteric space, while a fistula probe is traversing the fistula tract. The fistula tract is ligated with absorbable sutures and divided. The rectovaginal septum of the rectum and vagina can also be imbricated. A rectal advancement flap can be added to the procedure. If there is no sphincter defect, the wound is irrigated and closed in layers.

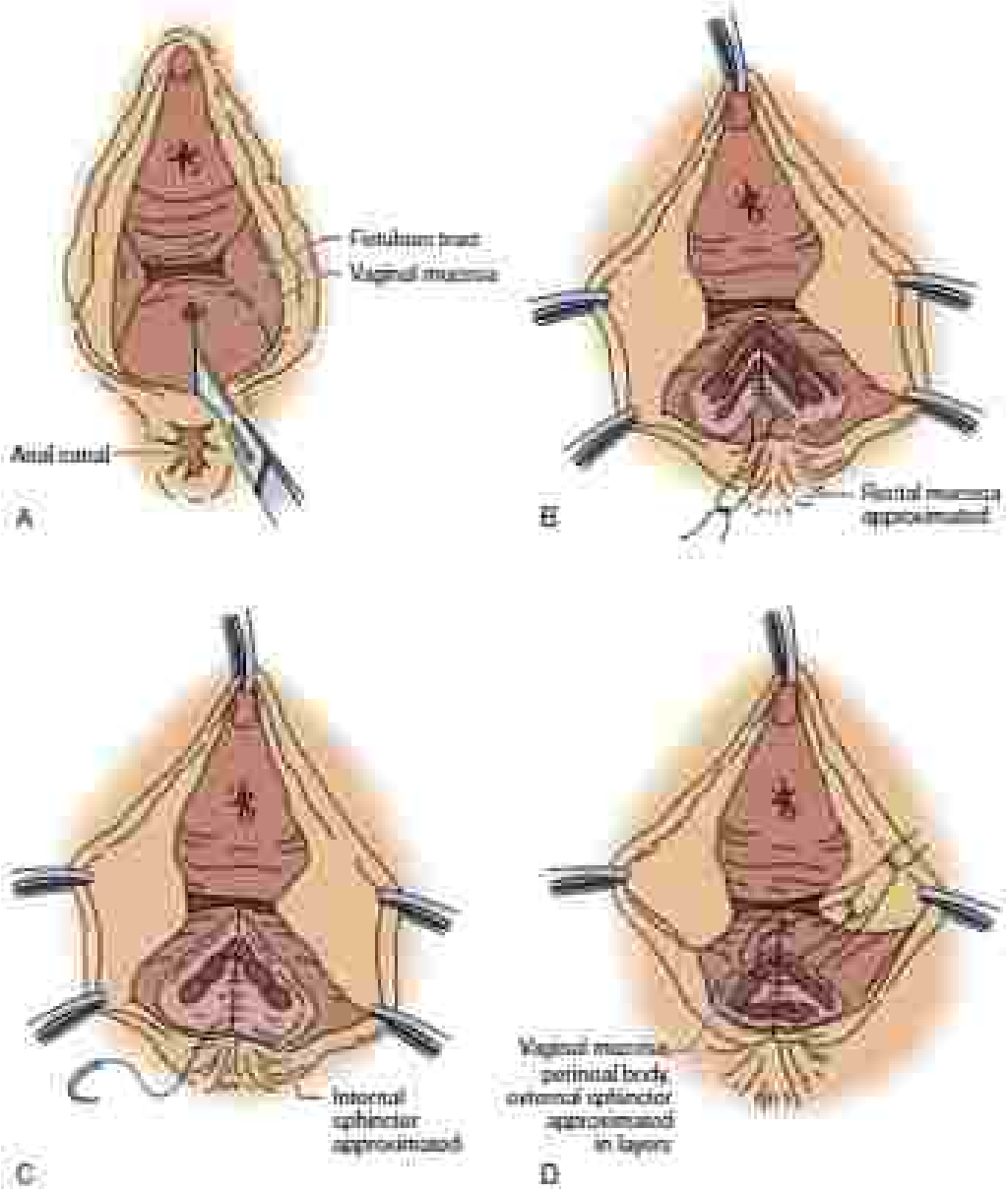

FIG. 4 Perineoproctotomy. (A) The patient is placed in the lithotomy position. The fistula is identified and excised from a full-thickness laceration. (B) The layers are dissected and repaired, first repairing the rectal mucosa. (C) The repair continues, approximating the internal sphincter. (D) The external sphincter is identified and repaired. Many patients will not have a discernible plane between the internal and external sphincters, in which case the internal and external sphincters may be repaired together. The vaginal mucosa is approximated. [From Beck DE, Roberts PL, Saclarides TJ, et al. Fistula-in-ano and anorectal fistulas. In: Cameron JL, Cameron AM, eds. Current Surgical Therapy. 12th ed. Philadelphia: Elsevier; 2017.]

In women who have a sphincter defect (most often from obstetric injury), a sphincteroplasty should be performed as well. Healthy ends of the external sphincter muscle are identified and skeletonized. The sphincter then is mobilized in the midline to ensure overlap without tension. Often the sphincter is so attenuated at the site of injury that the healthy ends of the sphincter can be overlapped and sutured into position without the need to divide or excise any tissue. The sphincter is overlapped and sutured in place with 2-0 absorbable interrupted mattress sutures. The wound is approximated loosely with the center of the skin incision left open for drainage. The technique should achieve similar results of sphincteroplasty and, if it should fail, will not result in worse than preoperative incontinence. In addition, when a sphincter injury is present, the addition of an overlapping sphincteroplasty to the approach has been reported to increase both the rate of fistula closure and restore continence.

Finally, similar to the techniques described for EIAF repair, some authors advocate placement of a biologic graft to separate the vagina and rectum. Ellis described a transperineal repair with a graft made from porcine intestinal submucosa placed in the rectovaginal septum. He reported an 81% success rate (22 of 27).

Interposition Flaps

Tissue transposition repairs offer the advantage of interposing healthy, well-perfused tissue between the rectum and vagina, and are potentially useful following previous failed local repair attempts. They add bulk to the rectovaginal septum and physically increase the distance between the rectum and vagina, and bringing their own blood supply may aid in healing. A disadvantage of the techniques is the potential for dyspareunia. The gracilis and bulbocavernosus (Martius) flaps are the two most described pedicled flaps for RVFs. Although not mandatory, fecal diversion typically is recommended and generally is undertaken before the flap procedure.

Gracilis Muscle Transposition

Repair using a gracilis muscle transposition offers the advantage of providing a large bulk of well-vascularized muscle to separate the vagina and rectum. Its origin is near the perineum, which makes it a convenient donor. It is, however, associated with higher morbidity due to the mobilization and transposition of this large muscle. A gracilis flap was most often used to repair recurrent RVFs of various etiologies or in patients with poor native tissue

and to some studies has typically been combined with concomitant fecal diversion.

The operation involves a transperineal incision, in which the rectum and vagina are separated. The fistula is divided and both the rectum and vagina are closed primarily. Dissection should continue cephalad to the fistula until healthy tissue is reached. An interposition advancement flap can be added to the procedure as well. The perineal incision created does not differ from that in other transperineal approaches. The muscle of either leg can be used and is harvested through an incision in the medial aspect of the thigh. This can be performed with a long incision along the length of the gracilis, or with separate smaller incisions near the muscle's origin and insertion. The muscle is mobilized with division of the perforating vessels. It is divided just above its insertion. The harvested muscle then is tunneled through the subcutaneous tissue to the groin and maneuvered into the perineal incision. Care must be taken that the flap is not rotated excessively and its blood supply not kinked. The muscle is secured to the apex of the rectovaginal dissection and the transperineal incision closed with interrupted absorbable sutures. The success rate of the gracilis muscle flap has been reported to range between 47% and 92% with the largest series published by Pinto et al, reporting a 79% success in 24 patients.

Bulbocavernosus (Martius) Flap

The Martius flap, which involves harvesting of the bulbocavernosus muscle with the overlying fat in the labia majora, is based on the perineal branch of the pudendal artery and is placed in the rectovaginal septum in similar fashion (Fig. 5). As with all interposition flaps, this repair has the potential risk for increased postoperative dyspareunia, but labial function and cosmesis do not appear to be compromised. As described previously, the operation involves a transperineal incision, in which the rectum and vagina are separated and the fistula is divided and both the rectum and vagina are closed primarily. To harvest the donor tissue, a vertical incision is made in the labia majora. The labial fat pad and underlying bulbocavernosus muscle are dissected out from the surrounding tissues. The amount of muscular tissue varies from patient to patient and may not be visible in some. Dissection occurs in a lateral to medial direction, taking care not to injure the blood supply. The flap is transected superiorly and tunneled to the rectovaginal septum. The success rate with this procedure has been reported to vary from 50% to 93.8% with the largest case series by Patel et al. in 2011 using the Martius flap reported a 65% success rate in 23 patients, with 78% of the patients having been diverted.

Transabdominal Approach

Transabdominal repairs and rectal resections are generally reserved for patients with circumferential or stitching disease as in the case with Crohn's disease and for fistulas classified as high and complex (including recurrent fistulas following failed local repair). Additionally, this is the treatment of choice for radiation induced fistulas that have failed local flap repair. These tend to be fistulae that are located in the mid rectum with an internal opening at the fornix of the vagina, which can often be difficult to access from a perineal or endoluminal approach. This generally involves a low anterior resection, where the segment of rectum containing the fistula is resected and a colorectal or coloanal anastomosis is performed. Depending on the height of the fistula, this may be done transabdominally only, or with a transabdominal transanal approach and colonic pull through. The vaginal side of the defect can be closed primarily.

Primary Repair With Omental Interposition

Primary repair with omental interposition is a transabdominal approach is a repair best suited for high RVFs. These fistulas are usually a complication of surgical injuries or diverticulitis. The approach entails dissecting the rectum down to the level of the fistula, which is then divided to expose both the rectal and vaginal openings. If the rectal wall is healthy, the fistula tract can be debrided and closed primarily. The vaginal opening is also closed primarily, and a pedicled omental flap is placed between the two closures and held in position with interrupted sutures. Some described approaches advocate for additional transperineal dissection of the rectovaginal septum with inserting of the omental flap to the subcutaneous tissue of the perineum or even to the levator ani along the lateral pelvic walls for tension free interposition. If the surrounding rectum is indurated or diseased a sleeve advancement can be undertaken.

Rectal Resection/Advancement and Sleeve Advancement

Rectal resection/advancement and sleeve advancement is indicated in circumferential or stitching disease as in the case with Crohn's disease, radiation induced fistulas, and for fistulas classified as high and complex.

The sleeve advancement technique includes resection of the rectum proximal to the fistula, circumferential mucosectomy of the fistulized and distal rectum, pull through of healthy colon into the remaining muscular tube of rectum, and a coloanal anastomosis (Fig. 6). Several studies report a fistula healing rate of 75% to 79%, with 72% of patients reporting normal continence. Nonetheless, more recent studies demonstrate early and late postoperative complications rates to be 41% and 33%, respectively.

Other Surgical Considerations

Fecal Diversion

Preoperative fecal diversion has not been shown consistently to lead to better outcomes, but this again may represent selection bias in those patients chosen for diversion.

There is no consensus on the indication of proximal fecal diversion in RVFs, and fecal diversion has not been shown to decrease the rate of fistula recurrence, although this may well be because the patients that undergo fecal diversion have more complicated disease. When low rates of success are anticipated (e.g., multiple failed attempts at repair, poor tissue compliance), preoperative fecal diversion should be considered. Additionally, most surgeons are more likely to perform fecal diversion with complex repairs such as an omental pedicle flap and those approaches that require a low colorectal or a coloanal anastomosis.

"Choice of Repair"

Considering the diverse causes, the large number of surgical options, and the lack of good quality comparative studies, there is no clear guideline on the choice of procedures to undertake first for RVF repair. The choice of procedure is determined largely by the type of fistula (low or high, simple or complex), the cause, whether a sphincter defect exists, the number of prior failed attempts, and the functional status of the patient. In addition, in deciding on a surgical approach, the surgeon should evaluate the patient for continuing inflammation or ongoing pelvic sepsis. The anatomic location of the fistula will also dictate the approach to repair (local repair vs transabdominal approach). Fistulas located in the mid rectum and upper vagina will not be accessible via a local approach and should therefore be managed with a transabdominal approach. A proposed algorithm for first line treatment and subsequent repairs is explained later and listed in Fig. 7.

Reported success rates vary greatly for each procedure. Experience likely plays a large role in this; however, even in experienced hands a certain failure rate is expected; therefore, all attempts should be made to avoid sphincter division and anal canal scarring in early repairs.

The first decision point in a proposed algorithm is whether a sphincter defect and associated incontinence are present. Overlapping sphincteroplasty will address the fistula and incontinence and is first line treatment in this patient population, typically those with obstetric trauma. An EAUS can be added to increase the fistula healing rate.

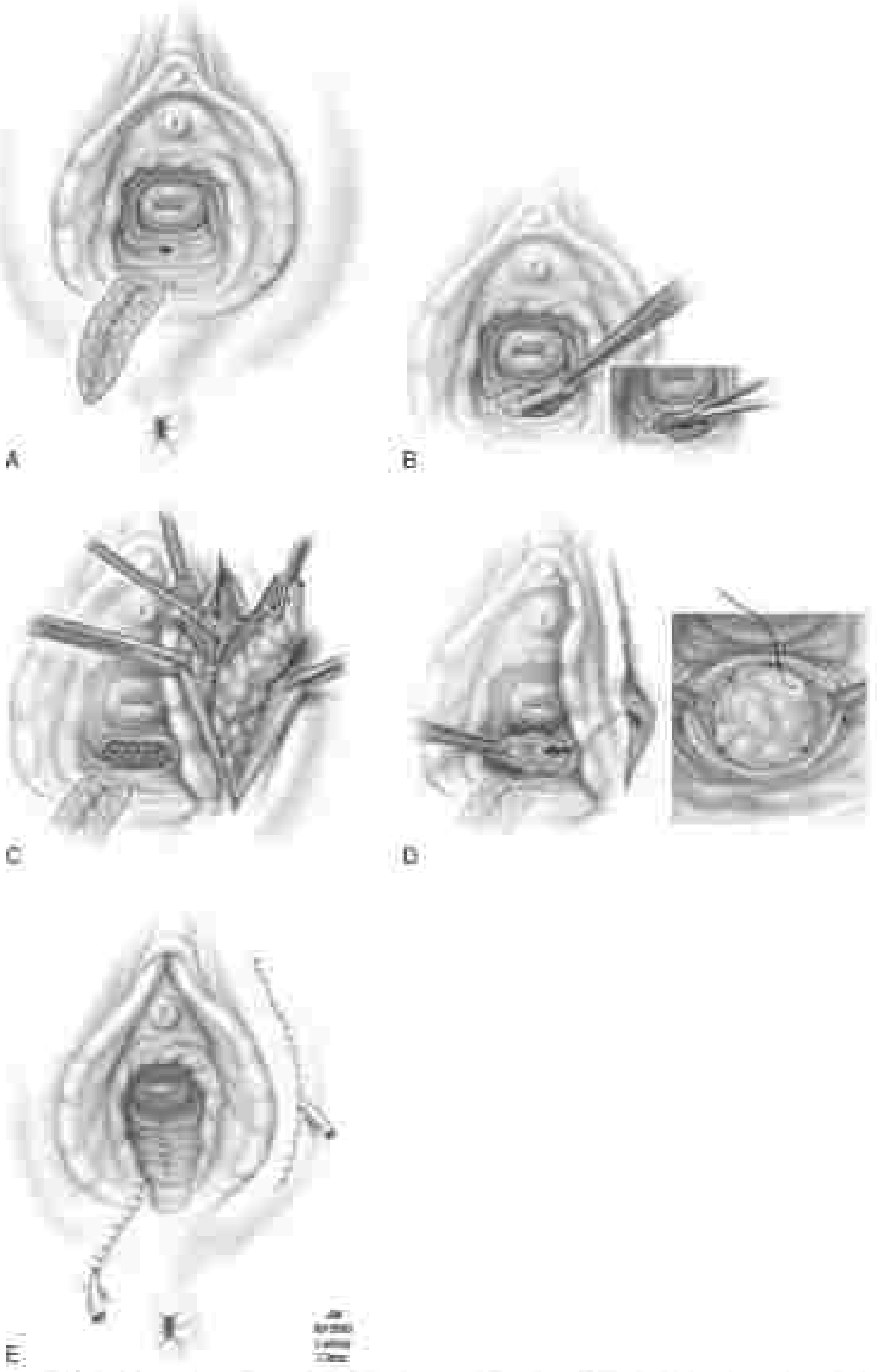

FIG. 5 Bulbocavernosus (Martius) flap. (A) The patient is placed in the lithotomy position, and a mediolateral episiotomy incision is made. (B) The vaginal side of the fistula is mobilized and excised. The rectal side of the fistula is closed. (C) Along the opposite labia majora, an incision is made and the bulbocavernosus muscle and tissue for graft are mobilized. (D) The bulbocavernosus muscle and tissue for graft are brought through a subcutaneous tunnel and secured to the previously closed rectal side of the fistula (here,). (E) The vaginal defect is closed, and the episiotomy incisions are closed. Drainage is accomplished with a Penrose or closed-suction drain. (Copyright 1999 Lahey Clinic, Burlington, MA. From Rosin JD, Kaufman HS: Anatomical and Acquired Issues of the Genitalia. In Wexner SD, Jorge JMN, Lowry AC, editors: Colorectal Surgery, 4th ed. Philadelphia: Elsevier; 2011.)

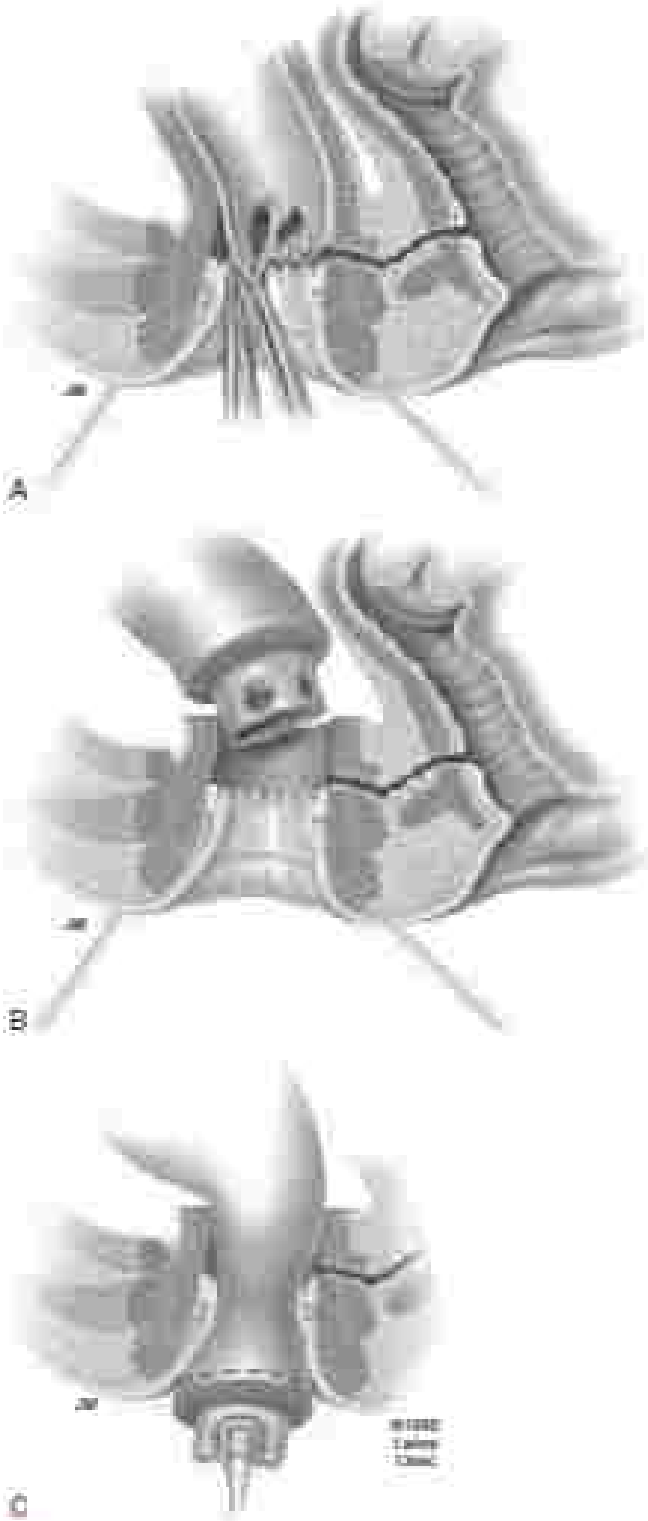

FIG. 6 Advancement flaps. (A) Connecting at the level of the dentate line, a circumferential dissection of mucosa and submucosa is performed, that leaving the stomach areas of the anal canal. (B) The dissection is continued cephalad and into the supralevator space, completing rectal mobilization. (C) The fistula can then be cored out and closed, and the distal cuff (rectal flap or the mucosa is preserved and sutured to the sphincter. (Copyright 1999, Lippincott Williams & Wilkins, from Wexner SD, Marchesa P, Jagelman DG. Anorectal and Colovaginal Fistula. In: Corman ML, ed. Colon and Rectal Surgery. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.)

In those patients without sphincter defect, either a rectal or vaginal advancement flap can be undertaken as first line options. Although the results for both procedures are thought to be similar, a rectal advancement flap puts the repair on the high-pressure side of the fistula but requires healthy rectal mucosa, whereas the vaginal flap saves the rectal mucosa from scarring and internal sphincter from disruption but places the repair on the low-pressure side of the fistula.

If either the rectal or vaginal flap fails, the subsequent step can be performing the opposite procedure versus proceeding with a more advanced repair such as a transperineal approach (sphincteroplasty or transperineal LIFT procedure) or a local interposition pedicled flap (either gracilis or Martius), with or without the addition of fecal diversion. If the local tissues are still healthy with minimal scarring, a repeat flap can be attempted. However, with every subsequent failed procedure, increased tissue ischemia is produced, and the chances of failure increase further. At this point, either a proctectomy or sleeve advancement may be necessary for definitive repair because this will resect the diseased rectum and bring healthy proximal rectum to the anal canal.

Because experience with biosynthetics is limited, there is no formal recommendation for their use currently. However, because biosynthetics rely on tissue ingrowth from surrounding tissue, a biosynthetic enhanced repair is not likely to succeed in an ischemic rectovaginal septum.

Radiation-Induced Fistulas

With the widespread use of radiation for locally advanced pelvic malignancies, the number of radiation-induced complications will continue to increase. The first step in management of radiation-induced RVFs is to rule out the presence of malignancy, either primary or recurrent. This requires detailed imaging and an examination with the patient under anesthesia with multiple biopsies of areas of irregularity or random biopsies if no irregularity exists. Once the presence of malignancy has been ruled out, the condition of the rectum, vagina, and surrounding perineal tissues must be evaluated.

It is recommended that no definitive repair be undertaken for at least 6 months after the completion of radiation treatment to allow for the resolution of the acute inflammatory effects of radiation and for the recovery of the surrounding tissue. If the local tissues are viable, a rectal or vaginal advancement flap can be attempted. The repair is less likely to succeed because it is performed in radiated tissue; therefore only one attempt at primary tissue repair should be undertaken. In the setting of primary repair failure, fistula repair may be attempted with muscle flap interposition, rectal sleeve excision with coloanal anastomosis, or proctectomy with coloanal anastomosis with or without fecal diversion.

Crohn's Disease

Most patients with Crohn's proctitis and an RVF will require an EUA and seton before definitive repair. Optimization of medical management is mandatory before surgical repair. Multidisciplinary management is critical; any repair is doomed to fail if all disease is not rendered quiescent. The Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease II study showed that patients who initially responded to infliximab (at least 50% reduction in fistula) had a 50% rate of full closure of the fistula. If medical management fails or is not an option, surgical treatment is undertaken, though successful surgical treatment of Crohn's-related RVF varies in the literature, with success rates ranging from 30% to 70%. Patients most likely to have a successful repair are those with an isolated RVF without other perianal disease and in whom their Crohn's disease is quiescent. If the rectum is healthy, either rectal or vaginal advancement flaps can be undertaken first. However, if the rectum is inflamed or scarred, vaginal advancement flap is the preferred first choice. There should be a low threshold for diversion in these cases. Crohn's disease–associated RVFs have an overall poor prognosis, with a recurrence rate

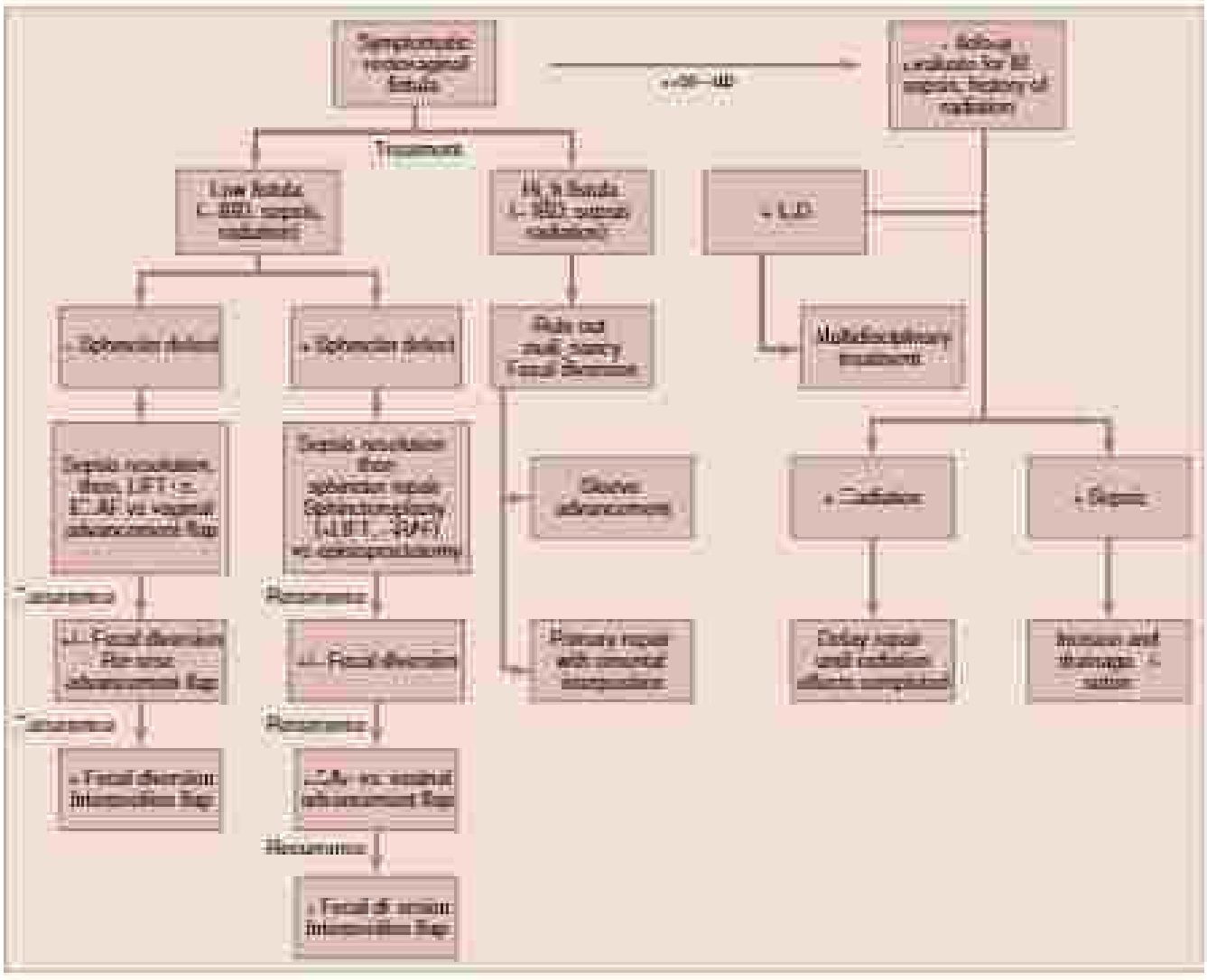

FIG. 7 Proposed algorithm for the management of rectovaginal fistulae. (ASIS, endoanal advancement flap; IBD, inflammatory bowel disease; LIFT, ligation of the intersphincteric fistula tract. *From Stone JF, Roehl KC. Rectovaginal and Complicated Fistulas. In the I.J. Stoker editorial: Surgery of the Alimentary Tract, 6th ed. Philadelphia: Elsevier; 2013.*)

that varies from 25% to 50%. It is therefore very important to appropriately counsel patients and set realistic treatment goals. In patients with poorly controlled proctitis, surgical options are very limited. Often, patients are symptomatic from the abscesses associated with the rectoanal fistulae and require optimization of medical management and prolonged setton drainage. With multiple failed procedures and recurrent fistulae, proctectomy with end colostomy is the definitive treatment of last resort.

Malignancy

The definitive treatment of malignant RVFs is an en bloc surgical resection of the malignancy, contiguous organs involved, and the fistula tract. This often requires a pelvic exenteration. A diverting stoma often is placed to control symptoms and decrease pelvic and perineal sepsis while the patient receives neoadjuvant therapy. The patient is reevaluated after neoadjuvant treatment to determine the extent of treatment response and to suitability to undergo a major operation. In patients with good performance status and a satisfactory response to neoadjuvant therapy, a pelvic exenteration can be considered. However, in most patients who are not suitable candidates for exenteration, the treatment focus is palliative.

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CONDYLOMA ACUMINATA

Raymond Yap, MBBS, BMedSci, MSurgSc, FRACS and John R.T. Monson, MD, FRCS, FACS, FASCRS

Condyloma acuminata (Fig. 1), commonly known as genital warts, is an extremely common sexually transmitted disease, with a prevalence of approximately 1%. The causative factor is human papilloma virus (HPV), a double stranded DNA virus with more than 120 genotypes identified. The most important clinical variants of HPV are split into two categories: those with minimal malignant potential (types 6, 11, 42, 43, 44) associated with genital warts, and high risk variants (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, etc, etc), which are associated with precancerous lesions and squamous cell carcinoma (SCC). Coinfection with multiple strains is common.

HPV typically arises through contact with virus laden secretions through breaks in the anogenital epithelium. The most common method of transmission is sexual intercourse, with a higher risk confirmed in those in the men who have sex with men and HIV populations. Condom use reduces the risk of transmission; however, transmission can still occur in areas of skin beyond the condom. Other forms of transmission such as through virus secretions in bathrooms, swimming pools, and autoinoculation are also possible, although less common. There is usually a long latent period before symptoms arise.

The clinical presentation is of warty outgrowths that do not cause much discomfort. Their appearance can be quite varied, with the cauliflower type most common. Other types include flat, dome shaped, or keratotic. They may present with itchiness or bleeding where the warts have been irritated. More significant is the psychological distress that accompany them. A rarer form of presentation is with giant condylomata also known as Buschke-Lowenstein disease (see the following section and Fig. 5).

Careful examination of the anogenital region with inspection, digital rectal examination, and anoscopy will reveal most lesions. Good lighting is essential. Inspection of the pubic area and oral cavity should also be performed. The differential diagnosis includes melanoma, SCC, SCC in situ, basal cell carcinoma, molluscum contagiosum, and seborrheic keratosis.

MANAGEMENT

Deciding on a management modality is dependent on factors such as the size and distribution of the condylomata as well as a patient's underlying physical state. Although spontaneous resolution of warts has been reported, complete response is uncommon, and most patients will need some form of intervention, whether in the form of topical therapy or operative management. There is little evidence to advocate one treatment over another in terms of success or recurrence rates. Table 1 outlines the various treatment modalities. Indeed, if the virus lies dormant within the basal squamous cells, recurrence is highly likely at some point in the patient's lifetime. Therefore, treatment goals are to treat all visible warts, preserve as much normal tissue, and to keep close surveillance for malignant change.

We have favored an operative approach to the management, with the patient either under conscious sedation or general anesthesia. Although we prefer a lithotomy position, a prone jack-knife position is also acceptable. This allows for meticulous inspection and examination for lesions. The entire genital region should be examined if possible, including the penis and scrotum in men and the labia majora and minor in women. Examination with an anal retractor such as a Pratt or Hills-Ferguson retractor should be performed for any anal canal lesions, which can be easily missed in the office. Representative biopsies are then taken for histopathologic examination to both confirm the diagnosis and detect if there is any premalignant (low or high grade dysplasia) or malignant change.

If there is a single large wart or the warts are confined to a small local area (approximately 1 inch in diameter), excision and closure with an absorbable suture such as 4-0 undyed Vicryl is appropriate in an interrupted fashion. We prefer the use of diathermy to excise the lesions to maintain a bloodless field (Fig. 2). Where the lesions are scattered, or widespread, monopolar diathermy is used to fulgurate the lesions. Once an eschar has been formed, the wart is then curetted, which may cause profuse superficial bleeding easily controlled with diathermy. As long the base of the wart is narrow and there is intervening healthy skin, the risk of anal stenosis is minimal. For perianal lesions, the use of a Lone Star retractor can be useful to enable better access to the lesion (Fig. 3).

Although the risk of transmission to the healthcare provider is minimal with the use of fulguration, we still recommend the use of an N95 respirator or similar grade face mask to further reduce this risk.

There are cases where staged operative management is indicated. If the affected skin is carpeted with lesions and affects more than 50% of the anal circumference, it is highly recommended to perform up to multiple visits to the operating room (OR) to clear the affected warts by excising or fulgurating a portion (no more than one third to one half of the anal circumference) and closing the wound if appropriate at each visit, the risk of anal stenosis is greatly reduced. The OR visits should be spaced out by 4 to 6 weeks.

Close surveillance is then required. Where no dysplasia or malignant change has been detected, after the initial postoperative visit, using the patient at the 3- and 6-month marks is appropriate. The recurrences that happen are usually few in number and easily treated with office based ablative procedures or topical therapy. Choice of therapy depends on both patient and physician choice.

SPECIAL CASES

Dysplastic Condyloma

Unfortunately, there is a rising incidence of anal cancer and dysplasia in the United States. Risk factors include men who have sex with men, HIV, transplantation, or other immunosuppression, cervical or vulvar neoplasia, smoking, and intercourse. The lesions are typically classified as low grade anal intraepithelial lesions (corresponding to anal intraepithelial neoplasia grade 1), high grade anal intraepithelial lesions (anal intraepithelial neoplasia grades 2/3), or as malignant (SCC).

Traditionally, anal cytology and high resolution anoscopy have been used for screening and surveillance of disease. Anal cytology is similar to cervical cytology in which a moist swab is inserted into the anal canal and smeared onto a slide. The pathologist may report one of five results: normal, insufficient, abnormal cells of undetermined significance, low grade, and high grade squamous intraepithelial neoplasia. The other modality is high resolution anoscopy. The area is swabbed with acetic acid and then examined with a high resolution microscope looking for changes associated with dysplasia. Unfortunately, the equipment is expensive and the learning curve is steep.

The utility of either of these methods in the prevention of SCC is unknown. Recent data from overseas suggest that without a visible lesion, progression to malignancy is extremely rare. In light of this, we recommend routine careful visual inspection and digital rectal examination, with OR examination and biopsies of any lesions are found. In the same vein, routine anal mapping with punch biopsies is also unlikely to be of benefit.

The initial management of dysplastic condylomata is similar to nondysplastic condylomata. Again, operative ablation with electrocautery is usually sufficient. A clear microscopic margin is not needed, macroscopic clearance is sufficient. Previously, wide local excision of the area was recommended, but because of high recurrence rates and its uncertain role in the prevention of malignancy, this has been

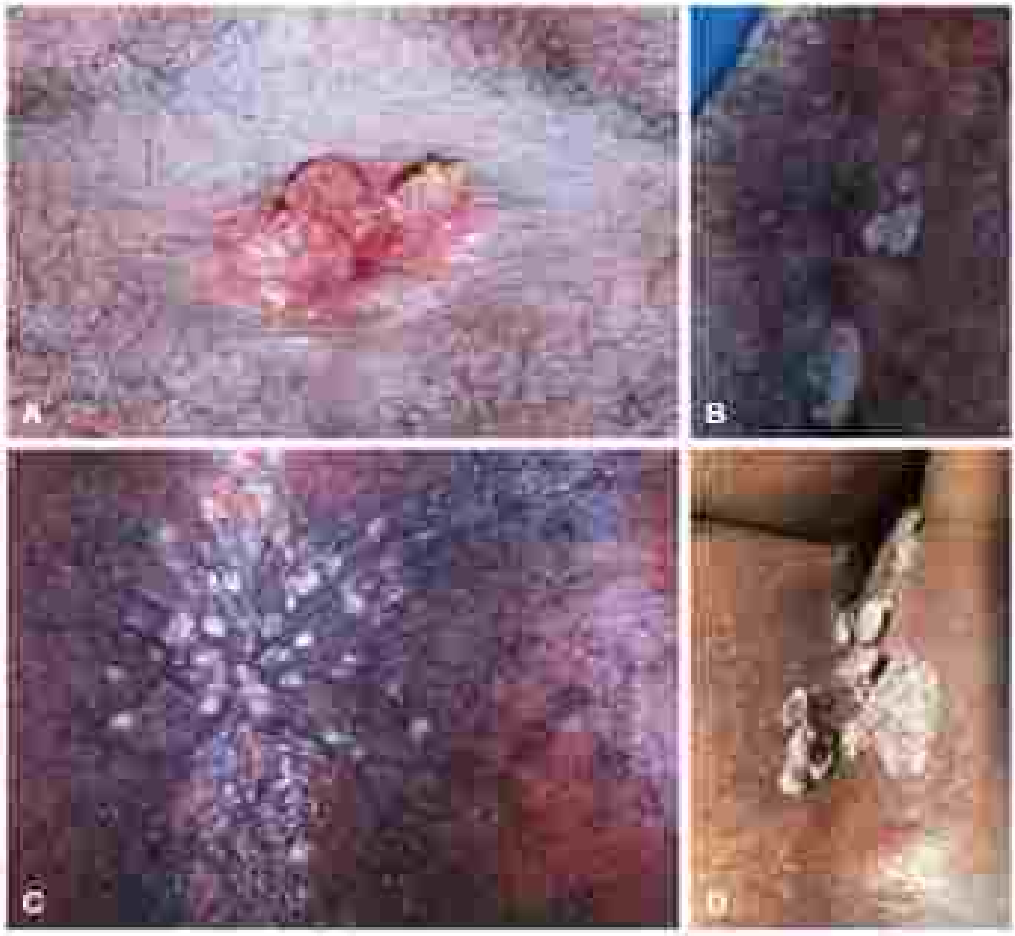

FIG. 1 Condyloma acuminata types. (A) Cauliflower, (B) flat, (C) dome, and (D) keratotic.

TABLE 1 Treatment Modalities

Treatment	Technique	Side Effects	Clearance Rate (%)	Recurrence Rate (%)
PATIENT APPLIED				
5-Fluorouracil (Efudex), 1% or 5% cream	1% cream twice daily for 4–6 weeks or 5% cream applied daily for 8–10 weeks	Pain, induration, erythema, ulceration	40–75	25–50
Imiquimod (Aldara), 5% cream	Applied overnight and washed off in morning 3 times per week for 12–16 weeks	Pain, induration, erythema, ulceration	50–80	10–20
Podofilox (Condylox), 0.5% gel	Twice daily for 3 consecutive days each week for 2–4 weeks	Pain, induration, erythema, ulceration	30–70	10–30
Sinecatechins (Veregen), 15% ointment	Applied 3 times per day for 12–16 weeks	Pain, induration, erythema, ulceration		
OFFICE MANAGEMENT				
Trichloroacetic acid (Tca Chloe), 80%–90% solution*	Apply directly to lesions, avoid surrounding skin; repeat monthly as required	Pain, irritation	70	20–40
Liquid nitrogen*	Apply with applicator until area white; repeat monthly as required	Pain, edema, eschesis, ulceration	70	2–40
Podophyllin (Podocon), 25% extract	Applied once per week, needs to be washed off 4 hours later, up to 6 treatments; do not exceed 0.5 mL per treatment	Pain, induration, erythema, ulceration. Can cause cancrin and CNS depression if systemically absorbed	50–70	30–50
OPERATIVE MANAGEMENT				
Electrocautery*	Fulgurate lesions, avoid normal skin	Pain, scarring	70–90	30
Laser*	Vaporize lesions, avoid normal skin	Pain, scarring	70–90	30
Surgical excision*	Excise lesions while preserving normal skin	Pain, bleeding, scarring, infection	70–90	40

*Safe to use in pregnancy.
CNS, central nervous system.

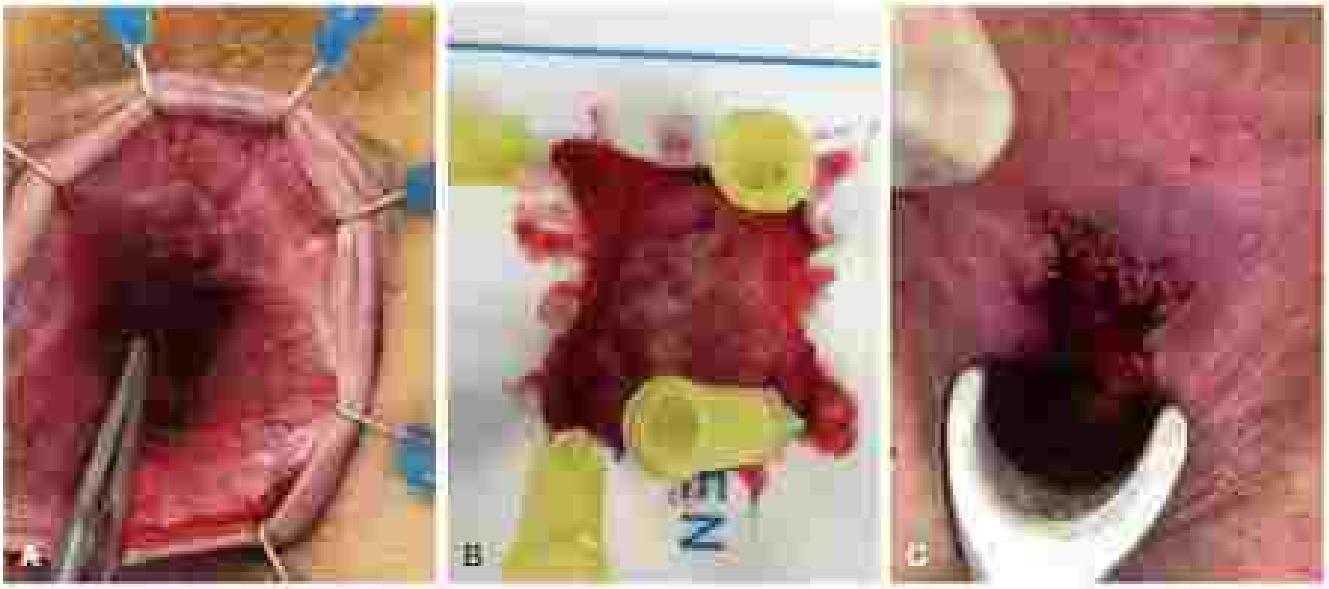

FIG. 2 (A) Immense cloak condyloma. Note how the Loop Star retractor provides excellent visualization for a lesion not otherwise easily accessible. (B) Specimen pinned out for histologic examination. (C) Closure of the defect.

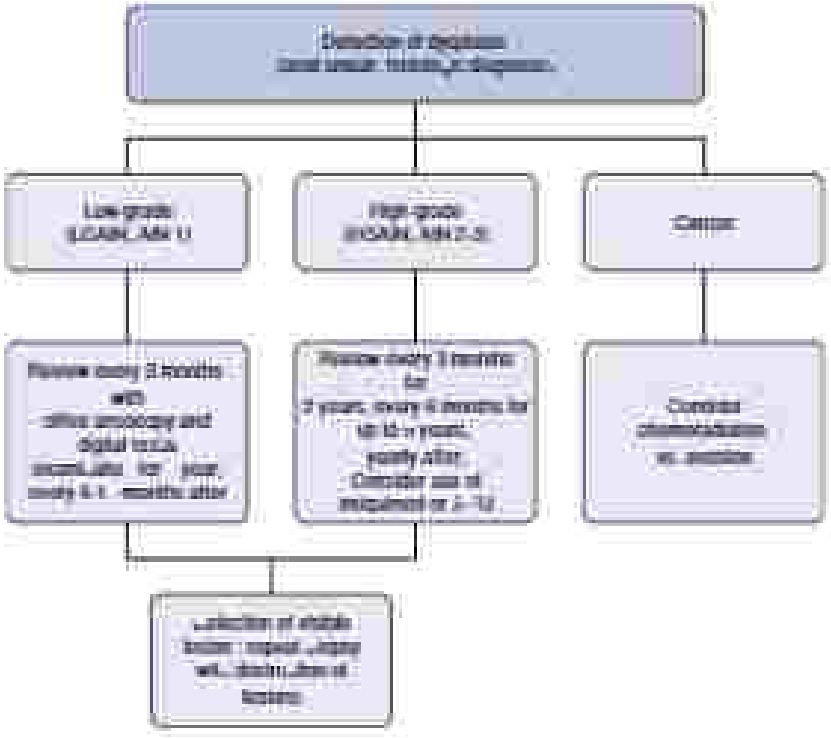

FIG. 3 Treatment algorithm for dysplastic lesions.

largely abandoned. Postoperatively, although the evidence base is only moderate, the use of fluorouracil 5% cream and imiquimod has been shown to reduce recurrence rates. Imiquimod is the most tested and has shown to be effective if used regularly, although cessation often results in recurrence. There is mixed evidence for either of these as a first-line treatment to better either downgrading of lesions or preventing malignancy and therefore the authors use it in the postoperative setting.

We would recommend close office surveillance of any patient with dysplasia. A suggested algorithm is outlined in Fig. 4.

Giant Condylomas

First described by Buschke and Lowenstein almost a century ago, this rare variant has local malignant potential with invasion into deeper structures. It is a slow growing, ulcerative, and large lesion that has up to a 50% risk of SCC. Wide local excision is the mainstay of treatment. The use of imiquimod is usually as an adjunctive therapy after excision is complete. Lesions may require the use of abdominoperineal resection. There are a few reports of the use of chemoradiation similar to those for SCC, although recurrence rates are high. An example is shown in Fig. 5.

FIG. 4 Electrocautery in excision of an irritated lesion.

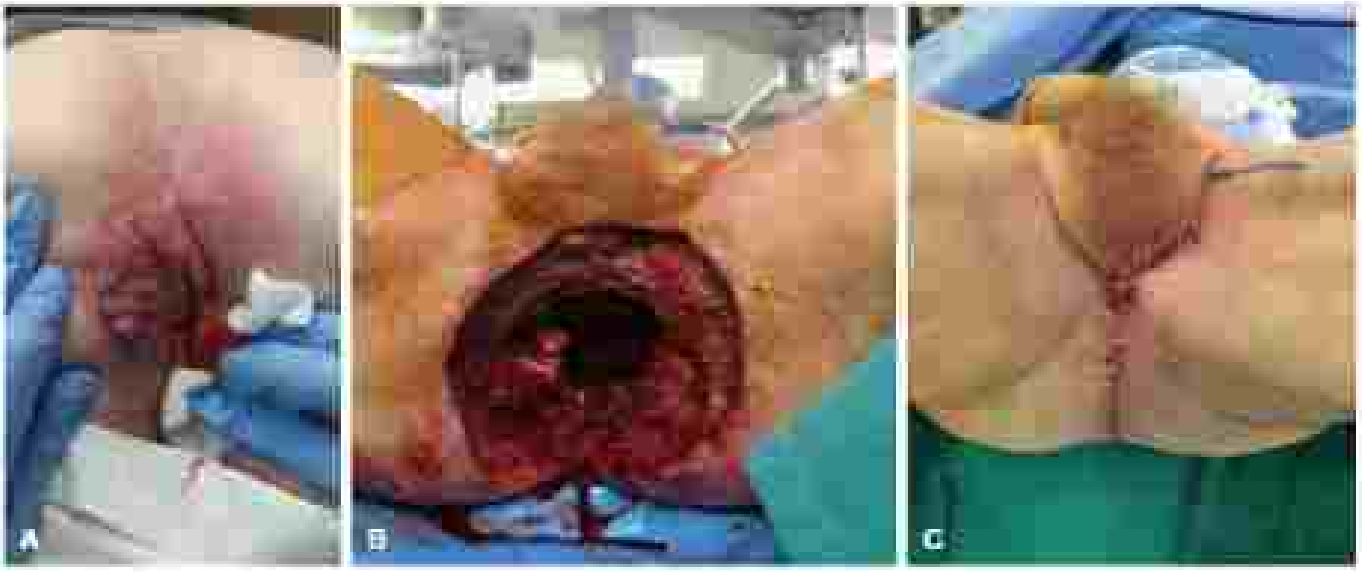

FIG. 5 (A) Giant condyloma with squamous cell carcinoma. (B) Defect left after abdominoperineal resection. (C) Use of bilateral gracilis flaps was required to provide a satisfactory result.

HPV Vaccine

Vaccination has very limited side effects and should be considered as a component of the management of HPV. Three vaccines are available in the United States: a quadrivalent vaccine (HPV4 Gardasil) targeting strains 6, 11,16, 18; a 9 valent vaccine (HPV9 Gardasil 9) targeting HPV 6, 11, 16, 18, 31, 33, 45,52, 58, and a bivalent vaccine (HPV2 Cervarix) targeting HPV 16 or 18. There are current recommendations to inoculate all young women and men. In women, the routine age is 11 to 12 years, or up to 26 years if not started previously. For males, routine administration should be at ages 11 to 12, or until age 21 if not started previously. In addition, if there are risk factors such as HIV, routine administration should be considered until age 26. There is some emerging evidence that the rates of dysplasia are reduced with the use of the vaccine, even in strains that are not actively protected against. Whether HPV vaccination arrests or downgrades the development of dysplasia is uncertain and therefore the efficacy of the vaccine in a therapeutic setting is unknown. A consultation with an infectious disease physician is recommended for these matters.

SUMMARY

Condyloma acuminata is a sexually transmitted disease, typically caused by HPV. Careful anoscopic inspection, digital rectal examination, and anoscopy are usually sufficient for diagnosis. Management aims are to eliminate all visible disease, exclude dysplasia and preserve normal skin, usually in the OR setting initially. Practitioners should be aware of the risk of dysplasia and the need for close surveillance if detected.

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Management of Pilonidal Disease

Naomi M. Sell, MD, MHS, and Todd D. Francone, MD, FACS, FASCRS

Pilonidal disease is a common, acquired inflammatory condition of the skin and subcutaneous tissue of the sacrococcygeal region. This disease most commonly affects young adults in their late teens and 20s, rarely presenting past the age of 40. Men are afflicted at three to four times the frequency than women. It has an incidence of 25 per 100,000, and most recent numbers describe 70,000 Americans seeking treatment annually. Its predilection for young adults harbors a unique socioeconomic burden because patients often require significant time away from work or school. Attention to the prevalence and social impact of this disease was brought to the public during World War II when 70,000 young American soldiers were admitted to US military hospitals for care typically requiring greater than 2 months of medical leave.

The disease can present acutely, often in the form of active infection or abscess, or individuals can live with smoldering, intermittent symptoms for many years. These various presentations have led to controversy among surgeons on the best treatment method, whether operative or nonoperative. Despite every surgeon's hope to eventually name one operation superior to others, it cannot be understated that each treatment decision for this disease should be patient specific because there are varying benefits to many of the options that will be described in this chapter.

ETIOLOGY

Acquired Condition

Pilonidal disease was first described by Herbert Mayo in 1833. His initial theory was that this disease was congenital in origin. However, after decades of controversy, research has now firmly established that pilonidal disease is not a congenital, but rather an acquired condition. There is no epithelial lining within the abscess cavity found in pilonidal disease, therefore, the cavity is not a cyst and the term "pilonidal cyst" is a misnomer. An abscess may or may not be present at certain points of the disease. When present, the abscess is simply a subcutaneous collection of debris and pus.

Name

The name pilonidal originates from two Latin terms: pilus, meaning hair, and nidus, meaning nest. Hair is a key component in the development of pilonidal disease. The other requirement being a deep natal cleft. Hair is often found within pilonidal abscesses. These hairs are not ingrown; rather, they are hairs that have been shed, either from the scalp or back, and have become lodged within this deep natal cleft.

Causes

Pilonidal disease is caused by the unfortunate alignment of all components of the disease being present at the same time. The three main components that lead to the development of this disease are: a deep gluteal cleft, loose hairs, and friction. The deep cleft facilitates entrapment of shed hairs, often from hirsute individuals, within that space. These loose hairs penetrate the skin and cause a foreign body reaction at that site. This reaction facilitates the dilation of midline pores and follicles through which additional debris accumulates, such as hair and shed skin. Friction, often in the form of sitting, aids this reaction by mechanically rubbing the hair into these openings. The entrapment of hair and debris leads to the development of midline pits and an eventual abscess. The moist environment of the deep cleft makes healing difficult and is welcoming of anaerobic bacteria.

A sinus tract develops when the body attempts to clear the infection. In an effort to remove the abscess contents, the body tries to expel the contents through a second external opening, often located at the cephalad aspect of the cleft. These sinuses are not the cause, but rather the byproduct of the disease.

Risk Factors

Although a few risk factors have been determined through small non-randomized studies, none constitute a direct cause and effect relationship. The risk factors associated with pilonidal disease include obesity, a sedentary lifestyle, and a hirsute body. Through appropriate questioning and by identifying these traits, lifestyle modifications may be used to deter the development of this disease.

MAKING THE DIAGNOSIS

The initial diagnosis of pilonidal disease is a clinical one based on a patient's history and physical examination findings in the gluteal cleft. Often, the disease either presents as an acute abscess or a chronic draining sinus. Pilonidal disease can be present for months to years before the development of symptoms.

Physical Examination

Characteristic physical examination findings reveal the sinus and fine pits found in the natal cleft (Fig. 1). The recognition of these pits, with or without a draining sinus, establishes the diagnosis of pilonidal disease. It is often difficult to see the midline opening; placing upward traction on the natal cleft can improve visualization. Shed hairs can often be seen protruding from these midline pits. In the setting of acute disease, examination may be painful and may be associated with cellulitis or an abscess. If an abscess is present, the swelling can make it difficult to visualize the midline pit. The pit can only sometimes be seen once the abscess has been drained and the edema resolves.

The presence of a draining sinus is indicative of chronic disease. Sinus tracts develop as the body's attempt to resolve and externalize the infection itself. Typically, the sinus opening lies outside the natal cleft, laterally either to the left or right; however, there are instances in which the opening is contained within the natal cleft (Fig. 2).

Differential Diagnosis

In making the diagnosis, it is important to distinguish pilonidal disease from alternative disease processes such as perianal abscess, perianal fistula, Crohn's disease, hidradenitis suppurativa, or unusual skin infections including tuberculosis, syphilis, or actinomycosis. Draining openings at the inferior aspect of the gluteal cleft can be either the result of a draining pilonidal sinus or a perianal fistula. Should an abscess be present and low lying near the anus, it can be difficult to distinguish acute pilonidal disease from a perianal abscess. It is important to perform a thorough anorectal exam to evaluate for concomitant fistulous disease or other anorectal pathology.

Imaging Studies

Imaging is often not beneficial, nor required, to confirm the diagnosis of pilonidal disease. There are cases of low lying sinus tracts that need to exclude the possibility of an anal fistula, in which magnetic resonance imaging may be useful. Probing easy to interrogate these openings are of little benefit. Magnetic resonance imaging is also helpful

FIG. 1 Multiple pits are present in the midline near cleft with evidence of hair shafts. (Courtesy Eric Johnson, MD, FACS, Cleveland Clinic, Cleveland, OH.)

FIG. 2 Chronic sinus tract is demonstrated with a probe in place to outline the tract between the midline pit and the anus. (Courtesy Eric Johnson, MD, FACS, Cleveland Clinic, Cleveland, OH.)

in rare circumstances of suspected actinomycetes of the sacrum in the setting of deep chronic infections.

ACUTE PILONIDAL DISEASE

Acute pilonidal disease typically presents as an abscess with or without cellulitis. Standard care is the same as for any other type of abscess, with treatment by adequate incision and drainage (Fig. 3). To allow for improved healing, the incision should be made off the midline over the area of fluctuance and should be either in an ellipse or crucial form. It is often difficult to visualize the midline pits in the setting of edema associated with the abscess. This procedure can be done in an office examination room under local anesthesia rather than an operating room. Packing of the wound is dependent on the depth of the abscess and risk of reepithelialization before complete wound healing. If it is difficult to reach area, to should packing be required, make sure to develop a plan for wound care with the patient's family member or visiting nurse service before being sent home.

If adequate drainage is achieved, then antibiotics are not necessary. Should the patient be diabetic, immunocompromised, or have other concerns for infection, then the use of antibiotics to cover gram positive skin flora and anaerobic bacteria is appropriate.

Wound care and close follow up are key points in the care of acute pilonidal disease. Sitz baths should be used by the patient at home several times a day for the week after drainage. Daily showers with soap and adequate drying are also beneficial. These steps help keep the wound clean and prevent recurrence. The patient should follow up within 2 weeks from incision and drainage to assess healing. Recurrence rates of this method are 15% to 40% because of the failure of simple incision and drainage to remove the debris from within the abscess cavity.

CHRONIC PILONIDAL DISEASE

Longstanding pilonidal disease can lead to the development of a sinus tract that drains contents from the midline pit to the outside world. These sinuses typically develop after a patient has suffered multiple prior acute abscesses, but, on occasion, draining sinuses have been the initial presentation in patients with mild disease. This tract most commonly opens cephalad to the natal cleft usually off to one side rather than directly in the midline.

Sinus tracts are often associated with chronic drainage and local irritation for which patients desire treatment. What differs from acute disease is that, in addition to the midline pit and abscess, the sinus tract must be addressed as well. Directing treatment only at the secondary opening will be inadequate and fails to address the underlying midline pits that are the true cause of this disease. Depending on symptom severity, there are both nonoperative and operative interventions available to treat this condition.

NONOPERATIVE MANAGEMENT

Asymptomatic patients and those with very minor symptoms should attempt to be managed nonoperatively. Conservative measures that include observation or simple hygiene optimization should be first line in those without significant pain or evidence of infection. The use of different hair removal techniques are a popular nonoperative land despite minimal clinical evidence. The goal of these interventions is to remove the hair seen as the stalks for the development of this disease process.

Hair Removal

Although not the distinct cause of disease, hair has a key role in the pathogenesis of pilonidals, which has led to the increased role of hair removal. It is used both as a sole nonoperative strategy and as adjunct to operative treatment. The most common technique of hair removal is by local hair shaving. Studies of this modality are limited. Although there is little proven benefit, hair shaving has been shown to be safe with minimal additional morbidity. Hair removal may actually be of most benefit before the development of pilonidal disease because the midline pits have not yet formed, however, there is no way of predicting who will or will not develop disease. There is no consensus on the frequency of hair shaving though the American Society of Colon & Rectal Surgeons recommends at least weekly.

Another method of hair removal is laser ablation. When used as an adjunct to surgical treatment of pilonidal disease, studies have shown decreased disease recurrence (<13%) compared with those

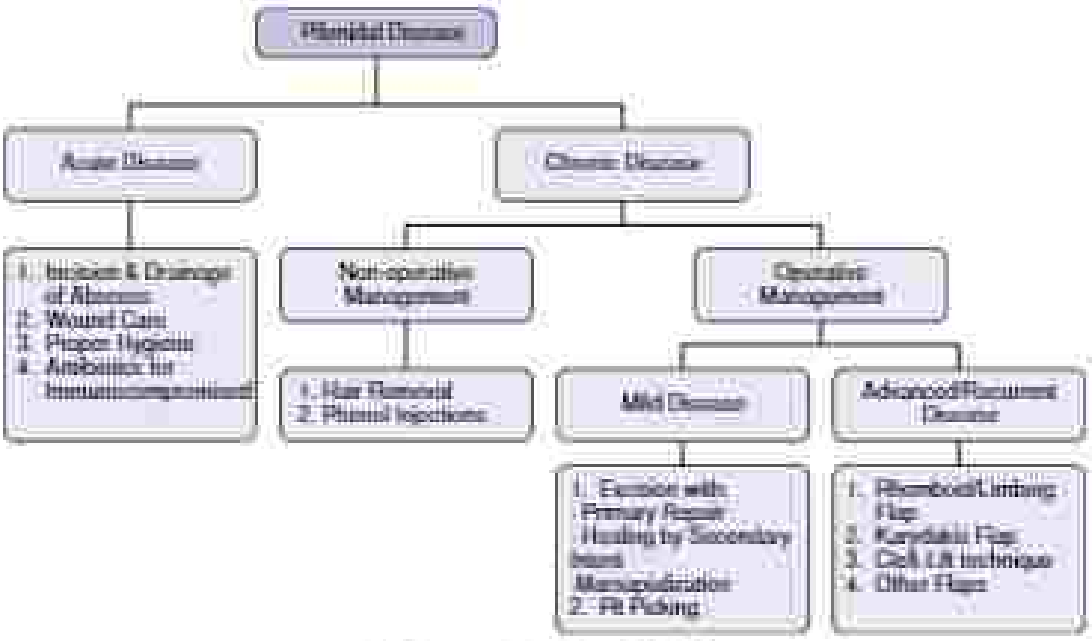

FIG. 3 Treatment algorithm for pilonidal disease.

without laser hair removal. Limitations to this method are that it often requires multiple treatments and may require local anesthetic. There are insufficient data to make recommendations for or against its utilization.

Phenol Injections

The use of phenol injections into the pilonidal tract can also be used rather than an operation. Phenol is a caustic substance that destroys the local tissue of the sinus tract. This procedure is performed by injecting 1 to 3 mL of 80% phenol into the pilonidal sinus. The solution is left there for 1 minute before being expressed out. The tract is then curetted to remove the broken down tissue, including the hair and debris that had been present. This can be repeated up to three times in a single setting, for up to 3 minutes of phenol exposure. A range of one to four separate procedures have been described as being necessary to achieve success. The procedure can be repeated as frequently as every 4 to 6 weeks.

The principle side effect reported is pain from the chemical. Local anesthetic must be used when performed in the outpatient setting. Other complications include burning of the surrounding skin and local wound infection. Compared with surgical tract excision, this procedure results in more rapid healing and return to normal activities. Disease recurrence rates are approximately 20% and more conclusive studies are needed before this becomes a standard treatment.

OPERATIVE MANAGEMENT

The indications for operative intervention include recurrent acute abscesses, symptomatic chronic pilonidal sinuses, and patient's preference. Many patients prefer surgical intervention even in the early stages of disease, given the uncertainty of disease recurrence and desire to prevent multiple life interruptions by recurrent episodes.

Early Disease

Early pilonidal disease can be treated with simple surgical excision rather than an extensive flap procedure. Some of these small procedures can be performed in the office under local anesthesia, whereas others require use of an operating room; however, all of these patients can return home the same day.

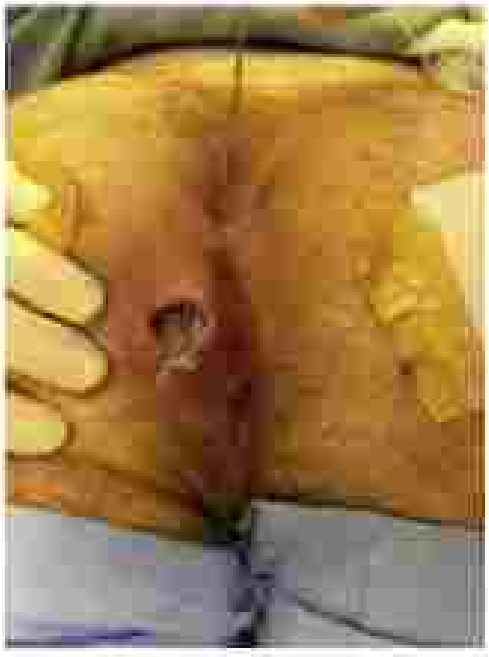

FIG. 4 A probe can be used to define the sinus tract to allow for unroofing. (Courtesy Eric Johnson, MD, FACS, Cleveland Clinic, Cleveland, OH.)

Excision With Primary Repair

Chronic pilonidal disease necessitates excision of the pit and associated sinus. Some advocate that for those undergoing their first surgical procedure for pilonidal disease, simple excision rather than a flap procedure should be used. Excision with primary repair is just as the name suggests. A simple midline excision of the dermis and associated subcutaneous tissue, typically to an ellipsoid fashion, that includes the midline pit and sinus, is removed. To remove the entire extent of the sinus tract, use of a lacrimal probe is beneficial. The probe is inserted through the lowest pit and is passed through the sinus until it exits at its most cephalad opening (Fig. 4). Either a knife or electrocautery can then be used to make a narrow elliptical incision over the probe, connecting the two openings. To prevent

FIG. 3 Sinus tract has been unroofed with subsequent marsupialization. (Courtesy Erik Johnson, MD, ACS Cleveland Clinic, Akron General, Akron, OH.)

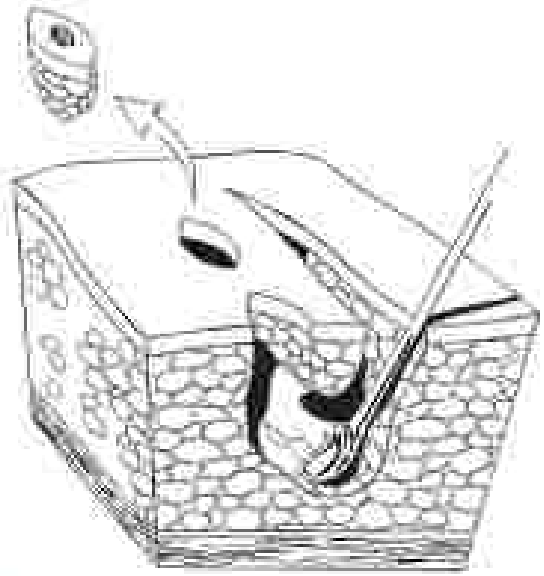

FIG. 4 Pit picking technique involves making an incision based on the pilonidal sinus cavity. This sinus cavity is usually connected with the pit being excised either en bloc or separately. (Modified from Hellinger J, Herold DeMeo S, Cornish J (Hellinger), editors. Principles and Practice of Surgery for the Colon, Rectum, and Anus. St Louis, 1992, Quality Medical.)

recurrence, a curette is used to remove associated debris and lining of the tract. The skin is then brought together primarily to close the defect in the midline. Small unroofings can be performed easily in the office under local anesthesia but, if there is any concern that the sinus tract may be too long to be well tolerated, then regional or general anesthesia in the operating room may be required. The benefit of closing the wound is that there is less need for continued wound care and therefore less pain. Small studies have also demonstrated faster healing rates compared with letting a wound close by secondary intention. Unfortunately, primary closure in the midline has a significantly higher recurrence rate than those who are packed and heal by secondary intention. A 2010 Cochrane review found that healing by secondary intention decreased disease recurrence rates by 50% when compared with primary repair. Both have similar surgical wound infection rates.

Excision With Healing by Secondary Intention

When chronic pilonidal disease has concomitant cellulitis, it is best to excise the wound, lay the tract open, and let it heal by secondary intention. This is a slower healing process compared with primary repair and can lead to much frustration with patients. This open wound requires daily wound care, which is cumbersome. The average healing time for these wounds is 2 months but can take up to 4 to 6 months. Given the burden on patient quality of life, the use of this style of intervention should be used selectively.

Excision With Marsupialization

The third variation of this simple technique is excision followed by marsupialization. After excision of the diseased tissue, the cavity is debrided to remove all residual hair and debris. The skin margins are then sutured to the primeval fascia at the edge of the wound bed (Fig. 5). This is meant to decrease the surface area that is left open to heal by secondary intention, which decreases healing time. It also prevents abscess formation and minimizes the chronic recurrence risk seen with primary closure.

Pit Picking

An alternative office based procedure is "pit picking." Pit picking is an option for patients with an acute abscess, several midline pits, or even those with a short sinus tract. This technique uses two incisions to address all components of the disease (Fig. 6). First, a small elliptical incision is made around the midline pit. This can be done with a fine 11-mm blade or even through use of a 2-mm punch biopsy. Care is taken not to go too wide around the pit. The small ellipse is then closed with a simple 3-0 monofilament suture. Next, a deeper lateral incision is made that is 1 to 2 cm off the midline location of the pit being addressed. This lateral incision allows access to the underlying abscess cavity and/or sinus tract. The incision is taken down to the abscess and then a curette is used to debride the underlying cavity and remove all debris and abscess/sinus contents. This incision is left open to drain. Packing is typically not required. Patients should follow up in 1 week for a wound check and removal of the suture. The wound typically heals in 3 to 4 weeks.

Advanced Disease

For patients with recurrent or refractory disease, more advanced surgical intervention is the most treatment option. The goal of surgery is to thoroughly remove all components of the disease to prevent recurrence, but to do so in the least disfiguring way. Historically, surgeons used to perform wide excisions of the natal cleft encompassing the midline pits and sinus tracts and excising as deep as the sacrococcygeal fascia. Although thorough, this would leave large open wounds that took months to properly heal. The extensive daily wound care required after this type of excision has significant limitations on patient quality of life, particularly given the young median age of this disease. Fortunately, there have been many advances in the use of rotational flap techniques that are able to excise disease, reduce the depth of the cleft, and provide less disfiguring, quicker wound healing. As a result, these techniques have become the recommended treatment option for complex pilonidal disease but require practiced hands to perform them successfully.

Rhomboid/Limberg Flap

The rhomboid, or Limberg, flap is the first rotational skin flap used to treat chronic pilonidal disease. Alexander Limberg first introduced this flap in 1946 to close midline wounds. This incision is in a diamond shape with 60 degree angles and traditionally lies over

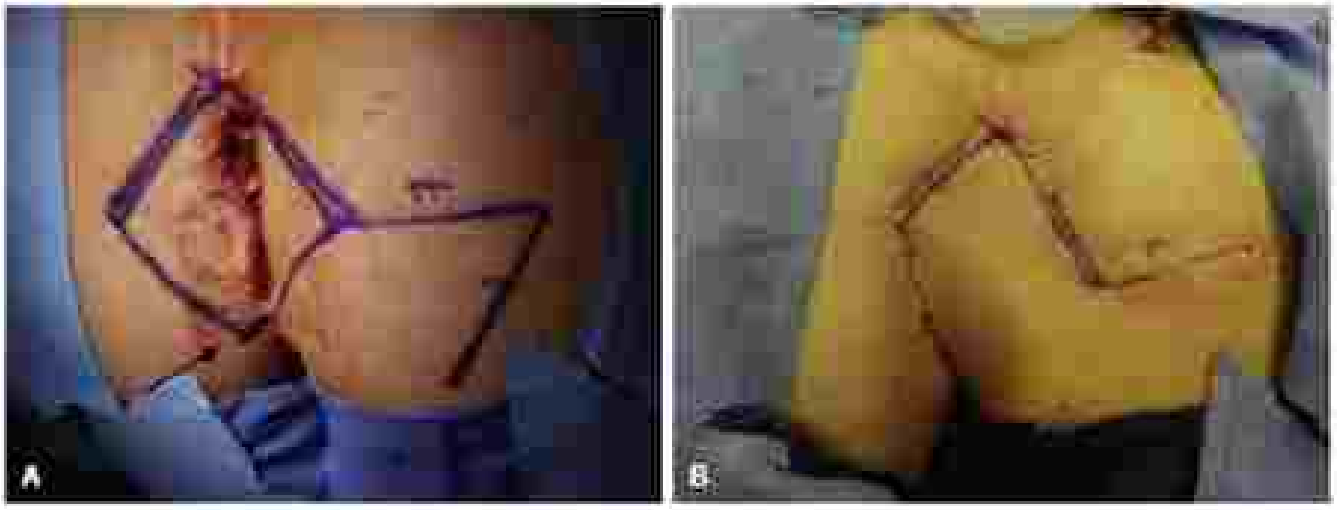

FIG. 7 (A) A rhomboid or diamond pattern delineates the area of excision in preparation for performing a Limberg flap. (B) Completion of the Limberg flap allows for flattening of the previously deep natal cleft. *Courtesy of Dr. Steven Bell, FACS, Jackson Clinic, Cincinnati, OH.*

the midline natal cleft (Fig. 7A). The excision is taken down to the presacral fascia to include all associated pits, abscesses, and sinus tracts. To cover this defect, a full thickness flap in a rhomboid shape is created to retain and cover the excisional defect (Fig. 7B). This pattern allows for flattening of the natal cleft. One recommendation is to use the modified, or oblique, variations in which the orientation of the diamond is rotated off midline in a diagonal manner. With this amount of tissue mobilization, the primary complication is wound dehiscence. The majority of these complications heal without recurrence; however, they do require prolonged wound care.

Karydakis Flap

The next flap procedure introduced for pilonidal disease was by George Karydakis in 1973. His technique uses a lateral, off midline, incision that serves as an advancement flap. The center (or apex) of the ellipse should be approximately 2 cm off midline to allow for completeness of excision and adequate closure. The excised piece of skin contains the midline pits and associated chronic abscesses and/or sinus tracts. The skin and subcutaneous fat from across the cleft is mobilized as an advancement flap to close the wound. This flap is fixed to the underlying sacrococcygeal fascia as well as the opposing skin. These fascia sutures help close the space and prevent recurrence in the midline. To minimize the dead space, a closed suction drain is left under the flap and exits at the superior lateral portion of the wound. The success of this operation has been shown with recurrence rates of less than 1%. This technique does result in 7% to 8% risk of wound complications, most commonly being surgical site infection or seroma formations that require drainage. Predictors of wound complications include obesity and smoking. Unfortunately, this procedure does result in postoperative pain that can necessitate hospital admission. Multiple studies have demonstrated the Karydakis flap to be superior to open excision and healing by secondary intent.

Cleft Lift Technique

Developed by Dr. John Bascom in 2002, the cleft lift technique was the next advancement of rotational flap technique. While utilizing the lateral incision of the Karydakis procedure, this reduces the depth of the midline natal cleft. Compared with the deep excision of the prior flaps shown to fascia, the only tissue excised here is an ellipse of the skin. This minimizes the removal of healthy tissue which allows a "fill" of the once deep natal cleft. This has become the surgical procedure of choice for advanced pilonidal disease and therefore will be explained in further detail.

Before bringing the patient to the operating room, the patient should be marked to allow for proper flap approximation. The patient should stand to allow assessment and marking of the true gluteal cleft. The cleft is defined by where the skin from each buttock makes contact. Next, the patient should be asked to sit upright and a horizontal line should be marked where the patient's buttock meets the chair (Fig. 8A, B).

This procedure is best performed in the operating room under general anesthesia in the prone position. The buttocks should be spread apart with each cheek taped with gentle lateral tension (Fig. 8C, D). Because these patients are most often hirsute, the surrounding hair of the lower back, buttock, and natal cleft should be trimmed with hair clippers. An additional field block of local anesthesia with epinephrine helps postoperative pain control and limits bleeding in the surgical field.

Before making an incision, the surgical excision site should be marked. An asymmetric ellipse should be marked on one side of the natal cleft that includes all midline pits and the sinus opening. The proximal end of the ellipse should be 2 cm superior to the natal cleft, whereas the distal aspect will end in a curve toward the posterolateral anus. The medial edge of the ellipse should be just barely across midline to make sure to involve all midline pits but leave as much skin as possible for reconstruction. The lateral edge should closely approximate the skin marking that was drawn preoperatively (Fig. 8E). If a patient has undergone prior pilonidal surgery, excision is improved if the more scarred side is removed, as long as this does not compromise wound closure.

The incision should start at the superior apex and not extend deeper than the dermis. It should be carried along the midline to the lowest pit. Once the last midline pit is reached, the incision should extend caudally in a crescent shape that points toward the posterolateral aspect of the anus.

Next, a skin flap is elevated on the opposite side of the natal cleft. This should be taken as far lateral as the preoperative skin contact marking. The superior aspect of the flap should be kept thin, approximately 3 to 5 mm, but gradually thicken as it approaches the distal aspect. At the distal end, just superior to the anus, the sacrococcygeal fascia overlying the coccyx should be exposed and the anococcygeal ligament divided. Special care must be taken to avoid injury of the rectum. The division of this ligament allows the flap to rotate and provide adequate coverage.

Once the flap is fully mobilized, attention should shift to the piece of skin chosen to be excised. Begin at the medial aspect within the natal cleft and dissect the skin off the underlying subcutaneous tissue extending toward the lateral marking. Do not yet make the lateral incision and remove the skin. In contrast to the Karydakis procedure, the excised tissue should be only as thick as the dermis, leaving the subcutaneous fat in place to avoid the creation of dead space. Before

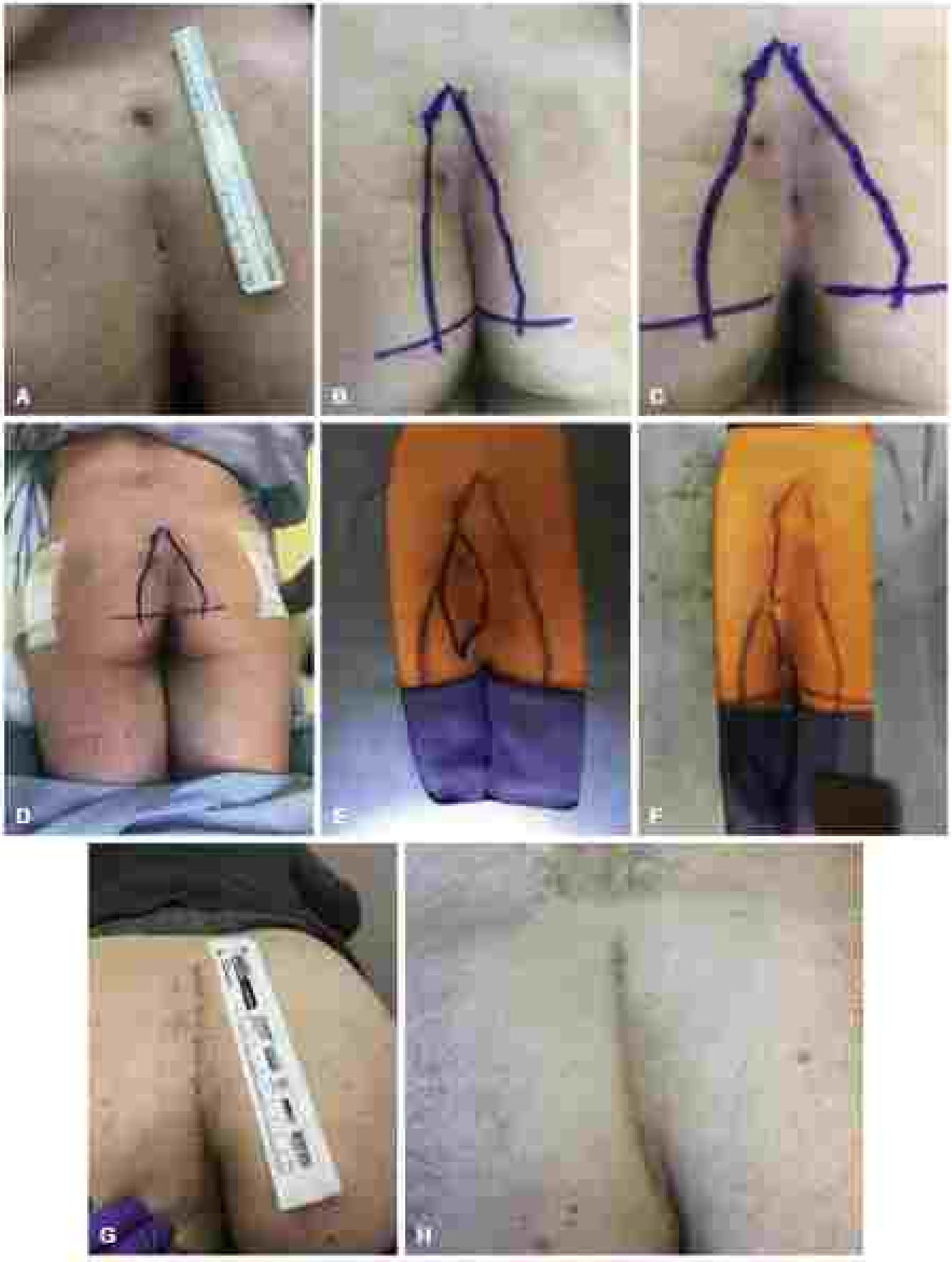

FIG. 8 Cleft-slit technique. (A) Preoperative photo demonstrates multiple midline pits in the natal cleft and a draining sinus located superior. (B) Operative planning markings demonstrate where the testicles meet the chair (horizontal line) and where the buttocks closely touch (vertical line). (C) The same markings are demonstrated with the buttock muscle spread to reveal the midline pits and sinus. (D) Patient positioning on the operative table. (E) Asymmetric ellipse is outlined on one side of the natal cleft that includes all midline pits and the sinus opening. (F) Postoperative appearance of the natal cleft following excision. (G) Four weeks after surgery. The natal cleft is much more shallow in comparison to before the operation. (H) Nine months after surgery. The incision is now well healed without recurrence. (Courtesy Michael Erdmann, MD, FACS, Newton Wellesley Hospital, Newton, MA.)

completing the excision, remove the tape from the buttocks. Have an assistant push the two buttock cheeks together and ensure that the advancement flap will cover the span of the wound. Once wound closure is ensured, the lateral aspect of the excised portion of skin can then be completely detached.

After removal of the skin, the underlying abscess cavity and sinus track can be viewed. These should each be unroofed and a curette used to clean out all debris without removing the abscess cavity itself. The cavity is left in place to prevent dead space and the collection of infected fluid within that space, which would compromise the flap. Instead, the cavity wall is divided into pieces through utilization of cross hatch incisions but remains attached to the underlying tissue. Thorough irrigation of the wound is critical at this step of the procedure.

Now the wound is ready for closure. Absorbable monofilament suture is used to sew the fibrofatty tissue of the buttock cheeks together. Multiple layers of closure are required to prevent dead space and decrease tension on the flap. A small vessel loop should be left under the flap to allow drainage of fluid. The vessel loop should be passed through a small stab incision at the superior lateral aspect of the flap and brought under the flap until it exits through the inferior incision near the anus. The superficial dermal layers should be closed with interrupted 3-0 absorbable suture and the final skin closure can be performed with running either a 3-0 or 4-0 monofilament suture (Fig. 8F). The two ends of the vessel loop should be tied to itself, similar to one in anal fistula procedures. Steri-strips and gauze can be used to cover the incision.

Patients can be sent home the same day but with clear wound care instructions. To prevent the accumulation of fluid, a family member or caregiver is instructed on how to apply a pressure dressing over the wound. It is also recommended to have this caregiver roll gauze slowly and gently over the flap three times a day to express fluid through the drainage openings. Given that these wounds are chronically infected before surgery and the abscess cavity is left in place, a 7- to 10-day course of broad-spectrum antibiotics is prescribed. Patients follow up should be within 1–2 weeks to assess healing and allow for removal of the vessel loop around day 10.

Bascom reported a 96% healing rate of his patients with refractory pilonidal disease (Fig. 8C, H). Complications include stitch abscess or wound dehiscence. Recurrence rates are similar to the Karydakis flap, but less wound complications arise. Improved short-term quality of life has been reported after a cleft lift procedure when compared with the Limberg flap.

Other Techniques

Additional closure techniques have been used for the treatment of chronic pilonidal disease. Common plastic surgery flaps, including the Z-plasty and V-Y advancement have shown promise when used at the hands of those trained in these procedures. The Z-plasty technique has been shown to have lower recurrence rates and lower morbidity when compared with excision with healing by secondary intent. However, when compared with the previously mentioned flap techniques, the Z-plasty has higher rates of wound infections and disease recurrence.

SUMMARY

Pilonidal disease is an acquired condition that most commonly affects young adults. The entrapment of hair and debris within a deep gluteal cleft often leads to the formation of an acute abscess at the site of a midline pit. Over time, these pits can develop a chronic pilonidal sinus that prevents simple healing of the wound. Early or first-time disease can attempt to be treated by nonoperative measures or simple surgical excision. For patients with advanced chronic or recurrent disease, a flap procedure may offer more benefit. Flap procedures allow for off-midline closure that reduces the depth of the gluteal cleft and decreases the risk of recurrence. Given the impact on the quality of life and frequent risk of recurrence, these advanced technical procedures should be performed by those with prior training.

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MANAGEMENT OF LOWER GASTROINTESTINAL BLEEDING

Peter Marcolesky, MD, and Alexandra Fisher, MD, FACS, FASCRS

Lower gastrointestinal bleeding (LGIB) is a complex problem that exists on a spectrum of severity with multiple etiologies. Defined as bleeding in the gastrointestinal tract originating from distal to the ligament of Treitz, possible sources include small bowel, large bowel, and the anus. Some newer resources define LGIB as specifically occurring distal to the ileocecal valve, with middle GI bleeding defined as a separate entity. However, this chapter defines bleeding distal to the ligament of Treitz as LGIB. It is estimated that 30% to 40% of all GI bleeding originates distal to the ligament of Treitz, with approximately 85% of LGIB originating in the colon. LGIB can be a difficult problem from both a diagnostic standpoint and an eventual management standpoint because of its many etiologies, evolving nature, and wide range of severity. Consequently, a systematic and multidisciplinary approach toward diagnosis and management is recommended (Table 1, Fig. 1).

EVALUATION AND DIAGNOSIS

History and Physical Examination

Evaluation should begin with a thorough history and physical examination. Important parts of the patient's history include the frequency, volume, and description of the patient's blood per rectum, as well as other associated symptoms such as presence of abdominal pain, dizziness, weakness, nausea, vomiting, symptomatic arrhythmias, or changes in diet and bowel habits. The patient should also be asked about any recent surgeries, prior gastrointestinal bleeds and, if so, what was the etiology; details about any previous colonoscopies and endoscopies; whether he or she is taking anticoagulants or antiplatelet medications; history of recent trauma; and if there is a personal history of colon cancer, inflammatory bowel disease, arteriovenous malformations, immunosuppression (either organic or iatrogenic), or hemorrhoids.

The physical examination should consist of a thorough abdominal examination, including digital rectal examination. It is important to look for the presence of abdominal masses or hernias and abdominal tenderness, specifically rebound tenderness, guarding, or other signs

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Management of Lower Gastrointestinal Bleeding

Peter Marcolesky, MD, and Alessandro Fichera, MD, FACS, FASCRS

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The physical examination should consist of a thorough abdominal examination, including digital rectal examination. It is important to look for the presence of abdominal masses or hernias and abdominal tenderness, specifically rebound tenderness, guarding, or other signs

of peritonitis. On digital rectal examination, the clinician should inspect for sources of blood, including hemorrhoids, fissures, or masses that may be palpable on examination. In addition, the quality of the stool in the rectal vault, whether it is impacted, melanotic, maroon colored, or frank blood, should be noted. Finally, the clinician should pay specific attention to the patient's vital signs because tachycardia or hypotension are signs of larger volume loss.

Further Studies

After initial examination of the patient, additional studies should be obtained for both diagnostic clarity and further management pearls found in the history.

Anoscopy

If the patient is complaining of blood covered stool, perianal pain, pain with defecation, or sensation of incomplete defecation, then anoscopy can be a quickly performed initial examination to search for hemorrhoids, anal fissures, fecal impaction, or local trauma to the anus. Anoscopy consists of inserting a tubular instrument into the patient's anus, this provides visualization of the anal canal and distal rectum. It is a quick method of visualizing the very distal most aspect of the lower GI tract for hemorrhoids, anal fissures, fecal impaction, or local trauma to the anus, and it can be done at bedside. If the patient has bleeding from internal hemorrhoids, then anoscopy can be used to assist with banding or other treatment of the hemorrhoids. Unfortunately, it is often uncomfortable for the patient, and it only provides limited visualization because it can only display a small segment of tract.

Rigid Sigmoidoscopy

In patients with a strong suspicion for distal LGIB, including the anus, rectum, and distal sigmoid, rigid sigmoidoscopy is also an initial option. The procedure is similar to anoscopy, except the instrument is longer and often has the ability to pump a small amount of air into the rectum to insufflate the bowel to provide better visualization of the mucosa. It is like anoscopy in that it is technically simple and can quickly assess the rectum and anus for bleeding sources, however, it is also uncomfortable for the patient and provides inferior visualization to a flexible sigmoidoscopy or full colonoscopy.

Colonoscopy

If there is a strong suspicion for a colorectal source of the LGIB, colonoscopy is usually a reasonable place to begin. Indicators that the bleeding may be from a colorectal source include anemia, hematochezia or maroon colored stools, tenesmus, chronic changes to bowel habits, palpable mass on digital rectal examination, older age, and history of diverticulosis or colorectal angiodysplasia. Ideally, the patient would undergo bowel prep before colonoscopy so the colon and rectum could be adequately visualized. If the bleeding is chronic in nature, then bowel prep is absolutely indicated because the differential diagnosis includes neoplasia and adequate visualization is necessary. If the bleeding is more acute and the patient is stable, then colonoscopy should occur within 24 hours of clinical presentation, and bowel prep should be attempted. The study consists of pushing a flexible scope through the entirety of the anus, rectum, colon, and usually past proximal to the ileocecal valve. Colonoscopy can detect an endoluminal source of bleeding such as neoplasia, bleeding diverticulosis, hemorrhoids, or angiodysplasia, in addition to diffuse sources of bleeding including inflammatory bowel disease, ischemic colitis, radiation proctitis, or infectious colitis. Furthermore, colonoscopy can be therapeutic as well as diagnostic because bleeding lesions can be either cauterized, clipped, coagulated with argon plasma, or injected with epinephrine to obtain hemostasis. Colonoscopy should be deferred if there is suspicion for active diverticulitis because this increases the risk of bowel perforation. In addition, if the patient has a heavy stool burden or is unable to tolerate bowel prep, then it may be difficult to sufficiently visualize the colon and rectum. Risks include bowel perforation, damage to mucosa, and the general risks of sedation.

Computed Tomography Angiography

Patients with active bleeding at a rate greater than approximately 0.5 mL/min can be visualized with a computed tomographic angiography (CTA). The study consists of injection of intravenous contrast while the patient is scanned by a multidetector helical CT scanner. The timing of the contrast is such that active arterial extravasation from a vessel into the lumen of the small bowel can be visualized on the study. A CTA can be rapidly obtained, is minimally invasive, and does not require any bowel preparation like a colonoscopy. Consequently it is very useful in hemodynamically unstable patients who are either only minimally or transiently responding to resuscitation and do not have time to undergo bowel preparation prior to intervention. CTA can also assist with the diagnosis of other causes of LGIB, such as mesenteric ischemia or ischemic colitis. To confirm and localize the

TABLE 1 Differential Diagnosis of Gastrointestinal Bleeding: Origin Site

Origin of Bleeding	Expected Symptoms/History/Findings
Small intestine	Melena/maroon colored stool Anemia
Colon/rectum	Melena/maroon colored stool/hematochezia History of diverticulosis Anemia Changes to bowel habits
Anus	Hematochezia/blood coated stool Palpable or visible hemorrhoids Anal fissure Pain with defecation Sensation of incomplete voiding of stool

FIG. 1 Evaluation based on severity of gastrointestinal bleeding.

bleeding, the patient must be actively bleeding at the time of the study, otherwise no extravasation will be visualized. Other disadvantages of CTA include possible allergic reaction to intravenous contrast, nephrotoxicity of intravenous contrast, exposure to radiation, that no therapeutic intervention is performed simultaneously with the study, and the difficulty with precisely localizing a small bowel source.

Nuclear Scintigraphy With Technetium 99m

Similar to the CTA, nuclear scintigraphy allows for radiographic visualization of the location of bleeding. In the study, the patient's red blood cells are tagged with technetium 99m, a radiotracer, and then injected back into the patient. The patient is then imaged to see where extravasation of the tagged red blood cells is occurring. Nuclear scintigraphy is a more sensitive test than CTA because it can detect bleeding down to a rate as low as 0.1 mL/min. It is also advantageous in that the radiolabeled red blood cells remain detectable in the patient for approximately 24 hours after initial labeling, so if the patient has a site of bleeding that is only intermittently active, then the patient can be rescanned over the course of the day which increases the sensitivity of the test. However, it is even less accurate at localizing the source of the bleeding than CTA. Pooled studies estimate a 25% false localization rate; therefore, it is more frequently used to screen for bleeding than to target a localized intervention.

Angiography

Should CTA or nuclear scintigraphy demonstrate active extravasation in the patient, an angiogram is a possible intervention to both further localize and potentially stop the bleeding. The patient is lightly sedated, and then intraarterial access is gained, usually through the femoral artery or other major artery. A catheter is inserted into the lumen of the artery and then guided through the aorta to the suspected bleeding artery. Contrast is injected through the catheter and then fluoroscopy is used to search for active extravasation. If the extravasation is localized, then that vessel can be embolized. If venous bleeding is suspected, the same process of embolization can be used in the venous system. Angiography can detect bleeding down to a rate of 0.5 mL/min or greater. Angiography is usually reserved for hemodynamically unstable patients or patients with a continued transfusion requirement only. The risks of angiography include the risks of undergoing sedation in an actively bleeding patient, vascular perforation, contrast allergy, contrast nephropathy, and pseudoaneurysm or bleeding at the access point. Provocative angiography is similar to angiography; however, during the procedure, the patient is given some form of anticoagulation with the goal of provoking an intermittently bleeding lesion into actively bleeding so that it can be captured on angiography. The lesion is then embolized, or at least identified for surgical resection, such as in the case of a hypervascular tumor. One single-center study demonstrated a 31% success rate with identifying a bleeding lesion with provocative angiography, without bleeding complications. Furthermore, the bleeding lesion was able to be successfully embolized or resected in all cases. Provocative angiography can be beneficial when searching for an intermittently bleeding lesion, but it does come with the standard risks of angiography, as well as the additional risk of hemorrhagic complications from giving a patient at high risk of bleeding a therapeutic dose of anticoagulant.

Capsule Endoscopy

Capsule endoscopy is a useful study for a hemodynamically stable patient who has chronic or episodic GI bleeding often associated with chronic anemia despite a negative workup of both upper and lower GI source because it can visualize the entirety of the small bowel. The patient swallows a pill-sized capsule that contains a camera, the camera then takes intermittent photographs as it moves through the patient's digestive tract. The images are reviewed to determine the source of bleeding. The test is relatively sensitive for detecting a source of bleeding, with some studies demonstrating a sensitivity of up to 90%. Capsule endoscopy does not have any therapeutic abilities because it is only a diagnostic test. However, it can help obtain a diagnosis, and determine appropriate future studies or management with its findings.

Balloon Enteroscopy

Similar to capsule endoscopy, double balloon enteroscopy allows for visualization of the small intestine. First, the patient is placed under anesthesia. The device used is an endoscope, but with an overtube that the endoscope can telescope in and out of. There are balloons on the distal aspect of the overtube and endoscope. The scope is advanced into the small intestine and then the overtube balloon is inflated and the overtube retracted, thus pulling the small bowel proximal to the endoscope and then allowing the endoscope to advance further into the small bowel. The endoscope's balloon is then inflated, and then overtube's balloon deflated, and the overtube advanced forward to meet the endoscope. The overtube's balloon is then inflated, allowing further retraction of the small bowel proximally. This process allows the overtube to retract small bowel, so the endoscope can be further advanced. The process is time consuming, but it does have the advantage over capsule endoscopy because the scope can be used to carry out therapeutic intervention, similar to a standard colonoscopy or endoscopy. Furthermore, the provider can begin the procedure from either the upper or lower ends of the GI tract. The study does come with the standard risks of endoscopy, including the risks of anesthesia and bowel perforation. Because it is so labor intensive, it is often unsuitable as are results of CTA, nuclear scintigraphy, or capsule endoscopy to plan a double balloon enteroscopy.

Nasogastric Lavage

Brisk bleeding from the upper GI tract, such as a bleeding peptic ulcer, angiodysplasia, or esophageal varices, can often manifest as visible blood in the stool, either hematochezia or maroon colored stool. Nasogastric lavage requires insertion of a nasogastric tube, and then the contents of the stomach are either suctioned, or saline is instilled into the nasogastric tube and then suctioned back to an effort to look for either blood or coffee grounds in the stomach. In a hemodynamically unstable patient, nasogastric lavage is a quick method of investigating the upper GI tract as a source of bleeding. Unfortunately, it is uncomfortable for the patient and it does not specifically localize the source of bleeding beyond identifying it as emanating from the upper GI tract. Furthermore, it does not have any therapeutic benefit.

Esophagogastroduodenoscopy

Endoscopic evaluation of the upper GI tract, including the esophagus, stomach, and duodenum, may be necessary if the patient's investigation of the lower GI tract is inconclusive. Esophagogastroduodenoscopy (EGD) is useful for diagnosing bleeding lesions, including peptic or duodenal ulcers, angiodysplasias, neoplasia, or inflammatory conditions that could be causing upper GI bleeding. Similar to a colonoscopy, the EGD has both diagnostic and therapeutic value. Additionally, ulcers can be inspected and biopsied to guide future medical management of peptic ulcer disease including PPI therapy and antibiotics for possible *Helicobacter pylori*. Its risks are similar to other endoscopic studies and includes perforation and any risks of sedation (Table 2).

MANAGEMENT

Initial management depends on the severity of the bleed. First, the quantity of blood in the patient's stool should be assessed, as should the patient's vital signs and associated symptoms. Because the acuity of management depends on the severity of the patient's bleeding and associated hemodynamics, we divide management into two separate categories for this chapter (Table 3).

Hemodynamically Stable Patient

A hemodynamically stable patient can present with a wide range of severity to his or her symptoms, including intermittent blood in the stool to someone with chronic anemia resulting from continued low rate of blood loss. Similar to a hemodynamically unstable patient, the clinician should begin with a history and physical examination. It is important to characterize the time course, amount of bleeding, appearance

TABLE 2 Evaluation of GI Bleeding by Site of Origin

Origin of Bleeding	Possible Etiologies
Small intestine	Neoplasm Angiodysplasia Inflammatory bowel disease Mesenteric ischemia Recent small intestinal surgery Meckel's diverticulum Dieulafoy's lesion Aortoenteric fistula Intussusception
Colon/rectum	Diverticulosis Neoplasm Angiodysplasia Inflammatory bowel disease Recent colorectal surgery/colonoscopy/biopsy Radiation proctitis Ischemic colitis Infectious colitis (EHEC, Salmonella, Campylobacter, Shigella, CMV, amebiasis) Rectal varices Fecal impaction Aortoenteric fistula
Anus	Hemorrhoids Anal fissure Inflammatory bowel disease Local trauma Perianal sexual abuse

CMV, cytomegalovirus; EHEC, enterohemorrhagic Escherichia coli; GI, gastrointestinal.

of the stool and associated symptoms, such as presence of abdominal pain, rectal pain, fever, weight loss, or changes in bowel habits. The physical examination should include a thorough abdominal examination searching for palpable masses, tenderness, or lymphadenopathy. A digital rectal examination should also be performed, taking care to note the presence of anal fissures, internal or external hemorrhoids, or any masses that are palpable in the anal canal. Anoscopy or rigid sigmoidoscopy can also be performed at this time if the patient tolerates it to gain better visualization of the anal canal, especially if there is suspicion for anal or rectal pathology or history and physical examination. If these examinations are not confirmatory of a diagnosis, then colonoscopy or flexible sigmoidoscopy should be considered as a next step.

In younger patients, blood on the stool is usually caused by internal or external hemorrhoids or anal fissure. Meckel's diverticulum is another possibility and is a frequent cause of painless bleeding in younger age groups. In older patients, malignancy is of greater concern, and therefore even if benign rectal pathology is uncovered on physical examination, the patient should be considered for colonoscopy. In older patients found to be anemic without a history of rectal blood loss in the stool, occult GI blood loss to stool, a possible etiologic, and EGD and colonoscopy should be considered for workup. Similar to a hemodynamically unstable patient, colonoscopy can be both diagnostic and therapeutic. If a bleeding polyp is noted, it can be removed either by forceps or resecting with a snare at the base of the polyp. Additionally, if the patient has a slow bleed from an angiodysplasia, argon plasma coagulation can be used during colonoscopy.

In a patient with intermittent bleeding, it can be useful to perform a tagged red blood cell scan because they can detect slower sources of bleeding. The radioactive tracer can remain in the patient's body for up to 24 hours, so he or she can be managed quickly should there be signs of further bleeding. Another option in an intermittently bleeding patient is provocative angiography to localize the lesion.

In a hemodynamically stable patient, surgical intervention can be warranted for several etiologies, including malignancy, inflammatory bowel disease refractory to medical management, bleeding hemorrhoids, or recurrent bleeding from a Meckel's diverticulum. If a bleeding Meckel's diverticulum is discovered, it is important to not only resect the diverticulum, but the adjacent bowel as well. The Meckel's diverticulum usually results in ulceration of the mucosa of the adjacent bowel resulting from the production of ectopic gastric contents from ectopic gastric tissue found in the diverticulum. Simple resection of the diverticulum without resection of the adjacent bowel will not control the source of bleeding.

Hemodynamically Unstable Patient

If the patient is found to be dizzy, tachycardic, hypotensive, or have other signs of hemodynamic instability or pending instability, then initial management should include obtaining vascular access with two large-bore intravenous needles, volume resuscitation, and baseline laboratory values, including hemoglobin, white blood cell count, platelets, liver function, renal function, and coagulation. The patient should be typed and crossed for blood products as well. An endoscopist should be consulted for possible colonoscopy, as well as EGD should there be suspicion for upper GI bleeding. Additionally, the clinician should consider placement of a nasogastric tube to perform nasogastric lavage if there is a concern that the bleeding could be coming from the stomach. If there is any coagulopathy or thrombocytopenia, then that should be corrected with vitamin K supplementation, fresh frozen plasma, and platelet transfusion. If the patient is taking any antiplatelet or anticoagulant drugs, they should be discontinued temporarily. Consultation with a cardiologist is recommended if the patient has had recent cardiac stent placement because discontinuation of dual antiplatelet therapy could result in thrombosis of the stent. Some sources recommend holding nonaspirin antiplatelet agents for 1 to 7 days while continuing aspirin in the setting of secondary prevention of cardiac ischemia. Goals of transfusion should be for a hemoglobin greater than 7.0 g/dL for patients without evidence of an active cardiac event, and more than 9.0 g/dL in patients with significant comorbidity including coronary artery disease. International normalized ratio should be corrected to a goal of less than 1.5. Platelets should be transfused for a goal of greater than 50,000/μL. If the patient requires a massive transfusion protocol, it is important to be mindful of maintaining a 1:1:1 ratio of units of packed red blood cells to platelets to fresh frozen plasma to ensure clotting factors and platelets are replaced in the setting of severe bleeding.

If the patient is responsive to initial resuscitation, then he or she should undergo EGD for evaluation of upper GI source because the upper GI tract is a more likely etiology for brisk bleeding than the lower GI tract. If the EGD is negative for a source of bleeding, then the patient should begin bowel prep to prepare for colonoscopy within the next 24 hours. At the time of colonoscopy, the entirety of the rectum, colon, and terminal ileum should be inspected by the performing physician for signs of active bleeding, as well as signs of recent bleeding, such as adherent clots or exposed blood vessels. If the source of bleeding is identified, then the bleeding vessel can either be cauterized, clipped, rubber band ligated, or injected with epinephrine to achieve hemostasis. Injection with dilute epinephrine, usually 1:10,000 or 1:20,000 dilution, is usually coupled with a second means of hemostasis, such as clipping of the vessel. In addition, the source of bleeding should be noted as a diverticular bleed versus angiodysplasia because angiodysplasia is amenable to argon plasma coagulation for hemostasis.

GI bleeding may be only part of the patient's hemodynamic instability; therefore, it is important to pay close attention to the patient's associated symptoms. For example, in acute mesenteric ischemia, the patient may be passing blood through the stool, but there are other factors present that are driving the patient's tachycardia and hypotension.

TABLE 3 Management of Gastrointestinal Bleeding

	Presentation	Diagnosis	Treatment
Diverticulosis	Maroon-colored stool or hematochezia Either painless or crampy pain Can be significant volume of blood in episodic bouts, usually occurs in older patients	Colonoscopy to identify bleeding diverticula	Most cases resolve without intervention Bleeding vessel can be clipped, cauterized, or injected during colonoscopy
Angiodysplasia	Low volume bleeding but can be more severe Hematochezia or maroon colored stool, either painless or crampy pain, usually occurs in older patients	Colonoscopy to identify bleeding vascular malformation	Argon plasma coagulation during colonoscopy Surgical resection is usually reserved for the case of continuous bleeding despite attempts at endoscopic management
Internal hemorrhoids	Painless bleeding with bowel movements Blood visible on stool, usually associated with frequent straining, constipation, pregnancy, or prolonged sitting	Digital rectal examination or anoscopy can visualize internal hemorrhoids	Conservative management includes stool softeners, high fiber diet, and limiting time spent on toilet If refractory to conservative measures, then they can either be rubber band ligated using anoscopy or excised surgically
External hemorrhoids	Pain with bowel movements Thrombosis of hemorrhoid usually results in continuous anal pain Blood present on stool or on toilet tissue, associated with frequent straining, constipation, pregnancy, or prolonged sitting	Visible on external aspect of anal canal and can be palpated on digital rectal examination	Conservative management includes stool softeners, high fiber diet, and limiting time spent on toilet Thrombosed hemorrhoids can be excised
Anal fissure	Pain with bowel movements, blood present on stool or on toilet tissue, usually associated with passing large/firm stools	Visible on external aspect of anal canal, usually tender on digital rectal examination	Conservative management with stool softeners, topical calcium channel blockers, topical numbing agents, topical nitroglycerine If refractory to medical treatment, lateral internal sphincterotomy can relieve sphincter spasm that can worsen fissure
Inflammatory bowel disease	Frequent, bloody bowel movements Crampy abdominal pain, anorexia, changes in bowel habits, diarrhea, weight loss, fevers, extraintestinal manifestations such as pyoderma, uveitis, erythema nodosum, primary sclerosing cholangitis, arthralgias	Colonoscopy can visualize the gross appearance of the intestine looking for cobblestoning, skip lesions, exhibition sag, or evidence of structuring or fistulizing disease; biopsies taken during colonoscopy often demonstrate inflammatory changes, noncaseating granulomas, or crypt abscesses	Inflammatory bowel disease can be medically managed with a combination of corticosteroids and other immunomodulating agents Regular endoscopic monitoring is needed because patients are at higher risk of neoplasia Surgery can be indicated for strictures, fistulas, or medically refractory disease Total abdominal colectomy is a definitive treatment in ulcerative colitis
Neoplasia	Occult bleeding, hematochezia/maroon colored stools, changes in bowel habits, weight loss, family history of neoplasia, personal history of inflammatory bowel disease, older patients	Colonoscopy can visualize the gross pathology and biopsy taken during colonoscopy confirms the diagnosis	Surgical resection can be curative, such as in the case of early stage anal benign disease, or it can be palliative, such as in the case of more advanced disease where complete resection is not possible
Ischemic colitis	Crampy abdominal pain associated with hematochezia or maroon-colored stools, older patients with coexisting coronary or peripheral arterial disease, usually precipitated by physiologic stress, such as surgery or illness	Flexible sigmoidoscopy or colonoscopy can diagnose ischemic changes or ischemic ulcerations to watershed regions of the large intestine, such as the sigmoid colon or splenic flexure	Supportive care with volume resuscitation and treatment of underlying insult Serial abdominal examinations are performed to monitor for worsening of intestinal ischemia, if the patient develops peritonitis, then surgical resection of the necrotic bowel should be performed

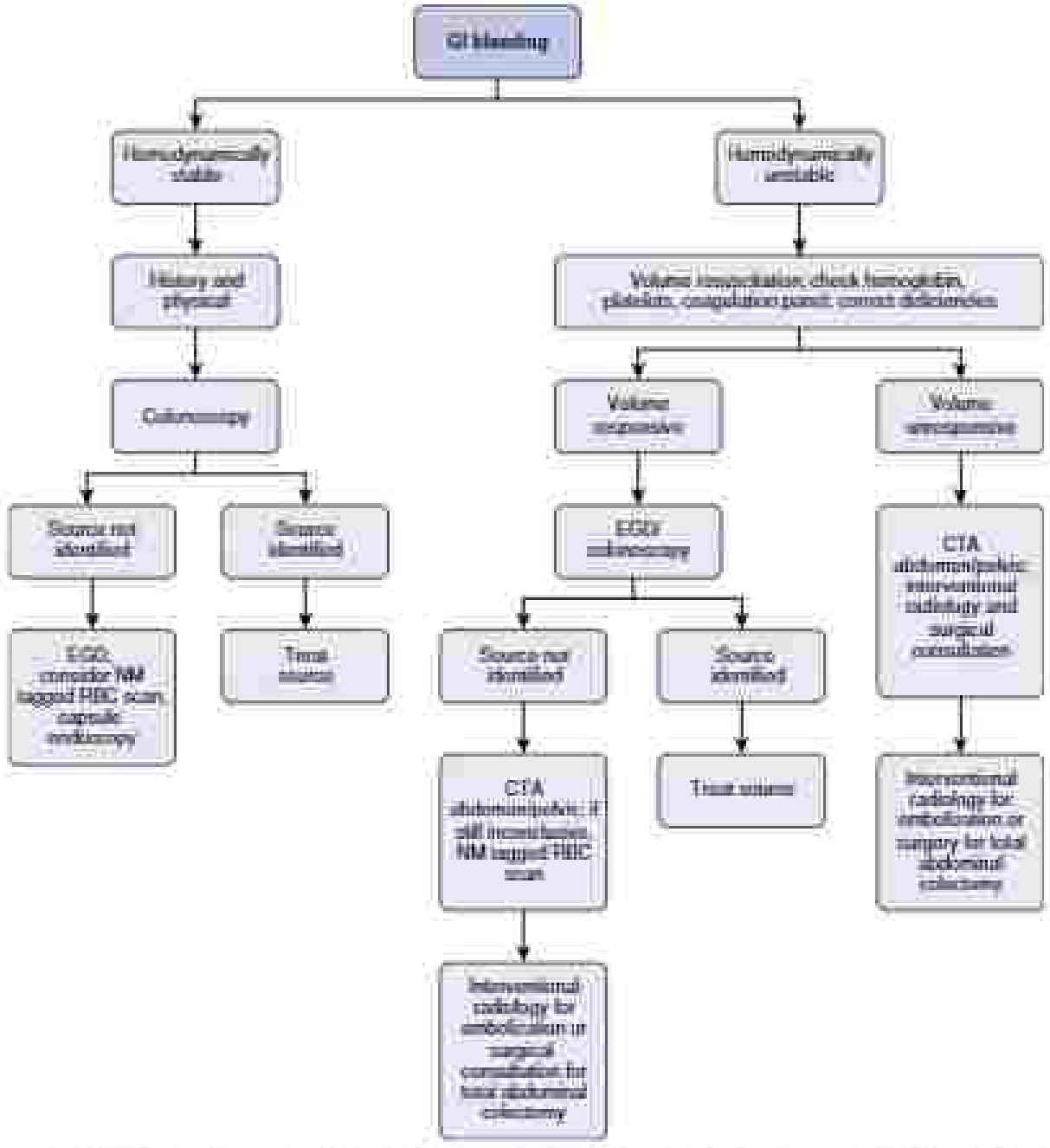

FIG. 2 Algorithm for treatment of gastrointestinal bleeding. CTA, computed tomography angiography; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; NM, nuclear medicine; RBC, red blood cell.

If the patient is transiently responsive to resuscitation, then the patient should undergo stat CTA, as well as consultation to interventional radiology for angiography and possible embolization pending the results of the CTA. If the patient is only minimally responsive to resuscitation, then direct consultation of interventional radiology for angiography and embolization would be more appropriate. Emergent EGD should also be performed at this time as well. In a hemodynamically unstable patient with negative CTA and negative EGD/colonoscopy, the next step would be surgery as a salvage procedure. Additionally, if a patient undergoes EGD/colonoscopy that identifies the bleeding, but the bleeding is unable to be controlled endoscopically, then surgical intervention is also warranted. Surgical options include either a segmental bowel resection if the bleeding is identified preoperatively or intraoperatively, or a subtotal colectomy. The surgeon should have a low threshold to perform a damage control operation because the primary objectives would be to control the bleeding as quickly as possible, and then continue resuscitation of the patient in an intensive care setting. Surgical intervention for GI bleeding should be regarded as a salvage procedure and not first line because it carries a 40% mortality rate and is often difficult to localize the bleeding intraoperatively. If a patient were to have bleeding that could not be controlled endoscopically, one option would be to tattoo the segment of bleeding bowel endoscopically, so it could be identified intraoperatively. Finally, in the case of mesenteric ischemia, surgery would be indicated to remove any necrotic segments of bowel, as well as vascular surgical intervention to attempt to restore blood flow to the bowel (Fig. 2).

CONCLUSION

LGIB is a complex problem arising from a variety of etiologies with a range of severity. Consequently, it is important for the clinician to be thorough in his or her assessment, and to be mindful of concurrent resuscitation of the patient. Because approximately 80% of patients presenting with LGIB will spontaneously resolve, most patients may only require some degree of resuscitation and not require procedural intervention to achieve hemostasis. Endoscopic and interventional procedures should be first line for most episodes of GI bleeding that require intervention, with surgery usually reserved only for refractory cases of brisk bleeding. Furthermore, in a hemodynamically stable patient, endoscopic assessment is usually a reasonable method of obtaining a diagnosis. Surgical intervention can also be warranted in the setting of neoplasia, refractory inflammatory bowel disease, Meckel's diverticulum, necrotic intestine secondary to ischemia, or hemorrhoids.

Suggested Readings

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Enhanced Recovery After Surgery

Alexis Gabre-Kidan, MD, and Jonathan Efron, MD

The key tenet of an Enhanced Recovery After Surgery, or ERAS, program is minimizing stress along the entire surgical care continuum from preoperative evaluation through postoperative follow-up. This requires several shifts to the standard approach to any given surgical patient. First, it must be accepted that outcomes depend on more than traditional preoperative cardiopulmonary optimization and surgical technique. Although we have made great advances in surgical technique, patients still suffer complications. This suggests that even as we continue to innovate and push the limits of our technical capabilities, we must also look beyond what happens in the operating room to make an impact on patient outcomes. Second, as we learned from multidisciplinary tumor boards in cancer care, a multidisciplinary approach with engagement of all stakeholders involved in the care of surgical patients is key. This starts, most importantly, with the patients themselves and includes outpatient surgical team members (i.e., nurses, support staff), surgeons, anesthesiologists, and inpatient care team members such as nurses, nutritionists, and physical therapy. Last, but perhaps most important, the adoption of an ERAS program requires a willingness to adopt evidence-based care that may be a departure from typical patterns of care. This is perhaps the most difficult and slowest step. However, as the emphasis on delivering high-quality, lower-cost care continues to grow, we must constantly evaluate and evolve beyond what dogma or preference dictates to ensure that we are delivering the best patient care possible.

This chapter reviews the standard elements of an ERAS program designed to minimize stress and, as a result, optimize patient outcomes. Past reviews have detailed each individual component of an ERAS program. Instead, we will outline the cornerstones of patient care in ERAS programs: minimizing fasting, judicious fluid administration, and optimizing analgesia. We will also demonstrate where each of these factors come in to play along the care continuum. Each element of ERAS affects one of these key tenets to ultimately minimize stress and decrease adverse outcomes.

EDUCATION

We propose that there is one additional key feature without which an ERAS program cannot succeed: education. This includes patient education as well as active engagement of all of the stakeholders that will participate in the patient's care along the care continuum.

An ERAS program may be a departure from what patients have experienced if they have had prior surgeries or even from their general expectations if they have not. Just as the adoption of ERAS by healthcare professionals requires a shift in the belief that patients who undergo major surgery need to be hospitalized longer, the common perception on the part of patients that surgery involves several days in the hospital for convalescence must also be adjusted. This begins with understanding patients' goals for surgery and educating them on the goals of an enhanced recovery pathway. It is important to explain the benefits of the ERAS pathway beyond simply reducing length of stay and avoiding terms such as *fast track* or *expedited recovery* because these do not convey the true goals of ERAS programs. Emphasis should be placed on decreasing complications, minimizing stress and anxiety, and guiding patients through their recovery as smoothly as possible. To this end, educational materials on preoperative instructions, what to expect during their hospitalization, and criteria for discharge are important to provide. Some programs use printed materials and give each patient an ERAS pamphlet to study before surgery, whereas others rely on Web-based materials. The most effective educational tools are written at an appropriate health literacy level and outline both daily milestones and overall goals for recovery (Fig. 1). These tools not only allow patients to take an active role in their care, but also expectation lower stress/anxiety and shorter hospital stays.

The creation and maintenance of a successful ERAS program revolves around a multidisciplinary, multimodal approach to care. This involves several team members, from anesthesiologists, surgeons, to nurses, and spans several settings from outpatient clinics to the operating room and inpatient wards. For many of these team members, the strategies used in caring for ERAS patients will signal a departure from their usual patterns of care. Similar to patient education, each team member must be educated on the overarching goals of the ERAS program and how his or her individual roles contribute to these goals. We will not review detailed steps on how to implement ERAS programs, because each implementation must be adapted to the culture and protocols of each institution. The first step, however, is education on the evidence that drives the various components of the pathway. Later in the chapter, we will discuss audit and compliance processes to ensure that ongoing education is taking place and any barriers are being addressed.

MINIMIZING FASTING

Perhaps the largest shift to caring for ERAS patients is the management of their nutritional status preoperatively and postoperatively. In

CONCLUSION

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We propose that there is one additional key feature without which an ERAS program cannot succeed: education. This includes patient education as well as active engagement of all of the stakeholders that will participate in the patient's care along the care continuum.

An ERAS program may be a departure from what patients have experienced if they have had prior surgeries or even from their general expectations if they have not. Just as the adoption of ERAS by healthcare professionals requires a shift in the belief that patients who undergo major surgery need to be hospitalized longer, the common perception on the part of patients that surgery involves several days in the hospital for convalescence must also be adjusted. This begins with understanding patients' goals for surgery and educating them on the goals of an enhanced recovery pathway. It is important to explain the benefits of the ERAS pathway beyond simply reducing length of stay and avoiding terms such as *fast track* or *expedited recovery* because these do not convey the true goals of ERAS programs. Emphasis should be placed on decreasing complications, minimizing stress and anxiety, and guiding patients through their recovery as smoothly as possible. To this end, educational materials on preoperative instructions, what to expect during their hospitalization, and criteria for discharge are important to provide. Some programs use printed materials and give each patient an ERAS pamphlet to study before surgery, whereas others rely on Web-based materials. The most effective educational tools are written at an appropriate health literacy level and outline both daily milestones and overall goals for recovery (Fig. 1). These tools not only allow patients to take an active role in their care, but also expectation lower stress/anxiety and shorter hospital stays.

The creation and maintenance of a successful ERAS program revolves around a multidisciplinary, multimodal approach to care. This involves several team members, from anesthesiologists, surgeons, to nurses, and spans several settings from outpatient clinics to the operating room and inpatient wards. For many of these team members, the strategies used in caring for ERAS patients will signal a departure from their usual patterns of care. Similar to patient education, each team member must be educated on the overarching goals of the ERAS program and how his or her individual roles contribute to these goals. We will not review detailed steps on how to implement ERAS programs, because each implementation must be adapted to the culture and protocols of each institution. The first step, however, is education on the evidence that drives the various components of the pathway. Later in the chapter, we will discuss audit and compliance processes to ensure that ongoing education is taking place and any barriers are being addressed.

MINIMIZING FASTING

Perhaps the largest shift to caring for ERAS patients is the management of their nutritional status preoperatively and postoperatively. In

keeping with the principle of decreasing the stress response to surgery, several components of the pathway are aimed at maintaining a metabolically fed state to decrease stress, which in turn decreases insulin resistance and catabolism.

The first intervention in an ERAS pathway aimed at decreasing the stress response to surgery is to avoid keeping patients without food or drink from midnight the night before surgery. Although the traditional rationale has been to decrease the risk of aspiration during induction of anesthesia, newer evidence from the anesthesiology community has shown that it is safe for patients to have solids up to 6 hours before surgery and clear liquids up to 2 hours before surgery. This allows the opportunity for patients to enter surgery in a metabolically fed state. Current ERAS guidelines recommend consumption of complex carbohydrate drinks up to 2 hours before the time of surgery. The advantage to this was first shown in animal studies that demonstrated that animals sustaining surgical trauma had better responses to stress than those that entered in the metabolically starved state. These findings were then confirmed when it was shown that patients taking preoperative oral carbohydrate solutions had 50% less insulin resistance and decreased loss of muscle mass, suggesting that the effects were not only limited to glucose metabolism but protein and fat metabolism as well. Subsequent studies and meta-analyses have suggested that preoperative carbohydrate loading is an independent predictor of length of stay. From a psychological standpoint, remaining without food or water for several hours is also uncomfortable, with many patients complaining of thirst and hunger. This creates additional unnecessary stress and anxiety preoperatively. Patients that are malnourished need additional nutritional optimization before surgery and would benefit from a structured plan to boost their nutrition in the days and weeks leading up to surgery.

The goal of minimizing stress and catabolism by encouraging oral intake continues through to the postoperative period. Patients are encouraged to take liquids the evening of surgery. In several studies even beyond the ERAS populations, early enteral feeds have shown to have beneficial effects and decrease overall postoperative complications. Again, in addition to decreasing patient discomfort and anxiety associated with remaining without food or water, this serves to decrease catabolism. Although some programs will advance patients to a solid or semisolid diet on the first postoperative day, others focus on nutritional supplements. The exact diet progression is likely not as important as having a structured plan for patients within a given program that minimizes fasting. To this end, routine use of nasogastric tubes is discouraged. Not only do nasogastric tubes cause patient discomfort and impede mobilization, but they have been shown to delay return of bowel function and are associated with increased pulmonary complications such as atelectasis and pneumonia. Last, for patients to continue oral intake, postoperative nausea and vomiting (PONV) must be well controlled. This starts preoperatively with risk stratification using scoring systems such as the Apfel score (Fig. 2) and appropriate preoperative prophylaxis. All patients should receive

Risk factors	Points
Female gender	1
Nonsmoker	1
History of PONV	1
Postoperative opioids	1
Risk score =	0...4

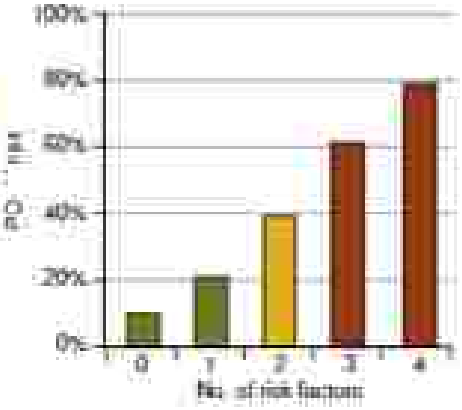

FIG. 1 Apfel score. PONV, postoperative nausea and vomiting.

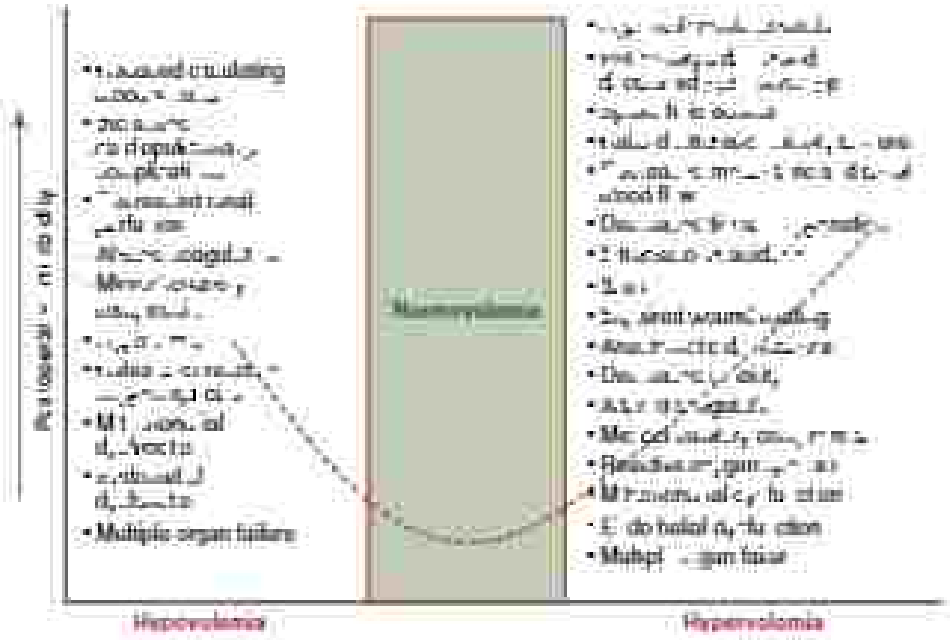

FIG. 2 Fluid balance.

dexamethasone before induction, ondansetron at the completion of surgery, and further interventions such as scopolamine patches based on their risk stratification. Several other intraoperative anesthetic factors affect rates of PONV and will be discussed in subsequent sections.

Despite measures to encourage early enteral feeding and decrease PONV, ileus remains a significant problem, and the most common reasons for increased length of stay in postoperative patients of all types. Prompt recognition of ileus and appropriate management is important to avoid delays in discharge and patient discomfort.

FLUID MANAGEMENT

Another large shift in the perioperative care of patients in the transition that fluid balance plays a large role in postoperative recovery. There are ample data to support the detrimental effects of both fluid overload and inadequate fluid resuscitation. The goal is to maintain patients in a euvolemic state by thoughtful and judicious use of intravenous fluids across the entire care continuum.

As discussed previously, patients are encouraged to take complex carbohydrate drinks up to 2 hours before surgery. This serves not only to minimize the stress response, but also to allow the patient to maintain fluid balance preoperatively. Another important consideration in preoperative fluid management is bowel preparation for colorectal surgery. The use of mechanical bowel preparation is meant to cleanse the colon to reduce fecal spillage and subsequently decrease infectious complications such as wound infections and anastomotic leakage. The literature regarding bowel preparation is mixed and controversial, with some studies demonstrating no benefit and others suggesting a benefit to mechanical bowel prep combined with oral antibiotic preparation. Strictly from a fluid management standpoint, mechanical bowel preparation leads to large preoperative fluid losses and patients potentially enter surgery in a hypovolemic state. This can lead to reflexive administration of additional intravenous fluids to compensate for preoperative losses. Several strategies have been advocated to minimize the routine use of mechanical bowel preparation for all patients undergoing colon and rectal resections, including the use of enemas for rectal resection and omitting preparation for right-sided resections entirely. However, multiple other studies have shown significant reduction in surgical site infections when mechanical preparations are used in conjunction with oral antibiotics. This requires further investigation and is an area where variability still remains, even within ERAS programs.

Intraoperative fluid balance is critical both within and outside of ERAS programs. Patients that leave the operating room in either extreme of fluid balance are at risk for postoperative complications. Recent emphasis has been on avoiding fluid overload because it has been shown to increase adverse outcomes such as pulmonary edema and ileus. Although the benefit of goal directed therapy has been demonstrated outside of ERAS programs, studies to date have been unable to show a benefit in ERAS programs. It is unclear if this is due to the increased use of laparoscopy or because ERAS programs already emphasize judicious use of intravenous fluids. Regardless, strategies to avoid fluid overload include tight titration with intravenous pumps, administration of a combination of balanced crystalloids and colloids, and use of pressors rather than fluids in hypotensive patients that appear euvolemic for other clinical indications. Several factors affect intraoperative fluid balance including the use of laparoscopy, thoracic epidural anesthesia, blood loss, and insensible losses. It is important that interventions that is administered thoughtfully in the intraoperative period because patients that enter the postanesthesia care unit and surgical wards in a state of fluid imbalance are at risk of deviating from the ERAS pathway.

Meta analyses have shown that fluid management is an independent predictor of outcome in ERAS programs, and the postoperative period is as important to overall fluid management as the intraoperative fluid balance. Fluid balance postoperatively should be oriented toward encouragement of oral intake of fluids and decreasing the use of intravenous fluids with a goal of between 1.75 and 2.5 L/day. Counter to traditional postoperative care, if oral intake is tolerated, intravenous fluids should be decreased or entirely discontinued on postoperative day 1.

The importance of effective management of fluids cannot be understated because it crosses all phases of care and involves all members of the team from patient to nurse. Improper use of fluids can lead to decreased end organ perfusion or pulmonary/bowel edema, both of which translate to slower recovery, increased morbidity, and increased length of stay.

ANALGESIA

Improving analgesia is an intuitive way to decrease the stress response to surgery and is a cornerstone of successful ERAS programs. As opposed to a more traditional approach to pain control, ERAS programs emphasize preemptive analgesia along with a multimodal approach to optimize response and minimize opioid use.

The method of preemptive analgesia most consistently demonstrated to decrease opioid use and alter the stress response to surgery is thoracic epidural analgesia. An epidural catheter is placed in the thoracic region preoperatively and maintained through the postoperative period, usually for up to 48 to 72 hours. Early ERAS data in open colonic surgery showed a strong benefit to epidural analgesia, but more recent studies with a higher percentage of ERAS patients undergoing laparoscopy have failed to show a benefit. Epidural analgesia is also not without its complications and contraindications and requires a pain management team to follow patients postoperatively, potentially posing a barrier to implementation. This has led to increased interest in other strategies for regional blocks such as transversus abdominis plane blocks administered by either the surgical or anesthesia team before surgery. Transversus abdominis plane blocks are generally performed with long-acting anesthetic agents. There has been increased interest in liposomal bupivacaine because it has been reported to provide analgesia for up to 72 hours after infiltration. It is unclear whether this provides additional narcotic sparing benefits beyond what is traditionally used in an ERAS program. However, this warrants further investigation because it may potentially be an avenue to limit opioid use which is highest in the early postoperative period.

In the absence of epidural analgesia, infusion of intravenous lidocaine intraoperatively has been shown to improve postoperative pain control, reduce opioid consumption, and is associated with quicker return of bowel function. Evidence for preemptive analgesia with acetaminophen and nonsteroidal antiinflammatory drugs remains unclear but there is more evidence to support the use of gabapentanoids preoperatively to decrease postoperative opioid use. Many centers also use alvimopan, a peripheral mu opioid antagonist, to decrease rates of ileus. There have been several studies across many surgical specialties showing that use of alvimopan can decrease rates of ileus and length of stay. Although the studies specifically investigating the benefit of alvimopan to an ERAS pathway are limited, they are promising and suggest that it can provide additional benefit in limiting ileus.

Multimodal analgesia is started preoperatively. Use of nonsteroidal antiinflammatory drugs and acetaminophen postoperatively has an opioid sparing effect. These medications should be used on a scheduled basis and do not have the same effects when used as needed. Use of these opioid sparing medications also secondarily decrease rates of PONV and ileus. Decreasing PONV and ileus in turn leads to earlier oral feeding and earlier mobilization.

There are two other ERAS recommendations that affect postoperative pain/discomfort and should be mentioned: urinary catheters and use of drains. Early removal of catheters, in some instances at the end of surgery, is encouraged. Not only does prolonged use of urinary catheters increase the risk of urinary tract infection, it also causes patient discomfort and impairs mobility. In the absence of significant pelvic dissection, it is recommended to remove catheters on the first postoperative day even in the presence of epidural catheters. Routine intraabdominal drainage is similarly discouraged and has never been

supported in the colorectal literature as a method of preventing or detecting potential complications. As ERAS guidelines continue to be developed for other surgical subspecialties, the literature specific to that field pertaining to the use of drains will need to be reviewed. If drains are used, early removal is advocated.

OUTCOMES/AUDIT

The success of any individual ERAS program relies not just on the initial implementation of the program, but also constant assessment of patient outcomes and program adherence. There is a clear stepwise association between adherence to the ERAS protocol and postoperative outcomes. When more than 70% of the ERAS elements are followed, symptom defying discharge, 30 day morbidity, and readmissions are significantly decreased. It is important to have an ongoing audit process to ensure that goals for the program are being met. Similarly, regular meetings with members of the ERAS team are important to discuss areas that may need improvement.

FUTURE DIRECTIONS

Although the most robust literature regarding ERAS pertains to colonic surgery, there has been an adoption of ERAS across several subspecialties (Table 1). There are 12 surgical subspecialties with separate ERAS guidelines from the ERAS Society and several more underway. Future study should be directed at the potential benefit of ERAS when applied to traditionally high risk surgical candidates such as the frail elderly population. For example, there is emerging interest in prehabilitation programs designed to optimize preoperative functional capacity to better prepare vulnerable patients to withstand the stress of surgery. The early data on these programs are mixed, and it is unclear whether they will offer additional benefits beyond ERAS or could be incorporated into ERAS programs. Last, the long-term benefits of participation in an ERAS program remain to be seen. Studies focusing on cancer specific outcomes suggest that adherence to ERAS protocols may be associated with increased 5 year cancer specific survival, but more studies of this nature are needed.

There is no doubt that implementation and maintenance of an ERAS program requires a large investment in resources, personnel, and time. However, with continued adherence, the benefits are clear and provide an opportunity to further improve the care of our surgical patients.

TABLE 1 Current ERAS Guidelines

Procedure and Topic	Year of Publication
Colonic resection	2012
Rectal resection	2012
Pancreaticoduodenectomy	2012
Cystectomy	2013
Gastric resection	2014
Anesthesia protocols	2015
Anesthesia pathophysiology	2015
Major gynecologic (pelvic)	2015
Bariatric surgery	2016
Liver resection	2016
Head and neck cancer surgery	2016
Breast reconstruction	2017
Hip and knee replacement	Under production
Thoracic noncardiac surgery	Under production
Esophageal resection	Under production

ERAS, Enhanced Recovery After Surgery.

SUGGESTED READINGS

Fearon KC, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24(3):466–477.

Gustafsson UO, Hausel J, Thorell A, et al. Adherence to the Enhanced Recovery After Surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg*. 2011;146(5):571–577.

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Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: a review. *JAMA Surg*. 2017;152(3):292–298.

PNEUMATOSIS INTESTINALIS AND THE IMPORTANCE FOR THE SURGEON

Paula Ferrada, MD, FACS, and Jason H. Delgado, MD, FACS

Pneumatosis intestinalis (PI) is defined as gas or air filled cysts on or in the bowel wall. This is a radiologic sign, not a disease, and it can be associated with multiple factors ranging from bowel ischemia to a more incidental finding. For the past decade, much research has been done to determine the significance of this sign, how to distinguish clinically when PI is pathologic or benign, and when it is the optimal time to perform surgery when patients have PI secondary to ischemia.

There is a likely a difference between PI identified on plain radiographs and the occurrence of this finding via more advanced radiologic methods such as computed tomography (CT). The latter imaging modality is more detailed and therefore can more sensitively identify pathologic PI in the early stages of ischemia, when it may still not be related to transmural necrosis. For this reason, it is important to note that PI should be evaluated in a clinical context that includes associated examination and laboratory data so that negative exploration on nontherapeutic laparotomy be avoided when possible.

This chapter presents an algorithm on how to identify patients who require an operation in the context of PI.

BENIGN PI

Benign PI presents as an incidental imaging finding without associated clinical signs/or indicative of ischemia. For example, some connective tissue disorders such as scleroderma have been associated with formation of cysts within the bowel wall not associated with ischemia. In the case of rupture of one of these cysts, the patient can even complain of abdominal pain that is self-limited, localized, and without any other clinical findings.

CLINICAL PRESENTATION OF PATHOLOGIC PI

Pathologic PI is present when there is associated ischemia. This can be associated with transmural necrosis. In pathologic PI, the patient usually presents with abdominal pain. If the abdominal pain

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PNEUMATOSIS INTESTINALIS AND THE IMPORTANCE FOR THE SURGEON

Paula Ferrada, MD, FACS, and Joseph Dutton, MD, FACS

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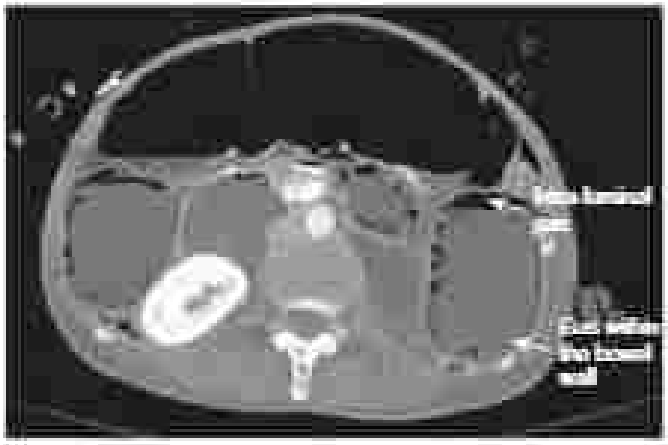

FIG. 1 Gravity assist the intraluminal gas asymmetry and the gas in the bowel wall can be distinguished because it is surrounded the entire loop of bowel.

is generalized, the parietal peritoneum is not yet inflamed. This is a reassuring sign that can signify lack of transmural involvement.

Patients with bowel ischemia have an identifiable cause in the majority of cases. These etiologies can include low-flow states in patients requiring hemodynamic support with multiple pressors, hypovolemia combined with proximal atherosclerosis, hypercoagulopathy, or other causes of shock states that compromise perfusion of the intestines in a more global fashion. Other pathologies, particularly acute thrombotic or embolic mesenteric arterial events, may result in more focal regions of ischemia. Mechanical compromise of perfusion, including strangulated small bowel obstruction, are other common etiologies. Severe compromise of venous mesenteric outflow, as can occur with significant portal venous or mesenteric venous thrombosis, can also prove a devastating cause of mesenteric ischemia.

LABORATORY FINDINGS

Patients with leukocytosis, increased lactate, and/or shock on vasopressors should be strongly considered for a surgical exploration because all of these have been shown to predict pathologic PI with transmural necrosis. Dubose et al. identified a lactate of 2.0 mmol/L or greater as the strongest independent predictor of pathologic PI on a retrospective multicenter trial. Ferraris et al. performed a prospective multicenter trial validated lactate higher than 2.0 mmol/L as a strong predictor of necrosis.

On the prospective multicenter trial, other laboratory findings such as elevated international normalized ratio and decreased hemoglobin where found to be predictive of ischemia. These are typical findings of patients that have bleeding in cases of pathologic PI secondary to necrosis of the bowel mucosa.

Other studies have examined dynamic renal function tests also to be predictive clinically, this correlates with patients that are septic and underresuscitated.

READING A CT SCAN WITH PATHOLOGIC PI

Gravity forces intraluminal air superiorly, however, gas within the bowel wall (PI) will completely surround the loop of bowel (Fig. 1). This can make it easier for the surgeon to identify PI on a CT scan.

After making the clinical diagnosis of pathologic PI, looking at the CT scan can help weigh the relative benefit of emergent surgical exploration versus initial resuscitation and physiologic optimization.

Ascites is an ominous sign if combined with pathologic PI because this is likely to be associated with third spacing and bowel inflammation secondary to transmural necrosis.

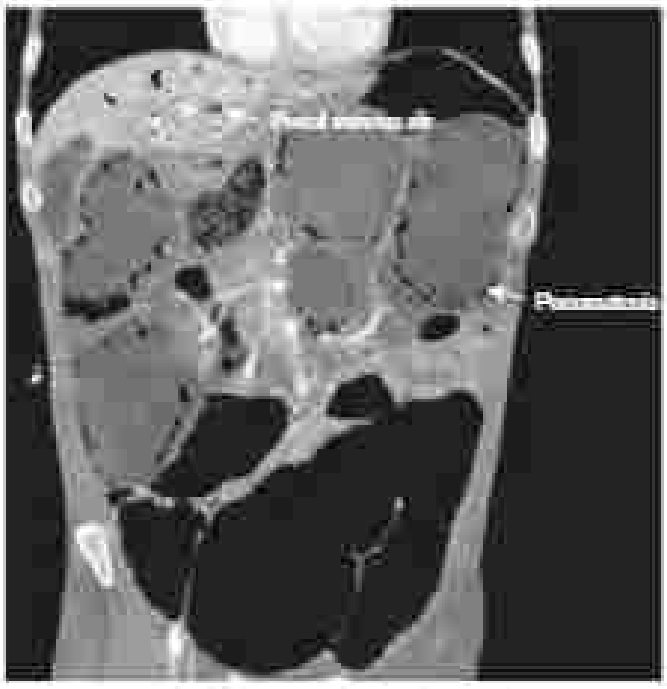

FIG. 2 Pneumatosis and portal venous air.

Small bowel pathologic PI is more likely to be associated with transmural necrosis than large bowel. The bowel, large or small, dies from the inside out. First, the mucosa becomes ischemic and necrotic. It sloughs off and, in some cases, passes as currant jelly stool. Patients then can lose blood and become anemic, with an increased international normalized ratio. Because the small bowel is thinner, it is more susceptible to these layers reaching the outer wall and perforating. The colon is thicker; therefore, the mucosa can be ischemic without showing signs of transmural necrosis on surgical exploration.

Portal venous gas is an ominous sign when associated with pathologic PI (Fig. 2). The physiopathology of portal venous gas is not well understood, although some of the theories proposed include the role of gas-forming bacteria in the portal venous circulation following necrosis and transmural dislocation of organisms from the enteric tract.

TECHNICAL RECOMMENDATIONS

Once the decision has been taken for surgical exploration, the surgeon has to keep in mind the principles of damage control resuscitation and understand the physiology of the patient.

Several key considerations are paramount to optimal outcome:

Constant communication with the anesthesiologist. If the patient is in shock, anesthetic can result in a further insult. Ensuring that further sedimentation is kept at a minimum can help the patient's perfusion.

Resuscitation as euvolemic. Hypovolemia will increase the chances of further necrosis and renal failure. Hypervolemia will result in further bowel swelling; goal directed resuscitation using methods such as arterial line waveform analysis or echocardiogram are advisable to maintain strict euvolemia.

How much to resect. These patients are usually in a state of shock. Minimizing blood loss and operative time is imperative. Consider resecting just the areas of necrosis and leaving the patient in discontinuity if necessary to allow for better resuscitation. These patients are often sick. Consider also minimizing dissection and blood loss and staying in the operating suite for the shortest necessary time.

Consideration for avoiding or delaying an anastomosis: Unless the cause of ischemia is mechanical, and it is diagnosed and treated in the operating room, consider that the bowel might still be in the process of continued ischemia. This can be disastrous for an anastomosis that can fail and place the patient at risk for a second source for intraabdominal sepsis.

Suggested Readings

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Liver

Cystic Disease of the Liver

Victor M. Zaydfudim, MD, MPH, and Reid B. [illegible], M[illegible]

L[illegible] [illegible] and [illegible] The [illegible] majority [illegible] [illegible] in the general [illegible] [illegible] [illegible] [illegible] [illegible] and [illegible] in patients with autosomal dominant polycystic kidney disease. Asymptomatic, simple, or polycystic liver cysts do not require intervention, while management in symptomatic cysts depends on patient presentation, extent of cystic disease, and available center-specific treatment options. Patients with polycystic liver disease should be evaluated and treated at experienced referral centers using a multidisciplinary approach. Neoplastic liver disease, including cystadenoma, cystadenocarcinoma, and intraductal papillary mucinous neoplasm of the bile duct [illegible], is also rare. The carcinogenesis pathway between cystadenoma and cystadenocarcinoma is poorly understood. The decision to proceed with resection or surveillance in cystadenoma is multifactorial and depends on patient and imaging specific factors. [illegible] has a high risk of malignant transformation or malignancy on presentation and resection is recommended. Other etiologies of cystic disease are rare and are frequently cystic primary or secondary malignancies, such as cystic-appearing hepatocellular carcinoma, cystic-appearing primary liver sarcoma, cystic colorectal, neuroendocrine or other metastases with features masquerading as simple cysts. [illegible] essential considerations and diagnoses for radiographic findings of liver cysts [illegible] are summarized in [illegible]. Appropriate treatment depends on the following: [illegible] making deliberate and correct diagnosis, [illegible] if symptomatic, determining whether symptoms are related to the cyst, [illegible] and [illegible] selecting the best individualized treatment option for each patient.

[illegible]

[illegible] genetic [illegible]

A simple liver cyst is the most common liver parenchymal imaging abnormality present in up to [illegible] of the population. The vast majority [illegible] of patients with simple cysts are asymptomatic and do not require treatment. The cysts are spherical or ovoid with a smooth cyst wall without radiographic features such as thickening, nodularity, or asymmetry. Cysts can range in size from a few millimeters to greater than [illegible] centimeters. The cyst wall is lined by a smooth single layer cuboidal or columnar epithelium and most of the cysts do not communicate directly with the biliary system. Cyst fluid is often simple serous, and straw colored but can be brown in patients with prior intracystic hemorrhage or bilious in patients with intracystic biliary communication. While rare, simple cysts can become infected particularly in patients with prior biliary tract or cyst instrumentation and/or significant comorbid conditions (e.g., poorly controlled diabetes, congestive heart failure, and others).

Ultrasonography (US) is diagnostic in most patients with simple cysts. Typical sonographic characteristics include a sharply demarcated well circumscribed lesion with a thin, almost imperceptible wall, a homogeneous anechoic pattern typical for simple fluid, and posterior acoustic enhancement (Fig. 1A). Atypical cyst wall characteristics (wall asymmetry or thickening, mural nodules) are concerning for a neoplastic diagnosis. Echoic material within the cyst fluid may suggest intracystic hemorrhage but this ultrasonographic finding should be corroborated by clinical presentation or with cross-sectional imaging.

Liver cysts are also frequent incidental findings during computed tomography (CT) and magnetic resonance imaging (MRI). The typical features on contrast-enhanced CT are similar to those found on ultrasound. Simple cysts have a well-defined, thin, almost imperceptible cyst wall. The cyst is filled with a homogeneous, hypoattenuated fluid with low Hounsfield units similar to water (Fig. 1B). There is no wall enhancement on either pre- or post-contrast images. Small lesions (<[illegible] cm) are not well characterized with CT and are better evaluated with US or MRI. The accuracy of MRI for diagnosing cystic lesions is very high. In addition to the well-defined thin cyst wall without worrisome features, simple cysts demonstrate intracystic fluid signal intensity that is very low on T1-weighted sequences and very high on T2-weighted sequences. When MRI features confirm the diagnosis of a simple cyst, additional studies and follow-up are not required in the asymptomatic patient.

An advantage of MRI over US and CT, when prototypical features of a simple cyst are not present, is the ability to characterize the fluid. Fluid signal characteristics different than water suggest hemorrhagic products, proteinaceous/mucinous fluid, or the presence of subtle mural nodules/projections. Similar to US or CT, an enhancing cyst wall or solid element on MRI is concerning for a neoplasm.

Despite adequate imaging, diagnostic challenges can arise. By definition, simple cysts are just that, simple. When a cyst is other than simple, by definition complex, this raises the concern for a neoplastic process. However, diagnostic dilemmas can be seen when a simple cyst has lobulated borders, for instance when the cyst expands around a hard intrahepatic structure such as a portal pedicle. Similarly, two simple cysts that are adjacent can share a cyst wall giving the appearance of a complex cyst with an internal septum. These radiographic findings can be challenging to distinguish from a true complex cyst. Finally, any findings of ductal involvement, such as intrahepatic ductal dilatation or mass effect on the intrahepatic or extrahepatic biliary system, also raise concern for neoplasia.

Management

Patients with incidental findings diagnostic for a simple liver cyst do not require intervention or surveillance. Symptomatic cysts are rare and more typical in patients with large cysts (≥ 10 cm or larger) particularly if there is stretching of Glisson's capsule. Cyst growth is typically gradual and vague symptoms such as abdominal fullness, early satiety, dull pain, and discomfort are more common than acute pain syndromes. In patients with small cysts and in those in whom imaging findings are discordant with subjective symptoms, other potential etiologies for pain including biliary, pancreatic, gastrointestinal, renal, musculoskeletal, and pulmonary sources should be considered. Rarely, patients will have hemorrhage into a simple cyst. This can cause acute pain and rapid enlargement of the cyst. If a preexisting simple cyst has been seen on prior imaging, the diagnosis of hemorrhage into a simple cyst typically can be made on follow-up imaging. However, if this is the initial presentation, distinguishing a hemorrhagic simple cyst from a complex one is difficult.

Simple cyst aspiration is rarely useful. The diagnosis of a simple cyst is established without fluid analysis, as patients with worrisome radiographic features fall into the complex category and should be treated with a presumptive diagnosis of a neoplasm. Diagnostic aspiration can be considered in patients with discordant imaging findings and symptoms; however, it is unclear how often subjective improvement in symptoms after cyst aspiration is related to a placebo effect. Despite this uncertainty, we have found this useful for decision making in some patients. Therapeutic aspiration without sclerosis does not provide adequate, durable treatment.

TABLE 1 Differential Diagnosis of Liver Cysts

Benign liver cysts:	Simple cyst Polycystic liver disease
Infectious/inflammatory	Pyogenic abscess Amebic abscess Echinococcal disease
Neoplastic liver cysts	Cystadenoma Cystadenocarcinoma Intraductal papillary mucinous neoplasm of the bile duct Primary liver cancer (e.g., cystic hepatocellular carcinoma, cystic primary liver sarcoma) Cystic metastases to the liver (e.g., primary colorectal, neuroendocrine, gastrointestinal stromal tumor, squamous cell, and others) Dilated hepatic foregut cyst
Miscellaneous	Hepatic pseudocyst Traumatic cysts

Sclerotherapy

Image-guided cyst aspiration and sclerosis can provide durable cyst drainage and resolution. US-guided sclerotherapy is a multistep process involving cyst access, insertion of a drainage catheter with partial cyst decompression, contrast cystography, and instillation of sclerosant (such as 95% ethanol, minocycline, tetracycline, hypertonic saline, or others). Sclerosing agents destroy the lining epithelium, preventing further fluid secretion, and therefore recirculation, into the cyst. For large cysts multiple sequential sclerosing treatments might be required. Current success for sclerosis of solitary liver cyst exceeds 85%. Aspiration and sclerosis, however, diminishes for very large cysts; the exact cut off for "very large cyst" (0.1, vol.2 [...n>3) is debatable. Aspiration of bilious cyst fluid and/or communication with the biliary system identified during contrast cystography precludes safe cyst sclerotherapy.

Conclusion

Laparoscopic cyst fenestration provides durable treatment for patients with symptomatic simple liver cysts. Large liver cysts compress and displace adjacent hepatic parenchyma with distortion of major vascular and biliary structures. Polycystic hepatic parenchyma is frequently

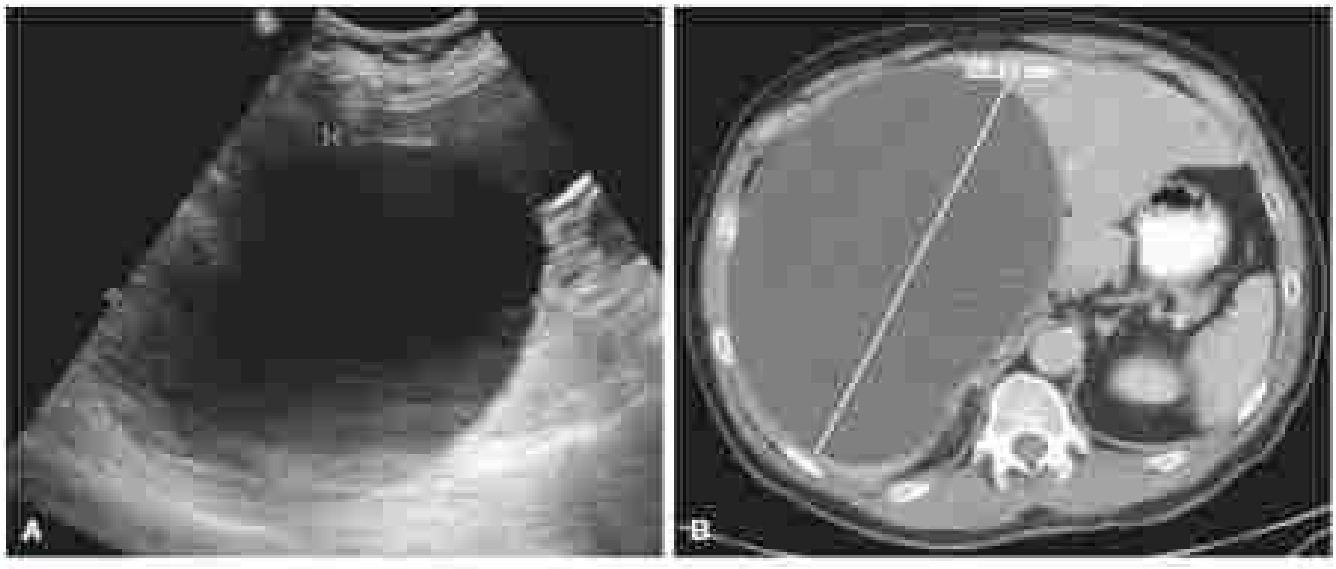

FIG. 1 (A) Ultrasound image findings consistent simple [illegible] (B) [illegible]

asymptomatic and both pericholangitis as well as major hepatic veins can be adjacent to the intrahepatic portion of cyst wall. As such, the goal of fenestration is to remove the portion of the cyst wall that is largely extrahepatic without injury to the intrahepatic portion of cyst wall, which may abut major vessels and bile ducts. First, the cyst is entered and aspirated to facilitate dissection and exposure. Next, the extrahepatic portion of the cyst wall is excised with an endovascular stapler or energy device (Fig. 2). Bile duct radicles can be present along the transection line, thus inspection following cyst wall resection for a bile leak is important. If present, this should be oversewn to avoid a postoperative bile leak. Following completion of cyst wall resection, the intrahepatic portion of the cyst wall is ablated to reduce secretions by the remaining epithelium. Ablation is safely and effectively performed with the argon beam coagulator, which coagulates the remaining cyst epithelium without penetration through the cyst wall into underlying structures. If bile is encountered during initial cyst entry and aspiration, communication with a biliary radicle along the intrahepatic portion of cyst wall is likely. The bile duct orifice should be identified and suture ligated to prevent a postoperative bile leak. At the completion of fenestration and ablation, an omental pedicle can be used to fill the space, although its benefit is not supported by data. Intraperitoneal drainage is not necessary. The resected cyst wall should be submitted for frozen and permanent pathologic examination to rule out a neoplastic cyst. If pathologic evaluation demonstrates features of a neoplastic cyst, complete resection of the cyst is appropriate and recommended.

FIG. 2. Laparoscopic cyst fenestration. The cyst is entered and aspirated to facilitate dissection and exposure. The extrahepatic portion of the cyst wall is excised with an endovascular stapler (shown), or energy device. The intrahepatic portion of the cyst wall is ablated with the argon beam coagulator to reduce secretions by the remaining epithelium.

Similar to current results with sclerotherapy, long-term success for fenestration of simple liver cysts exceeds 90%. Choice of initial approach (fenestration vs. sclerotherapy) depends on center experience and patient preference. Sclerotherapy is particularly useful for patients with significant comorbidity and high operative risk as well as for patients with large volume cysts located deep within the hepatic parenchyma. Fenestration is the preferred approach with very large cysts that can be accessed peripherally as well as in patients with biliary communication. In general, simple cysts do not require consideration of formal hepatic resection.

Polycystic Liver Disease

Phenotypic Features and Diagnostic Evaluation

Autosomal dominant polycystic liver disease (PLD) most frequently occurs in patients with autosomal dominant polycystic kidney disease (ADPKD) but also can develop in patients without ADPKD as a separate genotypic entity. While PLD is the most frequent extrarenal manifestation of cystic disease in patients with ADPKD, cystic disease of the kidneys is the most frequent extrahepatic manifestation of patients with PLD not associated with ADPKD. Histologic features of liver cysts associated with PLD are similar to simple cysts. Phenotypic and radiographic findings are individual, all and can vary from numerous cysts to innumerable cysts. Phenotypic manifestations of individual patients with PLD are dependent on second hit somatic mutations (in addition to the inherited autosomal dominant predisposition), which results in significant heterogeneity of these cystic diseases.

Most patients with PLD are asymptomatic and do not require treatment. When symptoms develop, they usually result from the mass effect of the accompanying hepatomegaly. Typical symptoms include abdominal fullness, early satiety, and pain, leading to long-term effects on the patient's quality of life. The other common complications are infection, frequently a result of cyst or biliary instrumentation or immunosuppression in kidney transplant recipients, and hemorrhage into a cyst(s). Complications of rupture or symptomatic vascular compression are very rare. Intrinsic hepatic function is preserved regardless of cystic extent or hepatomegaly.

Adequate PLD cyst characterization often requires contrast-enhanced CT or MRI. Imaging evaluation includes not only size and location of the cysts but, importantly, the extent of hepatic parenchymal preservation and vascular involvement. A number of classification systems have been proposed to assist in management of patients with PLD. The 2009 Mayo Clinic classification is particularly useful as it categorizes patients based on presence of symptoms, cyst or extent of normal liver parenchymal preservation, and the patency of hepatic venous outflow and hepatic venous outflow (Table 2 and Fig. 3). This classification system allows for individual all treatment decision making based on patient- and disease-specific factors. Patients with PLD should be managed with a multidisciplinary approach to determine the most appropriate operative or nonoperative treatment strategy. Other extrahepatic manifestations of ADPKD, in particular

TABLE 2 2009 Mayo Clinic Classification of Polycystic Liver Disease

Type	Symptoms	Cyst Characteristics	Sectors With Relatively Normal Liver Parenchyma	Hepatic Venous Outflow Obstruction or Portal Hypertension
A	Absent or mild	Any	Any	Any
B	Moderate/severe	Limited # of large cysts	≥2 sectors	Absent
C	Severe or moderate	Any	≤1 sector	Absent
D	Severe or moderate	Any	Any	Present

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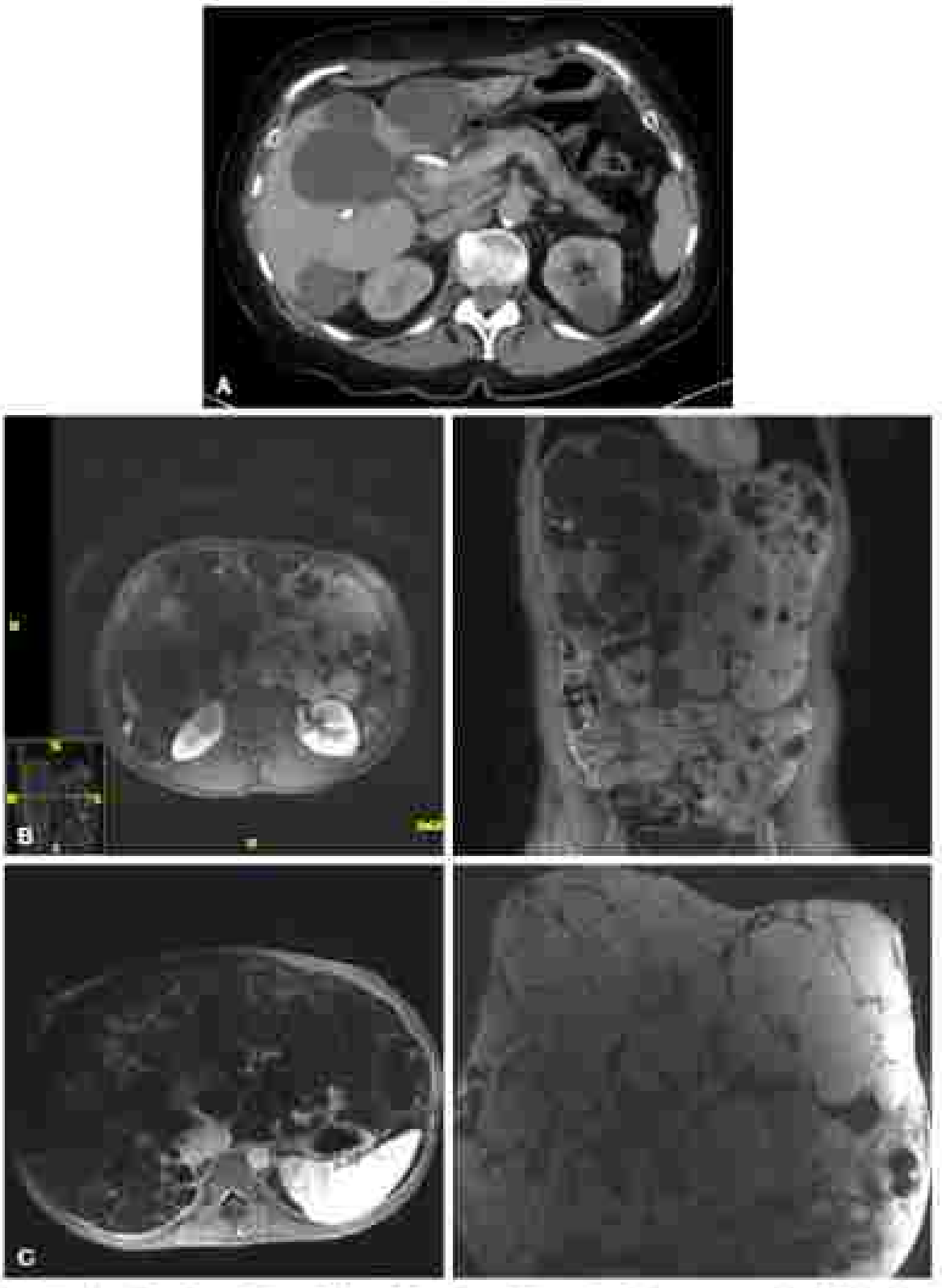

FIG. 3. Patients with polycystic liver disease (PLD) type A (A), type C (B), and type D (C) cyst distribution. Note preservation of left hepatic vein and relative sparing of left lobe hepatic parenchyma in a patient with type C PLD (B). Presence of symptoms consist of hepatic parenchymal and vascular problems (as summarized in Table 2) almost uncommon combination. Patients with PLD should be managed with a multidisciplinary approach to maximize the most appropriate treatment strategy. (*Left to right*) Courtesy Dr Vasiliki Rahaniotis.

evaluation and treatment of cerebral aneurysms, should be performed prior to considering liver directed therapy.

Management

Patients with type A cysts typically require no treatment or are considered for medical management. Use of long acting release octreotide decreases the total liver volume in patients with PLD and improves health related quality of life. Use of mTOR inhibitors, as monotherapy or combined with somatostatin analogues, have not been shown to improve outcomes when compared to long acting octreotide. To date, long acting release octreotide is the preferred medical management supported by published data. Select patients with PLD develop symptoms either from a dominant, infected, or hemorrhagic cyst. If such a cyst is identified, percutaneous cyst aspiration with subsequent sclerosis should be considered.

Patients with type B cysts should be considered for fenestration. In general, these patients have a limited number of large cysts with preservation of over half of the normal hepatic parenchyma. Fenestration without major parenchymal resection allows cyst unroofing and epithelial ablation. Fenestration of peripheral cysts usually can be achieved safely with a laparoscopic approach. However, despite large cyst volume and a relatively small number of cysts, an open rather than laparoscopic approach is favored if deep intraparenchymal cysts are selected for fenestration. Major vascular and biliary structures such as segmental portal pedicles or large hepatic vein branches can occupy the septa between neighboring cyst walls and be prone to injury. This requires meticulous division of septa between adjacent intrahepatic cysts to maintain hemostasis and bile stasis, avoiding significant bleeding, bile leak, or inadequate drainage of symptomatic disease.

Patients with type C cysts can be considered for anatomic hemihepatectomy of the dominantly affected liver lobe and concomitant fenestration of cysts in the remaining parenchyma. A clear understanding of the vascular anatomy, particularly hepatic inflow and outflow must be established by preoperative imaging to allow preservation of the liver remnant vasculature during the course of the operation (Fig. 2e). Due to the extent of cystic disease, parenchymal transection largely is performed through cysts and intracystic septa. Similar technical caveats discussed for type B cyst fenestration apply. Technical challenges in these patients result from the grossly distorted anatomy making identification and verification of vascular and biliary structures difficult. Postoperative complications such as ascites with or without venous outflow obstruction, bile leaks, and bleeding are more common than after fenestration alone. Hence, liver resection for type C cysts should be undertaken at centers with technical and multidisciplinary expertise.

Patients with type D cysts can be considered for liver transplantation. It is rare for a patient with PLD to have biochemical liver disease, thus even with massive cysts and hepatomegaly the vast majority of patients do not qualify for a deceased donor liver allocation under the current Model for End Stage Liver Disease (MELD) system. Recertification for select patients is possible with MELD exception point allocation, which is at the discretion of regional Organ Procurement and Transplantation Network review boards. Combined liver and kidney transplantation has been used in patients with ADPKD with both end stage renal disease and severe symptomatic PLD. Previous operative management of cystic liver disease increases morbidity of liver transplantation emphasizing the importance of a multidisciplinary approach and centralization of care for patients with PLD.

Cystic Hepatobiliary Neoplasms: Cystadenoma, Cystadenocarcinoma, Intraductal Papillary Mucinous Neoplasm of the Bile Duct

Phenotypic Features and Diagnostic Evaluation

Hepatobiliary cystadenoma is the most common cystic neoplasm of the liver with phenotypic similarity to pancreatic mucinous cystic neoplasms (MCN). Approximately 80% to 95% of all resected cystadenomas contain ovarian type stroma similar to MCN; patients with cystadenoma with ovarian type stroma are women. Cystadenoma without ovarian type stroma can occur in both men and women. Unlike simple cysts, the epithelium of cystadenoma consists of either columnar or cuboidal glandular lining with papillary projections and crypt like invaginations. Cystadenoma, with and without ovarian type stroma, can contain epithelial dysplasia, atypia, or metaplasia and both are considered to have neoplastic potential. The neoplastic cyst is surrounded by a dense pseudocapsule that pushes and displaces adjacent hepatic parenchyma allowing for enucleation. Typically, cystadenomas are at least partly intrahepatic and solitary but can be multilobulated. Usually, no communication exists between the cyst cavity and biliary system; however, bile ducts can be directly abutting the cyst pseudocapsule resulting in the possibility of fistulization. The true incidence of cystadenoma is unknown. Diagnosis cannot be confirmed without resection and there is likely an imaging overlap between a large proportion of patients with simple cysts and those with small cystadenomas without worrisome features. It is not uncommon to resect or biopsy a small incidental cyst during an unrelated liver directed operation and establish an incidental diagnosis of cystadenoma.

Cystadenocarcinoma is very rare and comprises less than 1% of primary hepatic malignancies. In a recent multiinstitutional study spanning 30 years, approximately 10% of patients with worrisome hepatobiliary cystic neoplasms who were selected for resection had cystadenocarcinoma and not cystadenoma. Factors associated with neoplastic progression to cystadenocarcinoma are poorly understood. Two possible pathways to malignancy are a time dependent malignant transformation from cystadenoma to cystadenocarcinoma and/or a different initial mutational composition that predisposes some cystic neoplasms to progress to carcinoma while others do not grow or transform. While there are case reports of cyst growth, progression of worrisome imaging findings including cyst complexity, mural nodule development, and/or wall thickening and enhancement, longitudinal studies evaluating a cohort of patients with biliary cystadenoma that allow an estimate of growth rate and the risk of malignant degeneration are not available.

Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is a solid mucin producing neoplasm that originates within the biliary tract of the hepatic hilus or intrahepatic bile ducts. Past descriptions included papillary cholangiocarcinoma and intraductal peripheral cholangiocarcinoma. IPMN-Bs are histologically and phenotypically similar to pancreatic IPMN. Papillary growth and mucin formation results in upstream biliary dilatation of the affected lobar or sectoral biliary system and can cause cystic dilatation of the peripheral bile duct to resemble a large neoplastic cyst. Unlike cystadenoma, IPMN-Bs demonstrate direct communication with the biliary system since it is involved by the neoplasm. Multiinstitutional resection series demonstrate a significant proportion (up to 90%) of high-grade dysplasia and invasive carcinoma in patients with IPMN-B and resection should be considered for all patients with this neoplasm.

Diagnosis of cystadenoma rather than simple cyst is suspected based on imaging. Both ultrasonography and contrasted cross-sectional imaging (CT and/or MRI) demonstrate findings typical for a complex cyst (Fig. 4). US findings concerning for a neoplastic cyst include internal septations, mural nodules or projections, intracystic debris, and/or a thick cyst wall. CT findings are similar with additional findings including Hounsfield units denser than water, fluid fluid levels, enhancing mural nodules or septations within the cyst, and/or an enhancing cyst wall. Advantages of MRI over US and CT is the ability to definitively characterize small cysts and intracystic fluid features. Fluid signal characteristics different than water suggest hemorrhagic products, proteinaceous/mucinous fluid, or the presence of subtle mural nodules/projections. Similar to CT, an enhancing cyst wall or solid element is concerning for a cystic neoplasm. The most common imaging findings in patients with cystadenoma include multilocular architecture and/or internal septations; these imaging findings are present in the vast majority of patients. Complex cyst wall features including nodularity and intracystic solid projections are less common and are concerning for malignant transformation.

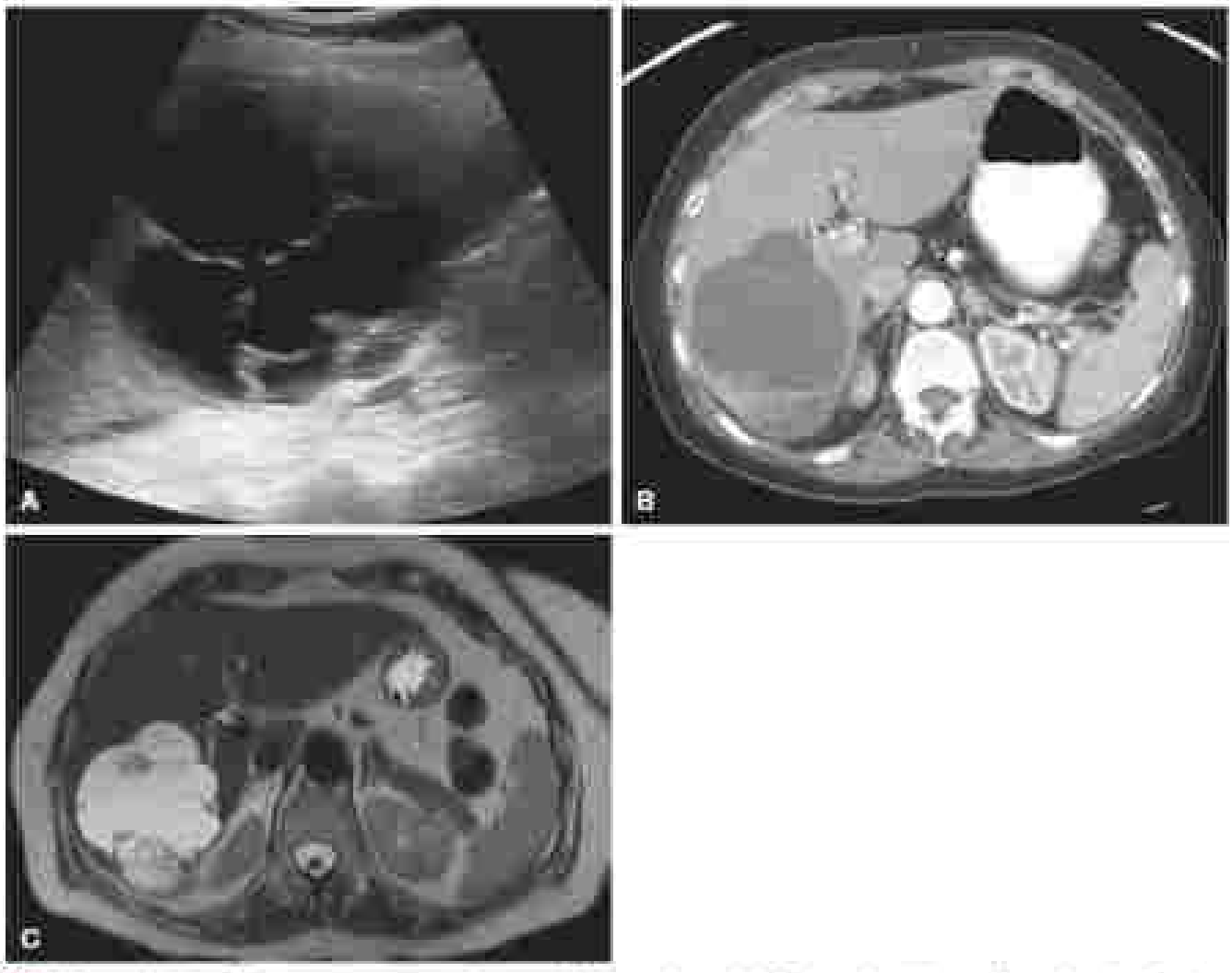

FIG. 4. Ultrasound (A) image findings consistent with complex cyst typical for cystadenoma including internal septations and hyperechoic projections and debris. Corresponding computed tomography (B) and magnetic resonance (C) images demonstrating multicystic intraductal complexity.

While no specific imaging findings are diagnostic for cystadenocarcinoma, increasing complexity of the cyst with soft tissue components including asymmetrical wall thickening with a solid component, a mural nodule, and/or papillary projections are concerning for malignant degeneration particularly if comparisons to previous imaging are available and these findings are new.

IPMN-B by definition involves the biliary system and communication with the bile ducts is frequently evident on imaging. Patients with intraductal papillary neoplasm only within the main biliary system have imaging findings consistent with pure biliary cholangiocarcinoma (Fig. 5). Patients with a cystic component from upstream biliary obstruction develop cystic dilatation with radiographic communication to the central bile ducts (Fig. 6). Endoscopic retrograde cholangiography can be useful in evaluation of IPMN-B. Papillary neoplasms can be directly visualized with cholangioscopy and the macroscopic neoplastic extent can be defined with cholangiography.

Cyst fluid analysis similar to fine needle aspiration of neoplastic cysts rarely assist with diagnosis or impact management. Carcinogenic antigen 19-9 (CA19-9) is expressed by normal biliary epithelium and is frequently elevated in patients with both simple cysts and neoplastic cysts. No specific value has been shown to discriminate between simple cysts and cystadenoma or between cystadenoma and cystadenocarcinoma. Other tumor markers are similarly neither sensitive nor specific. Biopsy of high risk features such as complex cyst wall components could be considered but is unlikely to change management in a patient considered for resection.

Management

The majority of patients with cystadenoma have imaging demonstrating a multilocular cyst wall or thin intracystic septations without worrisome cyst wall complexity. Management of these patients is controversial. The chance of malignancy in patients with these imaging findings is low; cross-sectional studies report the proportion of carcinoma in patients with cystic neoplasms selected for resection ranges between 2% and 10%. Long-term surveillance studies are lacking, but many patients with cystadenoma without worrisome features can be observed. Surveillance can be particularly prudent if the patient's age or comorbidity increases the risk of resection. If surveillance is selected for patients who would be candidates for resection, pragmatic adherence to a surveillance program is important. A number of case reports highlight the possibility of cyst growth and malignant degeneration over long (>10 years) surveillance intervals. Consequently, a recommended surveillance duration is undefined.

Among patients with cystadenoma selected for resection, enucleation is an appropriate and the most commonly used operative strategy. The plane between the cyst pseudocapsule and

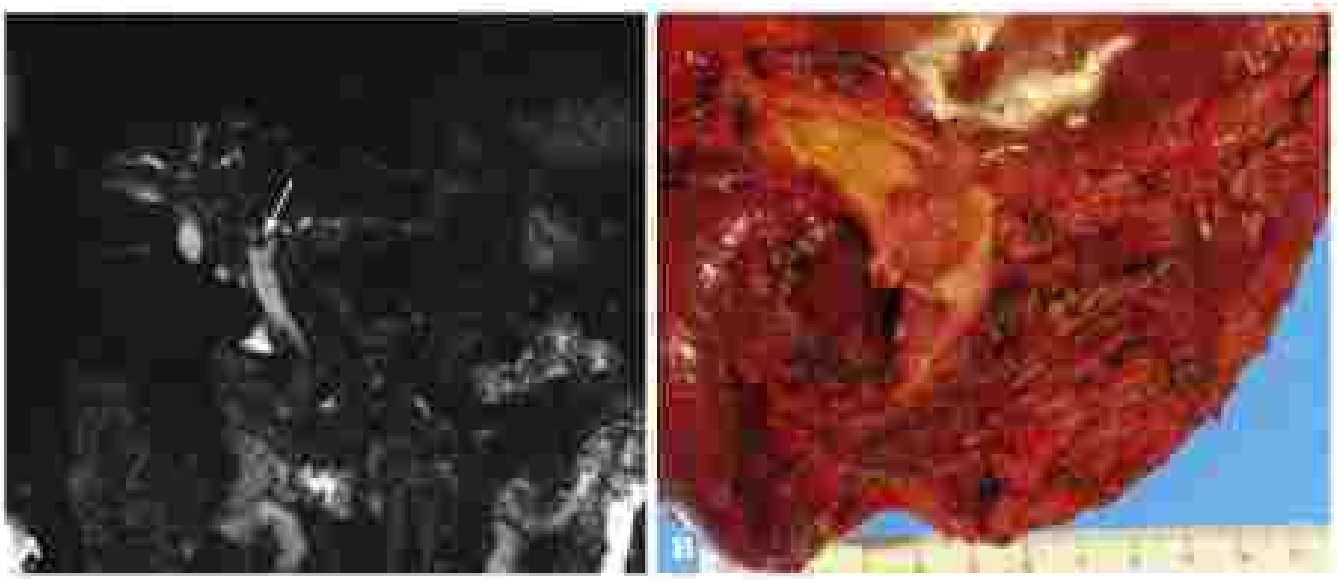

FIG. 5 Magnetic resonance cholangiography demonstrating a soft tissue filling defect at the bile bifurcation (A, arrow) typical for patients with intraductal only IPMN-B and corresponding neoplasm after resection (B).

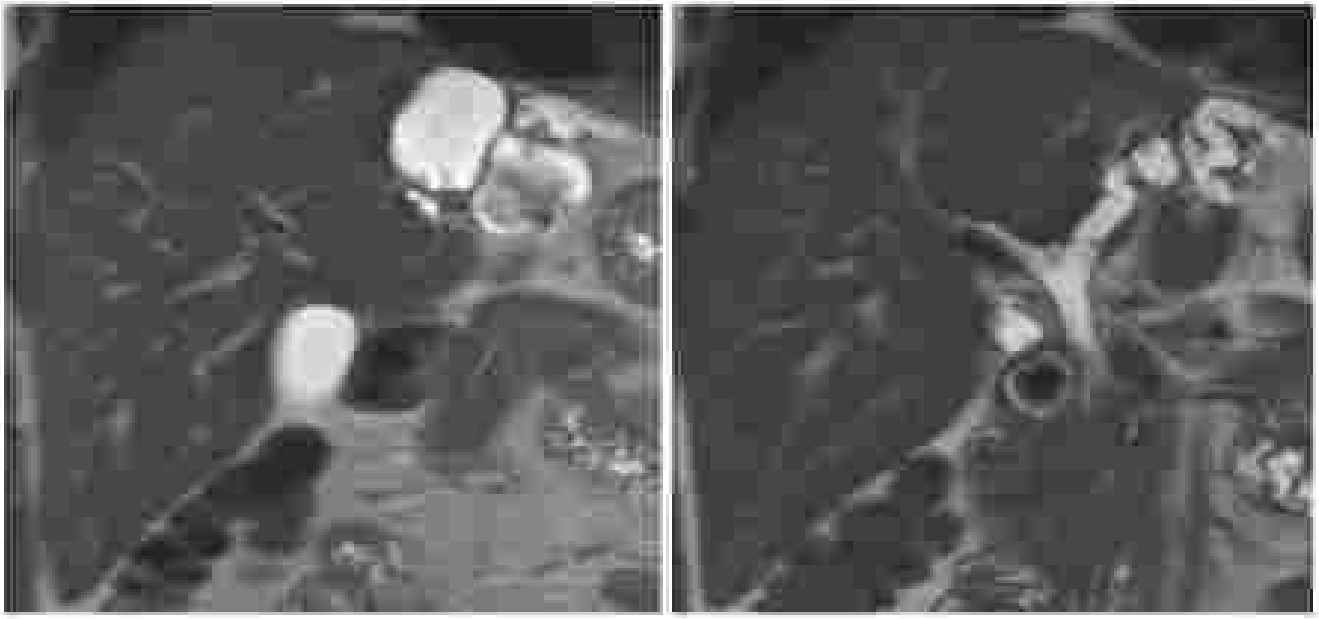

FIG. 6 Magnetic resonance imaging demonstrating IPMN-B with both cystic component and involvement of left hepatic duct. Left hepatectomy is indicated for resection of both left ductal and cystic components.

adjacent hepatic parenchyma is entered and pericystic dissection can be completed in a fairly avascular plane. Vascular and biliary structures frequently abut the intrahepatic portion of the pseudocapsule and, similar to the mass effect seen with simple cysts, both portobiliary pedicles as well as major hepatic veins can be distorted by cystadenoma. Pericystic dissection should aim at removing the cyst with preservation of major surrounding structures. Structures entering the pseudocapsule or densely adherent to it can be ligated. If a fistula with the biliary system is encountered, the intrahepatic radicles should be repaired or ligated to avoid a bile leak. Formal hepatic resection is rarely required for peripheral cystadenoma, but may be necessary for deeper intrahepatic cystadenomas. Since, by definition, the aim of cystadenoma resection is to eliminate the risk of malignancy or malignant transformation, cyst fenestration is contraindicated.

Patients with complex cyst wall features concerning for malignancy are considered for formal resection. If there is concern for malignancy, liver resection of both the cystic neoplasm and surrounding parenchyma to ensure a margin negative resection is performed. Similarly, patients with IPMN-B are treated by resection. Resection for IPMN-B depends on the location and extent of papillary portion of the neoplasm and the duct involved; resection should not be limited to the cystic component alone. Resections for main duct IPMN-B can include pancreaticoduodenectomy, common bile duct complex resection, or a combined hepatectomy and bile duct complex resection with reconstruction (just like cholangiocarcinoma type operations). Resection of intrahepatic IPMN-B typically requires anatomic hepatectomy to include both the biliary ductal and cystic components of the neoplasm. Resection of the cystic component without the intraductal component can result in tumor recurrence.

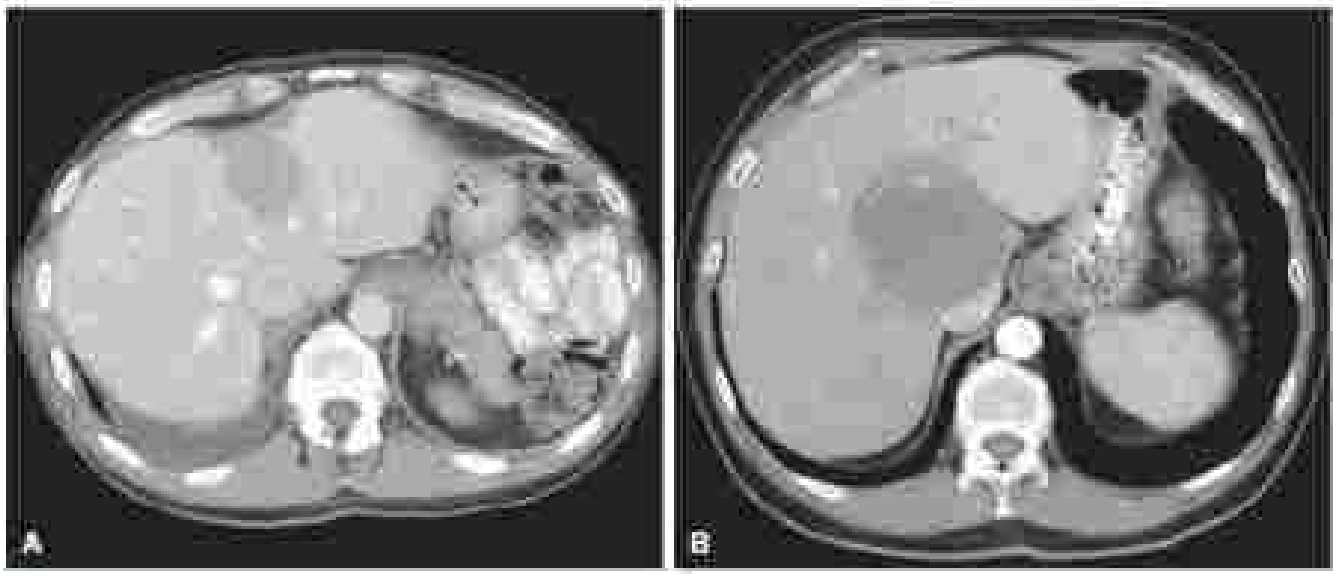

FIG. 3. Patients with malignancy can present with imaging characteristics that can be misinterpreted as cystic disease; both clinical history and imaging characteristics such as capsular retraction (A, patient with metastatic squamous cell cancer) or hepatic wall enhancement (B, patient with metastatic gastrointestinal stromal tumor) should raise suspicion of malignancy.

Cystic Malignancies

Both primary liver cancer (such as hepatocellular carcinoma and primary liver sarcoma) as well as metastases to the liver from primary colorectal, neuroendocrine, squamous cell, gastrointestinal stromal tumor, and others can demonstrate cystic features. The cystic wall of these lesions is complex, and they are distinguishable in most cases by any imaging modality from a simple cyst (Fig. 3). The combination of clinical history and imaging findings should raise suspicion for a cystic malignancy in patients with a personal history of cancer. Benign cysts typically do not grow (or do so slowly) and do not contain evolving and/or worrisome intracystic components during cancer surveillance. Persistent diagnostic equipoise between cystic malignancy and a simple liver cyst after review of cross sectional imaging is rare but can be resolved by biopsy. If the diagnosis remains elusive and the patient is a candidate for resection of a hepatic primary malignancy or metastatic disease, treatment planning should proceed as if these were malignant and not simple cysts, in other words, by a formal hepatic resection.

Miscellaneous Cysts

Biliary Hepatic Foregut Cysts

Ciliated hepatic foregut cysts (CHFCs) are very rare. CHFCs are typically located in segment four and abut the gallbladder. Histologic diagnosis is confirmed by presence of ciliated, pseudostratified, columnar epithelium covered by three layers of connective tissue, smooth muscle, and a fibrous capsule. The majority of patients with resected CHFCs present incidentally; symptoms, if present, are similar to patients with other cystic diseases of the liver. Patients with imaging findings atypical for a simple cyst or symptoms have been selected for resection. If resection is pursued, enucleation rather than fenestration should be performed. To date, five cases of squamous cell carcinoma presumably as a result of malignant transformation from squamous metaplasia within CHFCs have been reported.

Traumatic Cysts

Traumatic cysts are a rare complication of prior hepatic trauma or invasive procedures. They may result from resolving hematoma or a contained bile leak (biloma). Consequently, these are pseudocysts and lack an epithelial lining. The imaging appearance is similar to simple cysts, except a fluid–fluid level may be present if blood products are present in the cyst. The majority are incidental and do not require treatment. Rare patients with a symptomatic cyst (usually from mass effect) are treated similar to simple hepatic cysts. Percutaneous drainage can be attempted. If a biloma is identified, percutaneous drainage and endobiliary decompression will frequently lead to resolution. If cyst resolution cannot be achieved with percutaneous techniques, either laparoscopic or open cyst fenestration is reasonable. Similar to the operative management of simple cysts, if a biloma is present, identification, and suture ligation, of the biliary radicle should be performed to prevent bile leak or recurrence.

Hepatic Pseudocysts

Also rare, hepatic pseudocysts can develop during an episode of acute pancreatitis. These cysts have no epithelial lining. They are thought to occur as a result of fluid dissection into the hepatoduodenal ligament and the leaves of the gastrohepatic ligament. No therapy is necessary, as these typically disappear following resolution of the pancreatitis.

Suggested Reading

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MANAGEMENT OF ECHINOCOCCAL CYST DISEASE OF THE LIVER

[illegible] and D[illegible], MD, MRA, FAC[illegible], and Ibrahim Yakubu, MD, PhD

Human echinococcosis is a zoonosis caused by larval forms of tapeworms, cestodes found in the small bowel of carnivores. Hydatid cysts are most commonly caused by two species in humans, *E. granulosus* and *E. multilocularis*, which cause cystic and alveolar echinococcosis, respectively. The life cycle of the echinococcal parasite involves a definitive host (a dog or a cat) and an intermediate host (commonly a sheep). Humans become accidental intermediate hosts. Hence, the disease is endemic in sheep-grazing areas of the world such as Mediterranean, the Middle East, South America, Australia, and East Africa.

EPIDEMIOLOGY

Cystic Echinococcosis

Cystic echinococcosis is caused by the larvae of parasite *E. granulosus* (Table 1). The hydatid cyst is mainly located in the liver (60%) or lungs (30%), but occasionally also found in the kidney, spleen, and brain in about 2% of cases. The oncospheres (the larvae) transform into the metacestodes, which implant into the organ and grow into cysts with germinal, outer, and laminated layers. Echinococcal cysts are surrounded by pericyst (adventitia) from the peripancreatic tissue that surrounds the larval endocyst. The endocyst is composed of an outer acellular layer and an inner germinal layer that forms protoscolices and host capsules (Fig. 1). Protoscolices are infectious agents that develop into the adult tapeworm. A significant amount of these scolices floats freely in the hydatid fluid forming the so-called hydatid sand. The hydatid liquid is alkaline, with containing Na, K, Cl, and CO_3, similar to that of the host's serum.

Alveolar Echinococcosis

Echinococcus multilocularis is a small cestode (0.5–4.5 mm) that lives in wild carnivores (sylvatic cycle) or domestic dogs and cats (synanthropic cycle) (Table 1). The adult tapeworm reside in the small bowel of the definitive hosts, where gravid proglottids release eggs that are passed in the feces. Humans, aberrant intermediate hosts, become infected by ingestion of embryonated eggs. It can happen through direct contact with the definitive host or through indirect contamination of food or water. The parasite travels through the blood and settles in the liver in 70% of cases by developing an alveolar structure made up by several vesicles with the diameter range from less than 1 mm up to 15 to 20 cm. Each vesicle has a wall consisting of a germinal and a laminated layer. These lesions may be complicated by central necrosis, producing a cavity or pseudocyst after it liquefies. This disease is characteristic to the Northern Hemisphere, with the main endemic regions being Central Europe, Russia, Turkey, China, Japan, and North America. This form of disease clinically corresponds to a slow growing liver cancer with 75% of lesions located in the liver primarily. Alveolar echinococcosis (AE) is fatal in the absence of appropriate treatment, with 5 year mortality reaching 70% and 10 year mortality rate reaching 90% in untreated patients.

PRESENTATION AND DIAGNOSIS

The disease has characteristic long asymptomatic phase of growth. The larval growth averages about 1 to 15 years. It usually starts in the right lobe of the liver where metacestodes establish themselves. With time, the infection metastasizes via blood to lung, brain, and bones as well as becomes locally advanced to the abdomen, retroperitoneum, and diaphragm. In advanced stages, patients present with symptomatic disease with complaints of fatigue, weight loss, hepatomegaly, cholestatic jaundice, and abdominal pain. Occasionally, liver failure may occur resulting from portal hypertension, ascites, and splenomegaly from the compressive effect of the mass.

Clinical evaluation and noninvasive radiologic imaging are critical for decision making in the management of most patients with hydatid liver disease. Addition of the epidemiologic findings, exams, and detection and serology helps to provide a complete picture of disease.

Liver lesions are usually clinically silent and detected incidentally on abdominal ultrasonography (US) or computed tomography (CT) performed for other clinical reasons. Occasionally, in endemic areas, the disease can present with symptoms suggestive of the hydatid disease if there is a history of exposure to sheepdogs. Abdominal US is considered the gold standard for evaluation of the disease extent including the number of cysts, location, dimensions, and viability. The World Health Organization (WHO) established a standardized classification system for hepatic cysts based on US imaging (Table 2, Fig. 2). Color Doppler may be incorporated in ideal light on biliary connection or vascular infiltration.

US features of AE are consistent with a huge lesion with large central necrosis surrounded by a hyperechogenic ring corresponding to the parasitic fibrous tissue. AE also can present as a nodular homogeneous form of a hyperechogenic nature ("young AE") or as a pseudocystic form ("a huge AE with massive necrosis"). Abdominal CT confirms the morphologic aspects of AE. It is helpful to specify the number, size, and localization of the lesions in the liver. It is the best technique to identify the pattern of calcification and to delineate the mass precisely particularly the posterior border. It typically features a lesion with irregular borders, a heterogeneous content with a mosaic of various densities without significant enhancement with intravenous contrast administration. Magnetic resonance imaging is considered the standard to further delineate anatomy and adjacent structures as well as to ascertain cases with noncalcified lesions. The multifocal form is considered pathognomonic of AE. This is best visualized on T2 weighted sequences as a bunch of grapes of honeycomb-like pattern at the periphery corresponding to the parasitic vesicles. They are also the best to most closely differentiate between necrotic liquefactions and areas of fibrosis and parasitic tissue.

Preoperative cholangiography can be recommended in certain cases to assess the presence of communication between the biliary tree and the alveolar lesions. In cases with alveolar echinococcosis it is imperative to rule out extrahepatic involvement by obtaining a chest x-ray and CT scan of head. Recent studies also advise to obtain fluorodeoxyglucose positron emission tomography scanning to evaluate the parasite metabolic activity.

The WHO developed a so called PNM, microscopically recognized classification system to standardize disease diagnosis and treatment strategies in which P refers to the extent of parasite localization inside the liver, N establishes the involvement of neighboring organs, and M evaluates the absence (M0) or presence (M1) of distant metastases (Box 1).

Immunodiagnosis has a complementary role to a radiographic diagnosis that is used for initial diagnosis and a follow up of treatment. The enzyme linked immunosorbent assay replaced all other traditional immunodiagnostic methods such as Casoni intradermal test, complement fixation test, indirect hemagglutination test, indirect immunofluorescence antibody test, immunoelectrophoresis and latex agglutination test.

It is based on detection of the hydatid antigens extracted from the cyst such as fluid antigen B and antigen 5 (Ag5) from *E. granulosus*. It is more specific for *E. multilocularis* using Em2plus-enzyme linked immunosorbent assay which is based on Em2 antigen form metacestode and EMY-162 recombinant antigen. However, this test remains positive for years in inactive lesions after medical treatment because

TABLE 1 Hydatid Disease: Epidemiology and Characteristics

	Cystic Echinococcosis	Alveolar Echinococcosis
Causative agent	*Echinococcus granulosus*	*Echinococcus multilocularis*
Definitive hosts	Dogs and other canids (coyotes, dingoes, red foxes)	Red foxes, arctic foxes, coyotes, dogs, and cats
Intermediate hosts	Ungulates	Rodents
Geographic distribution	Worldwide	North America, northern and central Eurasia
Worldwide incidence	1–200/100,000	0.03–1.2/100,000
Organ localization	Mainly liver and lungs	Mainly liver
Characteristics of hydatid lesions	Large cysts, spherical, fluid filled, multilocular vesicles (diameter: 1–15 cm) Old cysts: internal septations, daughter cysts Three layered structure: germinal layer, laminated layer, pericyst	Alveolar-like pattern, with numerous vesicles (1–4 mm: 15 μm to diameter) and surrounding dense connective tissue; no cyst fluid, sometimes central necrosis
Type of growth in human organs	Concentric expansion	Tumor like, infiltrative behavior
Therapeutic options		Surgery, chemotherapy, endoscopic percutaneous interventions

From Vuitton L, et al. Hepatic echinococcosis: Clinical and therapeutic aspects. World J Gastroenterol. 2015;21(10):2984–2998.

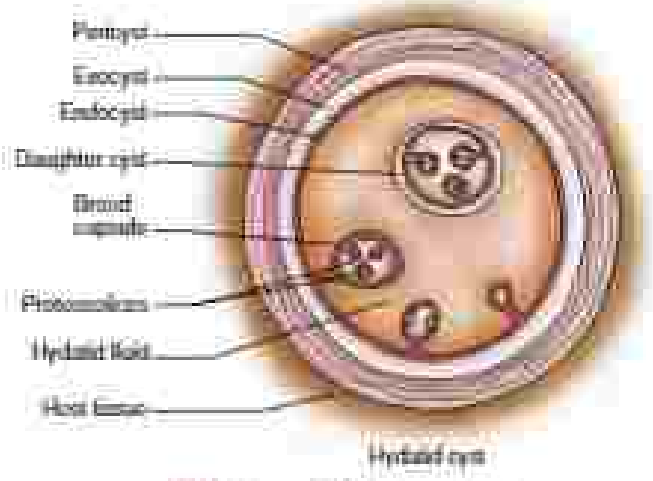

FIG. 1 Structure of echinococcal cyst.

8.6, coming from the laminated layer of the parasite, which persists in the calcified lesions. The surgical excision of the inactive lesion would unconvert a lesion to negative.

Em18 and Em18, new antigens, were developed to differentiate between active and inactive lesions. All lesions are classified into three groups based on serologic and US data: active hepatic lesions; calcified lesions; and without any evidence of hepatic lesions. Some studies identified elevated levels of immunoglobulin G1 and immunoglobulin G4 antibodies that become seronegative with treatment and recur with disease reactivation.

Liver needle biopsy can be performed in uncertain cases to help with histopathological diagnosis. Polymerase chain reaction of the specimen can identify DNA, whereas reverse transcriptase polymerase chain reaction can assess parasite viability with a good positive predictive value.

TREATMENT

There are several therapeutic modalities available to treat hepatic hydatid disease with the goal to achieve complete control of disease by eliminating the parasite and prevent recurrence. It involves chemotherapy, surgery, and percutaneous treatments. The recent development in chemotherapy and surgery improved life expectancy from 5 years in 1970s to 20 years in 2005.

Chemotherapy

The two benzimidazoles that are the most commonly used chemotherapeutic agents for hepatic hydatid disease are mebendazole and albendazole. Their mechanism is based on disruption of the absorption of glucose through the wall of the parasite, causing the glycogen depletion and degenerative changes in echinococcal mitochondria and endoplasmic reticulum. It is a parasitostatic treatment. Albendazole has better bioavailability because of better absorption in the gastrointestinal tract. It is recommended to be used alone in small CE1/3m liver cysts or for inoperable patients. More typically, it is used in combination with puncture, aspiration, injection, and respiration (PAIR) or surgery to prevent secondary disease. No medical treatment is recommended for the inactive or calcified asymptomatic cysts. The typical dose of albendazole is 10 to 15 mg/kg per day in two divided doses for patients weighing less than 60 kg and in a dose of 400 mg twice daily for patients weighing more than 60 kg. Mebendazole is given as a daily dose of 40 to 50 mg/kg in three divided doses administered continuously for 3 to 6 months. Their efficacy can be further enhanced with administration of praziquantel at 40 mg/kg once a week.

The size and stage of cysts are the key factors determining the duration of treatment and the likelihood of response to chemotherapy. Complete cure is observed to only about one-third of patients with chemotherapy alone. Treatment effect is evaluated both clinically and radiographically (reduction in cyst size >25%, membrane separation, or cyst calcification). The most common side effects include nausea, hepatotoxicity, neutropenia, alopecia, and leukopenia. Pregnancy, chronic hepatic disease and bone marrow depression are contraindications to chemotherapy. "Watch and wait" strategy is recommended for CE4 and CE5 cysts.

Surgical Management

PAIR

This approach was first proposed by a Tunisian team in 1987 as an alternative to the surgical treatment. Since its development, more

TABLE 2 World Health Organization Informal Working Groups on Echinococcosis Classification of Hepatic Echinococcal Cysts

Class	Ultrasound Features	Status	Fertility	Size	Treatment Approaches
CL	A unilocular active lesion with uniform anechoic content not clearly delimited by a hyperechoic rim, round or oval, usually small	Active	Nonfertile	CLa: <5.0 cm, CLm: 5–10 cm, CLE: >10 cm	Needs diagnosis
CE1	A unilocular simple active cyst with uniform anechoic content, may exhibit line echoes resulting from shifting of hydatid capsules called hydatid sand or *rive flake* sign, with visible cyst wall, round or oval	Active	Usually fertile	CE1a: <5.0 cm, CE1m: 5–10 cm, CE1E: >10 cm	<5 cm: ABZ >5 cm: ABZ + PAIR
CE2	A multivesicular, multseptated active cyst with separations producing *wheel like* structures, and daughter cysts (*rosette like* or *honeycomb like*)	Active	Usually fertile	CE2a: <5.0 cm, CE2m: 5–10 cm, CE2E: >10 cm	PT or surgery + ABZ
CE3	A unilocular transitional cyst that may contain daughter cysts, appears as an anechoic cyst with the detachment of laminated membrane from the cyst wall visible as floating membranes or as water lily sign, may be less rounded because of decreased intracystic fluid pressure	Transitional	Starting to degenerate	CE3a: <5.0 cm, CE3m: 5–10 cm, CE3E: >10 cm	PT, PAIR, or surgery + ABZ
CE4	A heterogeneous hyperechoic or hyperechoic multicystic cyst without daughter cysts, may show a *bull's eye* sign indicative of degenerating membranes	Inactive	Nonfertile	CE4a: <5.0 cm, CE4m: 5–10 cm, CE4E: >10 cm	Surgery + ABZ, or watch and wait
CE5	An inactive cyst with thick calcified wall that is arch shaped, with a cone shaped shadow, diagnosis is usually uncertain	Inactive	Nonfertile	CE5a: <5.0 cm, CE5m: 5–10 cm, CE5E: >10 cm	Surgery + ABZ, or watch and wait

ABZ, albendazole; *PAIR*, percutaneous intervention; *PAIR*, puncture, aspiration, injection, reaspiration; *PT*, percutaneous treatment.

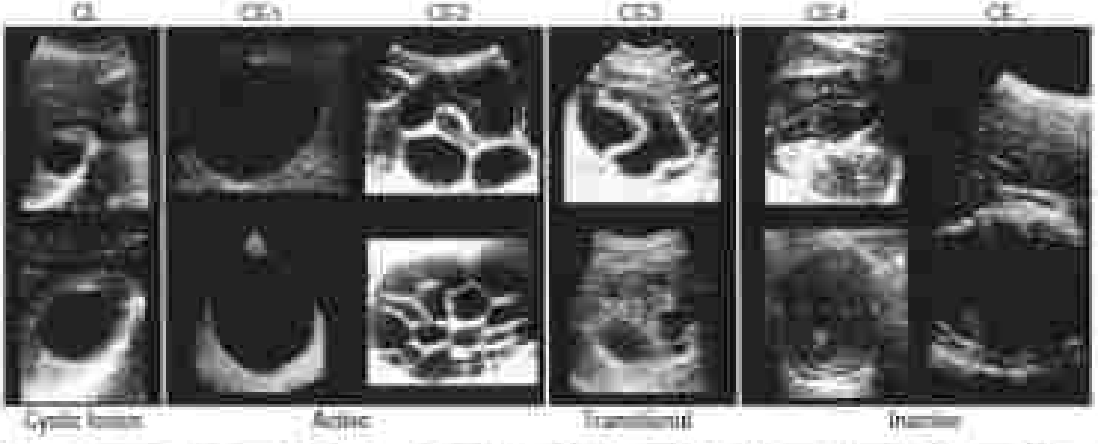

FIG. 2 [illegible]

than 3000 cases were published in the literature and discussed at the WHO Meeting during the XVIII International Congress of the Hydatidology Lisbon in 1997. It is a percutaneous drainage of echinococcal cysts located in the liver performed with a fine needle (for cysts <5 cm) or a catheter (for cysts >5cm), followed by the administration of a protoscolicidal agent in the cyst cavity for scolicidal effect. This technique can be further modified by placing and retaining the catheter in the cyst after the procedure for drainage or by curettage if numerous and large daughter cysts are present (percutaneous puncture with drainage and curettage). PAIR is usually performed under radiographic guidance using US or CT. Patients with the cystic echinococcal disease, with anechoic lesion 5 cm or greater in diameter

BOX 1 PNM Classification

PX Primary Tumor Cannot Be Assessed

1. P0 No detectable tumor in the liver
2. P1 Peripheral lesions without proximal vascular and/or biliary involvement
3. P2 Central lesions with proximal vascular and/or biliary involvement of 1 liver lobe
4. P3 Central lesions with bilateral vascular or biliary involvement of both lobes and/or with possible infiltration of 2 of 3 hepatic veins
5. P4 Any liver lesion with extension along the vessels (inferior vena cava, portal vein and arteries) and the biliary tree

NX Not Evaluable

1. N0 No regional involvement
2. N1 Regional involvement of contiguous organs or tissues like diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, parietal wall, muscles, skin, bone, pancreas, regional lymph nodes, liver ligaments, kidney

MX Not Completely Evaluable

1. M0 No metastasis to the lung and/or CNS (chest radiograph and cerebral CT negative)
2. M1 Metastasis to the lung and/or CNS

CNS, central nervous system; CT, computed tomography.

(CE1) in and 1) cysts with daughter cysts (CE2), and/or with detachment of membranes (CE3), multiple cysts and infected cysts are good candidates for PAIR. It is also recommended for pregnant women, children older than 3 years, patients who cannot undergo surgery, or those who fail to respond to medical treatment alone. The contraindications for PAIR are patients with lesions that are not accessible or to many locations in the liver, cysts communicating with the biliary tree, or open into the abdominal cavity, as well as inactive or calcified lesions.

PAIR has advantage of the minimally invasive approach, reduced hospitalization time and improved efficacy of chemotherapy. It comes, however, with the risk of anaphylactic shock, secondary echinococcosis associated with spillage of the protoscolices, chemical cholangitis, biliary fistulas resulting from the communication with the biliary tree, and systemic toxicity of scolicidal agent such as 95% alcohol or hypertonic saline (15% or more).

Chemical prophylaxis with albendazole is recommended 24 to 48 hours before intervention and 15 to 30 days after intervention to reduce the risk of disease recurrence and intraperitoneal seeding of infection. The procedure starts with aspiration of cyst fluid (1/3–1/5 mL) followed by the serologic tests for the presence of protoscolices and biochemical analysis of fluid. It is recommended to check bilirubin level in the cystic fluid on aspiration to rule out connection with the biliary tree before injection of the agent. Contrast medium is injected intracystically and confirmed by cystography. The solution is reaspirated after 5 minutes. The surveillance is performed using parasitologic, biochemical, serologic, immunologic, and US monitoring every week for the first month and every other month for the first year. Then, the interval is increased to every year for 10 years. Chest radiograph is recommended 1 year after PAIR and then every other year. CT scan of chest, abdomen, and pelvis should occur after 5 and 10 years. Endoscopic retrograde cholangiopancreatography with cystolithography is recommended if communication with the biliary tree is revealed during the procedure.

Surgical Resection

Surgery must be carefully evaluated for complicated cysts, particularly for: (1) large CE2 (CE3b) cysts with multiple daughter vesicles, (2) single liver cysts that may rupture spontaneously or as a result of trauma, (3) infected cysts, when percutaneous treatment is not available, (4) cysts communicating with the biliary tree, and (5) cysts exerting pressure on adjacent vital organs. It is contraindicated in inactive asymptomatic, difficult to access, and very small cysts.

Surgical options are further divided into radical and conservative approaches. Radical procedures include a total removal of the cyst, so-called pericystectomy. It carries an inherent higher operative risk but is associated with a lower risk of recurrence. A conservative approach with unroofing or capitonnage has a higher likelihood of recurrence, with ranges from 2% to 25%. Closed total pericystectomy removes the cyst in its entirety without spoiling the cyst. Open total pericystectomy encompasses procedure of sterilization of metacestodes with protoscolicidal agents, evacuation of the cyst content followed by removal of the pericystic tissue. Operative mortality varies from 0.2% to 4%. It is associated with major complications such as postoperative hemorrhage, cholangitis, sepsis, and fistula formation.

A benzimidazole agent is used to reduce the risk of anaphylaxis and secondary hydatid disease. It is administered 1 day before surgery to 1 month after surgery.

The first laparoscopic treatment was described in 1992. Since then, this approach has gained wider acceptance. It includes cystostomy and partial pericystectomy. The cystostomy involves aspiration of the cyst, instillation of a scolicidal substance, evacuation of the parasitic material, and partial resection of the pericyst. Several different methods are applied to the residual cavity; those most commonly described include marsupialization, capitonnage, omentoplasty, and internal drainage. The minimally invasive approach shortens the length of hospital stay to 1 to 8 days compared with open laparotomy; however, it is not different from the percutaneous drainage. The perioperative mortality varies from 0% to 0.5% for laparoscopic pericystectomy and 0% to 0.9% after percutaneous drainage. The most common complications are based on several factors, including age, size of the cyst, preoperative complications, and biliary cyst communication. The bile leak rate was reported to be about 6%, with most healed spontaneously without any additional intervention. The postoperative recurrence rate ranges from 0% to 11% for laparoscopic cases, 4.6% to 25% for open conservative surgery, and 0% to 0.63% to radical surgery.

The potential limitations of laparoscopic treatment are the fear of intraoperative spillage of cyst content, the possibility of anaphylactic shock, peritoneal seeding, and potential bleeding; however, clinical studies have showed a low incidence of intraoperative spillage. Despite that, laparoscopic approach suits better for peripherally and anteriorly location liver lesions.

The meta-analysis comparing laparoscopic to open approach showed no difference in cure rate, complications, mortality, and recurrences. The rate of conversion from laparoscopic to any type of open surgery ranges from 1.7% to 3.3%. The main reasons for conversion included a life-threatening bleeding, cystic rupture, irremovable residual daughter cysts, deep cystic locations or adjacent to the inferior vena cava, and intraoperative spillage of cyst contents. There are no prospective randomized trials directly comparing these two approaches.

A meta-analysis of 21 studies that compared 749 patients who received chemotherapy only and PAIR to 952 patients treated with surgery alone demonstrated that the former treatment approach is more effective than surgery. It was associated with lower morbidity and mortality, decreased recurrence risk, and a shorter hospital stay.

A small randomized trial on 50 patients that compared medical treatment with percutaneous drainage vs surgery alone concluded that percutaneous treatment is a safe and effective treatment choice for uncomplicated hydatid disease.

Management of Alveolar Echinococcosis

Approach to the alveolar echinococcosis differs from the *E. granulosus* as because it requires a multidisciplinary, more aggressive approach. Surgery is the first choice option for all qualified patients. Radical

resection of the entire hepatic lesion is the only curative approach. The likelihood of radical resection is determined by the WHO Informal Working Group on Echinococcus PNM classification system (Box 1). Unfortunately, only about 25% to 40% of patients have resectable disease. During the past 20 years, AE has become the fourth most common indication for liver transplant resulting from cholestatic disease in Turkey.

Palliative liver surgery is contraindicated; hence, liver transplant has been used since 1986 for advanced unresectable cases. The indications for liver transplant include the presence of liver failure and recurrent life-threatening cholangitis in the absence of extrahepatic manifestation of liver disease. Positron emission tomography is recommended to diagnose residual/recurrent lesions after liver transplantation. Presence of extrahepatic lesions before transplantation and prolonged immunosuppression are two main risks factors for recurrence. The suppression of cellular immunity leads to the uncontrolled growth of the parasite posttransplantation.

Chemotherapy should be carried out for at least 2 years after surgery and the patient should be monitored for at least 10 years because of high risk of recurrence in posttransplant immunosuppressed patients.

Therapy with benzimidazoles has resulted in an increased 10-year survival rate of approximately 80% compared with the 4% to 25% in historical untreated cohorts.

The largest study from one endemic center in Turkey reports results on 27 patients who underwent liver transplantation. The number of patients undergoing liver transplant for echinococcosis has decreased significantly in central Europe since early 2000s because of advances in imaging modalities. Recent systematic review (Abakhar- an et al., 2018) identified 36 studies describing their experience with liver transplantation. Of these patients, about 17% had undergone palliative partial hepatectomy before transplantation. Seventeen percent of patients had preoperative distant metastasis.

Six studies from China presented their experiences in ex vivo liver resection and autotransplantation for patients with end-stage disease that eliminates the need for immunosuppression. It usually involved the removal of the entire diseased liver with replacement of the infrahepatic vena cava by artificial blood vessels and transplantation of the normal liver tissue graft with reconstruction of hepatic artery and the portal vein.

Overall, earlier diagnosis for liver transplant, pretransplant and posttransplant benzimidazole therapy, minimal immunosuppression regimen, and close surveillance is crucial to achieve acceptable long-term results.

Suggested Readings

Brunetti E, Kern P, Vuitton DA, Writing Panel for the WI. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16.

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Management of Liver Hemangiomas

Ammar A. Jamil, MD, and Matthew J. Weiss, MD, FACS

Liver hemangiomas are the most commonly diagnosed solid benign tumors of the liver, with an incidence of approximately 20% in the general population. With advancements in imaging techniques and increased utilization of cross-sectional imaging, hepatic hemangiomas are now being diagnosed quite frequently. Females are most susceptible to having these tumors (female to male ratio of 5:1) and they tend to occur in the third to fifth decades of life. These tumors have a benign course, and therefore patient management is often driven by their symptomatology and the risk of complications.

PATHOGENESIS AND PATHOLOGY

The etiology of hepatic hemangiomas remains unclear. It is suggested that these tumors are either congenital lesions of the liver that are complicated with vascular ectasia or are an acquired abnormality of the normal hepatic vasculature resulting in atypical enlargement of these vessels. Though debatable, it has been proposed that angiogenic factors play an important role in the pathogenesis, which is supported by reports of tumor regression upon administration of antivascular endothelial growth factor antibodies. The strong predisposition for female incidence is also suggestive of a hormonal association. Estrogen receptors have been seen on the surface of hemangiomas and increased rate of growth has been observed when the patients are on steroid therapy, oral contraceptives, or during pregnancy. Currently, the mechanism by which these hormones contribute to the formation or progression of these tumors remains largely unknown.

Grossly, hepatic hemangiomas are well-defined, soft, and dark tumors, while microscopically they demonstrate a single layer of endothelium lining with dilated, cavernous, vascular channels surrounded by thin connective tissue containing occasional calcification and fibrosis. The most common location for hepatic hemangiomas is the right lobe of the liver; however, they can occur anywhere in the liver. At the time of diagnosis, a majority of these tumors are small (<3 cm) and are commonly referred to as capillary hemangiomas. A majority of these smaller tumors is diagnosed incidentally and only around 10% increase in size on follow-up. Symptomatic hemangiomas are more likely to be medium (3–5 cm) or giant (>5 cm) sized. Of note, large tumor size alone in the absence of symptoms is not an indication for surgical resection.

Clinical Presentation

The majority of hepatic hemangiomas are diagnosed incidentally on cross-sectional imaging (Figs. 1–4). Approximately 50% to 90% of patients are asymptomatic at the time of diagnosis. The likelihood of symptoms increases with the increased size of the lesion. Symptomatic lesions often present with vague, nonspecific symptoms including abdominal pain, nausea, vomiting, and early satiety. Giant hemangiomas can present with signs related to distortion of the hemangioma, stretching of a hepatic capsule, or diaphragmatic irritation including right shoulder pain or abdominal pain on deep inspiration. Additional symptoms due to mass effect on the stomach, duodenum, and the biliary tree include early satiety, gastric outlet obstruction, and obstructive jaundice. It is vital for the treating surgeon to evaluate these patients thoroughly for symptoms associated with the hemangioma, given that the symptomatic nature of the lesion is one of the most common indications for surgical resection.

One rare but life-threatening complication of large hepatic hemangiomas is a spontaneous rupture. It is associated with significant morbidity resulting from disseminated intravascular coagulopathy, hypovolemic shock, and a high mortality of over 30% has been reported. Another complication of large hepatic hemangiomas is Kasabach-Merritt (hemangioma thrombocytopenia) syndrome, which occurs when a large, rapidly growing lesion traps platelets, resulting in consumptive thrombocytopenia, which progresses to consumptive coagulopathy and eventually disseminated intravascular coagulation. Furthermore, when large liver lesions can lead to arteriovenous shunting that can lead to congestive heart failure.

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The majority of hepatic hemangiomas are diagnosed incidentally on cross-sectional imaging (Figs. 1–4). Approximately 50% to 90% of patients are asymptomatic at the time of diagnosis. The likelihood of symptoms increases with the increased size of the lesion. Symptomatic lesions often present with vague, nonspecific symptoms including abdominal pain, nausea, vomiting, and early satiety. Giant hemangiomas can present with signs related to distortion of the hemangioma, stretching of Glisson's capsule, or diaphragmatic irritation including right shoulder pain or abdominal pain on deep inspiration. Additional symptoms due to mass effect on the stomach, duodenum, and the biliary tree include early satiety, gastric outlet obstruction, and obstructive jaundice. It is vital for the treating surgeon to evaluate these patients thoroughly for symptoms associated with the hemangioma, given that the symptomatic nature of the lesion is one of the most common indications for surgical resection.

One rare but life-threatening complication of large hepatic hemangiomas is a spontaneous rupture. It is associated with significant morbidity resulting from disseminated intravascular coagulopathy, hypovolemic shock, and a high mortality of over 30% has been reported. Another complication of large hepatic hemangiomas is Kasabach-Merritt (hemangioma thrombocytopenia) syndrome, which occurs when a large, rapidly growing lesion traps platelets, resulting in consumptive thrombocytopenia, which progresses to consumptive coagulopathy and eventually disseminated intravascular coagulation. Furthermore, when large these lesions can lead to arteriovenous shunting that can lead to congestive heart failure.

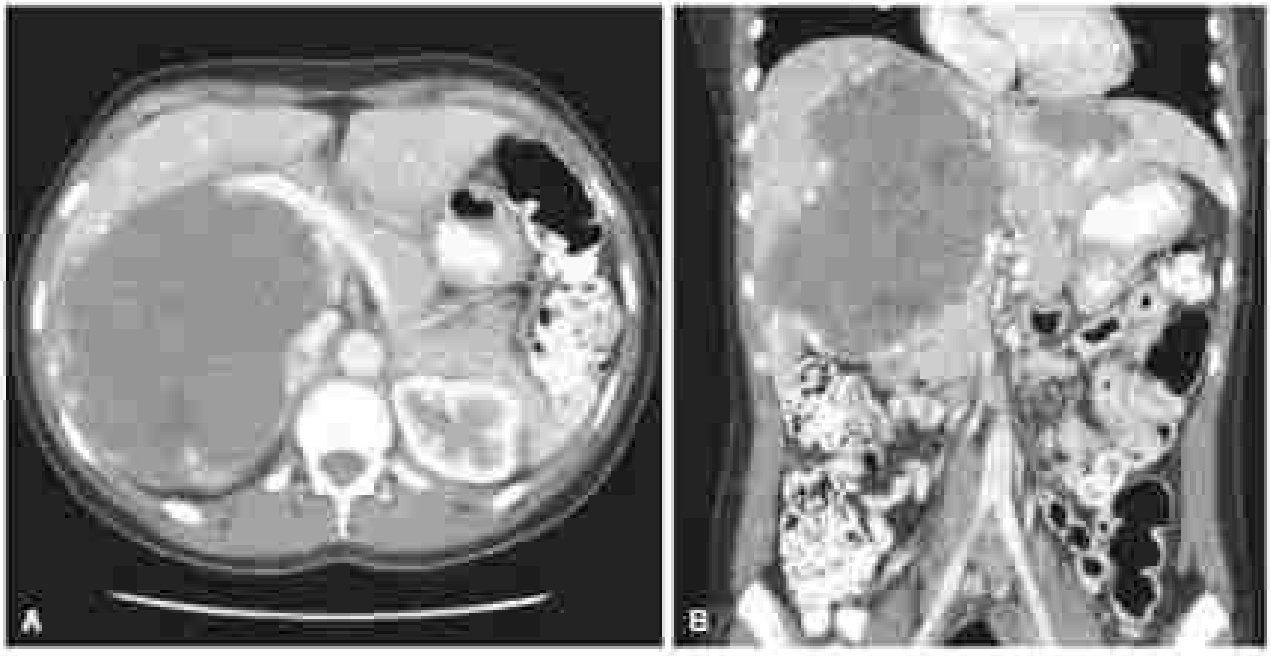

FIG. 1 Axial (A) and coronal (B) computed tomography demonstrating multiple hepatic hemangiomas in a 45-year-old woman. A large hepatic hemangioma is seen in the right lobe of the liver.

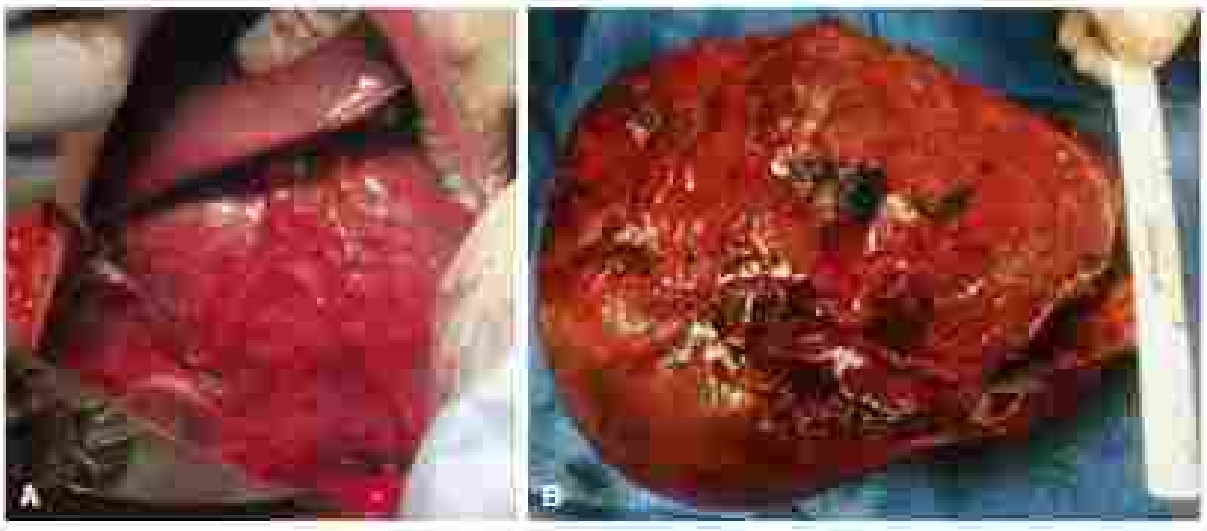

FIG. 2 Intraoperative images of a giant cavernous hepatic hemangioma in the right lobe of the liver extending into the caudate lobe. The patient was initially managed via surveillance; however the tumor grew significantly. On follow-up the patient reported epigastric pain, early satiety and was hypotensive and tachycardic upon lying down.

Physical examination is usually negative for findings unless the hemangioma is large enough that it becomes palpable in the right upper quadrant. Laboratory investigations including CA19-9 (carcinogenic antigen 19-9), carcinogenic embryonic antigen, and alpha-fetoprotein are generally within normal limits. If elevated, these lesions should be investigated further. In the case of Kasabach-Merritt syndrome, fibrinolysis can result in thrombocytopenia and coagulation abnormalities. Obstruction of the biliary tree can result in elevated bilirubin and alkaline phosphatase levels, although this is rare.

Diagnosis and Radiologic Findings

Accurate diagnosis of hepatic hemangiomas is imperative to avoid unnecessary procedures. Imaging-based diagnosis includes the use of ultrasound (US), contrast-enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI), angiographic, and nuclear scans (scintigraphic studies with Technetium 99m labeled red blood cells). These modalities can help differentiate hepatic hemangiomas from other benign (adenoma) or malignant (hepatocellular carcinoma [HCC], cholangiocarcinoma, metastasis, dysplastic nodules) hepatic tumors.

Ultrasound is the first step in the evaluation of hepatic hemangiomas. On US, they present as hyperechoic, homogenous, and well-defined lesions with posterior acoustic enhancement. This hyperechoic appearance is due to the presence of numerous interfaces between the endothelial tissue septa and the blood within them. Larger hemangiomas can also develop central necrosis and fibrosis, which makes them appear to be heterogeneous with mixed echogenicity. On Doppler US, most hepatic hemangiomas demonstrate

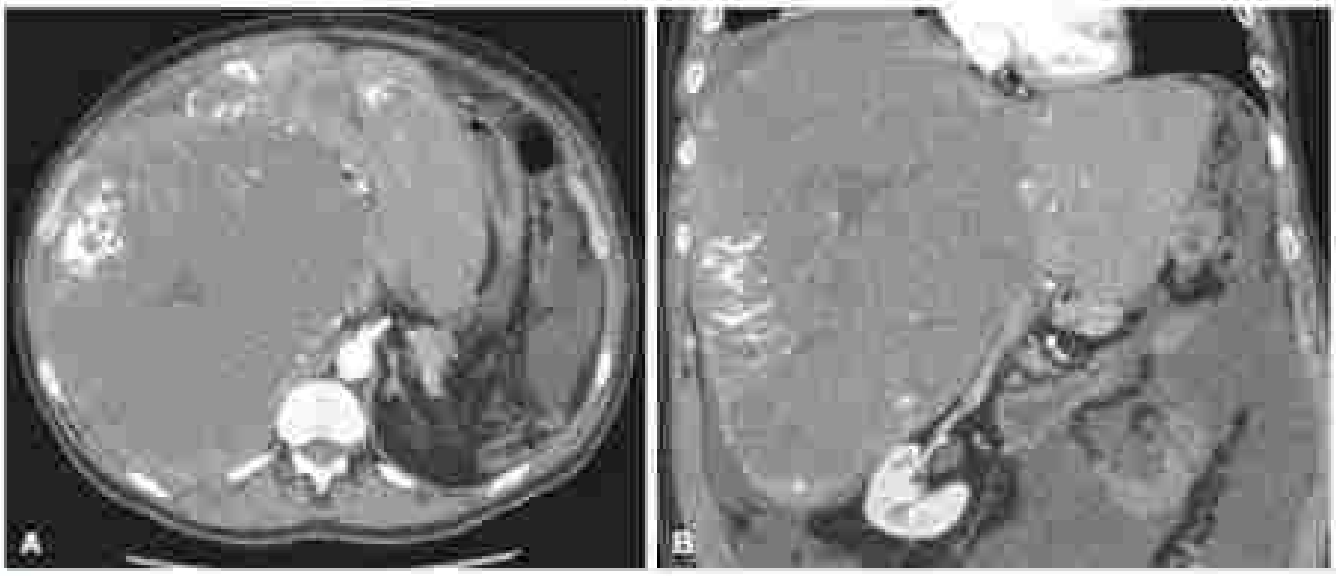

FIG. 3. Computed tomography of a 59-year-old male demonstrating a giant hepatic hemangioma in the right lobe of the liver. Axial (A) and coronal (B) view. The patient was initially managed via surveillance; however, the tumor grew and hepatic artery embolization was performed at an outside institution. Subsequently, he developed resulting bilateral pleural effusions and ascites requiring removal of 2 L abdominal fluid every 4 to 5 days. Additionally, he had lower extremity edema and pulmonary edema.

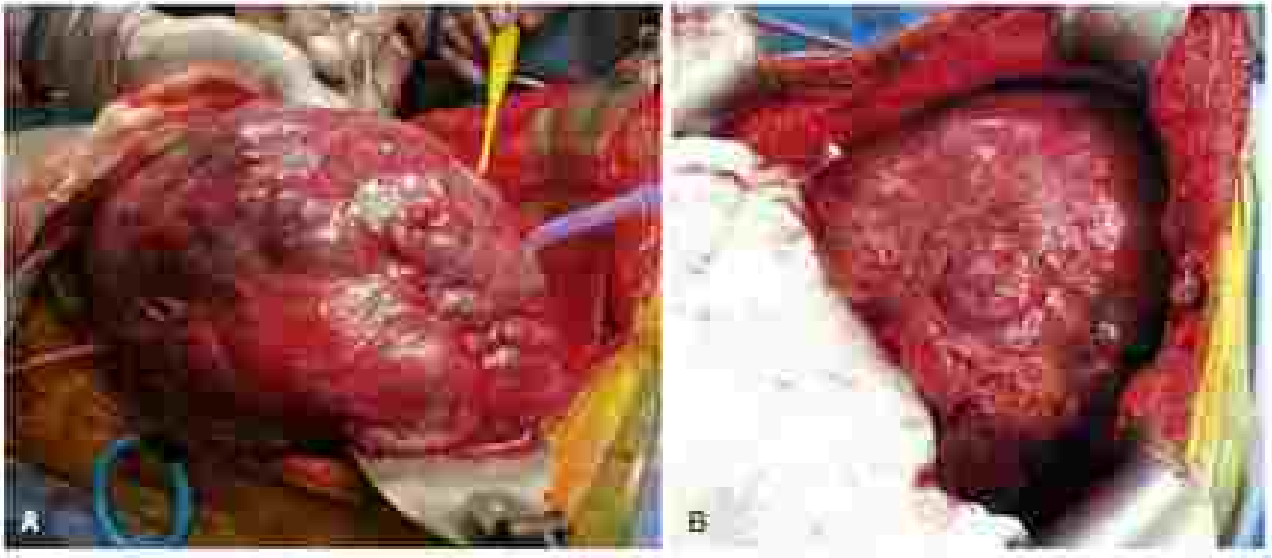

FIG. 4. Intraoperative image of a giant hepatic hemangioma in the right lobe of the liver.

minimal or no signal. The hyperechoic appearance on US can also represent other hepatic tumors; however, the absence of lesion blood flow on Doppler US can reliably differentiate hemangiomas from HCC, which frequently have intra- or peritumoral vascularity. The main limitations of using US are that it is highly operator and patient dependent, and when assessing a fatty liver a typical hemangioma can look hyperechoic relative to the liver parenchyma.

CT is the most commonly used modality for the diagnosis of hepatic hemangiomas. On unenhanced CT hepatic hemangiomas present as isodense liver lesions that are difficult to identify. However, contrast enhanced CT has a high sensitivity (98%) for diagnosing hepatic hemangiomas. On a noncontrast CT they are often hypoattenuating relative to the liver. On a contrast CT on the arterial phase, they show discontinuous, nodular, peripheral enhancement and in the portal phase they demonstrate progressive peripheral enhancement with centripetal fill in. Peripheral enhancement on the arterial phase, centripetal filling on venous phase, and contrast retention on the delayed phase, is highly suggestive of hepatic hemangioma. CT is particularly useful in differentiating hepatic hemangiomas from adenomas, focal nodular hyperplasia, hepatocellular carcinoma, or metastasis. The presence of these features is diagnostic; however, smaller lesions might not present with these findings. Giant lesions can present with central necrosis, thrombosis, or fibrosis, thus mimicking other hepatic lesions. When there is diagnostic uncertainty after CT other imaging modalities can be employed.

A dedicated hemangioma protocol MRI is the most specific (95%) and sensitive (99%) modality. Low signal intensity on T1 weighted imaging and bright signal on T2 weighted imaging with delayed relaxation times are characteristic of a hepatic hemangioma. This finding is known as a light bulb sign. CT can be equally effective in the diagnosis of hepatic hemangiomas and therefore MRI should only be performed when the diagnosis is unclear or when the patient cannot

undergo CT due to an allergy to contrast or renal disease. Additionally, MRI is the modality of choice for surveillance, as it reduces radiation exposure.

Percutaneous biopsies are contraindicated when hepatic hemangiomas are suspected, as it is associated with a high likelihood of serious complications and low likelihood of obtaining tissue for diagnosis. If diagnostic uncertainty exists after US, CT, and MRI, photon emission CT with technetium-labeled red blood cell scan or angiography can be used. Tagged red blood cell scans are limited for lesions located deeper in the liver parenchyma. Upon imaging a filling defect is observed in the liver, a finding similar to that in cases of other hepatic lesions. Therefore, the value of these modalities remains limited when diagnosing hepatic hemangiomas.

Management

Hepatic hemangiomas have a benign course; a majority remains stable on repeat imaging while 10% to 20% regress. The rate of hemangioma-related complications in patients managed via surveillance is similar to those undergoing surgical resection. Observation, therefore, can be an appropriate approach in patients with asymptomatic disease, even for women who are pregnant or are taking oral contraceptives.

Surgical resection is indicated when patients are symptomatic from their disease. These symptoms include extreme abdominal pain or signs related to mass effect leading to obstruction of the gastric outlet or the biliary tree. Other causes of these symptoms should be ruled out before proceeding with resection. If the patient presents with Kasabach-Merritt syndrome surgical resection is warranted despite the coagulopathy; many times resection results in reversal of the coagulopathy. Intensive care is often necessary to manage bleeding risk and prevent progression to disseminated intravascular coagulation. In the presence of hemangioma related complications, including intraperitoneal hemorrhage secondary to spontaneous or traumatic rupture, a surgery-first approach can be used. An alternative to a surgery-first approach is resection followed by embolization; however, if embolization is not successful emergent surgery should be performed.

Factors to be considered when a surgical approach is employed include the location and size of the tumor and the patient's comorbidities.

Surgical Approach

Surgical management of hepatic hemangiomas includes enucleation, anatomic or nonanatomic resection using an open or a minimally invasive approach. When performed by experienced surgeons these procedures are safe and feasible. The most common surgical approach is an enucleation, which is associated with reduced blood loss, shorter length of operation, lower risk of postoperative complications, and increased preservation of liver parenchyma. The minimally invasive approach has been shown to have similar outcomes when compared to open surgery; however, it may be challenging when resecting tumors on the right side of the liver.

To perform an enucleation, the hepatic artery inflow is controlled. For larger lesion ligation of the ipsilateral hepatic artery may be required, while for smaller lesions arterial flow can be controlled by ligation of more distal branches. A Pringle maneuver is useful to help attenuate the inflow in cases where the hemangioma is traumatically entered. It can also be used as a preoperative technique to decompress the tumor and facilitate resection. This maneuver is effective in cases of larger lesions. The maneuver is well tolerated if used for less than 30 minutes, and ischemic reperfusion injury is rare. If the enucleation requires more than 30 minutes periodic unclamping for 5 minutes is recommended. Clamping this portal permits pressure on the hemangioma limits the extent of resuspension of the lesion.

Upon entering the abdomen dissection begins with the incision of the Glisson's capsule to identify the plane of the pseudocapsule, which is relatively avascular. When the lesions are deep, an intraoperative US can be useful to identify them, and dissection of the normal parenchyma might be necessary to identify the pseudocapsule. Resection is then performed along the plane of the pseudocapsule, which reduces the risk of entering the hemangioma that can result in significant bleeding. In certain cases, the pseudocapsule may not be identifiable, making dissection difficult and parenchymal resection a more viable option.

Anatomic and nonanatomic liver resections are performed when there is diagnostic uncertainty, and there is a high suspicion for malignancy. Tumor size, location, and relationship with vasculature and biliary structures should be taken into account when selecting the appropriate surgical approach. Nonanatomic resection should be considered for smaller peripheral lesions. When performing liver resections inflow occlusion can be used to decompress the lesion, and assist with resection.

For unresectable tumors or patients with Kasabach-Merritt syndrome or coagulopathy, liver transplant can be the treatment of choice; however, this approach is employed infrequently.

Nonoperative Therapies

It is important to note that the majority of incidentally diagnosed hemangiomas require no intervention at all. The use of several nonoperative therapies has been described with limited success. Such therapies include transarterial embolization, percutaneous radiofrequency ablation, percutaneous ethanol ablation, and radiation therapy. Limited data are available on the use and outcomes of patients managed via these techniques. Elective embolization can result in transient pain relief, though tumor regression is rare and tumor recurrence and recurrent symptoms are common. Embolization is more effective for lesions that have actively identifiable arterial blood supply. Similarly, thermal ablation can result in transient relief in symptoms but complete ablation of the lesion is difficult due to the presence of nearby vessels and biliary structures. Ablation for giant tumors is typically associated with a high risk of complications and poor efficacy.

Nonoperative management of patients with hepatic hemangiomas should be considered in patients with symptomatic disease who are poor candidates for surgical resection due to comorbidities, or if the patients refuse resection. Additionally, a nonoperative approach can be adopted as the initial therapy in patients with spontaneous or traumatic rupture of the lesion to gain hemostasis.

Prognosis

Follow up using routine imaging is recommended for newly diagnosed hepatic hemangiomas that do not require surgical resection. The imaging modality of choice is an MRI due to reduced radiation exposure. It is recommended that an MRI is performed 3 months after the initial diagnosis followed by scans every 3 to 6 months for a year. If the lesion remains stable, imaging should be repeated annually, with less frequent follow up performed subsequently. Data on the impact of large hemangiomas on pregnancy are limited; however, follow up with ultrasounds is recommended.

Surgical resection is safe and feasible when performed by experienced surgeons and is associated with low morbidity and mortality. A majority of patients undergoing resection have reported a significant improvement in their symptoms postoperatively. Recurrence of tumors is rare and resection is almost always curative.

SUMMARY

Hepatic hemangiomas are the most common type of benign tumors of the liver that are now frequently being diagnosed due to an increase in the utilization of cross sectional imaging. The vast majority of hemangiomas present as small asymptomatic lesions, have a benign natural history, and can be observed with serial imaging. When under surveillance, larger lesions can very rarely develop spontaneous rupture, or result in Kasabach-Merritt syndrome, which should be diagnosed and managed in a timely manner, given the high rate

of morbidity and mortality associated with them. Surgical resection should be reserved for patients with symptomatic disease, or when there is a high risk of complications or an uncertainty in the diagnosis of disease. Surgical resection, performed via enucleation or nonanatomic or anatomic resection, is safe and feasible when performed by experienced surgeons. Resection is curative and long-term outcomes of all patients remain excellent.

Suggested Readings

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Management of Benign Liver Tumors

Derek J. Erstad, MD, and Kenneth K. Tanabe, MD

Benign liver neoplasms occur in 7% to 20% of the population and include simple cysts, biliary cystadenomas, hemangiomas, adenomas, and focal nodular hyperplasia (FNH). Most lesions are incidentally discovered during imaging for other indications and can be managed expectantly with routine surveillance. Surgical resection may be required if symptoms develop or if there is risk of rupture, hemorrhage, or malignant transformation. Surgeons should be familiar with the clinical workup, radiographic features, and indications for intervention for these benign liver neoplasms.

Radiographic Evaluation of Liver Lesions

The use of axial abdominal imaging has increased more than 10-fold in the past four decades, resulting in the increased incidental identification of asymptomatic liver lesions. The vast majority of these lesions are benign, particularly when found in younger patients. With advances in axial imaging technology, most benign lesions may be definitively diagnosed with imaging alone and do not require further intervention, such as percutaneous biopsy. Making the correct diagnosis is critical to preventing unnecessary surgery or the mistaken diagnosis of liver metastases in patients with a known primary malignancy.

Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are the most commonly used modalities to image liver lesions. Each has advantages that may complement the others, and more than one modality is frequently used to secure a diagnosis. US is commonly used in emergency departments for patients with vague upper abdominal pain and has the advantages of ease of use, short duration, and absence of ionizing radiation. Fluid-filled cystic lesions are easily identifiable on US, whereas solid masses will have variable degrees of echogenicity. The main disadvantage of US is the inability to establish a diagnosis for most solid lesions resulting from limited specificity, which can be further confounded by conditions that reduce the quality of US imaging such as steatosis and fibrosis. For these reasons, follow-up imaging with CT or MRI is typically required to confidently diagnose benign liver lesions. The use of CT scanning as the first choice for follow-up to US has markedly increased in recent decades as a result of increased availability, short turnaround time, and high diagnostic sensitivity and specificity for many conditions. For accurate diagnosis of liver lesions, intravenous iodinated contrast is necessary and provides three distinct phases of enhancement: early hepatic arterial phase, portal venous phase, and delayed hepatic venous phase. The majority of benign liver lesions may be diagnosed with a high-quality, contrast-enhanced CT scan; however, the limitations of CT include radiation exposure and contraindications to iodinated contrast in patients with reduced kidney function or contrast allergy. MRI also provides excellent resolution of the liver and has a high sensitivity and specificity for diagnosing hepatic neoplasms. MRI, however, is limited by decreased availability, long examination time, certain metal implants such as cardiac pacemakers, and contraindications to gadolinium-based contrast agents, most notably reduced kidney function. Table 1 summarizes the common radiographic findings of benign liver lesions using these three modalities.

Benign Liver Cysts

Pathogenesis

Simple liver cysts are predominately congenital in nature, arising from aberrant bile ducts that lack communication with the biliary tree for drainage. Accumulation of serous, noninfectious fluid creates a spherical, nonseptated cyst lined by a single layer of cuboidal or columnar biliary epithelium with a surrounding fibrous stroma. Simple liver cysts are usually small (< 5 cm in diameter) and remain stable in size, although growth may be observed because of continued production of serous fluid. Simple cysts are rarely symptomatic and nearly universally benign.

Presentation

Simple liver cysts occur in approximately 18% of the population. They are most often observed in adults and are usually discovered incidentally after abdominal imaging for another indication. There is a slight female predominance (1.5:1), and although cysts may occur throughout the liver, they are found more often in the right lobe. Simple liver cysts are asymptomatic in the vast majority of cases, although patients may develop symptoms resulting from enlargement, infection, hemorrhage, or rupture of the cyst. Liver function tests are usually within normal limits. Cysts larger than 4 cm, which are most frequently observed in elderly women, may on rare occasion cause pain, shortness of breath, early satiety, nausea, or vomiting. In extremely rare cases, large cysts may compress nearby vascular or biliary structures, the latter resulting in jaundice. Occasionally, large cysts might be palpable on physical examination. A self-limiting bleed into a simple cyst is more common in patients on anticoagulation, and typically causes acute upper abdominal pain that spontaneously resolves over hours to days. On rare occasions, cholangitis may cause secondary infection of a cyst and transformation into an abscess. Increased cyst size is associated with increased risk of rupture or hemorrhage, which

of morbidity and mortality associated with them. Surgical resection should be reserved for patients with symptomatic disease, or when there is a high risk of complications or an uncertainty in the diagnosis of disease. Surgical resection, performed via enucleation or nonanatomic or anatomic resection, is safe and feasible when performed by experienced surgeons. Resection is curative and long-term outcomes of all patients remain excellent.

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BENIGN LIVER CYSTS

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TABLE 1 Comparison of Imaging Findings for the Five Most Commonly Encountered Benign Liver Lesions

Lesion	US	CT	MRI
Simple cyst	Round, through-transmission, usually lacks septations Heterogeneity seen with hemorrhage	Well circumscribed, homogeneous, hypoattenuated Limited contrast enhancement	Well circumscribed, homogeneous T1: hypointense T2: very hyperintense Limited contrast enhancement
Biliary cystadenoma	Round, anechoic, ±thick cyst wall, internal septations May have mural and septal nodules	Well circumscribed, unilocular, unenhanced Mural and nodular enhancement with contrast	Well circumscribed, heterogeneous T1: hypointense T2: hyperintense Mural and nodular enhancement with contrast
Hemangioma	Homogeneous, hyperechoic, posterior acoustic enhancement Blood flow rarely observed	Well circumscribed, homogeneous Asymmetric peripheral pools of enhancement in arterial phase Centripetal enhancement and washout delayed phase	Well circumscribed, homogeneous T1: hypointense T2: very hyperintense Gadolinium enhancement pattern similar to CT
Adenoma	Well circumscribed, homogeneous, variable echogenicity	Isoattenuated noncontrast Hyperattenuated arterial phase, loss of contrast enhancement delayed phases (return to isoattenuation) Heterogeneous if necrosis or hemorrhage Hyperattenuated signal if active hemorrhage	T1: isointense to hyperintense T2: isointense to hyperintense Gadolinium enhancement pattern similar to CT Lesion not retained in delayed, hepatobiliary phase Fat saturation sequences demonstrate intracellular fat
Focal nodular hyperplasia	Variable echogenicity, central scar rarely observed Unreliable modality for diagnosis	Iso- or hyperattenuated noncontrast Hyperattenuated arterial phase, central scar remains enhanced during venous phase Loss of contrast enhancement in delayed phases (return to isoattenuation)	T2: hyperintense T2: hyperintense with hyperintense central scar Gadolinium enhancement pattern similar to CT Lesion retention in delayed, hepatobiliary phase

CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

can lead to shock, infection, and, in very rare cases, death. Polycystic liver disease is discussed in a separate chapter.

Imaging

In the majority of cases, US alone may be used to establish the diagnosis of a simple cyst, which appears as a circular or oval anechoic lesion with clearly defined smooth borders, posterior acoustic enhancement, internal septations, and absence of internal vascularity. Fluid layering, heterogeneity, and internal echoes mimicking septations may indicate cyst hemorrhage, whereas debris within the cyst fluid can be associated with infection or a prior bleed. The presence of internal septations or a thickened, irregular cyst wall with mural nodules and papillary projections or calcifications are concerning for biliary cystadenoma, which is associated with an increased risk of malignant transformation that requires surgical resection. In certain cases, CT or MRI imaging may be necessary to confirm the diagnosis of a simple cyst. On CT, simple cysts appear as well circumscribed, homogeneous, and hypoattenuated lesions that do not enhance with contrast injection (Fig. 1A). On MRI, simple cysts are hypointense with T1 weighted and hyperintense with T2 weighted imaging (Fig. 1B). Similar to CT, on MRI cysts lack contrast enhancement and appear as well circumscribed and homogeneous.

Management

The majority of simple cysts do not require intervention because most are asymptomatic. In cases in which the diagnosis is unclear (e.g., hemorrhage into simple cyst vs cystadenoma), follow-up scanning may be necessary. In the case of asymptomatic simple cysts, periodic surveillance imaging is not indicated. Surgical fenestration is recommended for symptomatic cysts. Sclerotherapy is an alternative for poor surgical candidates. Cyst aspiration is associated with a high rate of recurrence and is rarely indicated as definitive therapy for symptomatic cases in which the patient is unable to undergo other treatment modalities. Because it typically takes several days for cyst fluid to reaccumulate, however, cyst aspiration may be used as a diagnostic maneuver to determine whether symptoms are attributable to the cyst.

Surgical fenestration is a procedure to unroof a portion of the cyst to establish a permanent communication between the cyst and the peritoneal cavity for drainage. Fenestration can be performed by open or minimally invasive approach (laparoscopic or robotic). Cysts located in segments VII and VIII are more difficult to access by a minimally invasive approach. Laparoscopy is associated with reduced hospital stay, decreased postoperative pain, and reduced blood loss compared with an open procedure. Typically, the free wall of the cyst represented by the thinnest tissue is the resected portion. An energy device (e.g., harmonic scalpel) or surgical stapler is commonly used to cut through the cyst wall and liver tissue to minimize the likelihood of postoperative bleeding. In open operations, the resection margin can instead be oversewn with a running locked suture. The resected cyst wall is sent for pathologic evaluation to rule out malignancy. Securing a mobilized omental flap into the opened cyst helps reduce the likelihood of recurrence, which is a consequence of other tissue walling off the opened cyst (e.g., hemidiaphragm). Complete cyst wall excision

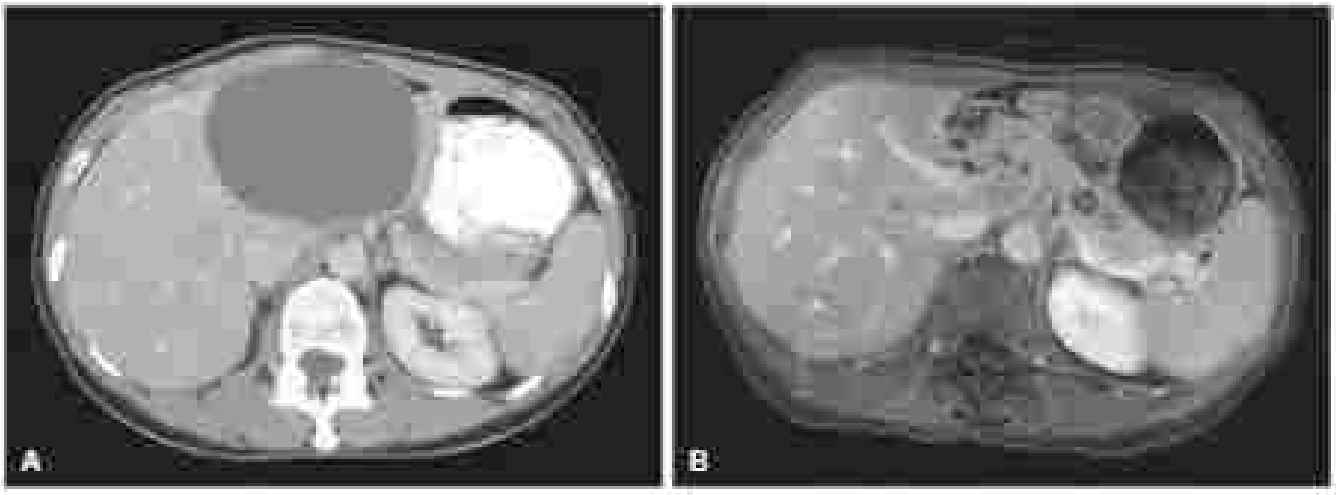

FIG. 1 (A) Axial computed tomography demonstrating a simple liver cyst in the left lobe of the liver in a 64-year-old woman. (B) Axial T1-weighted magnetic resonance imaging after cyst fenestration shows minimal hyperintense, residual fluid in the cyst cavity.

is rarely indicated and is reserved for instances when there is a high suspicion for biliary cystadenoma or cystadenocarcinoma. Complete resection can generally be performed with either a wedge or segmental resection. Recurrence rates are comparable between fenestration and complete resection, both approximately 10% to 15%. Morbidity for surgical fenestration or resection is approximately 15%, and mortality is less than 1%. Main complications include postoperative ascites, bile leak, hematoma, and surgical site infection.

For patients with multiple comorbid conditions who are unable to undergo a surgical procedure, sclerotherapy is an alternative treatment modality designed to destroy the biliary epithelial lining of the cyst wall, which is the source of fluid production. Sclerotherapy involves percutaneous placement of a drainage catheter into the cyst cavity under US guidance. Contrast is first injected to evaluate for communication with the biliary tree, which is a contraindication to proceeding. Other contraindications include intracystic bleeding and fistula to the gastrointestinal tract or peritoneum. Sclerosing agents include ethanol, tetracycline hydrochloride, and ethanolamine oleate. After an instillation duration of approximately 2 to 4 hours, the sclerosing agent is aspirated and the cyst cavity collapsed. Sclerotherapy is associated with a 20% recurrence rate within the first year, which is higher than surgical fenestration or resection, though is associated with lower morbidity and mortality. Postprocedural pain is common, though self-limiting.

BILIARY CYSTADENOMA

Pathogenesis

Biliary cystadenoma (BCA) is a cystic neoplasm of the biliary ductular system that may occur throughout the biliary tree, including both intrahepatic and extrahepatic locations. BCA is thought to arise from ectopic clusters of embryonic bile ducts, although a subset of lesions will also contain endocrine cells, indicating that BCA might also arise from intrahepatic peribiliary glands. BCA is typically a solitary, multilocular mass with fluid contents that is a distinct pathologic process from biliary intraductal papillary mucinous neoplasm. Unlike biliary intraductal papillary mucinous neoplasm, BCA lack papillary projections and a superficial spreading growth pattern, and histologically BCA have a cyst-in-cyst appearance characterized by multiple septa within the body of the lesion. BCA frequently contain ovarian-like stroma with estrogen and progesterone receptors and might therefore be hormone responsive. BCA has the potential for malignant transformation to biliary cystadenocarcinoma (BCAC) in approximately 20% of cases. BCAC is distinguished by the presence of proliferating, malignant-appearing epithelium on the tumor cystic layer.

Presentation

BCA typically occurs as a single mass, more often in the left lobe of the liver, and predominately affects women (90%) with a median age of diagnosis of 45 years. The majority of these tumors are identified incidentally and patients are asymptomatic, although some may present with abdominal pain or distension. Up to 20% of patients diagnosed with BCA will have elevated liver function tests, notably increased alkaline phosphatase and bilirubin. However, obstructive jaundice and cholangitis are rare and typically occur with extrahepatic disease. Cyst rupture and hemorrhage are reported but are also rare.

Imaging

On US, BCA appear anechoic with a thick cyst wall and internal septations. Intracystic debris is frequently observed, and mural and septal nodules may be present although are more common with BCAC, which contains foci of stacking malignant cells. On CT, BCA appear as well-circumscribed, multiseptated cystic lesions with mural and nodular enhancement on contrast injection. MRI provides similar architectural resolution, and BCA appear as low intensity on T1-weighted sequences and high intensity on T2-weighted sequences (Fig. 2A,B). The degree of T1 signal intensity in cyst fluid indicates the degree of protein and debris. Magnetic resonance cholangiopancreatography may aid in identifying cyst communication with the biliary tree. Although mural nodules, fluid debris, and wall thickening are more common with BCAC, there is currently no validated algorithm for reliably differentiating BCA from BCAC by imaging alone.

Management

Given the risk of malignant conversion of BCA to BCAC, surgical resection with negative margins is the current standard of care. Cyst aspiration, sclerotherapy, fenestration, and marsupialization leave behind premalignant or malignant tissue and are all associated with high recurrence rates (80%–90%) and should therefore be avoided when BCA is suspected. For extrahepatic BCA, complete removal of the cyst and surrounding bile duct followed by reconstruction with biliary diversion is required. For intrahepatic disease, technical factors including cyst location and size should determine the type and extent of resection. Peripheral lesions should be managed with segmentectomy or fenestration. For more central lesions near major vessels, formal resection may not be possible, in which case enucleation is an acceptable alternative. In extremely rare cases, orthotopic liver transplant has been used for BCA with good success.

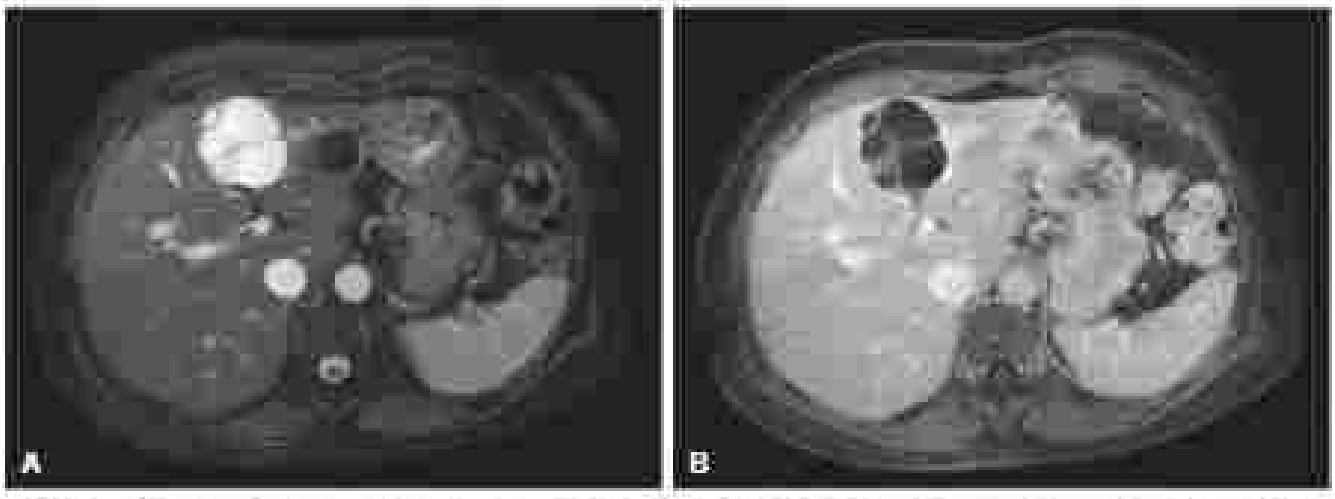

FIG. 1 (A) Axial T2-weighted image demonstrating a cystic mass in the left lobe of the liver in a 57-year-old woman. (B) Axial T1-weighted imaging of the same lesion reveals a hypointense, septated mass with clear borders.

HEPATIC HEMANGIOMA

Pathogenesis

Hepatic hemangiomas are the most common benign liver lesion, occurring in 5% to 20% of the population. They are congenital malformations comprising blood filled cavernous spaces lined by a single layer of endothelial cells and separated by fibrous tissue. They develop a round, well encapsulated shape and may grossly exhibit evidence of internal thrombosis or hemorrhage with calcifications. Hemangiomas have no potential for malignant transformation and, in contrast to adenomas, have an extremely low risk of spontaneous hemorrhage or rupture. Only a minority of lesions grow significantly over time.

Presentation

Hemangiomas occur predominately in women aged 30 to 50 years. Most patients present with a single lesion, though up to 10% of patients may present with multifocal disease throughout the liver. There is a slight predominance toward a peripheral location and the right lobe of the liver. In general, hemangiomas are small, ranging from several millimeters to several centimeters in diameter, although in rare cases lesions may be greater than 10 cm, which are referred to as giant hemangiomas. As with other benign lesions of the liver, hemangiomas are rarely symptomatic, and the majority of cases are incidentally diagnosed during abdominal imaging for other indications. With large hemangiomas, however, there is the potential for pain secondary to capsular stretch, or early satiety or nausea resulting from compression of the gastrointestinal tract. Giant hemangiomas in children may also result in a consumptive process called Kasabach Merritt syndrome, characterized by thrombocytopenia, hypofibrinogenemia, elevated fibrin degradation products, and coagulopathy.

Imaging

On US, hemangiomas appear as well demarcated, homogeneous, and hyperechoic lesions with posterior acoustic enhancement. On CT, hemangiomas appear as well circumscribed, hypodense lesions with postcontrast imaging. On MRI, hemangiomas appear as well demarcated, homogeneous lesions that are hypointense on T1 weighted imaging and markedly hyperintense on T2 weighted imaging (Fig. 3A). Following contrast injection, asymmetric peripheral pools of enhancement during the arterial phase followed by progressive centripetal enhancement and washout on delayed phases is pathognomonic for hemangioma (Fig. 3B). This enhancement pattern is similar to that observed with CT scan.

Management

The vast majority of hemangiomas are small and asymptomatic lesions that are managed nonoperatively. Indications for surgical resection include significant growth, significant symptoms that are unresponsive to analgesics and interfere with daily living, or, in exceedingly rare cases, rupture and hemorrhage. Perhaps the most difficult diagnostic challenge is to determine whether a patient's pain is caused by a known hemangioma. Unexplained abdominal pain are common, as are hemangiomas, and the two commonly coexist; therefore, it is important to carefully exclude other causes of abdominal pain before ascribing the pain to a known hemangioma. This task is challenging because pain caused by hemangiomas is typically nonspecific. The differential diagnosis commonly includes peptic ulcer disease, biliary colic, severe dyspepsia, and musculoskeletal pain. When choosing to operate for symptoms of pain, it is wise to inform the patient that his or her symptoms might not improve after surgery.

Resection can be completed by either open or minimally invasive approaches and involves tumor enucleation, wedge resection, or a limited segmental resection based on the size and location of the lesion in proximity to major biliary and vascular structures. Because of the large pseudocapsule often associated with hemangiomas, it is possible to perform an enucleation, sparing a parenchymal resection. Enucleation involves dissection in the plane between the normal liver parenchyma and pseudocapsule. Crossing vascular structures are individually identified and controlled with ties, clips, or an energy device. When operating on giant hemangiomas, a commonly used tactic is to first slowly squeeze the tumor to push out a majority of its blood. The tissue left behind is smaller and easier to grasp and manipulate. For large hemangiomas, preoperative hepatic arterial embolization has been used to mitigate intraoperative bleeding, though this is rarely necessary. Orthotopic liver transplant has also been used for large, unresectable lesions with good success. There are currently no effective medical therapies, though embolization and radiation therapy have been used for symptomatic patients who are not operative candidates.

HEPATIC ADENOMA

Pathogenesis

Hepatic adenomas are encapsulated tumors comprising sustained hepatocytes that exhibit minimal cellular atypia. Grossly, they appear as soft, tan lesions perfused by peripheral arteries on their outer surface, and necrosis may be observed centrally when the mass outgrows its blood supply. Because of their lack of encapsulation, adenomas are at increased risk of uncontrolled hemorrhage into the surrounding

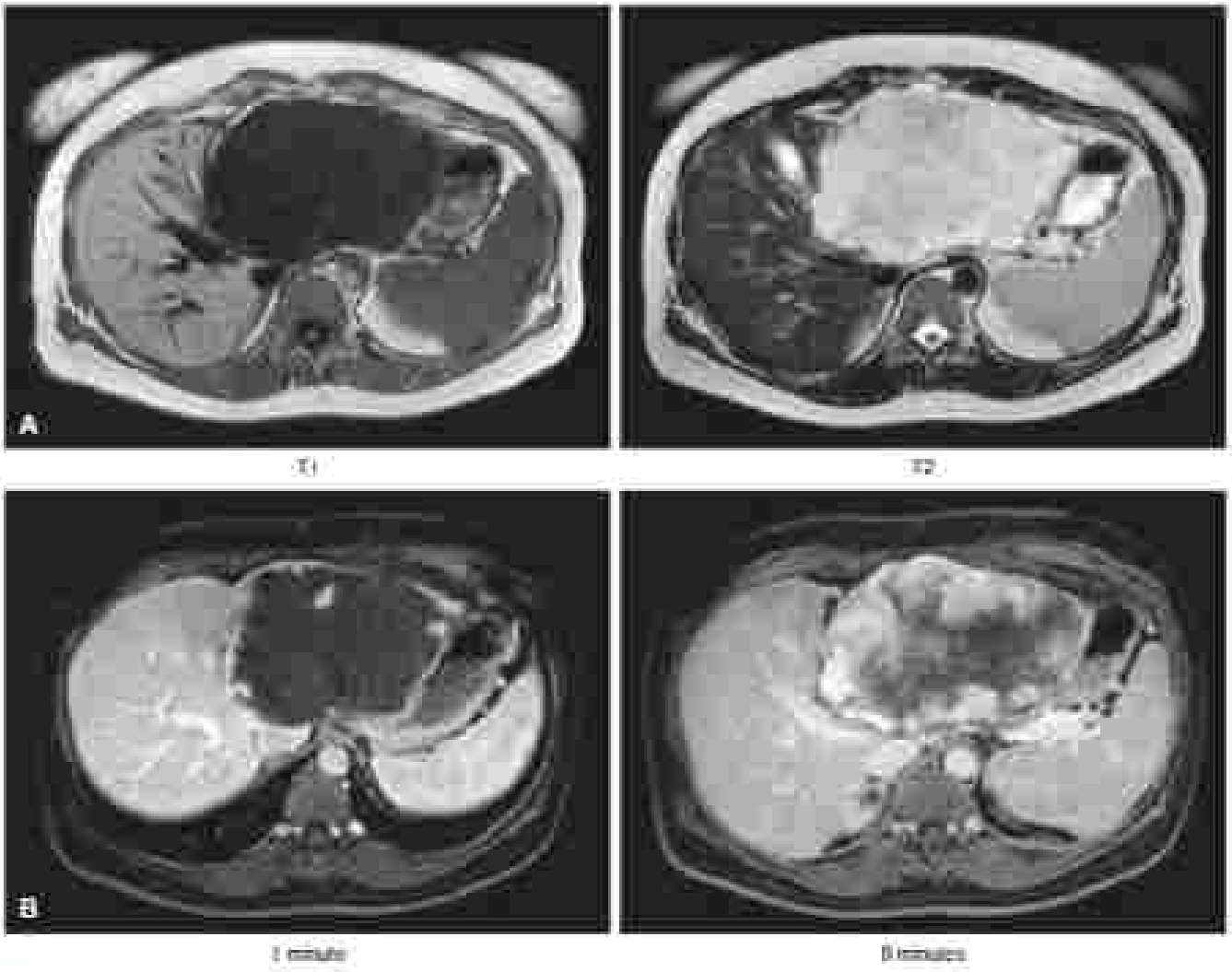

FIG. 2. (A) Homogeneous signal hyperintense on T1-weighted magnetic resonance imaging and hyperintense on T2-weighted images, as shown by this large left hepatic lobe mass in a 34-year-old woman. (B) Dynamic resonance imaging demonstrating centripetal contrast enhancement over time, which is pathognomonic for hemangioma.

liver tissue. Adenomas have a risk of malignant transformation. The risk is higher in men and for lesions larger than 5 cm in diameter. Adenomas generally occur in the absence of cirrhosis on a normal background liver, although steatosis and steatohepatitis are risk factors. Other risk factors include estrogens such as those in oral contraceptives, anabolic steroids, and type I and III glycogen storage diseases.

Adenomas may be categorized into four genetically distinct subgroups: HNF1 alpha–inactivated adenoma, inflammatory adenoma, beta-catenin–activated adenoma, and unclassified adenoma. The HNF1 alpha–inactivated subtype accounts for up to one third of all adenomas and is associated with spontaneous occurrence. These lesions exhibit macrovesicular steatosis and have a lower risk of malignant transformation. Inflammatory adenomas account for up to 60% of cases and are characterized by lymphocytic infiltrates, pseudoportal tracts, and abnormal activation of the JAK/STAT pathway. Inflammatory adenomas are associated with obesity-induced nonalcoholic steatohepatitis, which is rising in incidence in both men and women. The percentage of adenomas that are beta-catenin active is greater among men. These lesions exhibit greater cellular atypia than other subtypes, and their risk of malignant transformation depends on the type of beta-catenin mutation and the degree of constitutive downstream Wnt signaling. Finally, unclassified adenomas lack a clear mutational signature or inflammatory infiltrates. These lesions have been associated with the highest risk for spontaneous rupture.

Presentation

Adenomas can present as single or multiple simultaneous lesions and can range from a few millimeters to greater than 10 cm in diameter. The presence of 10 or more adenomas is referred to as adenomatosis. Adenomas occur most often in adult women aged 20 to 40 years, and less commonly in men. However, the epidemiology of adenomas has shifted in recent years. Historically, there was a significant association between adenoma formation and oral contraceptive use, which was determined by the duration of therapy and hormonal dosage; however, newer contraceptives have lower estrogen dosages, which has reduced the incidence of contraceptive-related adenomas. In contrast, obesity and the related metabolic disorders nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are risk factors for adenoma formation with rising global incidence for both genders. Finally, glycogen storage disease–related adenomas most commonly occur in young males less than 20 years of age.

Most adenomas are asymptomatic and discovered incidentally with abdominal imaging for other indications. Some patients present with acute onset right upper quadrant or epigastric pain secondary

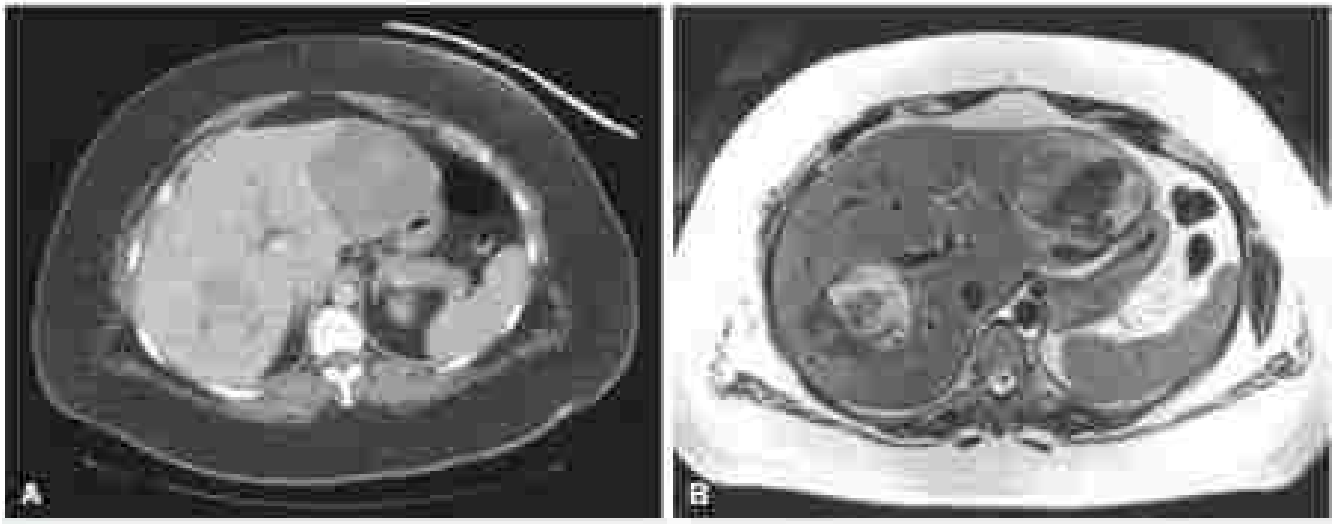

FIG. 4 (A) Axial computed tomography image of a 31-year-old female patient with two large adenomas with foci of hemorrhage. (B) Axial T2-weighted image of the same lesions shows mixed intensity signal that correlates with regions of hemorrhage.

to spontaneous adenoma hemorrhage. Bleeding is typically self-limiting; however, in rare cases, spontaneous hemorrhage and rupture may result in hypovolemic shock or death.

Imaging

Adenomas lack unique identifying radiographic features on US. They appear as well demarcated, heterogeneous masses with variable echogenicity, which can be difficult to differentiate from hepatocellular carcinoma or metastases. On CT scan, adenomas are hodgepodge relative to the surrounding liver parenchyma, and on contrast injection, will appear hyperattenuated during the early arterial phase with loss of signal during delayed phases. Depending on the degree of necrosis or hemorrhage, adenomas may have heterogeneous attenuation (Fig. 4A). On MRI, adenomas appear isointense to hyperintense on both T1- and T2-weighted sequences (Fig. 4B), with increased signal intensity on gadolinium contrast injection that is most prominent during the arterial phase. Gadoxetic acid contrast can help distinguish FNH from adenoma because FNH will typically retain contrast in the delayed hepatobiliary phase, whereas adenomas typically do not.

Management

The main risks of adenoma are bleeding and malignant transformation. For an adenoma less than 5 cm in diameter, the initial management strategy is cessation of hormonal contraceptives or anabolic steroids if present, followed by close surveillance. Weight reduction and improved dietary habits should be recommended for obese patients with fatty liver. The goal of cessation is to prevent further adenoma growth. In some cases, regression may occur although disappearance is unlikely and, if left in the liver, long-term surveillance is indicated. For patients in which the adenoma continues to grow or becomes symptomatic, or for adenomas greater than 5 cm, surgical resection is recommended. Ablative therapies have been used, but long-term follow-up data are lacking. The surgical approach to adenomas should be similar to that of a malignancy, with a goal of negative margins despite the benign nature of the lesion. The choice of an open or minimally invasive approach depends on technical factors and surgeon experience. Similarly, the decision between a formal anatomic resection versus a parenchymal-sparing approach should be determined by the size and location of the adenoma and the degree of suspicion of malignancy. For patients with multiple adenomas or unresectable lesions, close surveillance with MRI is the typical approach. Growth or worrisome changes on MRI of any specific lesion is an indication to resect that single lesion.

For patients who present with acute hemorrhage from a ruptured adenoma, treatment options involve vascular embolization or surgery, which depends on the stability of the patient. For patients with stable vital signs, the preferred approach involves selective arterial embolization by interventional radiology followed by elective surgical resection during the same hospitalization. For unstable patients or those not amenable to embolization, emergent laparotomy is indicated to control bleeding. The operation should be performed by an open laparotomy. Liver packing and inflow control with a Pringle's maneuver are used to gain control of the bleeding. If bleeding has been controlled before onset of hypotension, acidosis, hypothermia, or coagulopathy, resection may be performed at the same operation. Following hemorrhage into liver tissue, identification of the border between adenoma and liver can be difficult. In these situations, formal anatomic resection may be easier to perform than attempts to resect only the tumor. Finally, in cases in which bleeding cannot be controlled operatively despite Pringle, completing the operation leaving packing behind followed by selective embolization is indicated.

FOCAL NODULAR HYPERPLASIA

Pathogenesis

FNH is thought to be a hyperplastic response of normal liver tissue surrounding a congenital arteriovenous malformation and thus not a true neoplasm. Histologically, FNH appears as a proliferation of mature hepatocytes and bile ducts in a stellate pattern surrounding a central scar composed of fibrous tissue and malformed vessels. These lesions have no malignant potential and extremely low risk of bleeding or causing pain.

Presentation

FNH is the second most common benign liver lesion after hemangioma and occurs most often in reproductive age women aged 20 to 50 years. These lesions are typically discovered incidentally because they are nearly always asymptomatic, even when large; however, symptoms of vague right upper quadrant or epigastric pain may occur rarely. FNH usually presents as a single lesion, although multiple lesions may be observed in rare cases and are sometimes associated with a syndrome of vascular malformations. The majority of masses are less than 5 cm and approximately 80% will have evidence of a central scar.

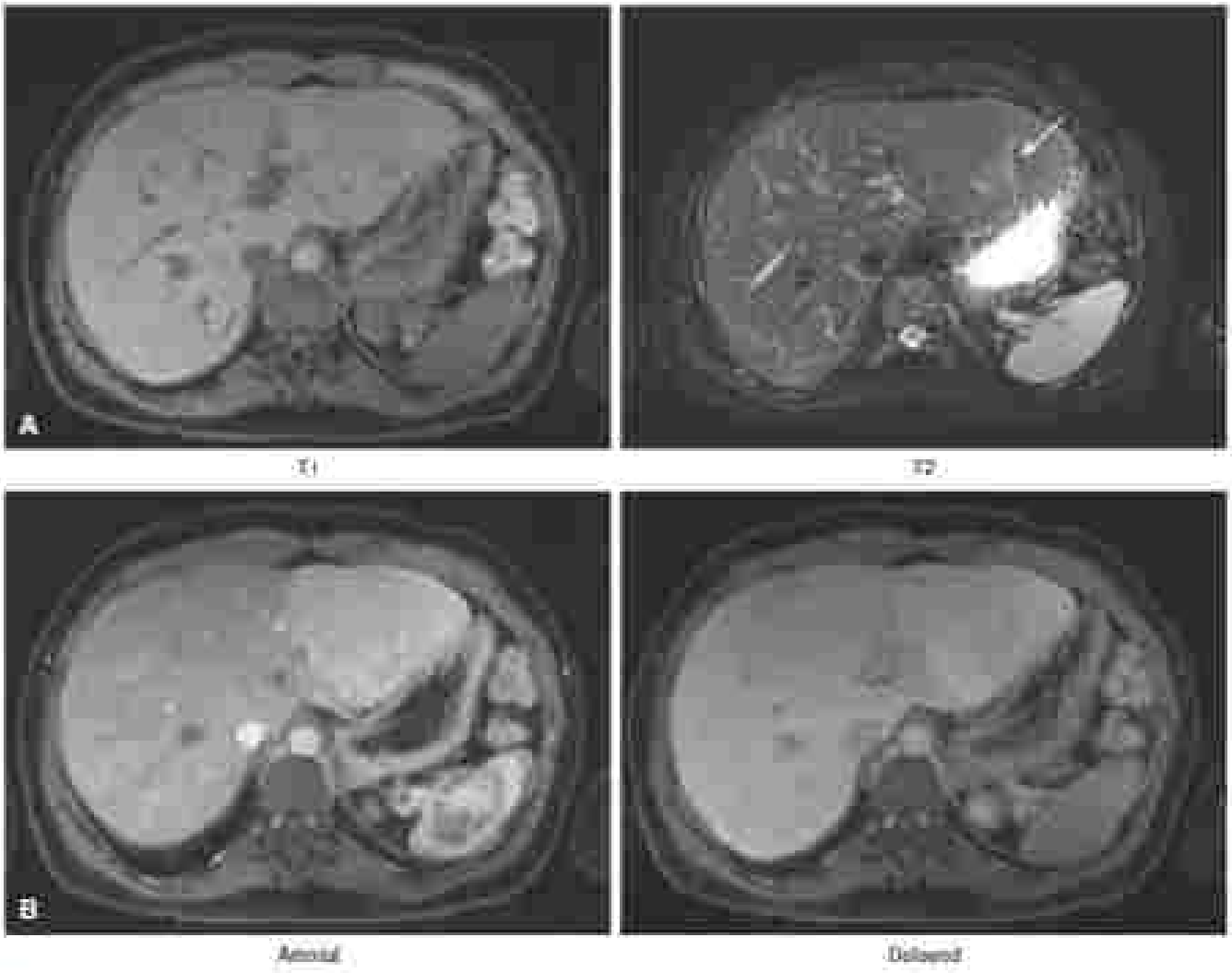

FIG. 3 (A) Focal nodular hyperplasia (FNH) appears hypointense throughout on T1-weighted magnetic resonance imaging whereas on T2-weighted sequence FNH is hyperintense with a hyperintense central scar (*left to right*). (B) FNH displays early arterial enhancement with rapid washout. During the venous phase, FNH is isointense with the central scar remains enhanced.

Twenty percent are "atypical" lesions that lack evidence of central scar and in rare cases, FNH greater than 10 cm has been reported.

Imaging

US is an available modality for the diagnosis of FNH, with an accuracy of approximately 80%. Multidetector CT and MRI are the standard of care for diagnosing FNH, which can be difficult to distinguish from other lesions, including adenoma or fibrolamellar carcinoma, particularly in the absence of a central scar. On noncontrast CT, FNH will appear isodense or hypodense relative to the surrounding liver parenchyma, and in some cases a hypodense central scar is visible. With contrast, FNH appears as a well-circumscribed, hyperattenuated mass during the arterial phase. During the venous phase, FNH is isodense, whereas the central scar remains enhanced. On T1-weighted MRI, FNH appears hypointense throughout, while on T2-weighted sequences, FNH is hyperintense with a hyperintense central scar (Fig. 3A). With gadolinium contrast, FNH will display early arterial enhancement (Fig. 3B). During the venous phase, FNH is isointense, whereas the central scar remains enhanced. Except for the findings of a central scar, these CT and MRI imaging characteristics are similar to those of hepatic adenomas, which is typically also in the differential diagnosis. Retention of gadoxetic acid on delayed hepatobiliary phase in FNH may be helpful in distinguishing it from adenoma. In some cases, biopsy is necessary to render a diagnosis, most notably when adenoma, fibrolamellar hepatocellular carcinoma, or metastases are possible diagnoses. There are no histologic features pathognomonic for a diagnosis of FNH, which often appears as fibrous and regenerative nodules, similar to cirrhosis.

Management

FNH almost never requires surgical intervention. There are extremely rare cases in which FNH causes pain unresponsive to analgesics that impairs quality of life, for which resection is indicated. Similar to the situation with purportedly symptomatic hepatic hemangiomas, ascribing symptoms of abdominal pain to an FNH can be fraught with inaccuracy. Both open and minimally invasive approaches are acceptable with a goal of negative margins. The extent of resection depends on technical factors, particularly the size and location of the lesion.

SUMMARY

There has been a substantial increase in frequency of incidentally discovered hepatobiliary masses because of increased usage of axial imaging modalities. The majority of these lesions are benign and

include simple cysts, HCA, hemangioma, adenoma, and FNH. Nonetheless, all incidentalomas require careful diagnostic evaluation to rule out malignancy or premalignant condition. Management of benign liver lesions does not typically require resection, with certain exceptions. Simple cysts should be observed unless symptomatic, in which case surgical fenestration is associated with the lowest rate of recurrence. HCA requires an oncologic surgical resection in all cases given the risk of malignant transformation. Hemangiomas have no malignant potential and harbor a low risk of hemorrhage; therefore, resection is not indicated except for rare cases of symptoms that adversely affect quality of life. Adenomas larger than 5 cm should be resected because of their risk of hemorrhage and malignant transformation. For smaller, asymptomatic adenomas, cessation of potential stimulants for growth including oral contraceptives, anabolic steroids, and obesity should be addressed in addition to observation with serial scans. Finally, FNH has no malignant potential and rarely requires surgical resection, except for cases of ongoing symptoms or inability to distinguish FNH from other potentially malignant lesions. The ability of surgeons to diagnose and appropriately manage benign liver lesions has taken on greater importance given the increasing frequency of incidentally identified liver lesions, now and likely in the coming decades.

Suggested Readings

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Management of Malignant Liver Tumors

Jordan M. Cloyd, MD, and Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS(Hon)

The most common malignant liver tumors are hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and metastatic colorectal cancer. In the Western world, metastatic liver tumors are more common than primary liver tumors.

Surgical resection is the mainstay of treatment for hepatic malignancies. Appropriate selection of patients for resection requires evaluation of the overall health status, oncologic appropriateness, and, finally, resectability of the disease. A lesion is considered resectable if negative margins can be obtained while leaving an adequate amount of functional liver parenchyma with intact hepatic arterial and portal venous inflow, venous outflow, and biliary drainage. If this cannot be accomplished, other liver directed therapies may be considered, such as tumor ablation, tumor embolization, and external radiation.

Tumor ablation can be performed with various techniques such as alcohol injection and thermal ablation with heat (microwave or radiofrequency ablation [RFA]) or cold (cryoablation). microwave and RFA are the most successful in hepatic malignancies. A newer technology called irreversible electroporation is emerging as an attractive alternative to thermal ablation for tumors near vascular structures. Irreversible electroporation uses short duration, high voltage pulses to create defects in the lipid bilayer that ultimately result in cell necrosis without the heat sink effect associated with thermal ablation when used near vascular structures. Tumor embolization includes transarterial blood embolization (TAE), transarterial chemoembolization (TACE), or radioembolization, typically using the radioactive isotope yttrium 90. Finally, external beam radiation therapy—either conformal or stereotactic—is emerging as another alternative for the treatment of malignant liver tumors not amenable to resection.

HEPATOCELLULAR CACINOMA

HCC is the most common primary malignant liver tumor worldwide. Although the incidence is highest in Asia and sub-Saharan Africa, the incidence in the United States has been increasing in recent years. Risk factors include cirrhosis of any cause, including hepatitis B and C. In the absence of cirrhosis, HCC usually is associated with hepatitis B, although a variant type, fibrolamellar HCC, occurs in patients with no underlying liver disease. HCCs are characterized by homogeneous enhancement in the arterial phase and washout of the contrast material in the portal venous phase on computed tomography (CT) scan and magnetic resonance imaging (MRI).

For patients with cirrhosis, liver transplantation will address both the HCC and the underlying liver disease. Because of limited organ availability and transplant associated risks, such as organ rejection and immunosuppression related complications, however, other treatment modalities often must be considered. The most widely used treatment modalities for HCC include TACE, ablation, and resection. Resection versus transplantation is addressed in a separate chapter.

Surgical resection of HCC is a good option when feasible. The presence and degree of fibrosis/cirrhosis correlates with the incidence of postoperative liver failure, as well as with long-term survival. Major liver resection is therefore generally limited to patients with no cirrhosis or cirrhosis classified as Child's A with no evidence of portal hypertension. In these patients, mortality rates are lower than 5%. Although 5-year survival rates range from 50% to 60%, recurrence rates are considerable among patients with cirrhosis, with recurrence noted in about one-third of patients within 5 years. Other factors negatively associated with long-term survival include invasion of major vessels, microvascular invasion, and both the number of tumors and tumor size; however, when adjusted for the presence of other prognostic features, tumor size is not a predictor of survival in patients with solitary lesions. Resection of tumors in patients with multifocal HCC and major vascular invasion are associated with poor prognosis and high recurrence rates (>85%) and should be considered only in highly selected cases.

In the appropriately selected patient, resection should be attempted only if negative margins can be obtained. Ideally, anatomic resections of portal territories, including sectionectomy, segmentectomy, and subsegmentectomy, should be performed, because HCC tends to spread via portal venous tributaries. Anatomic resections have been associated with reduced local recurrence and improved survival in patients with HCC in both randomized and observational studies. On the other hand, thermal ablation of small (<3 cm) HCC has been shown to have long-term outcomes that are equivalent to surgical resection in recent randomized trials, with less morbidity and mortality. These data should be interpreted cautiously, however,

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because these studies had small sample sizes and were not designed as noninferiority trials. Ablation can be accomplished percutaneously or through an open or laparoscopic operation. Finally, ablation of tumors larger than 4 cm or those close to major vascular structures should be avoided because this approach is associated with high rates of incomplete tumor destruction and recurrence, with local recurrence rates as high as 40%.

Embolization (bland, chemoembolization, or radioembolization) is used typically for patients who are not candidates for curative treatment by resection, transplantation, or ablation. Embolization also may be used as a bridge to liver transplantation or before ablation for tumors between 3 and 5 cm. In the latter group, the combination of TACE and RFA has been shown to improve survival when compared with either modality alone. Response rates with TACE are as high as 80%, but the treatment usually must be repeated every 3 to 4 months. A total bilirubin level greater than 3 mg/dL is a contraindication for these treatments. Portal vein thrombosis is a relative contraindication for TAE and TACE. These patients can be treated with radioembolization or external beam radiation. In the right setting, superselective embolization can be considered even if the ipsilateral portal vein is thrombosed. External beam radiation is an alternative for HCC with local control rates around 90%, although long-term data are limited.

Although surgical resection and transplantation are contraindicated in the presence of extrahepatic disease, liver-directed therapies may be used in the presence of limited extrahepatic disease, if the liver disease is thought to be rate limiting. For patients with significant extrahepatic disease, systemic therapy should be considered. Sorafenib, an oral multikinase inhibitor, remains first-line treatment, although the anti-PD1 agent nivolumab has recently been approved for second-line treatment of HCC.

INTRAHEPATIC CHOLANGIOCARCINOMA

ICC is the second most common primary malignant liver tumor, accounting for 10% to 20% of such cases. Its incidence has increased markedly over recent decades for unclear reasons. Risk factors for the development of cholangiocarcinoma include sclerosing cholangitis (10%–20% lifetime risk), choledochal cysts (15%–28% lifetime risk), and cirrhosis. Of the three gross subtypes of ICC—mass forming, periductal infiltrating, and intraductal—the periductal infiltrating type is associated with the worst prognosis and unfortunately is the most common. ICCs are typically low in attenuation on CT scan, with minor peripheral enhancement and upstream biliary dilation. Capsular retraction also may be noted. The diagnosis often is made when a liver lesion is found to be adenocarcinoma from biopsy and a workup for the primary (including upper and lower endoscopy and sometimes positron emission tomography scan) does not reveal a source.

Surgical resection with the goal of obtaining negative margins is the only curative option. The porta hepatis lymph nodes should be dissected formally because they are positive in about one third of patients. Survival rates for resected patients range between 40% and 60% at 5 years. Positive margins and positive nodes are associated with worse prognosis, and adjuvant chemotherapy and radiation may be beneficial in these cases. ICC is associated with a significant risk of peritoneal carcinomatosis, and diagnostic laparoscopy sometimes is considered in these patients. The presence of extrahepatic disease including lymph nodes beyond the porta hepatis is a contraindication for resection. Multiple liver lesions, which represent intrahepatic metastases, are associated with a poor prognosis, and resection should be considered only in highly selected patients. The presence of gross lymph node metastases in the hilum also is associated with worse prognosis, but some of these patients may benefit from resection and adjuvant therapy. For locally advanced tumors, TAE, TACE, or radioembolization can be used. Radiographic response can be seen in 25% of the patients. Whether regional therapy is better than chemotherapy in locally advance tumors remains to be determined.

METASTATIC COLORECTAL CANCER

Colorectal cancer is the third most frequent malignancy with approximately 150,000 new cases diagnosed every year in the United States. Synchronous or metachronous metastatic involvement of the liver will be diagnosed in about 50% of the patients with colorectal cancer. Consequently, colorectal liver metastases (CRLM) are far more common than primary liver tumors. These lesions are typically hypovascular and appear hypodense during the portal venous phase on CT scan. In this chapter, we focus on the resection of CRLM whereas other liver directed therapies are addressed in other chapters.

Surgical resection, when feasible, is the best curative option in patients with CRLM. The goal of the procedure should be to remove all metastases with microscopically negative margins. The optimal surgical margin width remains controversial but current recommendations are to aim for at least a 1 mm microscopic margin. Parenchymal sparing hepatectomies are preferred to major hepatic resections when applicable because these procedures are associated with decreased morbidity and increased rates of salvage ability in cases of recurrence, with no increase in recurrence rate or decrease in overall survival. For bilateral CRLM, major resection can be combined with wedge resection or ablation of the lesions on the contralateral side. These procedures may be performed at the same time or with staged operations, as dictated by the anticipated volume of the liver remnant. In patients with colorectal cancer and synchronous hepatic metastases, the primary tumor and the liver disease can be resected at the same time or separately. Concomitant liver and colorectal resection should be considered when only a minor liver resection is required or when the colon surgery is straightforward. Major liver resections should, however, be avoided when complex colorectal procedures are performed, such as those requiring extensive pelvic dissection or a low rectal anastomosis. In these situations, the hepatic metastases can be addressed first or after resection of the primary. Because the liver is usually the determining factor for complete disease resection, the "liver first" approach is an attractive option, especially for patients with extensive liver disease that may progress to unresectability and patients with rectal cancer that will require time between radiation and resection of the primary tumor. Occasionally, however, the primary tumor is symptomatic and must be addressed first. In contrast to patients with primary liver tumors, hepatic resection is often considered for patients with extrahepatic disease, as long as the extrahepatic disease is limited and resectable. This is a reflection of the very high response rates to the various systemic chemotherapy options currently available.

Preoperative chemotherapy is typically administered to assess tumor response and to address the potential micrometastatic disease not seen on imaging. A large randomized, controlled trial of perioperative chemotherapy for CRLM found improved progression-free survival compared with patients who received resection alone. However, prolonged, modern chemotherapy for colorectal cancer may be associated with significant injury to the liver, with increased risk of postoperative complications after liver resection. Specifically, irinotecan-based treatment is associated with steatohepatitis, whereas oxaliplatin-based chemotherapy is associated with sinusoidal congestion. Moreover, small (<2 cm) lesions may disappear with chemotherapy. If not surgically resected, these lesions will recur in up to 80% of the patients. The surgeon and the medical oncologist must work closely to determine optimal duration of preoperative chemotherapy and timing for the surgical procedure. In general, if preoperative chemotherapy is used, the duration should be limited to 4 to 6 cycles (i.e., 2–3 months).

Prognostic factors for patients who have undergone curative resection of CRLM include the disease-free interval between the diagnosis of the primary tumor and the metastatic disease, size of the largest hepatic tumor, presence of extrahepatic disease, mutation status (e.g., *RAS*, *BRAF*) and nodal status of the primary tumor. Overall and disease-free survival range from 30% to 60% and 20% to 40% at 5 years, respectively.

TABLE 1 Child-Turcotte-Pugh Score*

Measure	1 Point	2 Points	3 Points
Total bilirubin, mg/dL	<2	2–3	>3
Serum albumin, g/L	>35	28–35	<28
PT/INR	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grades I–II (sup. present with medication)	Grades III–IV (refractory)

*The scores are for clinical measures: class A, 5–6 points; class B, 7–9 points; class C, 10–15 points.
PT/INR, prothrombin time/international normalized ratio.

PREOPERATIVE ASSESSMENT

Patients should undergo preoperative optimization and risk stratification according to the presence of medical comorbidities. Liver function is assessed with evaluation of total bilirubin, prothrombin time, albumin, presence of ascites, and history of encephalopathy. The Child-Turcotte-Pugh scoring system (Table 1) is associated with perioperative mortality rates of 0%, 10%, and 50% in patients with classes A, B, and C, respectively. Thrombocytopenia (platelets <100,000/mm^3), splenomegaly, and esophageal varices are indicators of portal hypertension, which is associated with prohibitive rates of perioperative mortality after major liver resections.

The location of the hepatic lesions and their relationship to the main hepatic vessels and the biliary tree are determined with high-quality, contrast-enhanced CT scan or MRI. The volume of the future liver remnant (FLR) is then calculated to estimate the risk of postoperative hepatic failure. The minimal recommended volume of the FLR varies according to the quality of the liver remnant. For patients with a healthy liver, the FLR should be at least 20% of the standardized total liver volume. Patients with some degree of liver dysfunction, such as those with chemotherapy-induced liver injury, should have an FLR of at least 30%, whereas those with evidence of cirrhosis should have an FLR of 40% or more depending on degree of dysfunction. Volumetry is calculated with three-dimensional CT scan or MRI. The volume of nonfunctional liver (parenchyma that is either tumor-burdened or replaced by tumor) is subtracted from the total liver volume, which is especially important for patients with large lesions. Alternatively, the estimated total liver volume can be calculated with the patient's body weight or body surface area (i.e., total liver volume in cm^3 = −794.41 + 1267.28 × body surface area in m^2). Patients with insufficient FLR volumes should undergo portal vein embolization of the branches of the segments planned for resection to induce growth of the contralateral side. Volumetry is repeated about 4 weeks after portal vein embolization and in a few more weeks if the minimal recommended FLR has not been achieved. The degree of hypertrophy of the remnant (at least a 5% increase in the volume of the FLR or an increase of 2% per week or more) has been associated with decreased rates of postoperative liver insufficiency.

OPERATIVE APPROACH TO RESECTION

Liver resections can be categorized into anatomic and nonanatomic. Anatomic resections include segmentectomies, sectionectomies, hemihepatectomies, and extended hepatectomies (also known as trisegmentectomy). Although small peripheral lesions are usually amenable to nonanatomic resections, lesions that are large or centrally located often require anatomic resections. These procedures can be performed either through an open technique or laparoscopically.

Positioning, Incision, and Exposure

Patients are placed supine in 15-degree Trendelenburg position to decrease the risk of air embolism with both arms extended at 90 degrees. Intravenous fluids should be restricted until transection of the parenchyma is completed to decrease bleeding from hepatic veins. Central venous cannulation is often unnecessary but should be considered in patients with extensive comorbidities. If used, a central venous pressure less than 5 cm H_2O should be maintained. Once the parenchymal transection has been completed, intravascular volume should be restored to achieve euvolemia.

In the open technique, a right subcostal incision with an upper midline extension provides adequate exposure for most tumors. Alternative incisions include a midline, an inverted "T" (Makuuchi incision), or bilateral subcostal with midline extension (Mercedes-Benz incision). The xiphoid should be removed to facilitate mobilization of the suprahepatic inferior vena cava (IVC). The abdominal cavity is explored for the presence of extrahepatic disease. The round ligament is ligated, the falciform ligament is dissected up to the anterior surface of the hepatic veins. The gastrohepatic ligament is opened to expose the caudate lobe with care not to injure an accessory or replaced left hepatic artery. Intraoperative US is performed to identify all known lesions—as well as any new lesions—and their relationship with vascular and biliary structures, as well as the position of the main hepatic vessels relative to the transection plane.

Inflow and Outflow Control

For major hepatic resections, artery and portal vein inflow vessels can be dissected and controlled in the hilum of the liver, intraparenchymally, or through small hepatotomies (Fig. 1). The latter approach should be avoided if the tumors are close to the hilum (<2 cm). Selective inflow control before the transection will result in a vascular demarcation line that will guide the correct transection plane. After inflow has been controlled, control of the hepatic venous outflow is performed. This also can be done outside the liver or within the parenchyma during the transection.

Parenchymal Transection

Multiple techniques have been described for parenchymal transection. Because randomized controlled trials have suggested no differences between the various methods, in general, it should be determined by the expertise and comfort of the surgeon. A simple and frequently used technique is the crush clamp method in which the liver substance is gently "crushed" with a Kelly clamp exposing small vessels that can be divided with an energy device (Fig. 2). An alternative method is the two-surgeon technique, in which the surgeon dissects using the Cavitron Ultrasonic Surgical Aspirator and an assistant provides exposure and divides vessels. In general, small vessels less than 3 mm can be divided using electrocautery, medium vessels are controlled with titanium clips, and vessels larger than 5 mm are divided between suture. Caution should be given to overuse of linear staplers for parenchymal transection, because although simple and efficient, the technique is relatively blind and may lead to inadvertent biliary or vascular injury.

Right Hepatectomy

If a right hepatectomy is to be performed, further dissection of the anterior surface of the hepatic veins is carried out to expose the right hepatic vein. The right coronary and triangular ligaments then are divided, exposing the bare area of the liver as the right liver is mobilized and rotated to the left and the short hepatic veins draining directly to the IVC are ligated. The retrocaval ligament (Makuuchi's

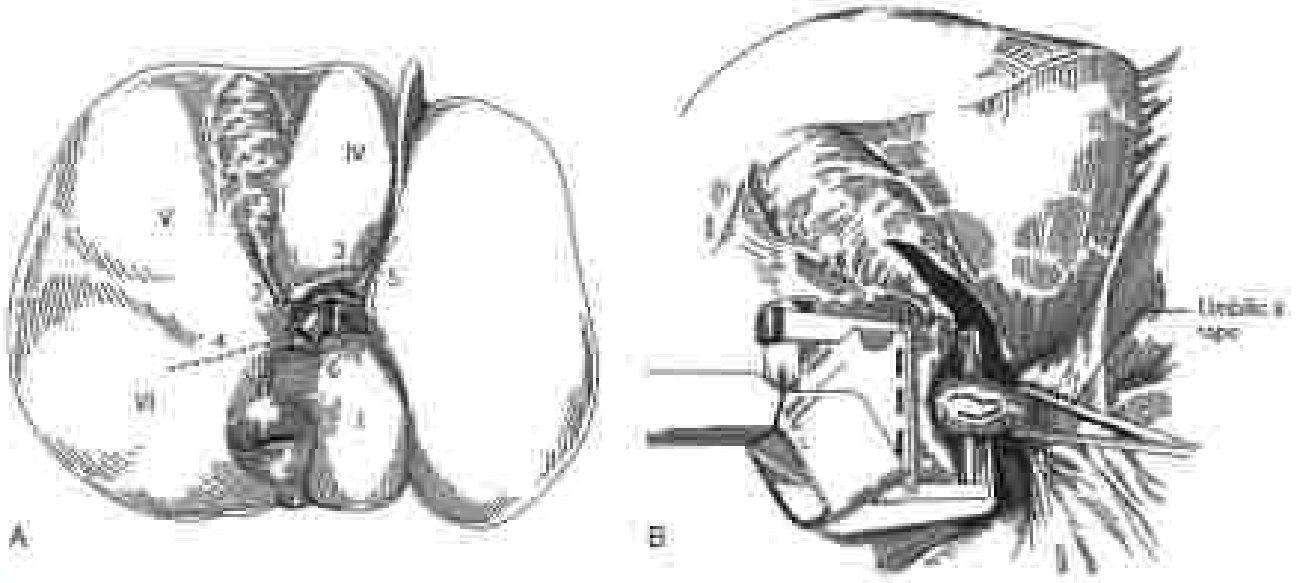

FIG. 1 (A) For the right portal pedicle to be accessed, hepatectomies are made in the gallbladder fossa (2) and in the caudate process (1). The pedicle is encircled with a metal pedicle clamp, and a vessel loop is passed around it. The vessel loop is used to retract the main portal vein/right portal vein to the left as a TA stapler is passed and fired. (B) to divide the right portal pedicle. [illegible]

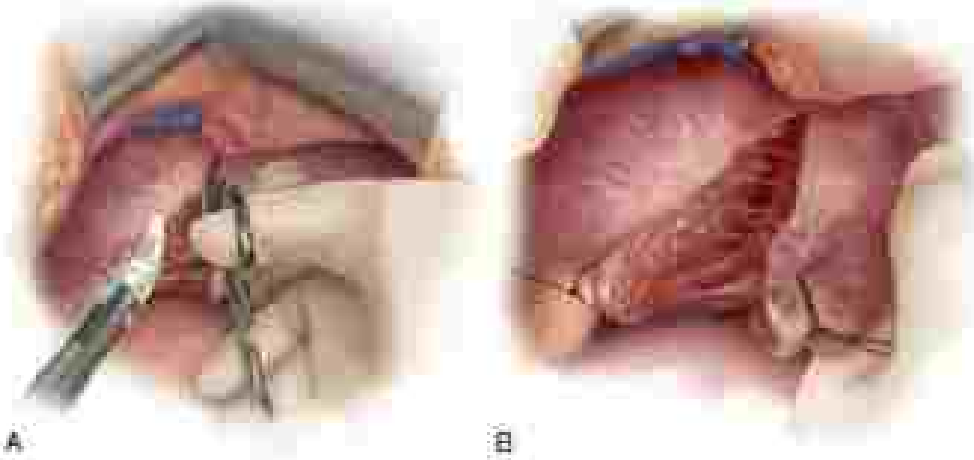

FIG. 2 (A) For division of the liver parenchyma, two stay sutures are placed for traction. The parenchyma is sequentially crush-clamped with a clamp. This demonstrates [illegible] (B) If the structure is <3 mm, the [illegible] are used. [illegible]

ligament) is identified and transected with a vascular stapler (Fig. 3). Further dissection between the liver and the IVC will expose the right hepatic vein, which is encircled. Attention is turned to the hilum, where the right hepatic artery and right portal vein are dissected and ligated. Alternatively, the right pedicle is controlled intraparenchymally as a large curved clamp is passed through an incision made in the left base of the gallbladder fossa, exiting through an incision at the junction of segment VII and the caudate process (Fig. 1). A clear line of vascular demarcation then can be identified. The right hepatic vein can then extraparenchymally be ligated with a stapler (Fig. 4). The transection plane follows the area of vascular demarcation leaving division of the right hepatic duct as the final step.

For large tumors in the right hemiliver that are adherent to the diaphragm and the retroperitoneum, an anterior approach can be used in which the parenchyma is divided before mobilization of the right liver. Inflow control initially is performed and the parenchyma is transected through the demarcated area until the anterior surface of the IVC is exposed. The right hepatic vein and short hepatic veins then are identified and ligated. The surgical maneuver, elevation of the liver by an umbilical tape passed between the anterior surface of the IVC and the liver, can facilitate this approach. The space between the right hepatic vein and the middle hepatic vein is initially dissected for 3 to 4 cm downward and a long clamp is passed gently 4 to 6 cm caudally from the anterior surface of the IVC to emerge between the right hepatic vein and the middle hepatic vein. An umbilical tape is passed behind the liver and is used as a guide to the transection plane.

Extended Right Hepatectomy

When indicated, segment IV can be resected along with the right liver. The initial steps are the same as previously described for a right hepatectomy. The transection plane is along the right side of the

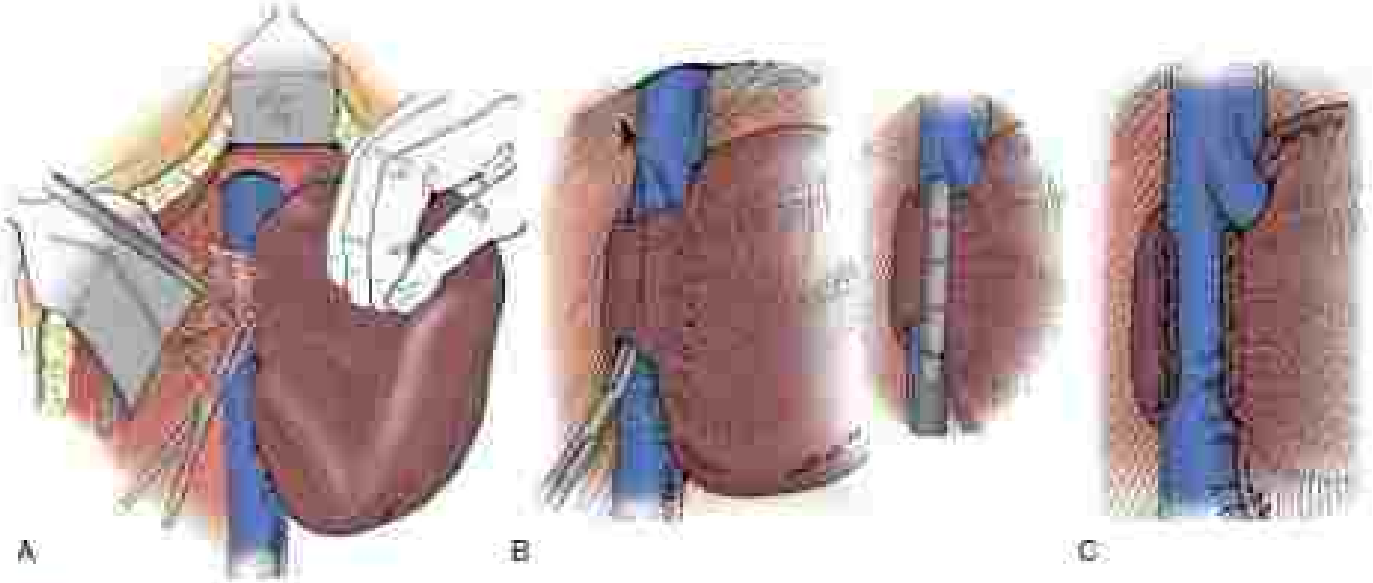

FIG. 3 (A) Division of the anterior vena cava ligament, (B) This ligament may contain liver parenchyma and/or a short hepatic vein and is therefore most safely transected with a stapler. (C) Transection will show exposure and control of the right hepatic vein. (From Blumgart LH, editor: *Surgery of the liver, biliary tract, and pancreas*, 4th ed. Philadelphia: WB Saunders; 2007. [194])

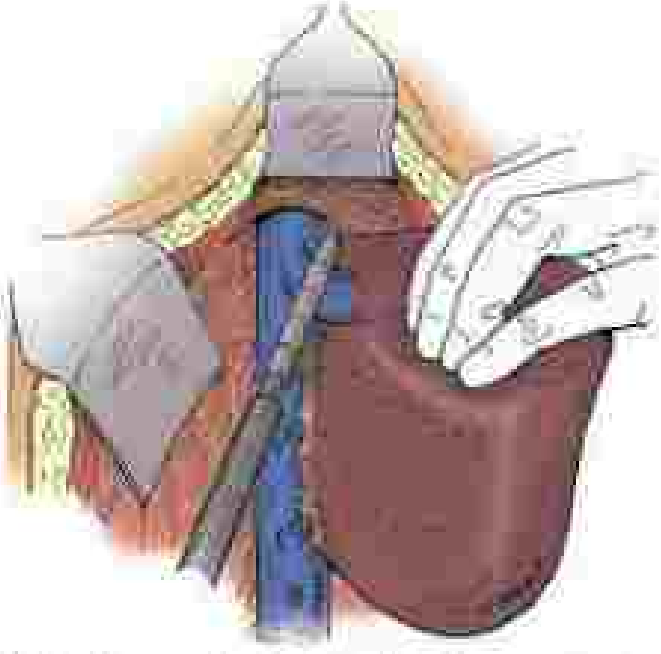

FIG. 4 Division of the right hepatic vein. With the liver retracted to the left, the right hepatic vein may be rapidly and safely divided using an Endo GIA stapler (Covidien) with a vascular load. (From Blumgart LH, editor: *Surgery of the liver, biliary tract, and pancreas*, 4th ed. Philadelphia: Elsevier; 2007. [194])

falciform ligament, from the groove separating the middle and left hepatic veins cranially to the right side of the umbilical fissure caudally, directed toward the medial aspect of the right hilar plate while avoiding the confluence of the left and right hepatic ducts. Inflow to segment IV is controlled during the transection, as is the middle hepatic vein as the surgeon moves cranially.

Left Hepatectomy

For a left hepatectomy, the triangular ligament is divided, exposing the IVC and the left hepatic vein. The round ligament is elevated and the parenchymal bridge between segments III and IVB is divided, exposing the left inflow at the base of the umbilical fissure. The left hepatic artery, portal vein, and hepatic duct are identified and ligated individually. For intrahepatic ligation of the pedicle, a curved clamp is passed through an incision that is 1 cm above the inflow to segment IVB to exit anterior to the caudate lobe (Fig. 1). The left lateral segment is rotated to the right, and the gastrohepatic ligament is divided. Exposure of the left hepatic vein is facilitated by dividing the ligamentum venosum at its insertion. The common trunk of the middle and the left hepatic vein is encircled as a clamp is passed between the left hepatic vein and the IVC, emerging between the right and middle hepatic veins. If the middle hepatic vein is to be divided because of tumor location, the common trunk is ligated with a vascular stapler. If the middle hepatic vein is to be preserved, the parenchyma between the left and the middle hepatic veins is transected and the left hepatic vein can be isolated. Alternatively, the left hepatic vein can be ligated intraparenchymally. The liver parenchyma is transected at the demarcated line. If oncologically feasible, the transection plane should run horizontally, approximately 1 cm above the hilum, from the area of transection of the left hilar plate to the left side of the gallbladder fossa, thus avoiding transection of an aberrant right anterior or posterior duct, and then turning vertical, parallel to Cantlie's line.

Extended Left Hepatectomy

When indicated, the right anterior sector (segments V and VIII) can be resected along with the left hemiliver. The initial steps are the same as those for a left hepatectomy. The main challenge is to define the transection plane, which is horizontal—extending from the right of the gallbladder fossa and anterior to the right hepatic vein toward the base of segment IV—without injuring the inflow to the posterior sector. The pedicle to the right anterior sector will be identified and ligated as transection of the parenchyma approaches the hilum.

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Hepatic Malignancy: Resection Versus Transplantation

Jaime M. Iskandar, MD, and Andrew M. Cameron, MD, PhD

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy worldwide. This aggressive and often lethal cancer frequently presents in the setting of underlying liver dysfunction. In 80% of cases, HCC is associated with cirrhosis or advanced fibrosis. It is three times more common in men and exhibits geographic variation, with the highest incidence seen in Asia and sub-Saharan Africa. The pathophysiology of HCC has been attributed to chronic inflammation secondary to cirrhosis. There is a pathologic progression from adenomatous hyperplasia to atypical hyperplasia and ultimately overt carcinoma. Risk factors for the development of HCC include viral hepatitis (hepatitis B infection even in the absence of cirrhosis), aflatoxin, aromatic amines, iron dysregulation, smoking, anabolic steroids, oral contraceptives, Budd-Chiari syndrome, α1-antitrypsin deficiency, hemochromatosis, alcoholic liver disease, and chronic Wilson's disease.

Incidences of HCC as well as the death rate related to the malignancy continue to increase in North America. As management of chronic liver disease improves, the number of patients living with compensated cirrhosis has risen. A recent study using the SEER (Surveillance, Epidemiology, and End Results) registry projects that the incidence of HCC will continue to rise until 2030. Metabolic disorders including nonalcoholic fatty liver disease and metabolic syndrome contribute more to the burden of HCC than the other risk factors including hepatitis C virus (HCV) infection. HCC is one of the leading indications for liver transplantation, with approximately 30% of patients awaiting liver transplantation in the United States carrying the diagnosis of HCC. The prognosis is poor if left untreated, with a 5-year overall survival of less than 10% and a median survival of under 6 months. Treatment options for HCC have expanded over the past few decades. In addition to liver transplantation and resection, locoregional therapies utilized as either monotherapy or as a bridge to surgical intervention have broadened the treatment options for patients. Unfortunately, only 20% to 30% of patients with HCC are candidates for either surgical or locoregional therapy at the time of presentation due to lack of adequate hepatic reserve or extent of disease. Tumor size, stage, number, location, patient's underlying liver function, and tumor pathology all must be measured when considering which treatment options to consider. Treatment mandates a multidisciplinary approach as multiple modalities may be used.

Evaluation

Patients who develop HCC are usually asymptomatic, outside of the sequelae of their chronic liver disease. Symptomatic patients may have upper abdominal discomfort, weight loss, early satiety, progression to decompensated cirrhosis, or a palpable abdominal mass. Paraneoplastic syndromes rarely occur but include erythrocytosis, polymyositis, hypoglycemia, hypercalcemia, and diarrhea. A thorough history and physical exam should focus on identification of underlying liver disease. History of ascites, gastrointestinal bleed, hepatic encephalopathy, and jaundice should be elucidated. Physical exam findings may include splenomegaly, caput medusa, ascites, gynecomastia, palmar erythema, and muscle wasting. Routine laboratory studies include coagulation factors, complete blood count, liver function tests, basic metabolic panel, alpha fetoprotein (AFP), and viral serologies.

The most common cause of death following resection for HCC is liver failure. Therefore, determining a patient's hepatic reserve preoperatively is essential for operative planning. The two commonly used measures of liver disease are the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) (Table 1). The Child-Pugh classification has been shown to be a better predictor of 30-day perioperative mortality following liver resection. Patients with class A cirrhosis are predicted to have perioperative mortality of less than 5% and can tolerate up to a 50% hepatectomy. Class B cirrhosis have a predicted mortality of 10% to 15% and should have no more than 25% of their liver volume resected. Class C cirrhosis is a contraindication to resection. The MELD score, which is comprised of bilirubin, international normalized ratio, and creatinine along with modifications for hyponatremia, prioritizes patients on the liver transplant wait list and predicts 90-day mortality. HCC patients with a MELD score higher than 9 benefit from liver transplantation.

Staging

A number of staging systems have been developed for HCC; however, no single system is universally accepted. Unlike other malignancies, tumor size and number do not adequately characterize the nature of the tumor nor do they capture the underlying liver dysfunction that accounts for significant morbidity. The American Joint Committee on Cancer Tumor Node Metastasis system provides prognostic information for patients with HCC following resection (Table 2). It

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Jaime M. Glorioso, MD, and Andrew M. Cameron, MD, PhD

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A number of staging systems have been developed for HCC; however, no single system is universally accepted. Unlike other malignancies, tumor size and number do not adequately characterize the nature of the tumor nor do they capture the underlying liver dysfunction that accounts for significant morbidity. The American Joint Committee on Cancer Tumor Node Metastasis system provides prognostic information for patients with HCC following resection (Table 2). It

TABLE 1 Child-Pugh Classification

Parameter	1 Point	2 Points	3 Points
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Slight	Moderate
Encephalopathy	None	1–2	3–4

Child-Pugh classification is calculated by summing the points per parameter. Class A = 5–6, class B = 7–9, class C = 10–15.
INR, international normalized ratio.

TABLE 2 AJCC UICC 2017 TNM Staging

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIa	T3	N0	M0
IIIb	T4	N0	M0
IIIc	Any T	N1	M0
IV	Any T	Any N	M1

T1a: Solitary tumor ≤2 cm.
T1b: Solitary tumor >2 cm without vascular invasion.
T2: Single tumor with vascular invasion, ≥ 2 cm, or multiple tumors, none >5 cm.
T3: Multiple tumors, any >5 cm.
T4: Single or multiple tumors of any size involving a major branch of the portal or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum.
N1: Regional lymph node metastases.
AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis; UICC, Union for International Cancer Control.

incorporates vascular invasion, as well as local, regional, and distant metastasis. However, it fails to account for the severity of the underlying liver disease and patient's functional status. The Barcelona Clinic Liver Cancer staging system has emerged as a standard staging system for HCC. It has the advantage of including patients' functional status and liver function in addition to the tumor-related variables (Fig. 1).

Imaging

Imaging studies play an essential role in the diagnosis of HCC. For individuals with cirrhosis, the annual incidence of HCC is 2% to 5%. As HCC is amenable to curative surgical intervention when identified early, routine surveillance is recommended for these patients and has been shown to significantly improve mortality rates. The American Association for the Study of Liver Diseases recommends that individuals with cirrhosis undergo screening ultrasound (US) at 6-month intervals with or without AFP. For patients with Child class C cirrhosis, surveillance is only recommended if they are a transplant candidate. For suspected HCC identified on surveillance imaging, diagnostic evaluation with multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) should be performed. Unlike many other malignancies, the diagnosis of HCC can be established noninvasively and tissue diagnosis is not required. The classic findings include arterial enhancement followed by venous washout. MRI is preferred in diagnosis of HCC, with a 91% specificity and 95% sensitivity compared to CT (83% and 91%, respectively). The Liver Imaging Reporting and Data System classification offers reliable probability of malignancy based on imaging findings and provides guidance for subsequent management. Cross-sectional imaging affords the advantage of visualizing tumor anatomy and assessing the potential liver remnant to assist with operative planning. If imaging findings are diagnostic for HCC, biopsy is not required to make the diagnosis due to the risk of bleeding, sampling error, and potential for seeding of the track.

Treatment

Liver Resection

The goal for hepatic resection of HCC is to resolve the patient cancer free while leaving them with an adequate functional liver remnant. Only 20% to 30% of patients have resectable tumors either due to underlying liver dysfunction or to the extent of disease. For patients who develop HCC without underlying liver disease, resection is the treatment of choice with 5-year survival reported to be as high as 70%. Imaging studies reviewed preoperatively determine resectability with regard to location, vascular involvement, and absence of distant metastases. Volumetrics can be obtained to estimate the liver remnant. If the liver remnant is thought to be inadequate (20%–30% for a healthy liver), portal vein embolization can be employed to induce hypertrophy of the future liver remnant. Intraoperative US is a useful adjunct to ensure negative margins can be secured and to evaluate for satellite lesions not seen on preoperative cross-sectional imaging. Due to the theoretical risk of intrahepatic metastases via the portal vein tributaries, anatomic resection is preferable to increase the likelihood of an R0 resection. Open or laparoscopic resection techniques are acceptable options. For patients with Child class A cirrhosis, no evidence of portal hypertension, and well preserved liver function, resection can be considered.

For patients that are referred for resection, it is important to identify prognostic factors. The main predictors of survival include tumor number, size, microvascular or macrovascular invasion, and grade. Vascular invasion is the strongest predictor of tumor recurrence and correlates with tumor number and size. For multifocal HCC with more than three nodules, Child Pugh status, microvascular invasion, and a positive margin were all negative prognostic factors, but tumor size was not. Approximately 70% of patients will develop disease recurrence within 5 years of resection; this is especially true for patients with cirrhosis.

Liver Transplantation

Liver transplantation is the gold standard for patients with HCC in the setting of Child-Pugh class B/C cirrhosis and limited hepatic reserve as it affords a significant survival advantage over liver resection. Transplantation allows for removal of the tumor and simultaneously corrects the extrahepatic manifestations of cirrhosis. Compared to partial hepatectomy, transplantation eliminates issues related to intrahepatic satellite lesions, margin status, and other anatomic limitations related to tumor location and future liver remnant volume that may otherwise deem an individual unresectable.

The outcomes for patients undergoing liver transplant for malignancy should be comparable to outcomes for patients with chronic liver disease without cancer. To ensure that this scarce resource is appropriately utilized, transplant criteria have been developed and validated. They include Milan, University of California San Francisco (UCSF), Barcelona Clinic Liver Cancer Group, Hangzhou, among others. These criteria are mostly based on size and tumor number; however, tumor biology remains an important factor. The Milan criteria have been the standard used in the United States; however, more expanded criteria, including UCSF, have demonstrated excellent results. Adherence to the Milan criteria (solitary tumor up to 5 cm or 3 tumors up to 3 cm each) has improved the 5-year survival rate to over 70% and decreased to post-transplant recurrence rate to less than 15%. The UCSF criteria include 1 tumor less than ≤5 cm or multiple tumors of which the largest is ≤3 cm and not exceeding 8

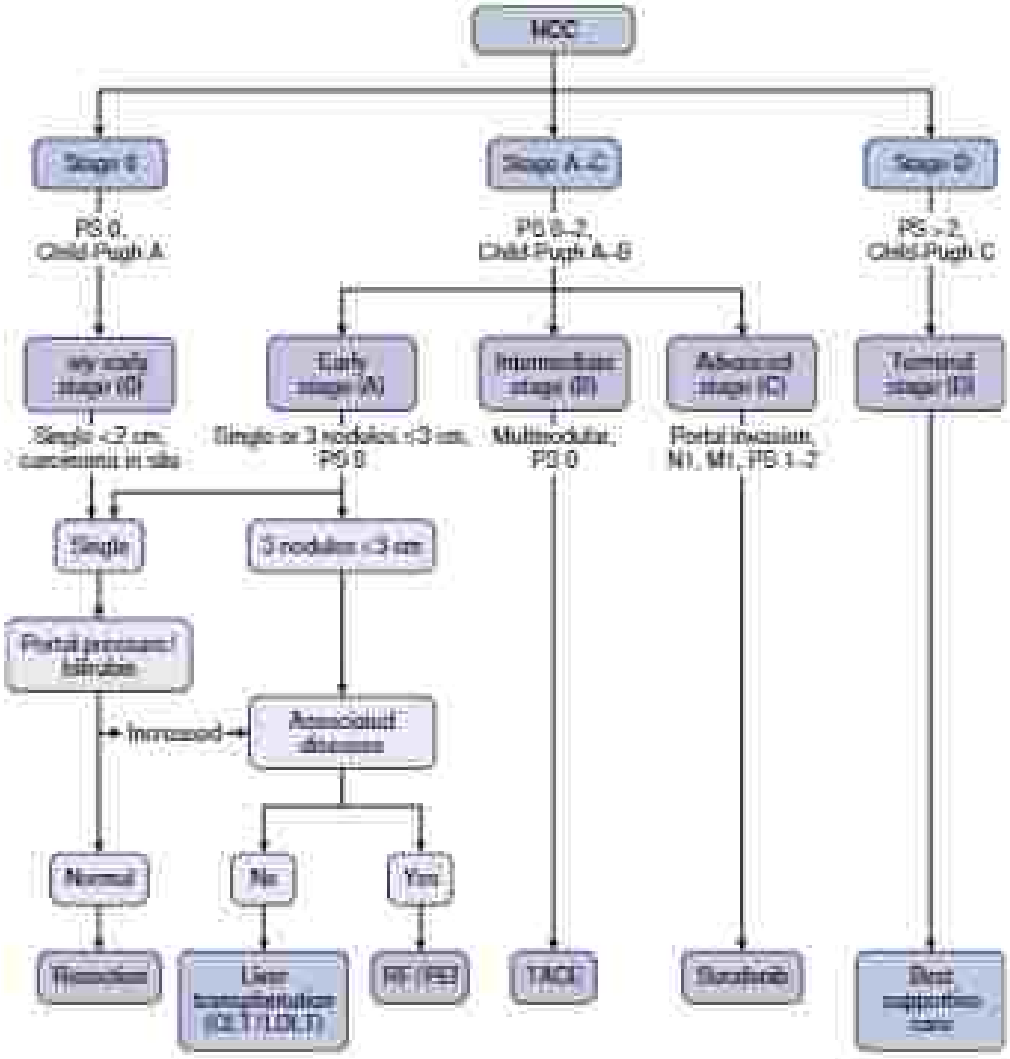

FIG. 1 Barcelona Clinic Liver Cancer staging system for hepatocellular carcinoma. CLT, Cadaveric liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; M, metastasis; N, node classification; PEI, percutaneous ethanol injection; PS, performance status; RF, radiofrequency ablation; TACE, transarterial chemoembolization. (From Cleveland D, Hussain *. Locoregional therapies in the management of hepatocellular carcinoma. [URL]; [URL])

can treat. While the Milan criteria serve as a surrogate for tumor biology, it may exclude some patients with favorable biology. AFP, tumor growth and progression, and response to locoregional therapy can all serve as surrogates for tumor biology.

The major limitation of liver transplantation for HCC is the waiting time to transplant, which can result in disease progression. Approximately 20% of patients awaiting liver transplant with HCC fall off the waitlist. Conversely, waitlist time also selects out those patients with unfavorable tumor biology or unrecognized metastatic disease who would not benefit from transplant. Patients are granted exception points 6 months after their initial listing that allow them to move up the waitlist despite maintaining a low calculated MELD score. For patients with a T2 or larger lesion, bridging therapy is used to prevent further disease progression prior to transplant. Transarterial chemoembolization, radiofrequency ablation, and other local therapies are available and vary by institution. The modalities also serve to downstage tumors that are initially outside of Milan criteria with favorable survival and recurrence rates.

While there are no randomized control trials comparing resection versus transplantation for HCC, there are a multitude of retrospective studies. Overall, the two surgical options have similar 1-year survival, but 3- and 5-year survival favors transplantation. In addition, liver transplant has better disease-free survival compared to resection. The equivalent 1-year overall survival is likely related to the perioperative morbidity associated with liver transplantation, but the oncologic benefit of transplantation is clear.

One approach for management of HCC in patients with cirrhosis is utilizing transplantation as a salvage therapy for HCC recurrence after liver resection. A few series have shown comparable survival; however, many report higher operative mortality, higher recurrence rates, and worse 5-year survival compared to primary liver transplantation. Salvage liver transplant remains controversial based on the unfavorable results and limited organ supply.

Cholangiocarcinoma

Resection is the standard of care for patients with hilar cholangiocarcinoma. Resection includes excision of the bile duct and concomitant liver resection to decrease the risk for recurrence. Unfortunately, the majority of patients are deemed unresectable at the time of diagnosis due to the severity of parenchymal disease, the inability to preserve vascular inflow and outflow from the associated tumor involvement, or inadequate remnant liver volume. Liver transplantation can overcome the above barriers in appropriately selected patients. Individuals with hilar cholangiocarcinoma are candidates for liver transplant if they present with an unresectable tumor but have no evidence of nodal or metastatic disease. They undergo a protocol including induction chemoradiation followed by operative staging and transplant. One-, three-, and five-year survival is 90%, 80%, and 75%, respectively at high volume centers that follow this highly selective and strict protocol. Transplantation for intrahepatic cholangiocarcinoma remains controversial.

Suggested Readings

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Ablation of Colorectal Liver Metastases

Kelly J. Lafaro, MD, MPH, and Yuman Fong, MD

The liver is the most frequent site of colorectal carcinoma metastases because of portal venous drainage. One-third of patients have liver metastases at the time of presentation, whereas more than half will develop liver metastases at some point during their disease course. Liver metastases are the leading cause of morbidity and mortality in cancer patients in the Western hemisphere. Surgical resection remains the mainstay of potentially curative treatment for liver metastases from colorectal carcinoma. New neoadjuvant chemotherapies, portal vein embolization, and multistaged resections together have expanded the indications for surgery in these patients. Despite these advances, a majority of patients with colorectal liver metastases are unresectable at the time of diagnosis. In addition, some patients are not surgical candidates because of prohibitive comorbid conditions or the need to preserve liver parenchyma to leave a sufficient amount to support posthepatectomy hepatic function.

Locoregional liver directed ablative therapies have emerged as a valuable adjunct to resection in patients with colorectal liver metastases who are otherwise unresectable and can even be curative for small tumors. Several ablation techniques have emerged starting in the 1980s and have evolved from cryoablation now to more effective and quicker techniques including radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE), and laser thermal ablation (LTA). This chapter summarizes the different ablation techniques and discusses patient selection, technical considerations, potential complications, and follow-up after ablation.

CRYOTHERAPY

First described in 1963, cryotherapy was initially introduced as a treatment for hepatocellular carcinoma; however, in the 1980s, its indication extended to colorectal liver metastases. At cryotherapy's inception, liquid nitrogen was used in direct contact with tumor surface, resulting in hypothermic cellular death. As the technology advanced, argon and helium gas replaced liquid nitrogen. High-pressure argon gas is passed through insulated probes followed by helium gas using the Joule-Thomson effect creating repeated freeze-thaw cycles resulting in protein denaturation, cellular dehydration, and ultimately tumor cell death. However, cryoablation is subject to substantial heat sink from surrounding hepatic vessels and has been linked to increased complications compared with other ablative techniques, including thrombocytopenia, disseminated intravascular coagulation, acute renal injury and "cryoshock," likely resulting from the repeated freeze cycles. As such, cryotherapy has largely been replaced by RFA and MWA.

RADIOFREQUENCY ABLATION

RFA has been the most widely used percutaneous liver ablative technology. It creates a closed-loop circuit between metal electrodes placed into the tumor, dispersive grounding pads placed on the patient, and the radiofrequency generator. This results in high-frequency alternating currents of 350 to 500 kHz and the friction from the agitation of ions within the tissue creates heat surrounding the probe and ultimately cell death from coagulative necrosis at temperatures higher than 60°C. If the tissue reaches greater than 100°C, carbonization or gas formation can char surrounding tissues and reduce ablative effectiveness secondary to high electrical impedance. Avoiding charring and high electrical impedance is important to maintaining more homogenous ablation zones and therefore avoiding incomplete tumor ablation and local tumor recurrence. Multiple commercial RFA electrode systems are available, including impedance controlled or temperature controlled systems. For example, the systems from Medtronic and Boston Scientific are impedance controlled, whereas AngioDynamics systems and Olympus CELON probes are temperature controlled.

RFA relies on passive conduction of heat into adjacent tissue, and the efficacy decreases with increasing tumor size. Multiple ablations can be performed for larger tumors; however, there is a risk of inadequate tumor destruction secondary to error in positioning the electrodes. Retrospective studies have shown similar rates for overall survival and disease-free survival in patients who underwent resection versus RFA for solitary colorectal liver metastases smaller than 3 cm; however, disease-free survival significantly decreased with RFA for tumors larger than 3 cm.

In addition to consideration of size, tissue composition and proximity of the lesion to hepatic vasculature are important factors influencing the outcomes of RFA. The flow of blood in large vessels creates a "heat sink," where the thermal energy created by the RFA probe dissipates and the cells surrounding the blood vessels remain at close to physiologic temperature, thus reducing the maximum temperature achieved and potentially leaving viable tumor cells.

There have been no prospective clinical trials comparing RFA with resection or other ablation techniques in the setting of colorectal liver metastases. Although retrospective studies show ablation site recurrences between 9% and 30%, the reader must keep in mind that such studies are easily susceptible to selection bias, and most frequently the data originate from patients who are not surgical candidates. Although initial retrospective data showed increased overall survival rates for patients who underwent surgical resection alone, compared with those who had a combination of surgical resection and RFA (65% vs 36%, respectively), more recent data comparing RFA in combination with resection showed comparable long-term outcomes to hepatectomy alone, with similar overall survival and disease-free survival rates. Thus, RFA is a useful tool when used alone in small tumors and complementary to surgical resection for patients with larger or bilobar tumors to achieve cure. To truly delineate the efficacy of RFA in comparison to other techniques, however, a prospective randomized clinical trial is necessary.

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In addition to consideration of size, tissue composition and proximity of the lesion to hepatic vasculature are important factors influencing the outcomes of RFA. The "heat sink" effect is large vessels creates a "heat sink," where the thermal energy created by the RFA probe dissipates and the cells surrounding the blood vessels remain at close to physiologic temperature, thus reducing the maximum temperature achieved and potentially leaving viable tumor cells.

There have been no prospective clinical trials comparing RFA with resection or other ablation techniques in the setting of colorectal liver metastases. Although retrospective studies show ablation site recurrences between 8% and 20%, the reader must keep in mind that such studies are easily susceptible to selection bias, and most frequently the data originate from patients who are not surgical candidates. Although initial retrospective data showed increased overall survival rates for patients who underwent surgical resection alone, compared with those who had a combination of surgical resection and RFA (46% vs. 34%, respectively), more recent data comparing RFA in combination with resection showed comparable long-term outcomes to hepatectomy alone, with similar overall survival and disease free survival rates. Thus, RFA is a useful tool when used alone in small tumors and complementary to surgical resection for patients with larger or bilobar tumors to achieve cure. To truly delineate the efficacy of RFA in comparison to other techniques, however, a prospective randomized clinical trial is necessary.

MICROWAVE ABLATION

MWA uses high-frequency oscillating electromagnetic fields of either 915 mHz or 2.45 GHz delivered through antenna probes. This induces rapid realignment of polar molecules to a lesser, increasing kinetic energy and heating the tissue. Water molecules are particularly affected and thus lesions with higher concentrations of water are more susceptible to heating by microwave ablation.

There are multiple advantages to microwave ablation over RFA. Studies comparing MWA and RFA have shown (1) faster ablation time with faster heating, (2) larger tumor capacity, and (3) increased and more consistent ablation zones, and fewer ablation site recurrences with MWA.

1. MWA was shown to be capable of reaching temperatures as high as 150°C, much faster than RFA. MWA is also not as susceptible to heat sink as RFA, making it ideal for tumors in the liver, particularly those situated near vessels. Ablation times for MWA averaged between 2 and 5 minutes in three studies, with most being less than 10 minutes, which is less than that of most RFA treatments.
2. The heat produced with MWA can be propagated through charred tissue better than RFA, in part leading to the success treating larger lesions.
3. Single or multiple probes can be used simultaneously, contributing to the larger ablation zones observed with MWA. Finally, no grounding pad is needed, making the procedure more feasible.
4. Finally, a retrospective matched cohort study comparing MWA and RFA for colorectal liver metastases showed lower ablation site recurrence rates for those treated with MWA (6% vs. 20% for RFA).

Although there are several advantages of MWA over RFA, the cables are bulkier and have been prone to heating issues in some cases. General anesthesia is typically required for both MWA and RFA to decrease motion and improve patient comfort. MWA, like RFA, can be performed under both computed tomography (CT) and ultrasound (US) guidance. Although US allows for real-time imaging of ablation zones and often decreases the amount of time per ablation, CT is useful for lesions that are not well imaged by US. Percutaneous, laparoscopic, and open MWA are used depending on the patient. Percutaneous ablations are especially useful in patients who are not a surgical candidate, whereas laparoscopic and open ablations are ideal for patients who have tumors in areas that cannot be reached percutaneously, and for situations in which a combination of resection and ablation will render the patient without evidence of disease.

In studies reviewing complications of ablation technologies, MWA had a complication rate of 4.4% and a mortality rate of 0.26%, comparable to RFA. The most common complications noted for MWA were hemorrhage requiring blood transfusion, portal vein thrombosis, bile leak, liver abscess, and pleural effusion.

In a recently published series of more than 800 microwave ablations for small liver cancer, durable response can be seen in more than 90% of subcentimeter lesions. For tumors 1 to 3 cm in size, only 9% of tumors recurred in 3 years (Figs. 1 and 2). Ablations can indeed be curative in small tumors.

IRREVERSIBLE ELECTROPORATION

IRE is a newer, nonthermal ablation technology, which was approved by the US Food and Drug Administration in 2008 for tumor ablation. IRE uses multiple electrodes, which deliver 2 to 3 kV direct current pulses lasting up to milliseconds. These currents cause damage to the surrounding cell membranes. Initially, the damage to the cell membranes is reversible, however, with increased time, this damage becomes irreversible, leading to apoptosis. Compared with MWA and RFA, ablation time used for IRE is very short. Although this decreases overall ablation time, care must be taken to position probes accurately because they cannot be adjusted midablation.

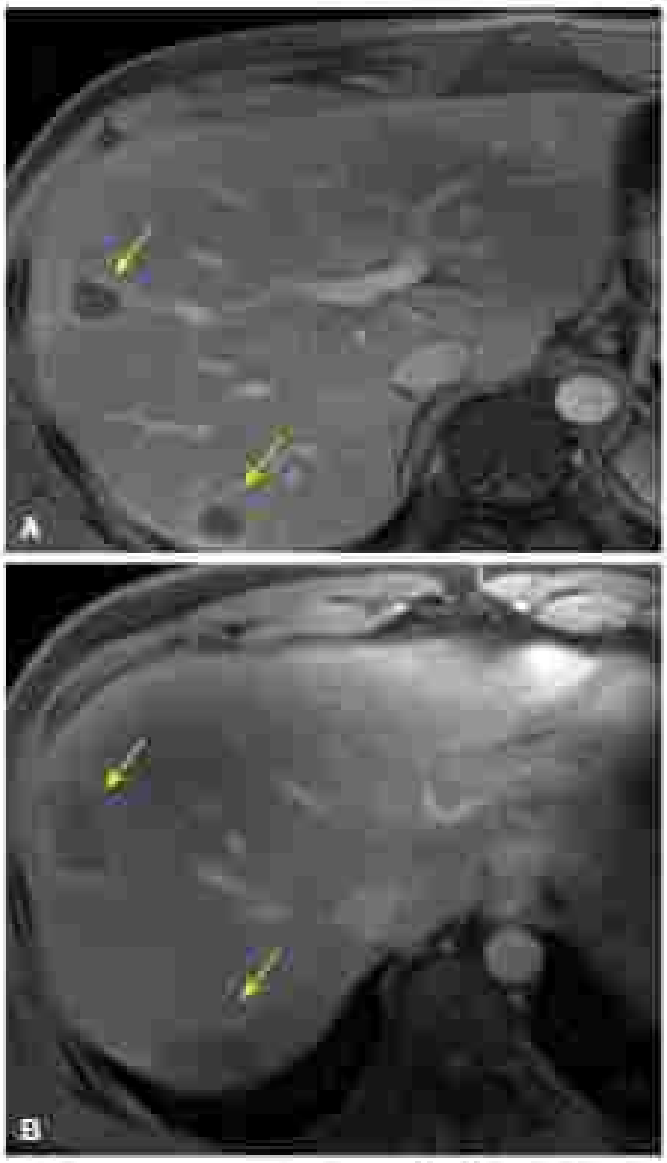
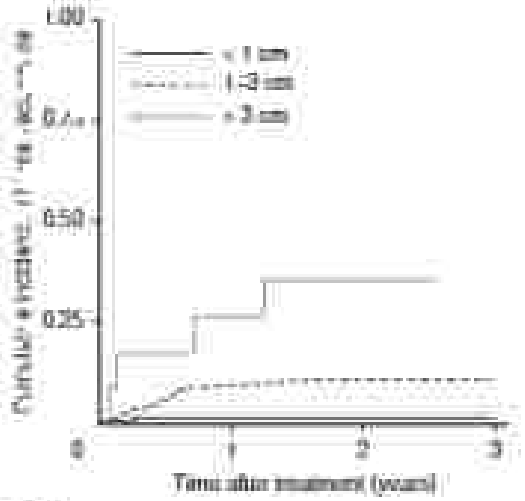


FIG. 1 Long-term appearance of microwave ablated lesions in the liver. (A) Classical portal venous phase appearance of metastatic colorectal cancer lesion (arrow): dark lesion with hypodense rim. (B) Unenhanced ablated area 3 years later.

Nonthermal technology has little destruction of surrounding tissues and adjacent tissue architecture is well preserved, and heat sink is not an issue with IRE. The combination of little destruction of surrounding tissues and lack of heat sink make IRE ideal for tumor situated near vessels or bile ducts. However, the multiple probes necessary to create the current are costly and can also be more technically challenging to position than other ablation probes (Fig. 3). The ablation zone created by IRE is often not evident by US for several minutes, making it difficult to ensure successful destruction of the tumor. In addition, IRE requires general anesthesia with paralysis because the currents can result in muscle spasms and arrhythmias. To decrease the chance of arrhythmias from IRE, the generator is linked to an ECG sensing triggering device, which signals pulses to be delivered in the cardiac refractory period.

IRE was first reported in the metastatic colorectal cancer patient population in 2014, when Silk et al. published a study of 22 metastatic lesions in 11 patients ranging from 1 to 4.7 cm in size. They reported an efficacy of 95% with local tumor recurrence in 1 of the 11 patients



No. of tumors at risk

< 1 cm	103	52	19	6
1–3 cm	381	157	52	19
> 3 cm	12	5	2	0

FIG. 2 Durability of microwave ablation. Treatment of <1 cm tumor was 98%; treatment of 1- to 3-cm tumor was 91%. (From Hong CL, et al.: Long-term outcome following microwave ablation for liver malignancies. Br J Surg. 2015;102:982.)

by 9 months. A larger study of 81 metastatic lesions, although not all colorectal in origin, reported a 67% primary efficacy. More recently, Engstrand et al. reported on 29 metastatic colorectal as well as neuroendocrine lesions, in which a 7.5% local failure rate was seen, with a time to recurrence of 66 to 150 days.

A study reviewing complications of IRE used in multiple organ ablations reported a 14% complication rate with the most common complications being pneumothorax, portal vein thrombosis, biliary obstruction, pleural effusion, and cholangitis. Arrhythmias were reported in 6% of the patients in this study. Of note, no uncontrolled muscle spasms were reported in this study in patients who were under general anesthesia with paralysis.

LASER THERMAL ABLATION

LTA uses optical fibers to deliver high energy laser radiation to the tissue, which reaches temperatures of 150°C, leading to coagulative necrosis. The penetration of light is optimal near the infrared spectrum; therefore, neodymium:yttrium aluminum garnet (wavelength 1064 nm) and diode (800–980 nm) lasers are the most commonly used. Flexible quartz fibers deliver light and a spherical thermal lesion of 12 to 15 mm in diameter. Up to four fibers can be used simultaneously to increase the ablation zone.

Although LTA is not as robustly studied as other ablative techniques, Vogl et al. reported on 549 patients with colorectal liver metastases up to 5 cm in diameter treated with LTA. The 3- and 5-year survival was 29% to 74.2% and 19% to 37%, respectively, which is comparable to RFA and MWA. However, LTA has not become a mainstay treatment for colorectal liver metastases in most institutions. The placement of fibers can be difficult and the technology is also affected by heat sink. The major downfall of LTA is the small ablation zone, making it less ideal than other ablation techniques to address metastases from colorectal cancer.

PATIENT SELECTION

Whenever feasible, surgical resection should remain the standard treatment for colorectal liver metastases; however, in patients who are not surgical candidates because of comorbid conditions or extent of disease, a combination of systemic and ablative therapies should be used. Systemic chemotherapies have improved significantly, with some regimens resulting in 70% response rates. Long-term durable response remains an issue, however.

As with all cancer care, patients should be evaluated by a multidisciplinary team including medical oncologists, surgical oncologists, diagnostic radiologists, interventional radiologists, and pathologists. Each case should be reviewed to determine surgical feasibility and, if not, the possibility of ablation. Before consideration for ablation, several factors must be taken into consideration including response to chemotherapy, tolerance of systemic therapies, comorbid conditions, presence of extrahepatic metastases, baseline hepatic function, and tumor specific characteristics. Older patients or those with significant comorbid conditions who would not tolerate surgical resection with liver only disease should be considered for ablation. In addition, patients with bilobar disease who are otherwise surgical candidates should be considered for partial hepatectomy of the portion of liver with higher tumor burden and ablation of lesions in the remnant, assuming there are only a few lesions remaining. All lesions should be able to be addressed during the combined resection and ablation to make it a reasonable option.

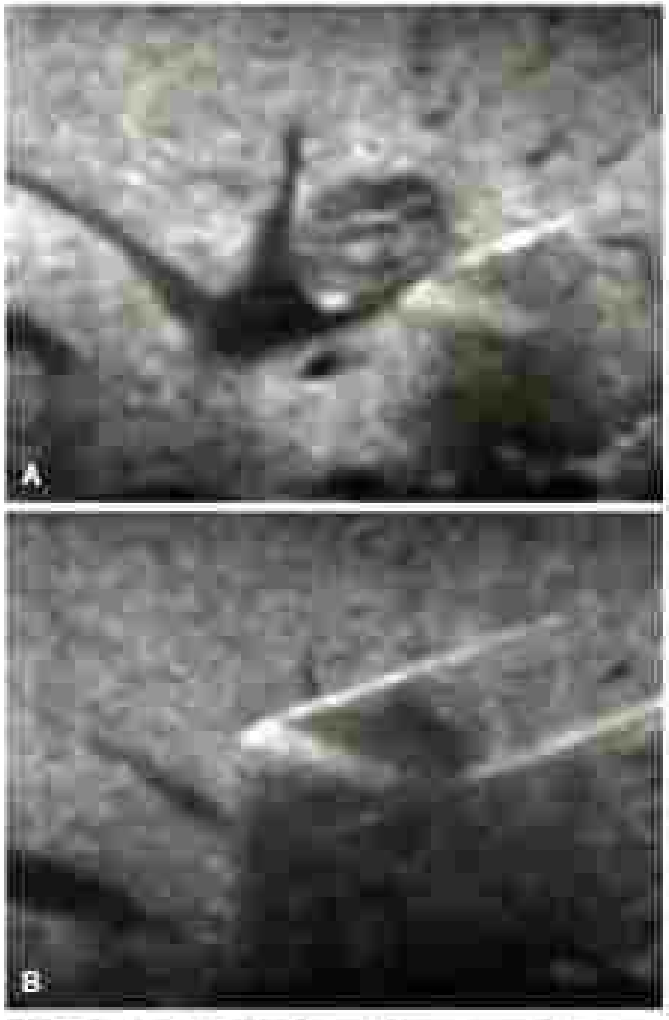


FIG. 3 Placement of needles for irreversible electroporation. (A) Tumors in a similar area were difficult to ablate with thermal ablation. Irreversible electroporation now allows perivascular ablation with good long-term outcomes. (B) Two needles are placed bracketing the tumor. Passage of needles into hepatic vein and vena cava is acceptable and will allow complete ablation.

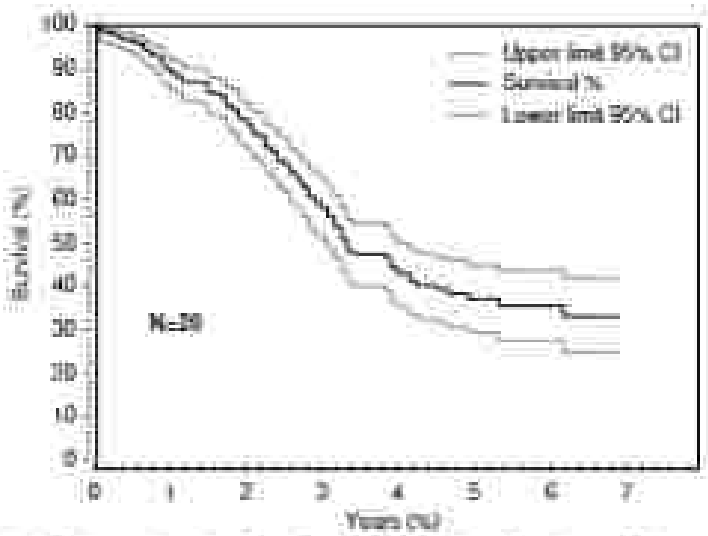


FIG. 4 Long-term survival after combined ablation and resection. Overall survival and 95% confidence interval (CI) curves for patients with liver metastases treated by resection in combination with intraoperative ablation. (From Hyun et al. Combined Ablation and Resection of Bilobar Colorectal Liver Metastases. PLoS One. 2016;11(1):e0147...)

BASELINE HEPATIC FUNCTION

In addition to a thorough metastatic workup, patients should also get a baseline evaluation of hepatic function before consideration of ablation. This hepatic liver function tests as well as evaluation of current radiologic scans for evidence of portal hypertension, cirrhosis or steatosis should be used. Chemotherapy-induced hepatic sinusoidal obstruction, which increases the risk of postresection liver failure, has not been shown to increase the risk of complications after liver ablation. However, portal hypertension and thrombocytopenia resulting from splenomegaly puts patients at increased risk of complications after ablation.

TUMOR-SPECIFIC CONSIDERATIONS

Radiologic studies including any CT or magnetic resonance imaging (MRI) scans should be evaluated and the size, number, distribution, and location of metastases within the liver noted. Ideal lesions for ablation include those smaller than 3 to 3.5 cm. Lesions larger than this require multiple probes or repeated ablations with overlapping ablation zones, which makes the tumor destruction less reliable and increases the chance of local recurrence. If there are multiple lesions within close proximity, surgical resection should be considered if the patient is a candidate. Lesions deep in the liver or within close proximity to major vessels or central bile ducts can be effectively ablated; however, the type of ablation technique should be chosen depending on location. If the lesion is close to major vessels, RFA should be avoided and MWA used to avoid substantial heat sink. Thus, ideal lesions for ablation remain small, deep lesions in the liver that do not lend themselves to surgical resection. While deciding whether to perform ablation percutaneously, laparoscopically versus open proximity to surrounding organs including the gallbladder, colon, stomach, diaphragm, and heart should be taken into account. When performed laparoscopically or open in combination with resection, these structures can be retracted to avoid thermal injury.

COMBINED ABLATION AND RESECTION

As surgeons have become more comfortable with intraoperative ablation, these procedures have extended the limits of surgical procedure for possible cure. When confronted with dominant disease on one side and small contralateral lesions, many surgeons now will perform a major liver resection along with ablation on the opposite side. Such experiences of combining ablation with resection from three different major centers were examined recently by Ward and colleagues. Such a combined procedure was found to be safe and produced very acceptable long-term survival given the bilateral liver disease (Fig. 4).

EXTRAHEPATIC METASTASES

According to current National Comprehensive Cancer Network guidelines, all patients diagnosed with colorectal cancer should undergo radiographic imaging to evaluate for extrahepatic disease, including a CT scan of the chest, abdomen and pelvis, and possible positron emission tomography CT. In terms of diagnosis of hepatic metastases, MRI with liver-specific contrast is the most sensitive modality. Similar to surgical candidates, patients with liver only disease remain the best candidates for ablation. Patients with pulmonary disease should be evaluated by a thoracic surgeon for possible lung-directed treatment. However, for small volume lung disease, the liver disease status dominates the clinical outcome. Thus, minimal lung metastasis is no longer a contraindication to liver tumor ablation. Patients with unaddressed peritoneal disease or bulky distant nodal disease should not be considered for ablation as it will add little benefit in this case.

TREATMENT APPROACH

Liver-directed ablative techniques can be performed under US, CT, or MRI using either percutaneous, laparoscopic, or open approach. For percutaneous procedures, patients generally require conscious sedation or general anesthesia for pain control as well as to minimize movement throughout the procedure. Prophylactic antibiotic usage has been debated and varies by institution. However, patients at high risk for liver abscesses, including those with a history of a biliary enteric anastomosis or biliary stents, should receive at least perioperative antibiotics and potentially a longer postprocedure course.

For those ablations performed laparoscopically or during laparotomy, a thorough intraoperative US of the liver should be used to identify any additional lesions present not seen on preoperative imaging. Up to 20% of patients are found to have extrahepatic disease not apparent on preoperative radiography. Once all the lesions are identified and mapped out, the placement of the ablation probes must be planned carefully to avoid major vessels and bile ducts, especially if using RFA. Surrounding organs should also be identified and retracted if possible. Cholecystectomy can be performed if the gallbladder is at risk of thermal injury. The probes should always be placed under US guidance into the lesion, taking into account where on the probe the particular ablation technique originates from. If multiple ablation zones are needed, the probe should be placed at the deepest portion of the lesion first. This is important as gas is created during the ablations, which is echogenic and can obscure the border of the tumors on US.

Once the probes are confirmed by US to be in position, the ablation is initiated. For RFA, tissue temperature is monitored to keep parenchyma between 100°C and 110°C to avoid charring, which affects impedance. For MWA, the frequency and time are chosen depending on the probe used and ablation zone necessary. Once the desired temperature and impedance for RFA or time duration for MWA are reached, the ablation is completed and probe is repositioned if necessary.

FOLLOW-UP

After liver ablation, liver function tests should be checked because they may acutely rise after ablation but should progressively return to baseline. Carcinoembryonic antigen should also be followed every 3 months as a rise in carcinoembryonic antigen is concerning for recurrence. Postablation imaging including CT scan or MRI should be obtained to determine efficacy of the ablation. Keep in mind that colorectal liver metastases are hypervascular in nature; therefore, it can be difficult to distinguish between residual tumor and necrosis resulting from the ablation. The current guidelines put out by the International Working Group on Image Guided Tumor Ablation recommend a baseline CT or MRI be obtained within 1 to 4 weeks postablation. The postablation and postablation imaging should be compared with look at size, shape, and location of the necrosis with ideally a 5- to 10-mm margin of ablation around the tumor. Once inflammation has subsided, positron emission tomography scans have been shown to be sensitive for detection of recurrent lesions. However, there must be at least 3 months allowed for inflammation to resolve. National Comprehensive Cancer Network guidelines recommend follow-up imaging every 3 to 6 months postablation for the first 2 years, followed by every 6 to 12 months.

COMPLICATIONS

For all the liver directed ablative techniques, complications range from minor skin burns to more serious ones including hemorrhage and bile leak. Historically, cryoablation has the highest complication rate, with some reports as high as 10% to 20%. Cryoablation has been linked to complications including thrombocytopenia, disseminated intravascular coagulation, acute renal injury, and cryoshock, likely because of the repeated freeze cycles. The high complication rates ultimately resulted in cryoablation being replaced to large part by RFA and MWA.

Both RFA and MWA have a lower rate of complications, ranging from 2.2% to 9.5%. The largest study evaluated 13,283 patients who underwent RFA of at least one liver lesion and had a complication rate of 3.3%, with the most common being hepatic infarcts, liver abscesses, bile duct injury, and bile leaks. Number complications include pleural effusions, burns to the skin, pneumothorax, intestinal injury, diaphragmatic injury, gallbladder injury, and cardiac tamponade. The most common complications reported with MWA were hemorrhage requiring blood transfusion, portal vein thrombosis, bile leak, liver abscess, and pleural effusion. Determinants of complication rates in RFA and MWA include tumor size, location, physician and institution experience, and approach (percutaneous vs. surgical). Reports of complications after IRE reach 16%, with the most common complications being pneumothorax, portal vein thrombosis, biliary obstruction, pleural effusion, and cholangitis.

SUMMARY

Surgical resection remains the mainstay of treatment of metastases from colorectal cancer. For patients who are not surgical candidates, ablation techniques offer significant disease free survival. In addition, ablation offers a potential cure for patients with small lesions that are located deep in the liver and would be technically difficult to resect. Ablation also allows us to extend resection criteria for patients with bilobar disease, which would previously have been deemed unresectable, such as a patient with a large left-sided lesion and two to three small ones in the right lobe. This patient may benefit from a left hepatectomy and ablation of the lesions on the right. Clinical trials are needed to better study patient selection and outcomes with current ablation technology. As current ablation techniques improve and new technology is introduced with larger, more consistent ablation zones, the indications for ablation of colorectal liver metastases will extend.

SUGGESTED READINGS

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MANAGEMENT OF HEPATIC ABSCESSES

Henry A. Pitt, MD

Hepatic abscesses are uncommon but remain lethal if not promptly recognized or adequately treated. Liver abscesses may be categorized as pyogenic, fungal, amebic, or mixed. Pyogenic liver abscesses (PLA) have multiple etiologies, are frequently polymicrobial, and their management has evolved significantly over the past 2 decades. Fungal abscesses are the least common, but their incidence is increasing especially in immunocompromised patients with cancer or who have undergone a transplant. Amebic liver abscesses (ALA) are caused by *Entamoeba histolytica* and occur most commonly in tropical, developing countries.

Mixed bacterial and fungal abscesses may occur especially when patients have been exposed to multiple antibiotic courses and/or to broad spectrum antibiotics. In addition, amebic abscesses may become secondarily infected with bacteria, but this situation is uncommon. Management of pyogenic, fungal, amebic, and mixed hepatic abscesses varies considerably. As with many areas within surgery, nonoperative and minimally invasive treatment options have become the norm. However, hepatobiliary surgery may be lifesaving when an abscess ruptures or when less invasive approaches are unsuccessful.

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outcomes improved. During this time, surgical drainage was required but evolved from extraperitoneal to transperitoneal approaches. Over the past 30 to 40 years, however, the evaluation of image-guided aspiration, percutaneous catheter drainage (PCD) as well as percutaneous and endoscopic biliary procedures and eventually invasive surgery (MIS) have dramatically altered PLA management. With all these advances, the outcomes for most patients with PLA have continued to improve. However, the development of advanced hepatopancreatobiliary (HPB) surgery, liver transplantation, and various ablative techniques for managing liver tumors has created new etiologies and treatment challenges.

Pathophysiology

PLAs may arise by several mechanisms including: (1) via the bile ducts, (2) via the portal vein, (3) by direct extension, (4) via the hepatic artery, (5) as the result of trauma, or (6) without an obvious cause, *cryptogenic*. In recent years, especially at western tertiary referral centers, PLAs of biliary origin are most common. Frequently, these patients will have a biliary malignancy that is being managed with biliary stents. Patients with benign biliary strictures, those with a prior biliary enteric anastomosis, and Asian patients with hepatolithiasis also are prone to PLA formation. In the first half of the twentieth century, appendicitis was the most common cause of PLAs. Currently, diverticulitis is the most frequent underlying infection that reaches the liver via the portal vein.

Severe forms of cholecystitis may cause a liver abscess by direct extension. Bacterial endocarditis may lead to multiple liver and/or splenic abscesses with the infection transmitted via the hepatic artery. Liver trauma may result in an intrahepatic hematoma that can become secondarily infected. Segmental hepatic infarctions following hepatobiliary surgery or ablative hepatic arterial therapies also may result in bacterial colonization and abscess formation. These various etiologies of PLAs require multiple therapeutic options and also are associated with different types of bacterial or fungal contamination.

The organisms most commonly associated with PLAs of benign biliary origin are *Escherichia coli*, *Enterococcus*, and *Klebsiella* spp. (Table 1). In patients with cholangitis and severe cholecystitis, anaerobes including *Clostridium perfringens* may also be isolated. In patients with biliary malignancies who have been exposed to many antibiotics, *Pseudomonas* spp., vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant (MDR) gram-negative aerobes, and yeast are also frequently cultured. In addition, these biliary PLAs often will be polymicrobial. In patients with diverticulitis or appendicitis, *Bacteroides fragilis*, other anaerobes and gram-negative aerobes are found most often in the associated PLA. The organisms isolated most frequently in patients with endocarditis are *Staphylococcus aureus* and *Streptococcus* spp. Similarly, if a liver abscess occurs as the result of a subcutaneous abscess, *Staphylococcus* spp., including methicillin-resistant *Staphylococcus aureus*, are cultured most often. Cryptogenic abscesses, especially in Asia, frequently grow *K. pneumoniae*, and anaerobes are also isolated more commonly in these patients.

Diagnosis

Almost all patients with PLAs present with liver and/or chills. Malaise and anorexia often are associated findings. The majority of patients will have some abdominal discomfort, frequently in the right upper quadrant. However, if diverticulitis or appendicitis is the underlying cause, the pain will be in the left or right lower quadrant, respectively. Nausea, vomiting, and weight loss also may be part of the presentation. In patients with a biliary etiology, jaundice may be present, but in those with biliary stents and cholangitis, PLAs may evolve without clinical jaundice. Physical examination will vary with etiology, but most patients will have no obvious abdominal findings.

The majority of patients with PLAs will have an elevated white blood cell count and some elevation of alkaline phosphatase. Mild increases of other liver function tests and hypoalbuminemia also are common. C-reactive protein usually is elevated, but serum lactate levels are normal unless the patient presents with septic shock. In some patients, pus may be seen in the liver on open abdominal surgery. Ultrasound (US) is helpful in screening for biliary pathology, but contrast-enhanced computed tomography (CT) is diagnostic in more than 95% of cases (Fig. 1). Magnetic resonance imaging (MRI) is equally sensitive and may provide additional useful information with respect to the biliary tree. In patients with indwelling biliary stents, direct cholangiography may also demonstrate the abscess(es) (Fig. 2). Culture of the bile in patients with abscesses of biliary origin will almost always be positive and can guide antibiotic therapy. In comparison, blood cultures will grow organisms in only half of the patients with PLAs.

TABLE 1 Typical Bacteria Associated With Underlying Etiologies of Pyogenic Liver Abscesses

Underlying Etiology	Typical Bacteria
Benign biliary	*Escherichia coli* *Enterococcus* spp. *Klebsiella* spp.
Cholangitis and severe cholecystitis	Anaerobes *Clostridium perfringens*
Biliary malignancies	*Pseudomonas* spp. VRE MDR aerobes Yeast
Diverticulitis, appendicitis	*Bacteroides fragilis* Other anaerobes Gram-negative aerobes
Endocarditis	*Staphylococcus* spp. *Streptococcus* spp.
Subcutaneous abscesses	*Staphylococcus* spp. MRSA
Cryptogenic	*Klebsiella pneumoniae* Anaerobes

MDR, Multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VR, vancomycin-resistant *Enterococcus*.

TREATMENT

Antibiotics

As with any serious infection, blood cultures should be drawn before antibiotics are initiated. If the patient presents with sepsis or septic shock, a serum lactate should be sent, and aggressive fluid resuscitation should be initiated immediately. The choice of antibiotic(s) should be based on the suspected underlying etiology and therefore the likely bacteriology (Table 1). Patient factors such as a known penicillin allergy or altered renal function should also influence the choice of antibiotic(s).

For PLAs of biliary etiology, a broad-spectrum penicillin with good coverage for gram-negative aerobes and *Enterococcus* spp. is one option for an antibiotic-naïve patient. However, broader coverage for anaerobes, *Pseudomonas* spp., VRE, and MDR aerobes is indicated for patients with indwelling stents who have received multiple prior courses of antibiotics. Ideally, these patients will have prior bile cultures that will guide antibiotic choices. In patients with diverticulitis or appendicitis, metronidazole to adequately cover *B. fragilis* should be part of the antibiotic regimen. If endocarditis or a subcutaneous abscess is the suspected source, vancomycin should be included in the antibiotic regimen until sensitivities are available. As blood, aspirate, or percutaneous drainage culture data become available, the

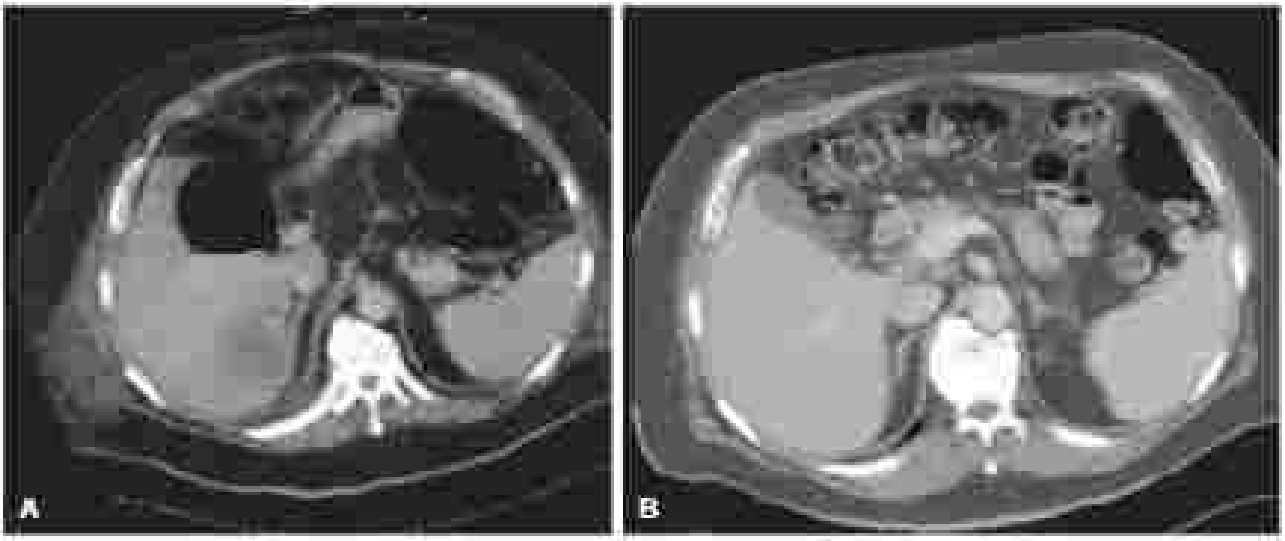

FIG. 1 (A) Computed tomography (CT) scan demonstrating a large pyogenic lung abscess (PLA) with an air-fluid level in segments [illegible] and 6. (B) CT scan 7 months later in the same patient, documenting complete resolution of the PLA after percutaneous catheter drainage.

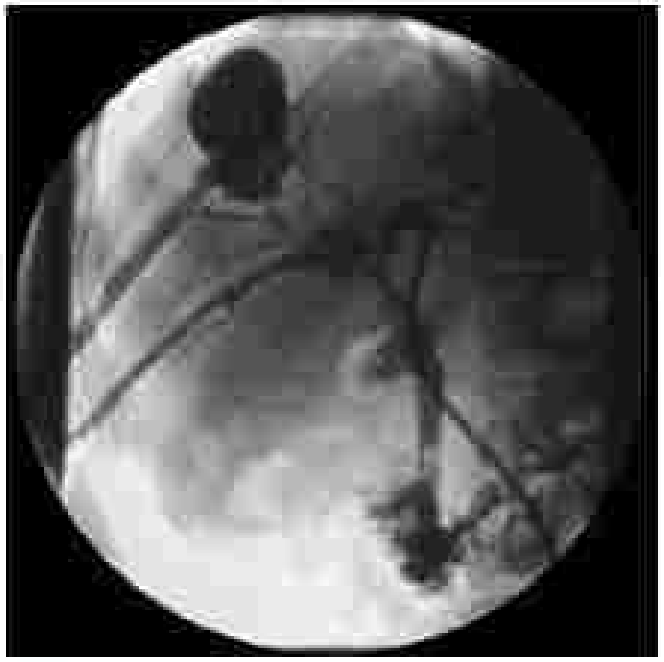

FIG. 2 Tube cholangiogram demonstrating a pyogenic liver abscess that has been percutaneously drained in a patient with an unresectable biliary malignancy and intrahepatic biliary stones.

antibiotic regimen should be tailored to cover the sensitivities of the isolated bacteria. Most experts recommend a 4 to 6 week antibiotic course, but a shorter regimen may be appropriate if adequate drainage and a good clinical response have been achieved. Also, if oral antibiotics will cover the isolated bacteria, not all patients will require home intravenous antibiotics.

Aspiration

Percutaneous image-guided aspiration should be performed to confirm the diagnosis and to obtain samples for culture in selected patients with a small, solitary, easily accessible abscess; aspiration and appropriate antibiotics may be adequate therapy. In these patients, repeat aspirations may be indicated if clinical response is slow. However, many patients will have a large abscess, a multiloculated abscess, thick abscess rim, and/or multiple abscesses. In these patients, aspiration alone will not be adequate and should not be undertaken. An alternate for patients with a larger, multiloculated, and/or viscous abscess is PCD.

Percutaneous Drainage

Over the past 3 decades, a shift has occurred so that the majority of patients with PLAs are managed with PCD. This procedure can be performed under US or CT guidance. Most of these procedures can be accomplished under local anesthesia with minimal sedation. After aspiration of pus for culture, a guidewire is placed into the abscess followed by placement of an 8Fr to 14Fr pigtail catheter (Fig. 3). Contrast is injected to define the cavity, but care is taken not to aggravate sepsis by over injection. The catheter is left to gravity drainage, but frequently, small volume irrigations with sterile saline solution are indicated to ensure catheter patency. Subsequent procedures to increase catheter size and/or to interrupt loculations may be indicated.

In recent series of PLAs, approximately 80% of patients have been managed by PCD. In addition, in most reports the success rate for intravenous antibiotics and PCD has been 90% or greater. Factors that may lead to failure include a chronic abscess with thick, fibrous walls; a cluster of smaller abscesses as opposed to loculation within one abscess; or biliary communication with proximal obstruction. Bilateral abscesses or a difficult location, for example, high in segments VII or VIII, may be contraindications to PCD. In addition, a ruptured abscess or association with an intraabdominal problem that requires laparotomy, such as appendicitis or infected peripancreatic necrosis, are situations in which surgery is preferred.

Surgical Drainage

In the preantibiotic era, several intraperitoneal approaches to abscess drainage were described. In the 1960s and 1970s, a transperitoneal approach was preferred and was said to have the advantage of providing the opportunity for an exploratory laparotomy to find an undiagnosed abscess source. This strategy became less necessary as cross-sectional imaging improved in the 1980s and 1990s. Since then, the evolution of MIS and intraoperative US have led to these techniques being preferred when surgery is required.

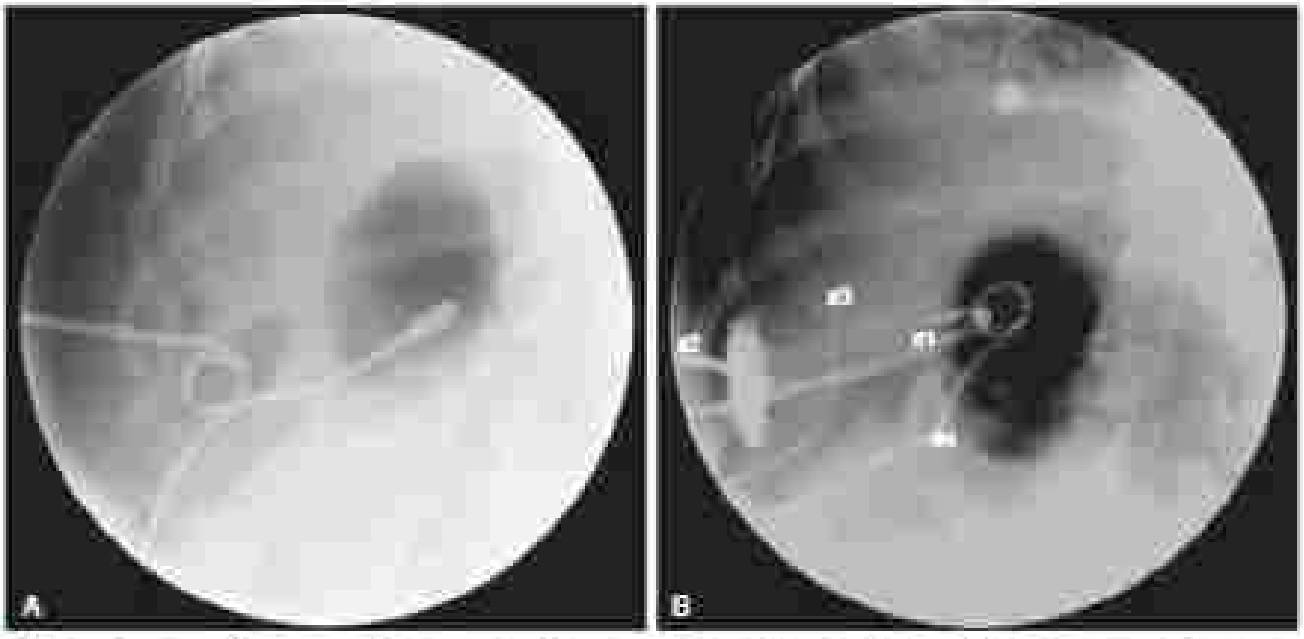

FIG. 3 (A) Initial placement of two percutaneous drainage catheters into the pyogenic liver abscess in the patient in Fig. 1. (B) Placement of two additional percutaneous catheters 4 days later to fully drain the large amount.

In those rare situations in which open surgery will be required, the choice of incision will depend on the abscess location. As these operations will be classified as "dirty," a wound protector should be used. The abscess should be localized with intraoperative US, and the adjacent peritoneum should be protected with laparotomy pads (Fig. 4). After aspiration for aerobic and anaerobic cultures, the liver capsule is incised. The cavity is then irrigated, and loculations can be disrupted gently with a finger being careful not to injure major vessels or bile ducts. Both soft Penrose and large suction drains are placed and brought out via a separate stab incision. In rare situations, hepatectomy of a very diseased segment or segments may be indicated. In performing these operations, care must be undertaken to avoid severe sepsis due to massive bacteremia caused by manipulation of the abscessed liver.

Outcomes

Historically, the majority of patients with PLAs died with outcomes being worst in patients with biliary abscess, malnutrition, and underlying malignancies. Currently, fewer than 10% of patients with PLAs die. However, patients with HPB malignancies and those who are immunosuppressed after liver transplantation are at greatest risk for mortality. For the remainder of patients with a relatively good prognosis, recent debate has centered around the relative risks and benefits of percutaneous needle aspiration (PNA) versus PCD. A recent systematic review and meta-analysis of five randomized controlled trials involving 306 patients clearly favored PCD. Compared to PNA, the success rate for patients with PCD was higher (96% vs 78%; $P < .01$); the time to clinical improvement was shorter ($< .001$); and the days to achieve a 50% reduction in abscess size was shorter ($P < .001$). Thus, when expert interventional radiologists are available, PCD should be performed.

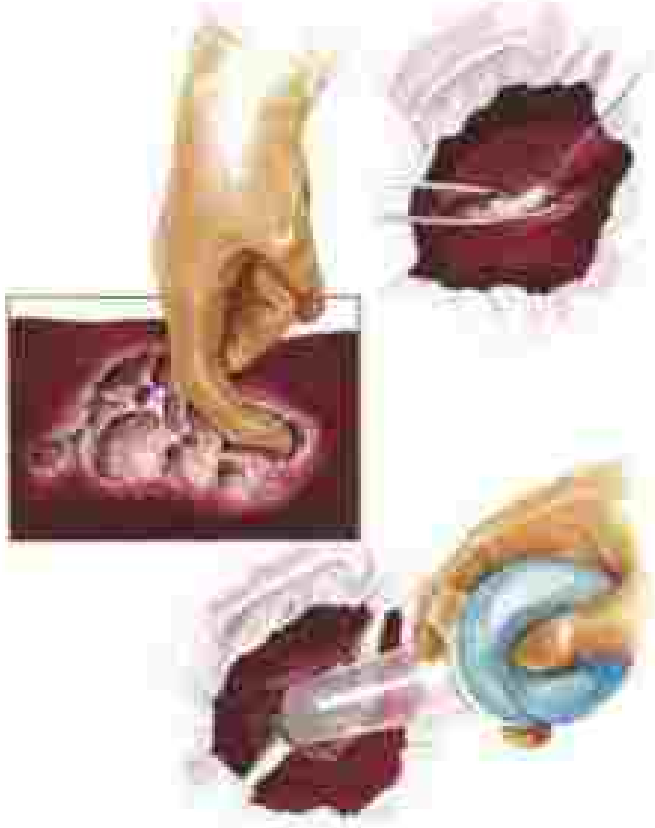

FIG. 4 Operative drainage of a PLA. Laparotomy pads are placed to prevent contamination when the abscess is incised and cultured (top). Loculations are gently disrupted with a finger (middle). The cavity is copiously irrigated (bottom) before large drains are placed. (From Lillemoe J, Jarnagin C. Atlas of Gastrointestinal Surgery v.2 E. 2nd ed. Shelton, CT: People's Medical Publishing; 2010.)

FUNGAL HEPATIC ABSCESS

Immunocompromised patients, including those receiving chemotherapy for an underlying malignancy and those who have undergone a liver transplantation, are more prone to develop a fungal liver abscess. Patients with biliary malignancies and indwelling stents, who receive multiple courses of antibiotics for recurrent cholangitis, also

ers at increased risk for mixed bacterial and fungal liver abscesses. Patients with hepatic tumors who undergo ablative procedures also have an increased risk for development of a fungal hepatic abscess.

Treatment

The principles outlined earlier for bacterial liver abscesses also apply to fungal hepatic abscesses. PCD should be undertaken as the preferred initial procedure. Biliary stent placement or change is also indicated when the underlying etiology is biliary obstruction. Approximately 80% of fungal abscesses will have *Candida* spp. In some patients, *Aspergillus* or *Cryptococcus* will be isolated. Historically, amphotericin B was the treatment of choice, but currently, micafungin and caspofungin should be utilized to treat these patients. Prolonged antifungal therapy is indicated, and oral fluconazole should be used only if *Candida* spp. are sensitive. In patients with mixed bacterial and fungal liver abscesses, appropriate antibiotic therapy also should be provided.

Outcomes

Patients with a pure or mixed fungal liver abscess are at high risk for mortality. Patients who receive adequate drainage and antifungal therapy still have a 20% risk of mortality. Patients who have fungemia and those with a delay in diagnosis who develop severe sepsis before adequate drainage and/or appropriate antifungal therapy is initiated are also at increased risk for mortality. As a result, approximately 50% of patients with a fungal liver abscess do not survive.

AMEBIC LIVER ABSCESS

Amebiasis is a common global parasitic infection caused by the protozoan *E. histolytica*. The vast majority of these infections occur in tropical and subtropical areas in the developing world including Africa, Indonesia, Central and South America. High risk groups in developed countries include immigrants, tourists who have travelled to endemic areas, sexually active homosexual men, institutionalized patients, and those with HIV. Amebiasis occurs with a bimodal age distribution, with one peak at age 2 to 3 years and the second peak in middle age. ALA is 10 times more common in men than in women. Low socioeconomic status and unsanitary conditions are independent risk factors for amebiasis.

Diagnosis

The vast majority of people who become infected with *E. histolytica* are asymptomatic. However, without symptoms, patients may shed amebic cysts for years. The most common form of invasive disease is colitis that presents with gradually worsening diarrhea, abdominal pain, and weight loss. In this setting, trophozoites may reach the liver via the portal system and cause focal hepatocytic necrosis and microabscesses. After coalescence, a single abscess will contain a thick liquid that typically is red/brown and has been described as "anchovy paste." Clinical presentation may be acute with fever and right upper quadrant pain or subacute with weight loss and intermittent fever and pain. Simultaneous presentation with colitis and an ALA is unusual. Clinical characteristics distinguishing patients with ALA from those with pyogenic hepatic abscesses are presented in Table 2.

Patients with an ALA will have a mild to moderate elevation of the white blood cell count. These patients also may have mild elevations of alkaline phosphatase and transaminases, but jaundice is rare. Stool samples for trophozoites may be positive in up to half of the cases. Chest radiographs will frequently demonstrate a pleural effusion, atelectasis, or elevation of the right hemidiaphragm. US, CT, and MRI are all excellent methods for detecting ALAs (Fig. 5). Approximately three fourths of ALAs appear as solitary lesions in the right lobe.

Another serology is highly sensitive and specific in differentiating ALA from PLA. Serum antibodies are positive in 99% of patients with ALA and in 80% of those with invasive colitis. Serologic data are usually available in 24 to 48 hours, therefore the need to aspirate a suspected ALA to establish a diagnosis is questionable. In addition, no level I data are available to demonstrate that aspiration of an ALA has a survival benefit. Thus, diagnostic aspiration is reserved for the rare patients with a negative serology or when secondary bacterial contamination is suspected.

TABLE 2 Clinical Characteristics of Patients With Pyogenic and Amebic Abscesses

Pyogenic	Amebic
Age >50 years	Age <50 years
Male/female 1:1	Male/female 10:1
No ethnic predisposition	Hispanic descent
No recent travel	Travel to endemic area
Underlying malignancy	No malignancy
High fevers	Fever
Pain unusual	Pain common
Tenderness uncommon	Tenderness common
No diarrhea	Diarrhea common
Jaundice occasionally	Jaundice rarely
Severe sepsis	Mildly septic

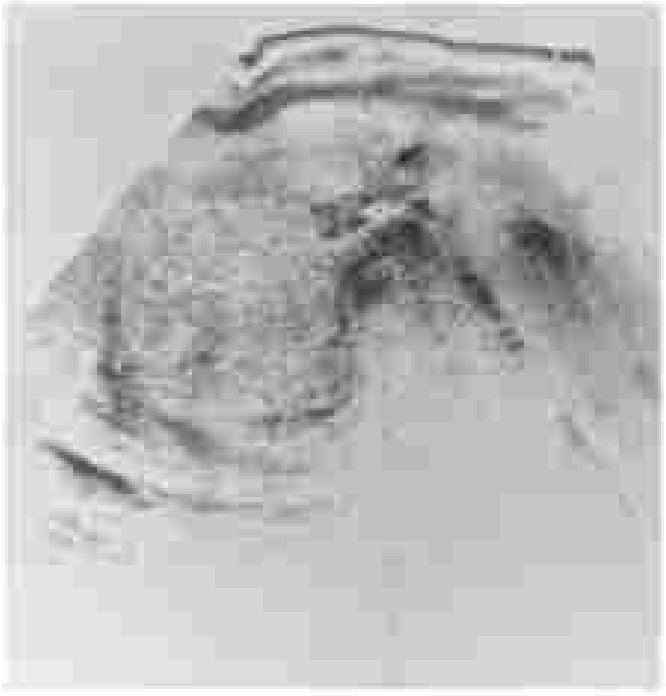

FIG. 5 Ultrasound demonstrating large amebic liver abscess in the right lobe.

TREATMENT

Antibiotics

Metronidazole is the antibiotic of choice for ALA. The oral dose is 500 to 750 mg three times a day for 7 to 10 days. The response to metronidazole is usually profound with symptomatic improvement in 3 to 4 days. At 5 days, 85% of patients with an ALA have responded and that rate increases to 95% at 10 days. Tinidazole 2 g orally for 5 days is an alternative for the rare patient with a metronidazole allergy. Another alternative

to metronidazole 2 g for 5 days to patients who do not tolerate the side effects of metronidazole. However, with metronidazole treatment, the parasites persist in the intestines in up to half of the patients. Therefore, an additional luminal agent such as paromomycin (35 mg/kg three times a day for 5 to 7 days), diiodohydroxyquin (650 mg orally three times daily for 20 days), or iliamycin furoate (500 mg orally three times a day for 10 days) should be utilized to eradicate intestinal colonization.

Therapeutic Aspiration

In 2003, Bennion and colleagues reported a prospective, randomized trial in patients with ALA, comparing oral metronidazole alone with US-guided aspiration plus oral metronidazole. ALA aspiration improved liver tenderness within the first 3 days, but no differences in other clinical findings or laboratory tests were observed between the two groups. The authors concluded that the minor clinical benefit was insufficient to justify routine needle aspiration. Thus, therapeutic needle aspiration is reserved for patients with (1) no clinical response after 5 to 7 days, or (2) a large abscess, especially in the left lobe, with increased risk for rupture into the peritoneum or pericardium.

Catheter and Surgical Drainage

In patients with a very large (>10 cm) ALA, PCD has been shown to be better than needle aspiration with respect to duration of clinical symptoms. PCD is useful in patients with pulmonary, peritoneal, or pericardial complications. However, large catheters are usually required because of the high viscosity of the amebic abscess fluid. Additionally, catheter drainage may lead to secondary bacterial contamination. Surgical drainage of ALAs is rarely required, and indications include (1) failure of response to more conservative measures, (2) erosion into neighboring organs including the stomach, duodenum, and colon, (3) sepsis related to secondary bacterial infection, or (4) life-threatening hemorrhage, not amenable to angiographic therapy.

OUTCOMES

The majority of patients with an ALA respond to oral antibiotics within 3 to 5 days. However, if the presentation is very late and subacute organ or free rupture has occurred, an ALA may be fatal. Factors associated with a poor prognosis include presentation with (1) encephalopathy, (2) a serum albumin of less than 2.0 g/dL, (3) a total bilirubin of greater than 3.5 mg/dL, (4) an abscess volume of greater than 500 mL, (5) multiple abscesses, (6) adjacent organ erosion, and (7) free rupture. Fortunately, these factors are present in only a small percentage of patients with ALA. The fact that most patients with an ALA, unlike many with PLA, are young, otherwise healthy, and unlikely to be immunosuppressed or have a malignancy, means that their likelihood for full recovery is excellent. Although clinical recovery is usually rapid, radiologic resolution of the abscess may take many months.

Suggested Readings

Bennion J, Hinds HH, Hung DM, et al. Treatment of amebic liver abscess with metronidazole alone or in combination with ultrasound guided needle aspiration: a comparative, prospective and randomized study. Trop Med Int Health. 2003;8:1030–1036.

Cai YL, ... Jing XZ, Liu J, Li JL. Percutaneous needle aspiration versus catheter drainage in the management of liver abscess: a systematic review and meta-analysis. HPB. 2010;12:393–401.

Huang CJ, Pitman FE, Sepulveda FA, et al. Pyogenic liver abscess changing trends over 42 years. Am Surg. 1998;223:605–606.

Ispahi PA, Huang CJ, Liberman RD, et al. Fungal hepatic abscess: characterization and management. J Gastrointest Surg. 1997;1:78–84.

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Transarterial Chemoembolization for Liver Metastases

Quang Nguyen, MD, and Christos S. Georgiades, MD, PhD

Transarterial chemoembolization (TACE) has become the standard of care for the treatment of unresectable hepatocellular carcinoma. In patients with hepatocellular carcinoma, catheter-based image-guided delivery of chemotherapy agents and embolization particles has been shown to result in significant improvement in objective tumor response, progression-free survival, cause-specific survival, and overall survival. TACE is also used to treat a number of secondary, liver-predominant malignancies. Studies have indeed shown many benefits for patients treated with TACE, including downstaging into resectability, improving survival and disease progression, and controlling symptoms. In this chapter, we describe how TACE can be incorporated into a multidisciplinary approach for the treatment of patients with metastatic malignancies to the liver. A variety of agents/transarterial modalities have been developed including bland transarterial hepatic arterial embolization (TAE), TACE, and selective internal radioembolization therapy. These therapies offer reduced systemic toxicity and more effective local tumor control. As a result, some procedures have been included in the National Comprehensive Cancer Network treatment guidelines.

CHEMOEMBOLIZATION OPTIONS

The efficacy of TACE relies on the fact that normal liver parenchyma is mainly supplied by the portal vein (~70%), whereas primary or secondary liver neoplasms are exclusively fed by hepatic artery branches (neo-angiogenesis) therefore, the intra-arterial delivery of a cytotoxic drug will primarily target neoplasms and spare liver parenchyma.

There are three slightly different options for treating patients using a catheter-based transarterial approach.

1. Bland embolization alone. Operators use embolic particles to effect complete stasis in the hepatic artery branch that feeds the target tumor. TAE is predicated on the assumption that all damage to the tumor is due to ischemia and that chemotherapy plays no role. Studies have shown TAE is nearly as effective as TACE; therefore, if chemotherapy administration is contraindicated (e.g., maximum lifetime doxorubicin amount reached, allergy), the patient may still benefit from TAE.
2. Lipiodol-based TACE. This is the originally described conventional TACE method. It involves the transcatheter delivery of a cocktail (chemotherapy and lipiodol) into the target tumor, followed by particle embolization. The chemotherapy cocktail consists of any combination of cisplatin 100 mg, doxorubicin 50 mg, and mitomycin C 10 mg. This is mixed with lipiodol (Ethiodol) in a 1:1 or a 2:1 volume ratio depending on flow characteristics. A 1:1 ratio is more viscous and used for high flow states, whereas 2:1 (chemo/lipiodol) is less viscous and used in low flow states.

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Lipsett PA, Huang CJ, Liberman KD, et al. Surgical hepatic abscess: characterization and management. J Gastrointest Surg. 1997;1:378–84.

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3. Drug-eluting beads (DEBs). The latest development are the introduction of sponge like particles that can be preloaded with chemotherapy. These particles are used to embolize the target tumor similar to conventional TACE, without the addition of lipiodol. Over a period of time, these particles elute chemotherapy, maintaining a high intratumoral dose and low plasma concentration. DEBs allow only one chemotherapy drug to be loaded, which is most commonly doxorubicin.

None of the three options has been shown to be superior to the others in terms of efficacy and the choice is operator dependent.

The secondary liver diseases most commonly treated with TACE are (in decreasing order of frequency):

1. Neuroendocrine cancer, if
   a. Symptomatic
   b. Results in clinically significant laboratory abnormalities such as hypoglycemia from metastatic insulinoma or hyperglycemia from metastatic glucagonoma
   c. Rapidly growing
   d. High Ki-67 index
2. Cholangiocarcinoma (CCA), if
   a. Systemic chemotherapy failed or in conjunction with systemic chemotherapy
   b. To target tumor portion along a precarious resection margin thus aiding surgery
3. Colon cancer
   a. If surgery or ablation is not an option and no systemic options left
   b. To maintain tumor size if planned surgery is significantly delayed
4. Other (breast, melanoma, pancreatic)
   a. TACE for such neoplasms is less well studied and should be tailored to each individual patient

A novel indication is the use of immunotherapy. TACE is believed immune response. Early studies suggest that circulating tumor related antigens after TACE, will result in augmented immune response. If checkpoint inhibitor administration is appropriately timed.

PATIENT PREPARATION

Patient selection is of paramount importance for patients with secondary liver disease as operator must coordinate with systemic options, consider potential drug interactions and potentiation of side effects and coordinate follow up and response evaluation, therefore a multidisciplinary input is necessary. In general, indications for liver-directed locoregional treatments for secondary malignancies include the following:

1. Liver predominant disease. TACE is reasonable if liver disease burden is the likely cause of the patient's demise should TACE be withheld. Minimal extrahepatic disease such as lymphadenopathy is not a contraindication to TACE.
2. Control of extrahepatic disease with systemic chemotherapy, with progression of liver disease.
3. To downstage or maintain a patient into criteria for resection. For example: a patient with resectable colon cancer metastases, whose surgery is delayed for other reasons. Or a patient with CCA with precarious surgical margin (i.e., tumor too close to a hepatic vein that must be preserved). Low level evidence suggests that incorporating aggressive locoregional treatments early in the treatment of CCA improves the chance for converting the patient into a candidate for resection.

A clinic visit is necessary during which the physician assess the patient's Eastern Cooperative Oncology Group status, explain the risk/benefit profile, set expectations, and answer the patient's questions. A complete blood count, comprehensive metabolic panel, and coagulation profile are reviewed to ensure there are no undue risks for TACE. A contrast-enhanced, cross-sectional study (preferably a magnetic resonance imaging [MRI] scan) is necessary for treatment planning and to evaluate for response after TACE. Contraindications to liver directed, locoregional therapies are summarized in Table 1 and aim to mitigate the risk of acute hepatic failure. Symptoms (encephalopathy, severe tumor related pain), signs (ascites) or labs (liver function tests [LFTs]), and poor performance status (hepatocellular carcinoma status >2) should prompt reconsideration of TACE.

TECHNIQUE/PATIENT CARE

1. Right lower fasting in preparation for conscious sedation or general anesthesia.
2. Premedication:
   a. Dexamethasone (20 mg intravenously), which reduces post-operative fever, anorexia, fatigue.
   b. Proton pump inhibitors, which reduce risk of gastric/duodenal ulcers and mitigate significance of nontarget embolization.
   c. Hydration, which reduces fatigue, nausea.
   d. Antibiotics. Not necessary unless sphincter of Oddi has been compromised. If prior biliary intubation or post Whipple, then antibiotic prophylaxis is necessary. Recommended regimen is moxifloxacin 400 mg by mouth daily beginning 3 days before and continuing for 17 days after TACE.
3. Vascular access. TACE can be performed either via common femoral arterial (CFA) or radial arterial (TRA) access. While still most TACEs use the CFA access, TRA which facilitates early patient ambulation is increasingly used. In both cases a 5Fr sheath is used. If TRA is performed, a Barbeau's test is performed first to minimize the risk of hand ischemia. Upon access, a cocktail of heparin and one or more vasodilators (nitroglycerin, verapamil, or nicardipine) is administered. The tumor is not necessary for CFA access.
4. Diagnostic arteriogram. The objective of diagnostic angiogram before delivery of chemotherapy is twofold:
   a. To delineate the vascular anatomy related to the tumor and how to best deliver the treatment
   b. To unmask any nontarget vessels at risk for inadvertent chemoembolization and plan approach to minimize the risk.

A superior mesenteric arteriogram is first performed. This excludes replaced/collateral vascular anatomy to the liver and shows whether the portal vein is patent or not. Then a celiac arteriogram is performed. This shows the target (hepatic artery branches) and nontarget vessels (i.e., left and right gastric artery, supraduodenal artery, cystic artery, umbilical artery) that must be protected (Fig. 1).

5. Treatment. Once the target arteries are clarified on, a microcatheter is used to obtain superselective access. The ideal location for the tip of the catheter is one that an infusion from that point would cover the entire tumor and, at the same time, spare as much of normal liver parenchyma as possible (Fig. 2). Once the catheter is in the optimum position, the treatment mixture is delivered. Whether lipiodol TACE or DEB TACE, this is done under continuous fluoroscopic observation. As the cocktail is given target arterioles embolize and flow dynamics may change. Over-aggressive embolization may result in antegrade reflux around the catheter and inadvertently reach nontarget organs. The ones most commonly at risk are the duodenum, stomach, and pancreas resulting from the proximity of their arterial supply to the hepatic artery. The technical objective is to deliver the entire treatment mixture into the target tumor and reach blood flow stasis within the artery that supplies it. Additional particle use may be necessary to achieve stasis. If multiple tumors are targeted, it is best to target each individual tumor as selectively as possible as

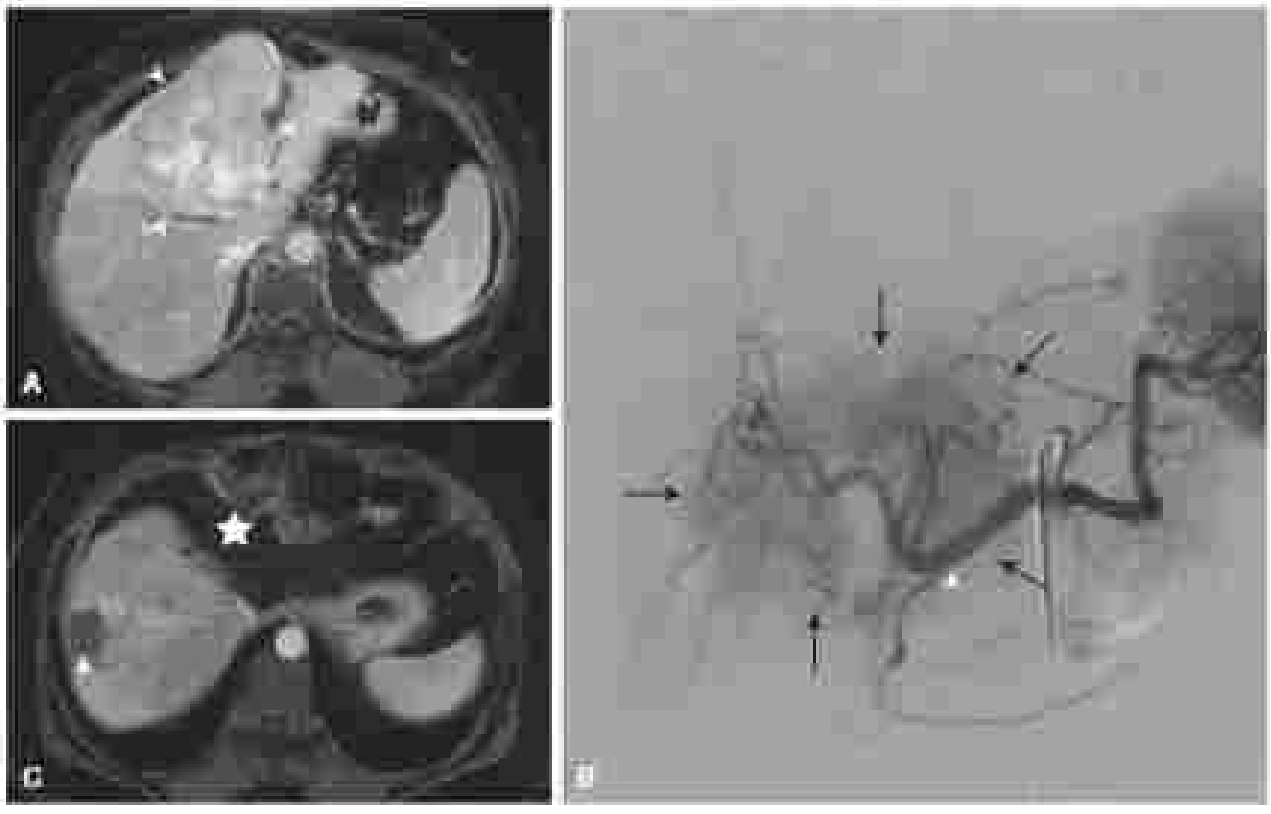

FIG. 1 A 51-year-old female with cholangiocarcinoma. (**A**) Axial contrast-enhanced magnetic resonance imaging shows a large hypervascular mass (arrow) in the liver with dominant unresectable tumors on the left of surgical margins. (**B**) Diagnostic angiogram during transarterial chemoinfusion after (TACE) shows the hypervascular mass (arrow) being fed by the hepatic artery (arrowhead). After a combination of locoregional treatments including many TACEs the patient became resectable. (**C**) Axial contrast-enhanced magnetic resonance imaging 2 years after initial diagnosis shows the remnant liver with no radiologic evidence of disease. A completely necrotic lesion (arrowhead) remains like after repeat TACE. See, Lin, h... [illegible]

opposed to treating an entire lobe. Though more time consuming and technically challenging, selective embolization carries a lower risk of liver injury and results in better response. Once the technical objective is reached, the catheters and sheath are removed and HOA hemostasis is obtained. The latter can be obtained by either a 15-minute manual compression or by the use of a vascular closure device. The use of vascular closure devices obviates the need for manual pressure and allow the patient to ambulate at 2 hours instead of at 6.

Note: In general, only one lobe (right or left) can be treated at any one time because TACE results in transient LFT elevation, with the treated liver recovering by approximately 2 weeks. During the recovery period, adequate remaining liver function must be ensured. In cases in which multiple subselective TACEs can be performed without affecting a significant portion of the normal liver parenchyma, bilateral lesions can be treated in one session.

6. Patient recovery. Patient recovery in short (<24 hours) and centered around symptom control and prevention. Postprocedure hydration, as-needed antiemetics, and pain control are the mainstay of recovery. The latter is optimized with patient-controlled analgesia pump. The most common symptoms include fatigue, fever, and abdominal pain, a triad that is termed the postembolization syndrome. They are reported in at least 40% of patients and gradually subside, on average, over 14 days. Other symptoms that could be encountered include nausea, anorexia, and rarer, alopecia (4%) and night sweats. Volume of embolization and degree of tumor necrosis are correlated with severity of symptoms. If lipiodol is used in the TACE mixture, a noncontrast computed tomography can be obtained after the procedure to indicate the distribution of treatment (Figs. 1, 2).
7. Patient follow-up. Irrespective of the embolization method used (conventional using lipiodol, Irinot, or with DEBs), follow-up protocol is usually preserved. It includes a repeat multiphasic MRI with intravenous gadolinium-based contrast, laboratory tests (comprehensive metabolic panel, complete blood count, international normalized ratio, relevant tumor markers) and a clinic visit to reassess the patient's performance status. Follow-up is generally at 3-month intervals but this must be tailored to each patient and according to treatment goals. There is no limit to the number of TACE treatments a patient can receive. Further treatment should be aborted, however, if any contraindications develop (Table 1), if the initial indication is no longer valid or if after 2 TACEs the targeted lesion failed to respond as expected. Studies have shown that failure of initial TACE does not predict failure of a second treatment, however, if two TACEs fail to result in tumor response, additional treatment is unlikely to have any benefit.
8. Toxicities/complications. Complications related to TACE are summarized in Table 2. A majority of patients (>60%) will have the described postchemoembolization syndrome. It is always self-limiting and only symptomatic care is indicated. The most feared complication is acute liver decompensation resulting from TACE-related acute liver injury. The related risk is small (<1%) and only considered when there is underlying liver disease (cirrhosis, severe steatohepatitis, significant history of systemic chemotherapy). Unilateral TACE all but eliminates this risk in cases of metastatic disease. Similarly, encephalopathy is also unlikely as TACE for secondary liver disease is usually

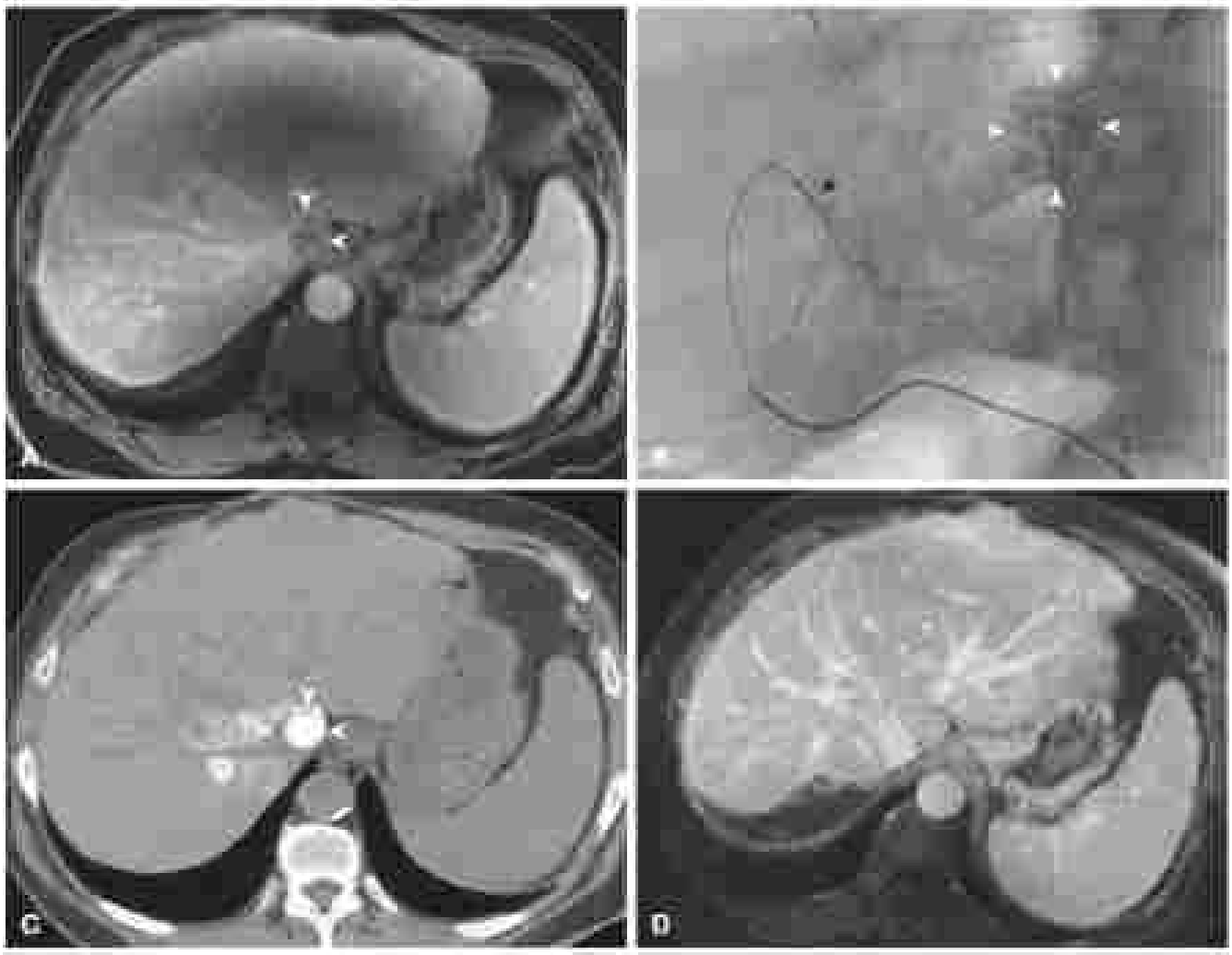

FIG. 2. A 64-year-old patient with history of colon resection for colon cancer. (A) Axial contrast-enhanced magnetic resonance imaging shows a single metastatic focal parenchymal abutting and compressing the inferior vena cava. The patient was deemed unresectable and had no extrahepatic systemic options. (B) Diagnostic angiogram during transarterial chemoembolization shows a subsegmental microcatheter (black arrowhead) and the hypervascular lesion (white arrowhead). (C) Noncontrast CT on postchemoembolization session 1 shows the dense lipiodol deposition in the targeted lesion (arrowhead). (D) Axial contrast-enhanced magnetic resonance imaging 3 years after treatment shows complete and persistent response with no radiologic evidence of disease.

performed in patients with intact liver function. Previous history of encephalopathy is the major risk factor for worsening encephalopathy. Both acute liver failure and encephalopathy risk can be further mitigated by selective treatments. Biliary complications include stricture and abscess formation. The biliary tree is supplied by the hepatic artery and overzealous embolization (especially with DEB) can result in ischemic strictures and hyperbilirubinemia. If the sphincter of Oddi has been violated (hepaticojejunostomy or biliary stent), there is a very high risk of intrahepatic abscess formation. Bacterial colonization translates into an abscess as a result of TACE-related biliary ischemia in more than 60% of such patients. Pre- (1 week) and post- TACE (2 week) treatment with broad-spectrum antibiotics (i.e., moxifloxacin 400 mg, by mouth every day) reduces the risk to less than 10%. Another potentially serious complication is inadvertent embolization of nontarget vessels. Performing a detailed diagnostic arteriogram before TACE and a selective TACE nearly eliminates this risk. Aberrant vascular anatomy further increases this risk with the vessels most at risk being left or right gastric arteries, supraduodenal artery, and the umbilical artery.

OUTCOMES

Colorectal Cancer

In a study by Vogl and associates in 2006, 863 patients with unresectable colorectal hepatic metastases that were refractory to systemic chemotherapy were treated with TACE (Fig. 2). By imaging characteristics, 68 patients (14.7%) had partial response, 223 patients (48.2%) had stable disease, and 172 patients (37.1%) had progressive disease. The 1- and 2-year survival rates after chemoembolization were 62% and 28%, respectively. Median survival times from date of diagnosis of liver metastases and date of first chemoembolization were 38 months and 14 months, respectively.

DEB-TACE as a new platform for intraarterial drug delivery in secondary liver tumors has been demonstrated in a retrospective analysis of 38 patients with metastatic colorectal cancer. Irinotecan-loaded DEBs were used and tumor response was assessed with modified Response Evaluation Criteria in Solid Tumor criteria in all patients. After an overall 47 procedures, 15% of the treated patients were classified as complete responders and 30% showed partial response, whereas 29% showed stable disease and 37% showed progressive disease. Most important, a median overall survival of 13.5

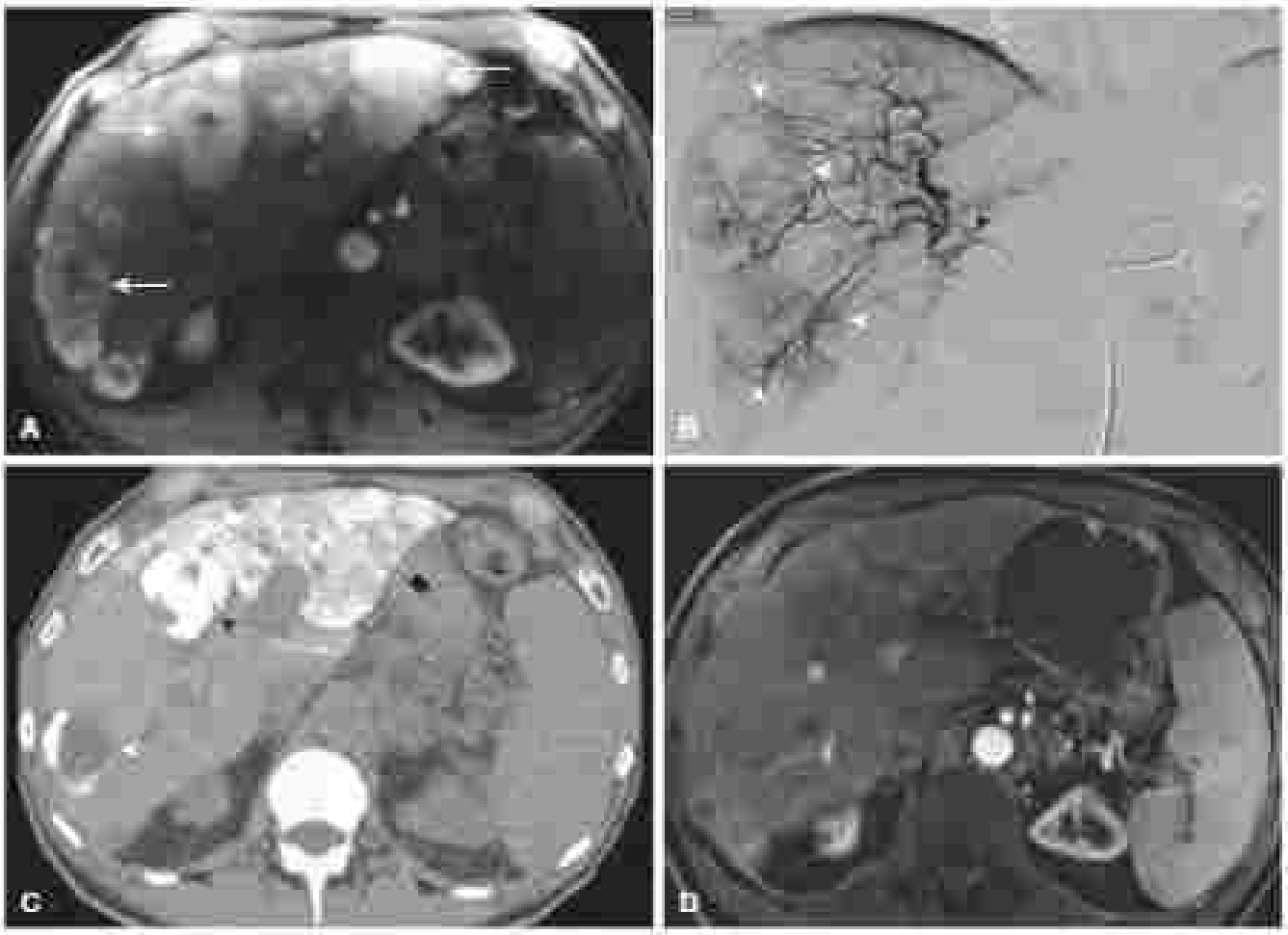

FIG. 3 A 70-year-old man with primary pancreatic neuroendocrine cancer (A) Axial contrast-enhanced magnetic resonance imaging shows extensive secondary neuroendocrine metastases in the liver (arrows). (B) Hepatic arteriogram of the right hepatic artery during segmental chemoembolization (TACE) shows the hypervascular tumor (arrowheads). The patient underwent a series of 4 TACEs over 6 months. (C) Abdominal computed tomography on post-TACE day 1 after left TACE shows dense lipiodol deposition in the hypervascular mass (black arrowhead) and a shrinking immediate proximity (curved) right hepatic lobe (white arrowhead). (D) Axial contrast-enhanced magnetic resonance imaging 2 years after treatment shows near-complete and systemic response with minimal radiologic evidence of disease.

TABLE 1 Contraindications to TACE

Contraindication	Comment
Total bilirubin >4	Superselective TACE can be performed
Rapidly rising total bilirubin	Deteriorating liver function
ECOG 3	Unlikely to benefit patient
Life expectancy <6 mo	Unlikely to benefit patient
Borderline liver function	Superselective TACE can be performed
Severe encephalopathy	Optimize medical treatment
Active bacterial infection	Treat and then TACE
Large tumor burden	
Renal insufficiency	Use CO_2 as contrast
Significant cardiopulmonary disease	
Biliary tube or hepaticojejunostomy	>40% risk of liver abscess ≤10% of prophylaxis is used

Contraindications to TACE are relative. A risk-benefit analysis must be applied to each patient, keeping the ultimate goal of treatment in mind. For example, if ECOG 3 status is temporary and unrelated to liver disease, TACE may be offered after recovery.
ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.

TABLE 2 TACE-Related Toxicities

	Risk (%)	Mitigating Factors	Comment
Liver decompensation	<1	Selective embolization	Underlying cirrhosis increases risk
Encephalopathy	<1	Selective embolization	Underlying cirrhosis or prior encephalopathy increases risk
Liver abscess	2–4		If intact sphincter of Oddi
	10–20	If pretreated with antibiotics	If compromised sphincter of Oddi/colonized biliary tree
	>60	If not pretreated	
Cholangitis	10–15	Symptomatic treatment	Higher with drug-eluting beads
Renal failure	<2	Hydration	Worse if chronic renal insufficiency
Nontarget embolization	<1	Perform diagnostic arteriogram; selective TACE	Variant anatomy increases risk

Acute liver failure from TACE is rare and even rarer with secondary disease. This is because the noninvolved parenchyma is not cirrhotic (unlike hepatocellular carcinoma) and patients have preserved liver function. Only when signs of borderline liver function exist (elevated bilirubin levels, encephalopathy), further toxicity can be mitigated if subselective TACE is feasible. In general, TACE is very well tolerated and significant complications are rare and mitigated by meticulous technique and proper patient selection.

TACE, transarterial chemoembolization.

months was achieved with this treatment, yet again proving the potential of DEB TACE.

CCA

In a recent study Alberti and associates described results from treatment of intrahepatic CCA with DEB TACE (Fig. 1). They reported good disease control with more than 90% of patients having no disease progression. In a previous smaller study, the same group reported a median survival of 13 months and 100% response evaluation criteria in solid tumors response from DEC head treatment.

Metastatic Neuroendocrine Tumors

Metastatic neuroendocrine tumors represent approximately 10% of metastatic disease of the liver (Fig. 2). Carcinoid and pancreatic islet cells have a predilection to metastasize to the liver, and these patients with liver metastases have a poorer prognosis and quality of life. Surgical resection is curative but is possible only in less than 10% of patients. Progression to hepatic metastases is accompanied by hormonal synthesis and release into the circulation that can lead to a constellation of symptoms known as carcinoid syndrome (rash, flushing, diarrhea, and electrolyte disorders). With this development, treatment of the liver would be for palliation of the carcinoid syndrome symptoms. TACE can be used in patients with unresectable, hormonally active neuroendocrine tumors and strongly contribute to the elimination of hormonal symptoms. A report by de Monte et al. summarized the efficacy of TACE in the setting of neuroendocrine liver metastatic disease. The authors reported 74% chance of symptom control, a 56% chance of biomarker response, and a 50% chance of objective tumor response. TACE was very well tolerated and disease progression was delayed by 12 to 18 months.

SUMMARY

Level 1 evidence shows that transarterial chemoembolization is the mainstay for treatment for unresectable hepatocellular carcinoma as it results in significant prolongation of survival. Though lower level, evidence exists that selected patients with secondary liver disease may also benefit from TACE.

Patient and tumor selection are important and case specific. For example, TACE may help downstage patients into criteria for resection (colon cancer) or ensure disease stability while more definitive treatments must be delayed. Additionally, for hormonally active disease TACE has demonstrated a very high efficacy in both symptom and hormonal control, along with objective tumor response.

Finally, because of the complexity and variability of secondary disease and the continuously emerging novel therapies, a multidisciplinary approach is necessary to optimize outcomes.

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PORTAL HYPERTENSION: ROLE OF SHUNTING PROCEDURES

Sharon R. Weber, MD, Shawn E. Ostrander, MD, and Mark S. Orloff, MD

APPROACH TO VARICEAL BLEEDING

β-Blockade is the primary therapy for prophylaxis against initial variceal bleeding from esophageal varices. In patients with acute variceal bleeding, endoscopic therapy is widely accepted for hemorrhage control and prevention of variceal rebleeding. Options include variceal sclerotherapy and band ligation. Both modalities are equally effective at controlling active bleeding, but ligation is preferred because of lower rates of complications, including esophageal stricture. Endoscopic therapies are augmented by pharmacologic vasoconstriction with octreotide or vasopressin. When endoscopic intervention is not readily available or is ineffective (as in 10% to 15% of patients with acute variceal bleeding), this pharmacologic vasoconstrictive can reduce portal flow with or without balloon tamponade (with a Sengstaken-Blakemore or Minnesota tube) as an effective temporizing measure.

For patients who have not responded to endoscopic and pharmacologic therapy, the TIPS procedure is typically the treatment of choice. Meta-analysis comparing TIPS with endoscopic treatment showed lower rebleeding rates in TIPS but higher rates of encephalopathy, with no ultimate difference in survival. The use of surgical shunts for refractory variceal bleeding has declined markedly with improving availability and long-term patency of TIPS.

In select patient populations, surgical procedures other than liver transplantation are used as salvage therapy when less invasive treatments fail. Surgical decompression may be considered for Child's class [illegible] and B patients who have recurrent bleeding after medical and endoscopic treatment, who have poor access to healthcare, or who have gastric varices. Surgical shunts also play a role for patients whose condition is refractory to medical and endoscopic treatment and who are not transplant candidates (nonabstinent patients, active alcoholics, elderly patients, and those with significant cardiovascular disease). Two groups of patients with compelling arguments for surgical shunts are (1) those with chronic noncirrhotic portal vein thrombosis, provided a patent and shuntable vessel can be identified (i.e., splenic vein or superior mesenteric vein [SMV]), and (2) those with Budd-Chiari syndrome with favorable anatomy. Patients with well-compensated cirrhosis and no ascites could benefit from a distal splenorenal shunt when they have limited access to interventional radiology, but these are very few patients in the current era.

TIPS

Widespread clinical utilization of TIPS began in the early 1990s. Transjugular access of the hepatic vein is performed under fluoroscopic guidance. The portal vein is then accessed through the liver parenchyma and a stent is placed in this channel. TIPS effectively relieves variceal hemorrhage, improves ascites, and prevents rebleeding. As a functional side-to-side portacaval shunt, it has

high rates of hepatic encephalopathy (reported to be about 25% in most studies), though this complication can usually be controlled with medical treatment and is nondebilitating for most patients. In many recent years, the introduction and ready availability of expanded polytetrafluoroethylene stents have decreased the need for acute intervention with improvement in patency rates and in several randomized controlled trials with 1- to 2-year outcomes have reduced rebleeding rates and improved survival compared with bare stents. The long-term effect of these stents on outcomes is not yet known. TIPS has the major advantage over surgical shunting procedures in that nonthrombotic placement permits in situ removal during liver transplant, whereas extrahepatic shunts must be ligated or resected at transplant should a patient be a suitable candidate for transplantation.

The role of TIPS as prevention for initial variceal bleeding has not been studied, and thus its indications is to treat acute variceal bleeding, prevent recurrent hemorrhage, and treat refractory ascites. Approximately 80% to 90% of TIPS procedures are performed electively, and treatment of ascites is the most common indication for TIPS. TIPS is also recommended for patients with Budd–Chiari syndrome who fail to improve with anticoagulation and have favorable anatomy. Contraindications to TIPS include moderate to severe pulmonary hypertension, occluded hepatic veins or portal veins, hepatic encephalopathy, Model for End-Stage Liver Disease score greater than 18, and bilirubin level greater than 5 mg/dL, all of which are significant predictors of poor outcomes.

The effectiveness and advantages of TIPS have been well reported. TIPS prevents rebleeding more effectively than endoscopic therapy, improves overall liver function, and effectively bridges patients to transplantation. Most episodes of rebleeding after TIPS have been linked to stenosis or thrombosis, necessitating follow-up care and intervention. In the setting of acute variceal bleeding, it has been suggested that TIPS may reduce treatment failure and mortality rate in high-risk patients, when compared with distal splenorenal surgical shunting procedures after bleeding, a randomized controlled trial showed no difference in variceal rebleeding, encephalopathy, shunt occlusion, and survival, although 80% of patients in the TIPS group required intervention to maintain patency. Long-term follow-up results from a randomized trial comparing TIPS with small-diameter prosthetic to graft portacaval shunt showed superior survival for Child's class A and B patients and longer time to shunt failure for those receiving surgical shunts. TIPS is currently indicated for patients with continued bleeding after failed medical and endoscopic management, prevention of rebleeding or ascites treatment in liver transplantation candidates, and prevention of rebleeding in patients who are not candidates for surgical shunt or liver transplantation.

TIPS is often follow up Doppler ultrasound to evaluate shunt function and frequently re-intervention to maintain shunt patency, with 1-year primary patency of 60% to 67%, 74% to 80% with revision of stenotic stents (assisted primary patency), and secondary patency rates of 95% to 100%. For this reason, it may not be the ideal treatment for patients with difficulty accessing medical care or with a history of poor compliance.

SURGICAL SHUNTS

The definitive surgical treatment for patients with variceal bleeding and underlying cirrhosis is liver transplantation. Before the advent of TIPS, patients who failed medical therapy were surgically shunted. In the TIPS era, surgical decompressive shunts remain a treatment option in those patients who (1) are not candidates for transplant because they have well preserved liver function and minimal hepatic encephalopathy; (2) are well-compensated cirrhotics without ready access to TIPS and without ascites; or (3) require bridging to transplantation resulting from variceal bleeding that has failed medical, endoscopic, and TIPS treatment.

Surgical shunts are classified by the extent of portal diversion and selectivity. Because variceal hemorrhage is the consequence of portal hypertension, these operative techniques are designed to shunt portal venous circulation to the systemic circulation to decrease hypertension. The anatomy of shunting can be nonselective or selective and the extent of diversion can be total or partial. Total nonselective shunts (e.g., end to side portacaval shunt) decompress all portal hypertension by diverting portal blood flow to the systemic venous system via the inferior vena cava (IVC) and thus are complicated by progressive liver failure and hepatic encephalopathy. Partial nonselective shunts, in contrast, preserve portal perfusion of the liver to minimize these effects and risk of liver failure. Selective shunts (e.g., distal splenorenal shunt, small caliber portacaval H graft) decompress a particular venous compartment to prevent variceal bleeding while maintaining portal perfusion to the liver, typically via the mesenteric circulation. A note for any selective shunt is the inevitable change in selectivity that occurs over time. Selective shunts are at risk of collateral development and subsequent loss of selectivity as portal systemic collaterals divert flow into a patent shunt. Conversely, selective shunts may narrow over time, thus decreasing the shunted blood flow and have been shown to have diminished primary patency compared to total shunts.

Total Nonselective Shunts

Total portal systemic shunts, or nonselective shunts, include any shunt greater than 10 to 12 mm in diameter between the portal vein (or its main tributaries) and the IVC (or feeding vessel thereof) because this likely results in total shunting of portal blood. This decompression of all portal hypertension results in excellent control of variceal bleeding at the cost of adverse effects on liver. Although bleeding and ascites are controlled in more than 90% of patients, total shunts can lead to hepatic encephalopathy in 30% to 40% of patients as well as progressive liver failure. The end to side portacaval shunt is the classic example of nonselective shunting and is the technique on which early studies are based. Today, it is largely of historical interest. Though complicated by hepatic encephalopathy this approach controls bleeding more effectively than medical therapy. Although studies showed no survival benefit with surgical shunting, results were biased by crossover to surgical management by patients who failed medical therapy.

A generous side to side portacaval shunt also acts as a total nonselective shunt. Early studies showed no differences in clinical outcomes compared with end to side portacaval shunts; however, it may play a role in select patient populations today. Specifically, it is indicated in patients with significant ascites and refractory variceal bleeding who are not transplant candidates, as well as in those with Budd–Chiari syndrome with ascites and portal hypertension without underlying or resultant cirrhosis. It should not be performed in patients who are potential liver transplantation candidates because the dissection in the porta hepatis complicates subsequent transplantation surgery with increased operative morbidity and intraoperative transfusions. In Budd–Chiari syndrome, in which a portacaval shunts cannot be performed because of caudate hypertrophy or hepatic IVC occlusion, a mesocaval shunt may be the more appropriate approach. Though mesocaval shunts have been described for this clinical scenario, they should be avoided because of shunt length leading to poor patency rates and inferior outcomes. Mesocaval and mesoatrial shunting procedures performed with prosthetic grafts suffer from 20% to 30% thrombosis rates; use of autologous internal jugular vein graft in the mesocaval setting may avoid this complication. In centers with extensive experience, TIPS for Budd–Chiari may be an effective treatment.

Budd–Chiari patients with a patent vena cava and relatively preserved liver function may best be served by a side to side portacaval shunt. The patient should be positioned with the right side elevated and explored through a right upper abdominal transverse incision. A self-retaining retractor and generous Kocher maneuver is required, as is complete mobilization of the vena cava and

portal. Care should be taken to avoid damage to the bile duct or any replaced hepatic vasculature. Generally, the anastomosis should be 2.5 cm in length and will require a side biting clamp, two right angle clamps, and 3- 0 or 4- 0 prolene suture. If it is not possible to perform the anastomosis without tension secondary to caudate hypertrophy, a side to side reconstruction can be performed with an 8- to 10- mm prosthetic graft beveled with the caval anastomosis oriented more inferiorly.

Partial Nonselective Shunts

Use of small diameter shunts, typically defined as 8 to 12 mm in diameter, results in a partial shunt and can be performed in the mesocaval or portacaval positions. Use of either polytetrafluoroethylene or Dacron grafts or vein autografts (e.g., internal jugular vein) acts as a conduit between portal or SMV and the IVC. The smaller shunt diameter compared with total shunts results in maintenance of portal perfusion in 80% of patients with equivalent bleeding control. These patients have lower incidence of hepatic encephalopathy and liver failure compared with total shunts. An interposition mesocaval shunt had no difference in clinical outcomes compared with side to side portacaval shunts in a randomized controlled trial. This approach suffers from a high thrombosis rate, but avoids portal hepatic dissection, an important consideration for future liver transplantation candidates.

In the setting of portal vein thrombosis with preserved liver function and a patent SMV and vena cava, the side to side mesocaval shunt provides effective decompression and a low rate of encephalopathy. A variety of incisions can be used. Visualization is aided by use of a self retaining retractor and the small intestine is retracted inferiorly and to the left with upward traction on the transverse mesocolon. Identification of the middle colic vein will direct the dissection to the SMV. Approximately 6 to 8 cm of the *SMV should be mobilized with ligation and division of small branches and vessel loop control of large branches. Lymphatics should be carefully tied. A window is made in the mesocolon, and the IVC is sufficiently dissected to allow clamping with a side biting clamp. The proposed conduit, either a 12 mm ringed polytetrafluoroethylene graft or autologous jugular vein, is sewn to the SMV with 5- 0 or 6- 0 prolene, suture line tested, and packed with heparinized saline. The graft will curve gently around the duodenum and should be tailored to be neither too short nor too long to prevent kinking when the retractors are released. Right angle vascular clamps are applied to the SMV, followed by a lateral venotomy, and the graft is beveled to run parallel with the venotomy (Fig. 11). The caval clamp is removed first and vented through the suture line before tying. The SMV clamps are removed and pressure used to control bleeding at the suture line. Sterile pressure tubing can be used to check pressures with the graft open and occluded (Box 2).

Selective Shunts

Selective shunts are designed to decompress esophageal varices while avoiding adverse effects of total diversion by selectively diverting blood flow to the liver, but maintaining portal perfusion. The canonical example is the distal splenorenal shunt (DSRS). Described by Warren and colleagues, it is commonly referred to as the Warren shunt. DSRS results in portal oxygen disconnection through an end to side anastomosis of the superior mesenteric end of the splenic vein to the left renal vein and ligation of collateral vessels. Decompression of the gastroesophageal venous system prevents bleeding, while the high pressure superior mesenteric venous system maintains perfusion of the liver. Variceal bleeding is well controlled in more than 90% of patients, but the risk of ascites persists and a DSRS may worsen ascites rather than relieve it. For this reason, it should be avoided in patients with advanced ascites. The preservation of hepatic function compared with total shunts remains debated, but selective shunting does result in a lower incidence of

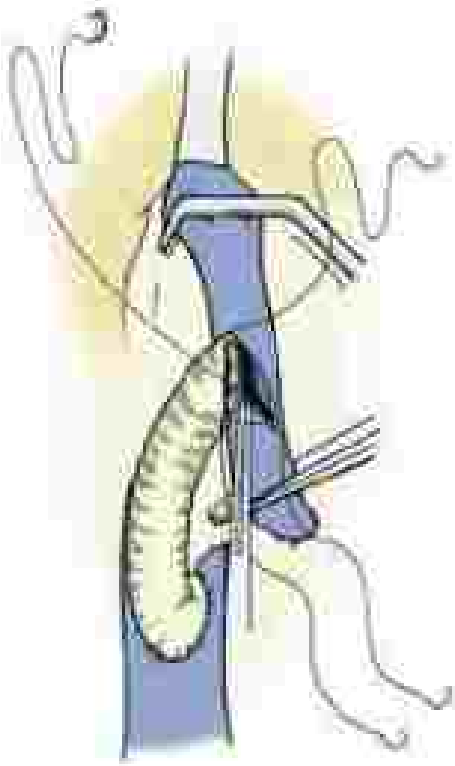


FIG. 1 After occlusion with vascular clamps, the superior mesenteric vein and splenic vein are transected at the confluence of the portal vein. (From Cameron JL, Zinner MJ, Ashley SW, Maingot's abdominal operations, ed 11, New York, 2013, McGraw-Hill Education.)

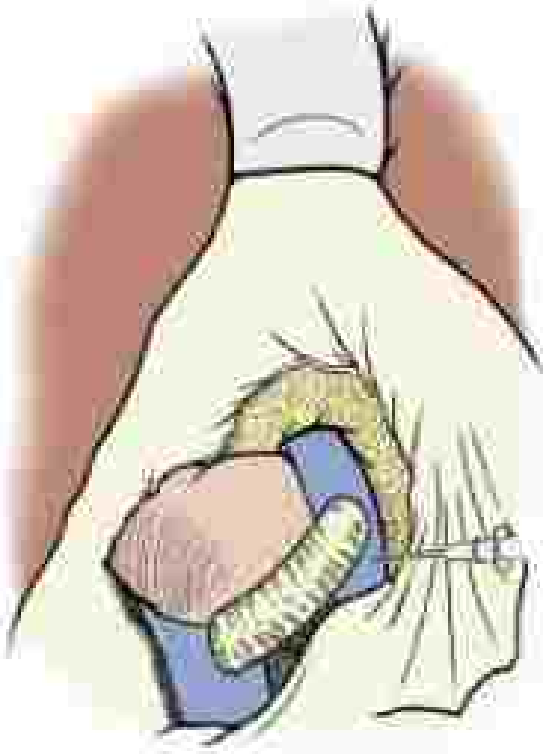


FIG. 2 After completion of the interposition mesocaval shunt, the portal splenic, and mesenteric veins are mobilized. The pancreas is mobilized from the superior mesenteric vein to the spleen by dividing the posterior parietal peritoneum along its inferior margin. (From Cameron JL, Zinner MJ, Ashley SW, Maingot's abdominal operations, ed 11, New York, 2013, McGraw-Hill Education.)

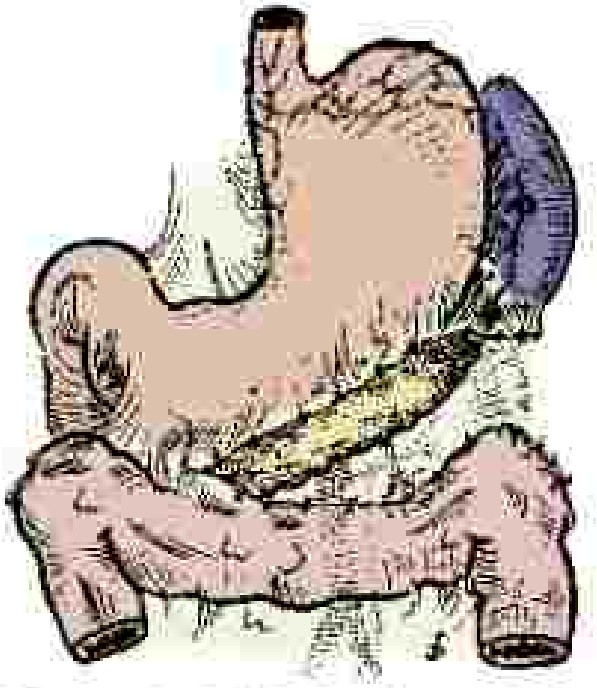


FIG. 3 The pancreas is mobilized from the superior mesenteric vein to the splenic by dividing the posterior parietal peritoneum along its inferior margin. (From Jarnagin W, editor: Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas, 6th ed. Philadelphia: Elsevier, 2017.)

hepatic encephalopathy, at least in short term results. Some evidence suggests these shunts become nonselective over time, although published series on the long-term outcomes for these procedures remains elusive. One disadvantage of this shunt is that it can only be performed in well compensated cirrhotics on an elective basis. For this population, however, it remains an excellent proximalpant shunt that avoids dissection in the porta hepatis that may complicate later transplantation.

The DSRS can be performed with a generous midline incision or bilateral upper subcostal incisions. The lesser sac is opened. While preserving the short gastric vessels, the gastroepiploic vessels as well as the coronary vein should be disconnected from the portal system. Adequate exposure requires mobilization of the colon, including splenic flexure, as well as elevation of the pancreas off the retroperitoneum. The inferior mesenteric vein is divided and the pancreas carefully dissected away from the splenic vein, any small tributaries can be divided with fine ligature (Fig. 3). Next the renal vein is mobilized by dividing the adrenal branch while preserving the other major tributaries. The splenic vein is clamped and divided from the portal system, which may facilitate further mobilization, if necessary (Fig. 4). Finally an end-to-side anastomosis is fashioned between the renal vein and splenic vein after applying clamps and using the splenic vein (Fig. 5).

Other Surgical Shunts

A few shunting procedures for portal hypertension are worth mention, although they are outside the scope of this chapter. Of historical interest are the side-to-side splenorenal shunt and the proximal end-to-side splenorenal shunt with splenectomy. Additionally, pediatric specific shunts deserve special mention. The Clatworthy shunt was described in the 1950s and was historically the most common shunt used in pediatric populations. A nonselective mesocaval shunt, a completed hydrous of the distal IVC and anastomosis of the proximal end to the side of the SMV. It has been replaced by the H-type mesocaval shunt, in which an autologous internal jugular vein graft is used

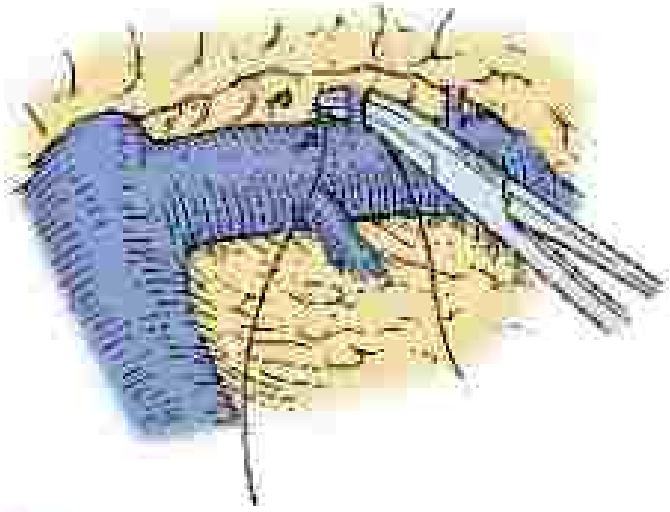


FIG. 4 Isolation of splenic vein from the pancreas near the splenic vein requires blunt dissection at right angles to the splenic vein. There are vein have this walls and require gentle dissection. (From Jarnagin W, editor: Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas, 6th ed. Philadelphia: Elsevier, 2017.)

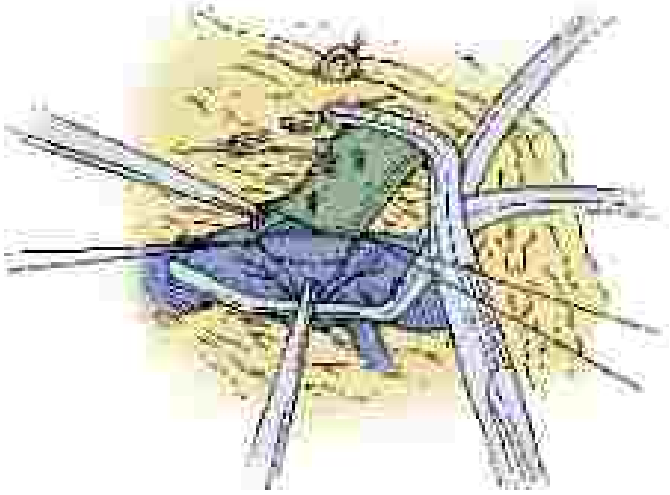


FIG. 5 This posterior anastomosis is made with a running suture. The clamps must be held for a tension-free anastomosis. (From Jarnagin W, editor: Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas, 6th ed. Philadelphia: Elsevier, 2017.)

to connect the SMV and IVC. The mesenteric-left portal venous bypass, or Rex shunt, evolved as a salvage procedure for living donor pediatric transplantation. It is used to treat children with extrahepatic portal vein thrombosis with portal hypertensive complications by restoring blood flow to the liver. An autologous jugular vein graft, or transposition of the dilated coronary vein, is used to shunt the SMV to the intrahepatic left portal vein.

CONCLUSIONS

Our recommendations for a management approach to variceal bleeding in portal hypertension are summarized in Fig. 6. The initial approach comprises medical management and endoscopic therapy. Temporizing measures, such as Sengstaken-Blakemore or Minnesota tubes, play a role as needed to bridge to more definitive therapy. In recurrent bleeding, the management approach diverges based on underlying liver function. Cirrhotic patients should undergo a

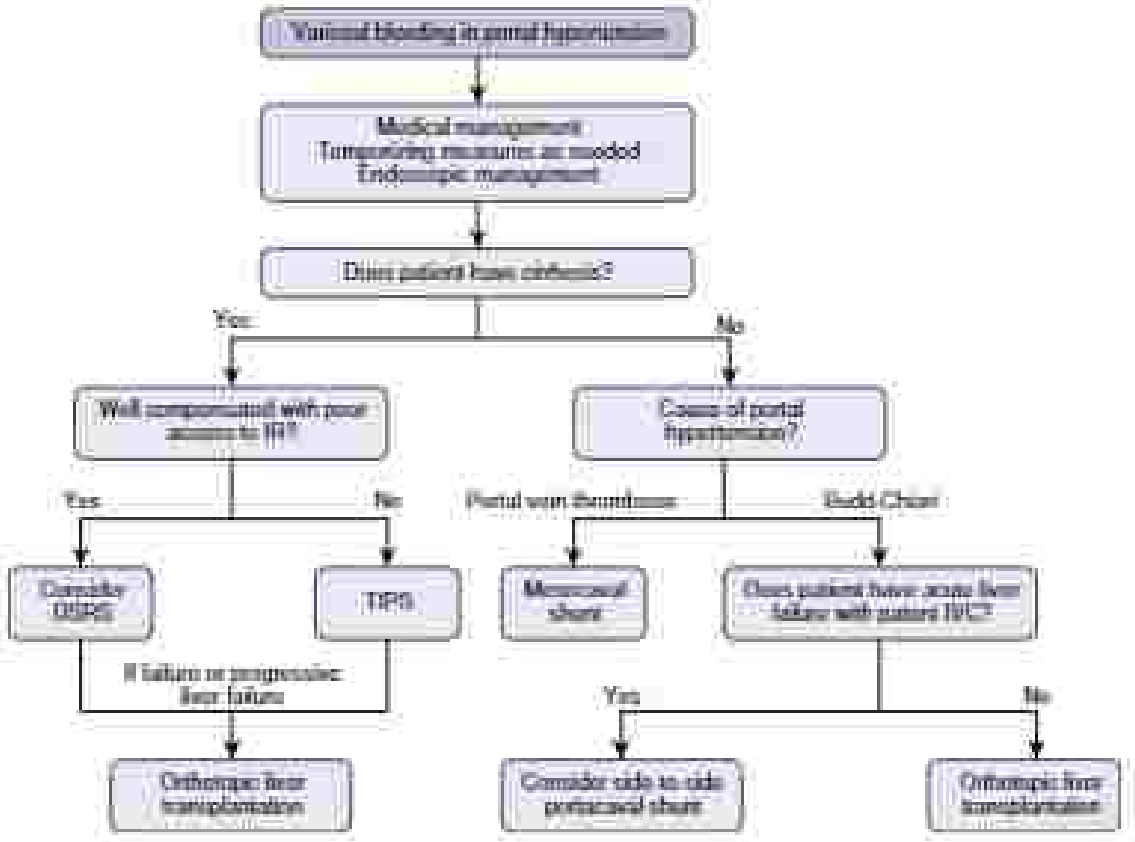


FIG. 8 *Management approach to variceal bleeding in portal hypertension. DSRS, Distal splenorenal shunt; IR, interventional radiology; IVC, inferior vena cava; TIPS, transjugular intrahepatic portosystemic shunt.*

shunting procedure as a bridge to orthotopic liver transplantation, either TIPS or, in those who are well compensated with poor access to care, a DSRS. In patients who do not have cirrhosis, the cause of portal hypertension dictates management. A mesocaval shunt is the appropriate therapy for those with portal vein thrombosis but with a patent mesenteric vein. Patients with Budd-Chiari syndrome should be managed with orthotopic liver transplantation, unless they have acute liver failure with a patent IVC, in which case a side-to-side portacaval shunt may be considered.

Suggested Readings

[illegible]

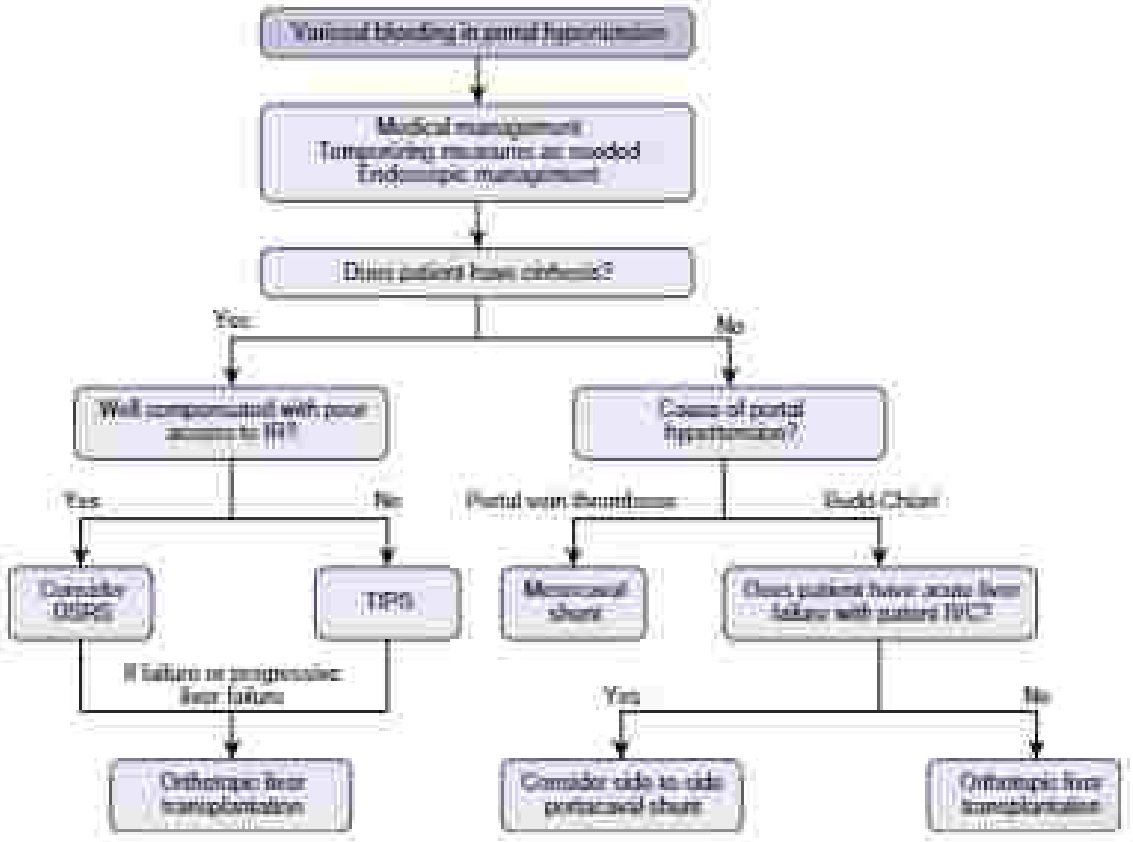
Role of Liver Transplantation in Portal Hypertension

Joseph DiNorcia, MD, and Ronald W. Busuttil, MD, PhD

Liver transplantation is a marvel of modern medicine, with the first successful transplant of the human liver performed by Thomas Starzl in 1967. Advances in surgical techniques, anesthesia and critical care, and immunosuppression have helped liver transplantation become the gold standard treatment for both adult and pediatric patients with decompensated cirrhosis and complications of portal hypertension.

INDICATIONS FOR LIVER TRANSPLANTATION

Although cirrhosis alone is not an indication for liver transplant, the presence of complications of portal hypertension suggests that the patient has decompensated cirrhosis, and liver transplantation can be lifesaving. Leading causes of cirrhosis in adults in the United States include nonalcoholic fatty liver disease, hepatitis C virus, and alcoholic liver disease, whereas chronic cholestasis from liver diseases such as biliary atresia is the most common cause of cirrhosis in children. Cirrhosis is late-stage fibrosis that results from repetitive injury and repair of the liver. This scarring impairs hepatocyte function, increases resistance to portal venous blood flow through the hepatic sinusoids, and ultimately leads to portal hypertension. Portal hypertension is defined by elevated pressure in the venous system draining the abdominal viscera. Although cirrhosis is the most common hepatic cause, obstruction of blood flow prehepatic (e.g., portal vein



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Suggested Readings

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Orloff MC. Fifty-three years' experience with randomized clinical trials of emergency portacaval shunt for bleeding esophageal varices in cirrhosis: 1958–2011. JAMA Surg. 2014;149(8):851–860.

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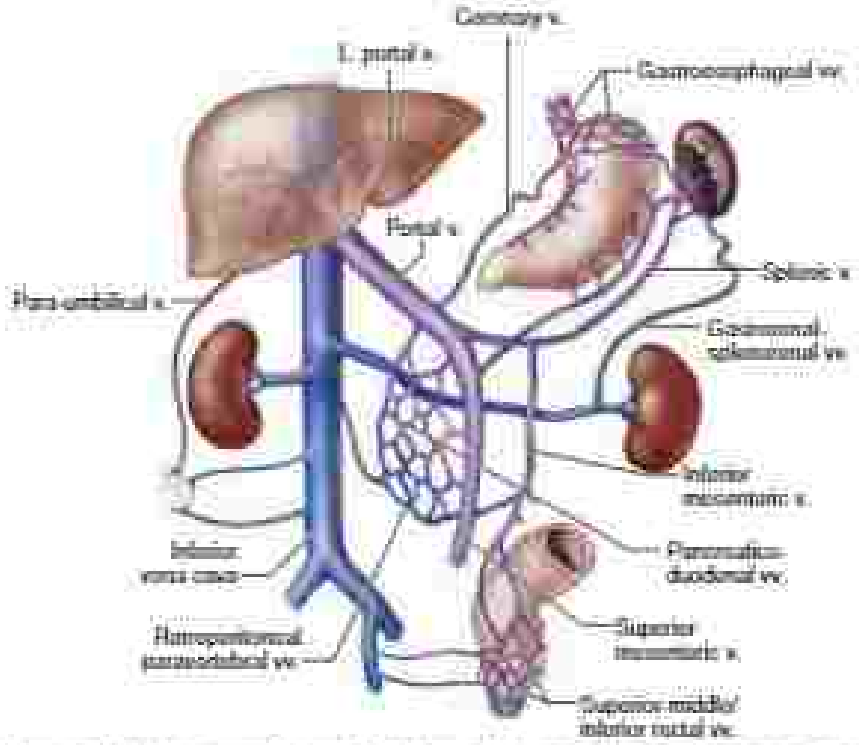


FIG. 1 Portal venous system. Anatomy of the portal venous system and the common portosystemic collateral pathways that develop in portal hypertension. (From Abbas [sic], Wilson CJ. Diagnostic Ultrasound Lab, Philadelphia, [source 20?]. p. 4 [6].)

thrombosis) and pathogens (e.g., Budd-Chiari syndrome) also can cause portal hypertension.

Normal portal venous pressure are 1 to 5 mm Hg greater than systemic venous pressure; in portal hypertension, portal pressures are 6 mm Hg or more above systemic venous pressure. This increased pressure in the portal system causes formation of portosystemic collateral venous pathways that manifest as prominent superficial abdominal wall veins, esophageal, gastric, retroperitoneal, and rectal varices; and portal hypertensive gastropathy, enteropathy, and colopathy (Fig. 1). Rupture of these varices can cause massive hemorrhage. The increased pressure also causes ascites, which can cross the diaphragm to form hepatic hydrothorax, and splenomegaly, which sequesters platelets to cause thrombocytopenia. The metabolic and hemodynamic effects of portal hypertension also can affect other organ systems, resulting in hepatic encephalopathy, cirrhotic cardiomyopathy, hepatopulmonary syndrome, portopulmonary hypertension, and hepatorenal syndrome.

The diagnosis of decompensated cirrhosis usually can be made by a thorough history and physical examination. Common manifestations of decompensated cirrhosis are outlined in ▬▬ 1. A history of confusion, memory loss, or personality change can indicate hepatic encephalopathy. Fetor hepaticus can be smelled on the breath, and asterixis can be elicited in the outstretched hands of patients with hyperammonemia. Temporal wasting and generalized sarcopenia suggest the protein wasting, catabolic state of advanced liver disease. Jaundice can be seen as scleral icterus and darkened skin. Spider angiomata or nevi, spider angiomata, and palmar erythema indicate dysfunction in the hepatic metabolism of estrogen and vasodilation. Decreased breath sounds at the lung bases may indicate hepatic hydrothorax, whereas low oxygen saturation or shunting of the fingers suggests significant hypoxemia from the intrapulmonary shunting of blood associated with hepatopulmonary syndrome. A history of hematemesis, hematochezia, or known bleeding esophageal varices suggests significant portal hypertension. Prominent superficial veins in the abdominal wall can form caput medusae around the umbilicus, and auscultation of a Cruveilhier-Baumgarten bruit over the umbilicus indicates recanalized umbilical or paraumbilical veins. Easy bruising or bleeding suggests coagulopathy or thrombocytopenia, and splenomegaly often can be palpated below the left costal margin. A history of diuretic use and paracentesis to control ascites or a history of spontaneous bacterial peritonitis are other common signs of decompensated cirrhosis. Uncontrolled, long-standing ascites can create umbilical or inguinal hernias that can incarcerate, leak, or bleed. Finally, hypoalbuminemia and fluid overload, due to chronic arterial, of end-stage liver disease can lead to marked peripheral edema. By the time patients present with any of these signs and symptoms, their liver disease is quite advanced, and these patients should undergo expeditious evaluation for liver transplant.

ALLOCATION OF LIVE ' ALLOGRAFTS

Liver transplantation is hampered by a limited supply of cadaveric liver allografts that cannot meet the demand. Approximately 14,000 patients are listed for liver transplantation annually, but only about 6000 to 7000 patients receive liver transplants per year in the United States. Currently, liver allografts are allocated based on a "sickest first" policy where the *Model for End-stage Liver Disease* (MELD) scoring system in adults (≥ 12 years old) and the *Pediatric End-stage Liver Disease* (PELD) scoring system in children (< 12 years old) provide objective assessments of 3-month mortality for patients with end-stage liver disease who do not receive liver transplant.

Originally developed to predict survival in patients undergoing elective placement of transjugular intrahepatic portosystemic shunts for complications of portal hypertension, the MELD score uses serum creatinine, total bilirubin, and international normalized ratio (INR) to provide a score ranging from ▬ to a maximum of 40. In 2016, serum sodium also was incorporated into the MELD score because decreasing sodium levels have been correlated with increasing mortality while on the liver transplant waitlist. The PELD score uses serum albumin, total bilirubin, and INR as well as growth failure (based on gender, height, and weight) and age at listing. Children with MELD/PELD scores higher than 25 and life-threatening complications of portal hypertension, such as severe encephalopathy or gastrointestinal bleeding requiring mechanical ventilation, red blood

BOX 1 Manifestations of Decompensated Cirrhosis

Hepatic encephalopathy
Jaundice
Sarcopenia
Cirrhotic cardiomyopathy
Hepatic hydrothorax
Hepatopulmonary syndrome
Portopulmonary hypertension
Hemostasis: esophageal varices, bleeding
Splenomegaly
Ascites
Hepatorenal syndrome
Peripheral edema

FIG. 2 United Network for Organ Sharing region map. The United States is divided into 11 regions, which are further subdivided into 58 donor service areas. In general, livers from deceased donors are allocated locally, regionally and then nationally to patients at each listed status. "Share 35" allocates livers regionally first to facilitate transplant in patients with Model for End-stage Liver Disease scores ≥35. *(Courtesy United Network for Organ Sharing, Richmond, VA.)*

cell transfusion of at least 30 mL/kg in 24 hours, or dialysis may be granted additional priority known as status 1B to expedite the allocation of an appropriate, size-matched liver allograft.

Patients are waitlisted according to blood type and ranked by MELD/PELD score and time on the list. The United States is formally divided into 11 regions made up of 58 local donor service areas, each of which is presided over by an organ procurement organization (Fig. 2). In general, liver allografts are allocated locally, regionally, and then nationally based on medical need (as determined by the MELD/PELD score) and distance from the donor hospital (to minimize cold ischemia time of the liver). For patients with MELD/PELD scores of ≥35 or higher, liver allografts are allocated regionally first, a policy known as "Share 35" to increase access to liver transplant and further decrease waitlist mortality for medically urgent patients. The current liver allocation system thus focuses on candidates with the greatest risk of pretransplant mortality (i.e., urgency) without consideration for maximizing patient survival after transplant (i.e., utility). In addition, disputes attempts to distribute the scarce resource of a liver allograft equitably, regional and national disparities in access to liver transplant persist. We can expect refinement and change to the current liver allocation system in the near future.

LIVER TRANSPLANTATION TECHNIQUES

Hepatectomy

The first phase of liver transplantation involves removing the diseased liver. The total hepatectomy can be broken down into four steps: incision and entry into the abdomen, mobilization of the ligaments of the liver, dissection of the porta hepatis, and dissection of the vena cava. We will discuss each step. Adequate exposure is essential, particularly in the setting of portal hypertension. Commonly used abdominal incisions include a bilateral subcostal incision with midline extension (the "Mercedes") and the inverted T incision. These large incisions provide excellent exposure but suffer from a weak point where the three lines of incision meet. Depending on the shape of the cirrhotic liver, degree of splenomegaly, and abdominal wall laxity, smaller incisions such as the "hockey stick," reverse L, or J shaped (the "Makuuchi") incisions also can provide good exposure (Fig. 3).

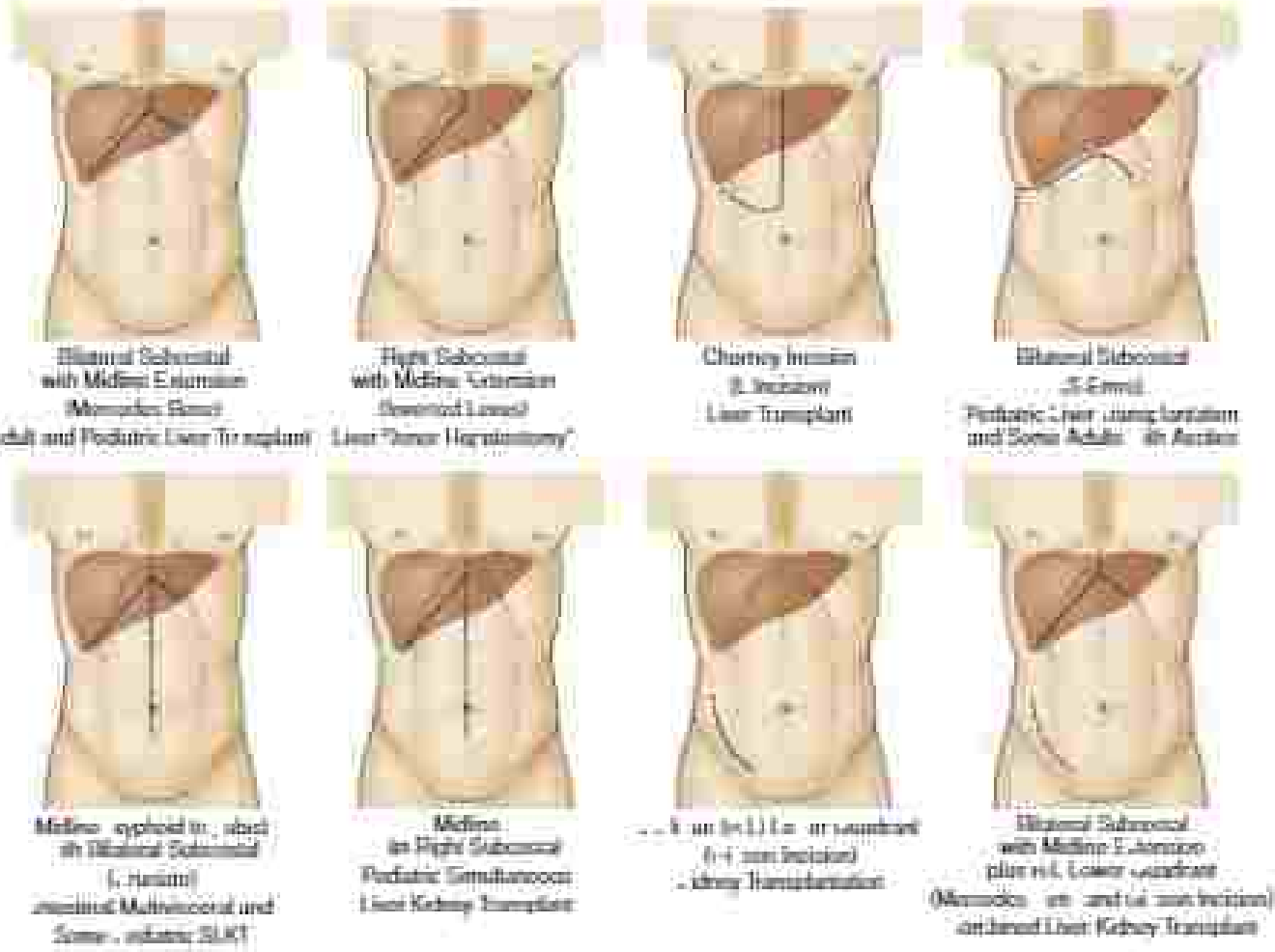
Sharp dissection through the subcutaneous tissue helps to identify, ligate, and divide prominent superficial veins to avoid bleeding early in the operation. Study of preoperative imaging can elucidate the point of entry into the abdomen to avoid recanalized paraumbilical veins or other large venous collaterals. Before entry, it is important to ensure there is adequate suction to evacuate ascites. Turbid or frankly purulent ascites should be cultured, offering the surgeon a moment to assess for active peritonitis, which should contraindicate liver transplant at that time. Patients with active peritonitis should be aborted and treated with appropriate intravenous antibiotics. They can be reexplored after 5 to 7 days of treatment when another liver allograft becomes available.

In portal hypertension, the ligamentum teres hepatis (i.e., round ligament of the liver) often carries recanalized paraumbilical veins that can become quite large as they shunt blood from the portal to systemic venous system. The ligamentum teres thus should be controlled securely with tie or stapler. The falciform ligament is divided to the hepatic vein followed by the left and right coronary and triangular ligaments to free the liver from the diaphragm and retroperitoneum. The gastrohepatic ligament may contain a replaced or accessory left hepatic artery and should be securely ligated and divided to expose the caudate lobe and left side of the vena cava.

The goal of dissection of the porta hepatis is to ligate and divide the bile duct, hepatic artery, and portal vein with minimal trauma and sufficient length for future anastomoses. These three structures are encased in nerves, lymphatics, and connective tissue, which must be dissected free. Particularly in cases of portal vein thrombosis, there can be large varices in the porta hepatis that require careful dissection to avoid significant bleeding. Although inflammation may distort the tissue planes, these planes provide safe passage around the vital structures and should be sought to allow efficient dissection.

After division of the cystic duct, the common hepatic duct is divided close to the biliary to maximize length. The bile duct is then sent down to the duodenum, taking care to preserve its blood supply. The hepatic artery is dissected with ligation and division of the right and left branches. The proper hepatic artery is carefully liberated, ligated and divided,[1] on the right gastric artery followed by the gastroduodenal artery, which is ligated with some length for the potential creation of a branch patch for later arterialization of the graft. The common hepatic artery is dissected free for a short distance along the superior border of the pancreas to provide space for clamping. A gentle vascular clamp can be placed on the common hepatic artery early in the dissection of the porta hepatis to prevent retrograde dissection of the artery. There can be large lymph nodes along the artery, which need to be handled with care to avoid bleeding. Finally, the portal vein is dissected free from the surrounding connective tissue from its bifurcation to the pancreas, which often requires division of the right gastric vein and superior pancreaticoduodenal vein. The portal vein is left intact until the dissection of the vena cava is complete.

In cases of portal vein thrombosis, it is necessary to remove the thrombus and ensure adequate portal flow before implantation of the liver. The thrombectomy requires control of the portal vein as close



* Some groups, including ours, have performed and published the use of a short (~ 10 cm) subcostal midline incision only or other MIS approaches for the donor hepatectomies.

as possible to the confluence of the superior mesenteric vein (SMV) and splenic vein (SV), depending on the degree and extent of clot. In cases of acute or nonocclusive thrombus, the clot usually can be lifted from the vein wall with minimal disruption to the intima of the vein. In cases of chronic, occlusive thrombus, the clot may be adherent and calcified and usually requires circumferential dissection to separate the clot and intima from the media of the vein to perform an adequate thrombectomy/endarterectomy. These maneuvers must be performed with the utmost care not to damage the portal vein. If the main portal vein is unusable because of complete thrombosis and cavernous transformation, it may be possible to excise the clotted portion of vein and sew an interposition graft of donor iliac vein to the SMV-SV confluence. If an interposition graft is not possible, the SMV should be dissected below the transverse mesocolon in preparation for a donor iliac vein bypass graft. In certain cases, large varices around the porta hepatis may provide adequate portal inflow to the liver allograft. Last resort options in cases of unusable portal vein, SMV, or collateral vein to usable portal inflow from the renal vein (if there is a large splenorenal shunt) or from the vena cava, known as cavoportal hemitransposition, but outcomes with such techniques are inferior (Fig. 6).

The dissection of the vena cava differs depending on the method of liver implantation. With the standard bicaval technique, the native liver is removed en bloc with the retrohepatic inferior vena cava (IVC) (Fig. 5). The retrohepatic IVC is completely mobilized as the suprahepatic and infrahepatic IVC are dissected free from the diaphragm and retroperitoneum to provide space for clamping. The right adrenal vein is ligated to allow adequate mobility of the infrahepatic IVC. With the dissection complete, the surgeon should alert anesthesia before clamping of the portal vein, suprahepatic IVC, and infrahepatic IVC. This complete clamping can cause hemodynamic instability as venous return decreases and the renal and splanchnic beds congest. In patients with severe portal hypertension who do not tolerate clamping, portocaval venovenous bypass may be necessary, which involves cannulation of the axillary, femoral, and portal veins to preserve venous return and decongest the splanchnic bed (Fig. 4). With the *piggy-back* technique, the native liver is dissected off of the IVC to remove the liver, thus preserving the IVC (Fig. 7). The hepatic veins are skeletonized anteriorly, and the short hepatic veins draining directly into the IVC are ligated and divided as the caudate lobe is mobilized off of the IVC up to the hepatic veins posteriorly. This piggy-back dissection requires division of the ligamentum venae (i.e., hepatic venal ligament) to completely liberate the liver from the IVC. The portal vein is clamped and divided high in the hilum before partially clamping the suprahepatic IVC and dividing the hepatic veins will take the liver to preserve length for future hepatic venous outflow reconstruction.

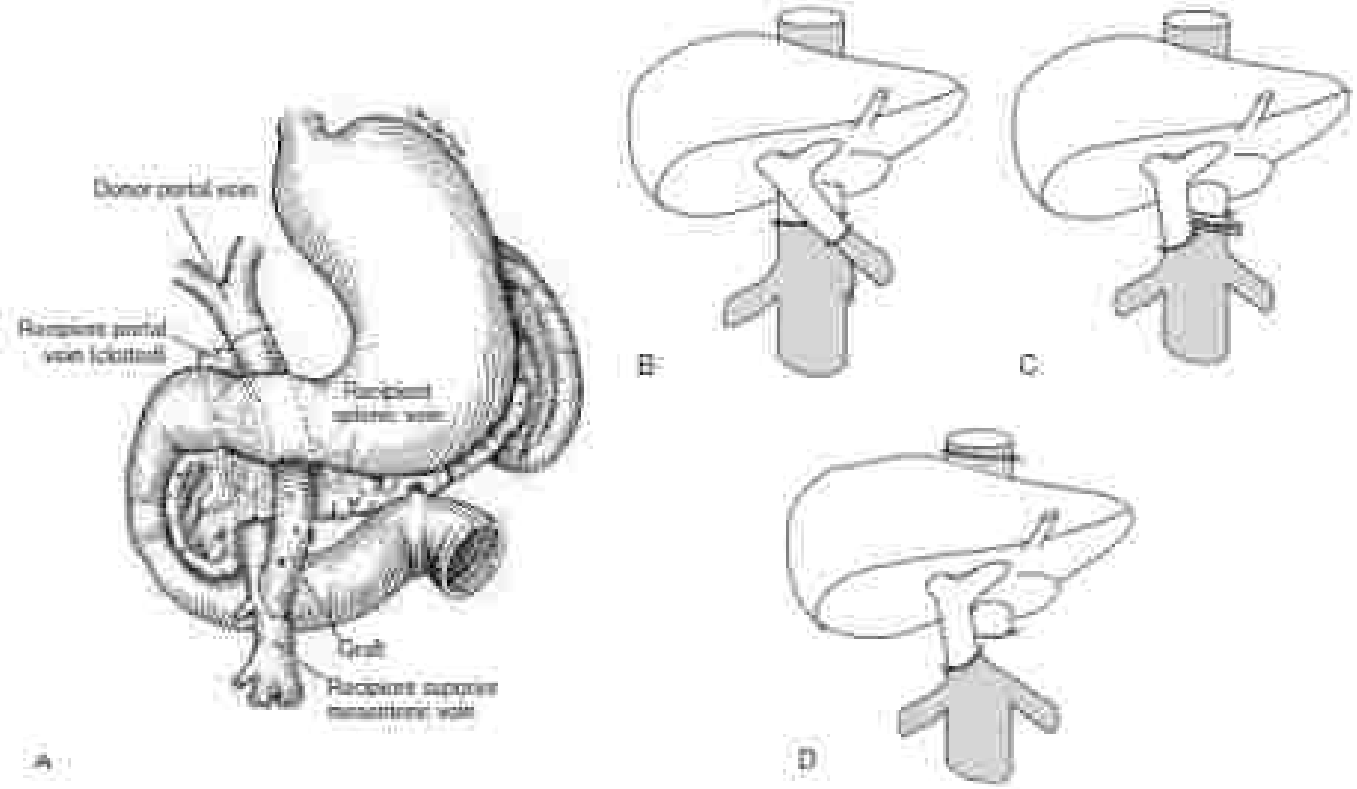


FIG. 9 Options for portal venous inflow in the setting of complex portal vein thrombosis. (A) As the vein graft from the donor can be sewn to the recipient superior mesenteric vein. (B) When a large splenorenal shunt is present, the recipient left renal vein can be sewn to the donor portal vein. As a last resort, the recipient inferior vena cava can be sewn to the donor portal vein. (C) donor iliac as side or (D) end to end, known as conjoint hemitransplantation. (Adapted from Abt, P. L., Crisalli, K. A., Martin, M., Reyes, J., Fontes, P., & Markmann, J. F. (2003). Liver transplantation in the setting of complex portal vein thrombosis. Liver transplantation, 9(6), 652–657. https://doi.org/10.1053/jlts.2003.50104)

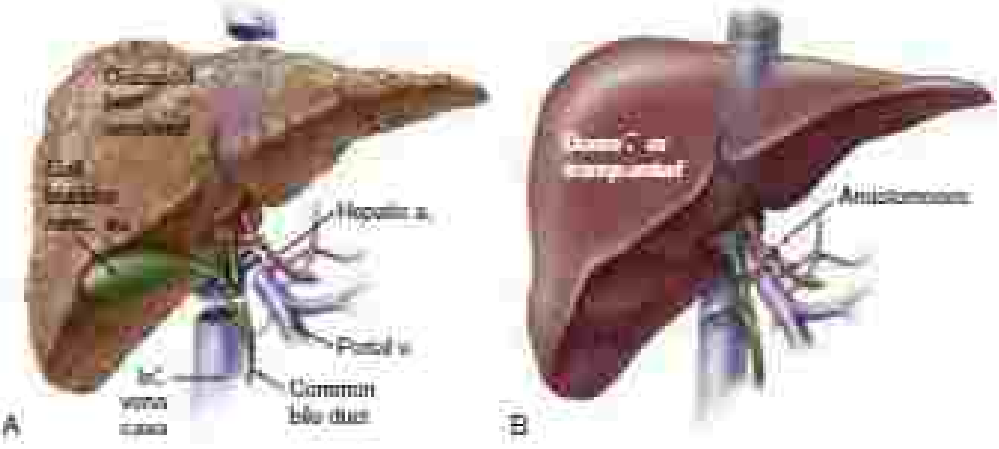


FIG. Classic bilateral liver transplantation. (A) The native liver is removed en bloc with the monohepatic vena cava, and (B) the donor liver with monohepatic vena cava is implanted orthotopically.

Implantation

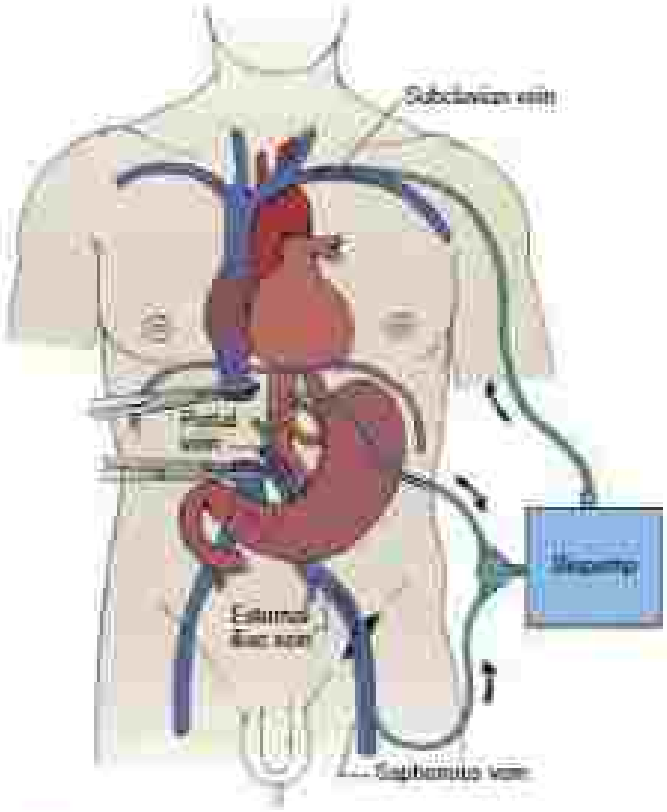


FIG. 6 Veno-venous bypass. Intracaval bypass is established before completion of the hepatectomy. The axillary, right atrium, and portal veins are cannulated. A centrifugal pump returns cystemic and portal venous blood to the heart via the axillary vein while the patient is anhepatic. (From Gilbert JD, Jaeg KM, Hug ... Oxford: ... J Int Pediatr Hepatol Gastroenterol. 2016;)

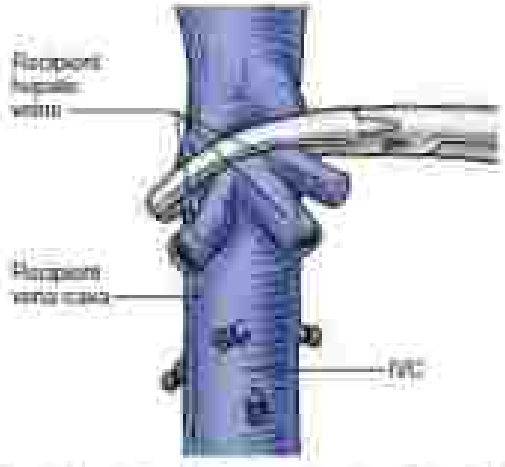


FIG. 7 Piggy-back technique for liver transplantation. During this hepatectomy, the diseased liver is freed from the recipient vena cava by ligating and dividing the short hepatic veins. The right, left, and middle hepatic veins are clamped and divided, and the liver is removed, thus preserving the vena cava. IVC, Inferior vena cava.

factor that allows for expansion of the portal vein after reperfusion to avoid stenosis. In cases of portal vein thrombosis described previously, anastomosis may involve donor portal vein to interposition graft between the ...eV – V confluence, the S...IV below the transverse mesocolon, large ... collaterals around the porta hepatis, left renal vein, or vena cava (Fig. 6). These techniques for portal inflow should be thoroughly analyzed and anticipated before reaching the operating room during study of preoperative imaging and undertaken with the utmost care. Occasionally in patients with significant portal hypertension, large portosystemic collaterals may continue to shunt blood away from the transplanted liver after reperfusion. It is important to find and ligate these collaterals to improve portal flow.

The liver allograft is reperfused once the portal vein reconstruction is complete. After a quick round of hemostasis to check for bleeding from the caval and portal anastomoses, the hepatic artery is reconstructed. The health of the biliary system is dependent on arterial tissue, and a perfect hepatic artery anastomosis is essential for excellent posttransplant outcomes. Common technical reasons for hepatic artery thrombosis include poor intimal apposition, dissection of the intima, misalignment of the artery lumens, entrapment of adventitia in the anastomosis, and narrowing of the lumen. The hepatic artery anastomosis thus should be sewn with meticulous handling of the artery and utmost precision to avoid these common pitfalls.

The donor hepatic artery usually includes the entire celiac axis with a patch of aorta. Aberrant donor arterial anatomy, such as a replaced right hepatic artery arising from the superior mesenteric artery, will require reconstruction during the back table preparation of the liver allograft. To prevent intraplasm thrombosis and retrograde bleeding that will interfere with the reconstruction, heparinized saline is instilled into the donor hepatic artery and the artery is gently clamped in the hilum. The hepatic artery is usually reconstructed in an end-to-end manner at a level where the diameters of donor and recipient arteries are well matched. Using fine polypropylene sutures, the donor celiac axis is commonly sewn to a branch patch of the recipient proper hepatic and gastroduodenal arteries, where they take off from the common hepatic artery. Branch patches can be fashioned at any major branch point along either the donor or recipient artery as length and quality of the artery allow (Fig. 5). A benefit of using branch patches in case of suturing a wider anastomosis without compromising the arterial lumen. If the donor hepatic artery is diseased or injured, it can be cleanly divided at a distal point of healthy arterial wall. If the recipient hepatic artery is not usable, more proximal dissection of the branches of the celiac axis can reveal a suitable segment of artery. Meticulous handling and preservation of length for both donor and recipient hepatic arteries during the organ procurement, back table preparation, and hepatectomy that are essential for an uncomplicated hepatic artery reconstruction.

Intimal dissection, atherosclerosis, or proximal stenosis are the most common reasons for poor hepatic artery inflow, which would require creation of a conduit directly from the recipient aorta to the donor artery using a donor iliac artery graft. The iliac artery conduit usually is sewn to the recipient infrarenal aorta because it is easier to access and safer to clamp. The conduit is then tunneled through the transverse colon mesentery behind the stomach to the porta hepatis. Alternatively, in cases of severe atherosclerosis of the infrarenal aorta or inaccessible retroperitoneal compartment, the iliac artery conduit can be sewn to the recipient supraceliac aorta. Exposure of and suturing to the supraceliac aorta can be challenging; clamping here temporarily occludes blood flow to the intestines and kidneys, which can be perilous. Rarely is it necessary to sew the donor iliac artery conduit to the recipient iliac artery for arterialization of the liver allograft.

The bile duct reconstruction is the final step in implantation of the liver. After the donor gallbladder is removed, the bile duct is reconstructed either by duct-to-duct anastomosis or ... hepaticojejunostomy or choledochojejunostomy using fine, absorbable sutures. The benefits of a duct-to-duct anastomosis (i.e., choledochocholedochostomy) include preservation of native anatomy and physiology and ease of access to the biliary system via endoscopy posttransplant. As with the portal vein, it is important to cut to appropriate length and align the donor and recipient bile ducts to avoid a redundant duct that might kink. Excision of the donor cystic duct and transection of the common hepatic duct ensures good blood supply to the end of the donor duct. Before cutting the donor duct, it is important to assess for aberrant duct anatomy, such as a right posterior sectoral duct draining directly into the common bile duct, to avoid cutting

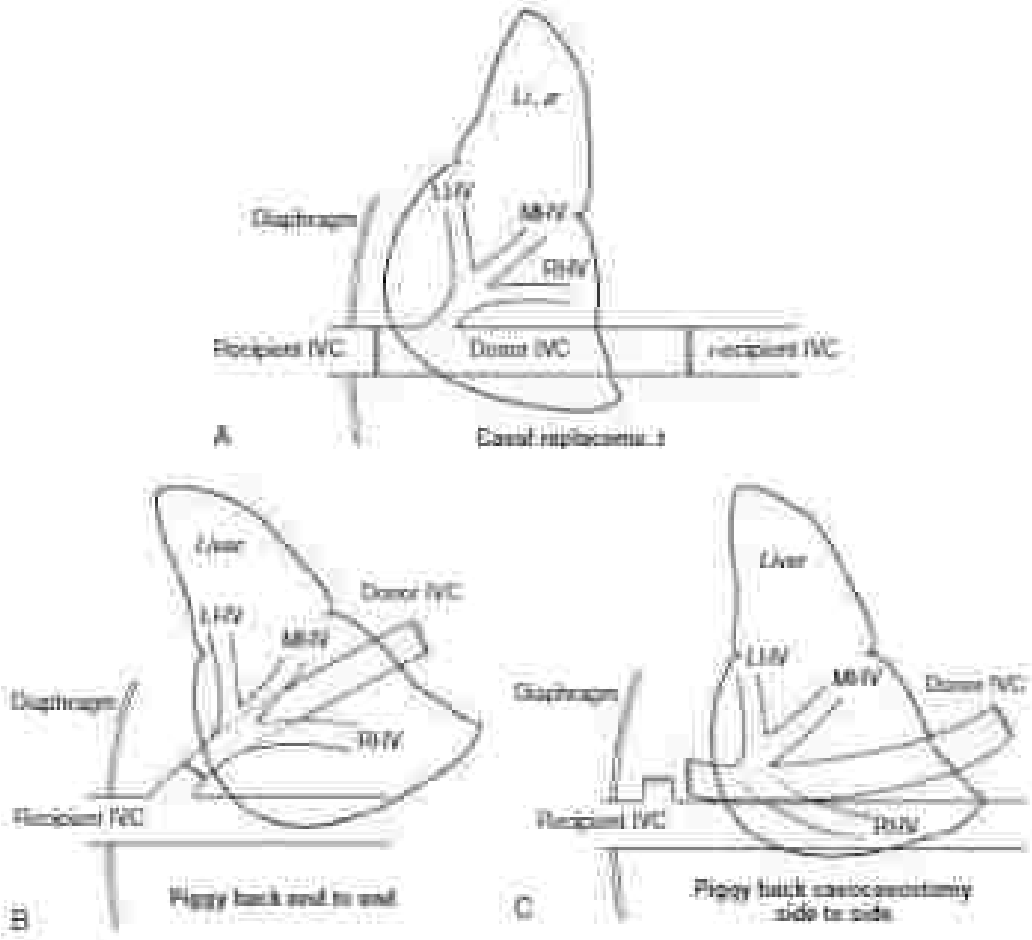


FIG. 8 Hepatic venous outflow reconstruction options. (**A**) The classic (orthotopic) technique of the donor and recipient supra- and infrahepatic vena cava (IVC) cuffs to reconstruct the hepatic venous outflow. (**B**) In the classic piggy-back (orthotopic) technique, the hepatic venous outflow is reconstructed by anastomosing the donor suprahepatic vena cava to a common orifice of the recipient hepatic veins. The donor infrahepatic vena cava is closed with a tie, suture, or stapler (—). In the modified piggy-back (orthotopic) technique, the hepatic venous outflow is reconstructed by anastomosing a cavotomy on the donor infrahepatic vena cava to a cavotomy on the posterior wall of the recipient vena cava. Both the suprahepatic and infrahepatic vena cava cuffs of the donor are closed. *IVC*, Inferior vena cava; *LHV*, left hepatic vein; *MHV*, middle hepatic vein; *RHV*, right hepatic vein.

above this insertion and creating two lumens that would need separate anastomoses. It also is important to probe the recipient bile duct to ensure that there is no distal obstruction or obvious problem at the ampulla of Vater. After trimming each duct to lumens with healthy, well-vascularized biliary epithelium, peri-duct vessels are controlled with fine polypropylene sutures before the reconstruction. In cases of mismatch of the diameters of the donor and recipient bile ducts, there are several options, including sewing down the larger duct (i.e., ductoplasty), creating a branch patch at the cystic duct insertion, or creating an anterior slit to widen the smaller duct on either the donor or recipient side (Fig. 10). When there is a significant size discrepancy, a side to side anastomosis can be performed between the donor and recipient ducts, though more commonly a Roux en Y hepaticojejunostomy anastomosis is performed. If the recipient bile duct is unusable for whatever reason (e.g., poor quality in patients with primary sclerosing cholangitis), Roux en Y hepaticojejunostomy anastomosis is performed.

Complications

The most common complications after liver transplantation are bleeding and infection. Complications specific to the liver transplant itself include problems with the liver allograft or with any of the anastomoses. These complications most often can be detected by clinical examination, serial monitoring of the hepatic function panel and INR, and liberal use of Doppler ultrasonography (DUS). If a problem is suspected, liver biopsy and cross-sectional imaging can confirm the diagnosis, whereas direct percutaneous venography/angiography can offer a chance for therapeutic intervention. Liver allografts can suffer from delayed graft function or primary nonfunction, the latter of which requires urgent retransplantation. Acute cellular rejection and antibody-mediated rejection also lead to graft dysfunction but can be managed with adjustments of immunosuppression.

Rarely, the hepatic venous outflow reconstruction can have thrombosis or stenosis, which may require hepatic venogram with angioplasty and possible stent placement. Portal vein thrombosis (“PVT”) and portal vein stenosis (PVS) are relatively rare outside of pediatric and living donor liver transplantation, in which size discrepancy and proper orientation lead to technical challenges, but can be catastrophic, resulting in early graft dysfunction and loss. Risk factors for PVT include technical issues (e.g., redundant vein), hypercoagulability, prolonged “cold” ischemia requiring intraoperative thromboendarterectomy, small portal vein diameter, and reconstruction with an interposition graft. Any PVT or PVS should be managed by reoperation to attempt graft salvage, if the graft is reversible. Reperfusion of an irreversible graft can cause massive cytokine release, coagulopathy, and hemodynamic instability; in these cases, retransplantation is contraindicated, and the patient should be relisted for liver transplant immediately. Late PVT or PVS may be amenable to percutaneous angioplasty with or without stent.

Hepatic artery thrombosis (“HAT”) is a dreaded complication of liver transplantation. Because the biliary system is dependent on arterial

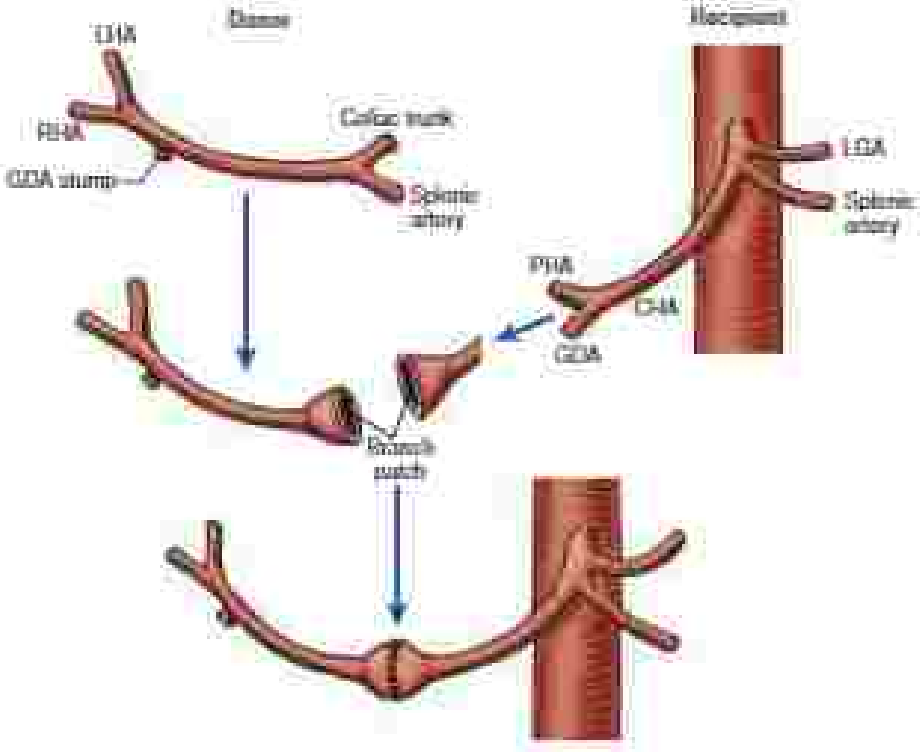


FIG. 9 Branch patch reconstruction of the hepatic artery. Branch patches can be created at points of bifurcation to maintain the diameter of an artery and facilitate suturing of an anastomosis without compromising the arterial lumen. CHA, Common hepatic artery; GDA, gastroduodenal artery; LHA, left hepatic artery; PHA, proper hepatic artery; RHA, right hepatic artery. *[From Gruessner R, Reed A: Surgical factors ... In Busuttil RW, Klintmalm GBG, eds: Liver and Pancreas Transplantation. Philadelphia, 2004, Saunders.]*

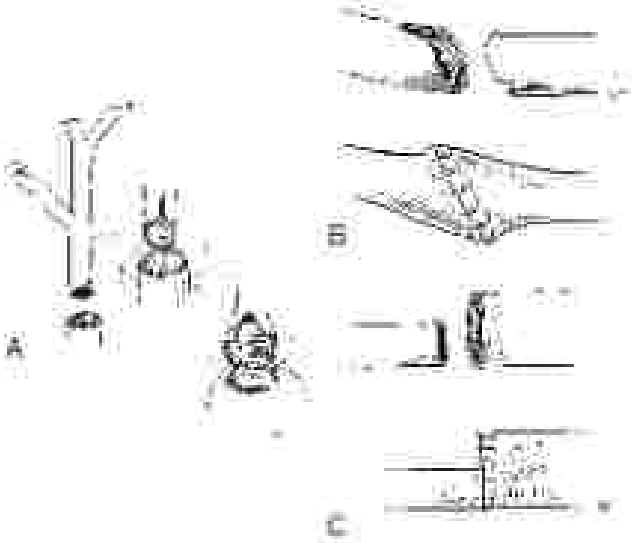


FIG. 10 Biliary reconstruction options. (A) When there is a size discrepancy between the donor and recipient bile ducts, an anterior slit can be made to maintain the diameter of the smaller duct. (B) When both bile ducts are small, slits can be made on both donor and recipient ducts to compensate for tissue that is ultimately lost in the suture line and to prevent stricturing. (C) Alternatively, the larger duct orifice can be partially sewn to create equal lumens for anastomotic leakage as a lateral duct-to-duct. *[From Busuttil RW, Klintmalm ... In Busuttil RW, Klintmalm GBG, eds: Liver and Pancreas Transplantation. Philadelphia, 2004, Saunders.]*

blood flow, arterial compromise leads to bile duct strictures, bile duct necrosis, liver abscesses, and, ultimately, graft dysfunction and loss. HAT thus requires a high index of suspicion and vigilance postoperatively to allow prompt recognition and management to ensure graft and patient survival. If HAT is diagnosed early enough, it is possible to salvage the graft by operative thrombectomy and revision or reconstruction of the hepatic artery. If diagnosed late, the patient most likely will need retransplantation. Hepatic artery stenosis (HAS) has a characteristic "parvus et tardus" (i.e., slow and late) arterial waveform on

IOUS and often presents clinically as unexplained, asymptomatic graft dysfunction. Early HAS may represent edema at the anastomosis and should be followed with serial IOUS until resolution. If HAS persists, surgical revision or percutaneous transluminal angioplasty with or without stent placement are options (Fig. 11). With advances in interventional radiology expertise, percutaneous transluminal angioplasty is first-line therapy for HAS at many institutions.

The two most common complications with the bile duct are bile leak and stricture. Many bile leaks will resolve without intervention as long as they are well drained. Abdominal pain, fever, and signs of peritonitis should prompt imaging to look for intraabdominal fluid collections. Fluid collections should be drained percutaneously and sent for bilirubin and culture. If the collection is indeed a biloma, the leak most often can be managed with intravenous antibiotics and endoscopic sphincterotomy and biliary stent placement. If the bile leak is severe, with suspected major disruption of the anastomosis, reoperation is necessary to revise the biliary reconstruction.

Bile duct strictures can be classified as anastomotic and nonanastomotic. Anastomotic strictures usually result from technical issues, including surgical technique, small caliber ducts, or thermal injury from electrocautery and can be managed with endoscopic balloon dilation and stent placement (Fig. 12). Short-duration internal biliary stenting for serial dilation and stent placement is very successful, and surgical revision is rarely needed. Nonanastomotic strictures can result from ischemia secondary to preservation injury or hepatic artery thrombosis, use of donors after cardiac death livers, rejection, or recurrent disease such as causes of autoimmune cholestatic liver disease. If the stricture involves the extrahepatic bile ducts, it may be possible to operate, excise the fibrotic segment, and convert to a Roux-en-Y hepaticojejunostomy. If the stricture involves the intrahepatic bile ducts, retransplantation usually is necessary.

Living Donor Liver Transplantation

We are able to perform living donor liver transplantation (LDLT) when a healthy person voluntarily donates part of the liver to a patient with indications for liver transplant, either an adult to a child or an adult to an adult. LDLT is founded on the principles of segmental anatomy and regeneration of the liver, which allow the procurement of partial liver allografts that will grow in the recipient while the remnant liver

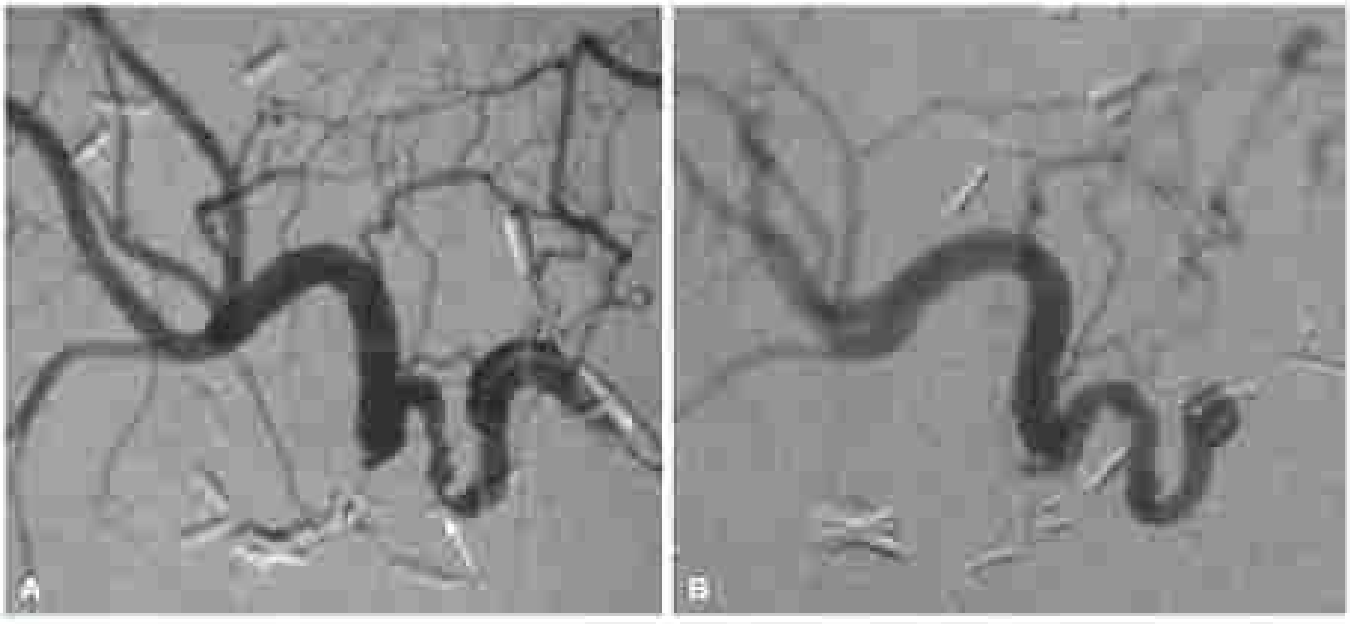


FIG. 11 Hepatic artery stenosis. (A) Hepatic artery angiogram shows a stenotic lesion (arrow) distal to the anastomosis. (B) Balloon angioplasty corrected the stenosis. (From Goodall MD, Atkinson LAC. Transplantation in Focus. Mosby; Philadelphia; Elsevier; 2011.)

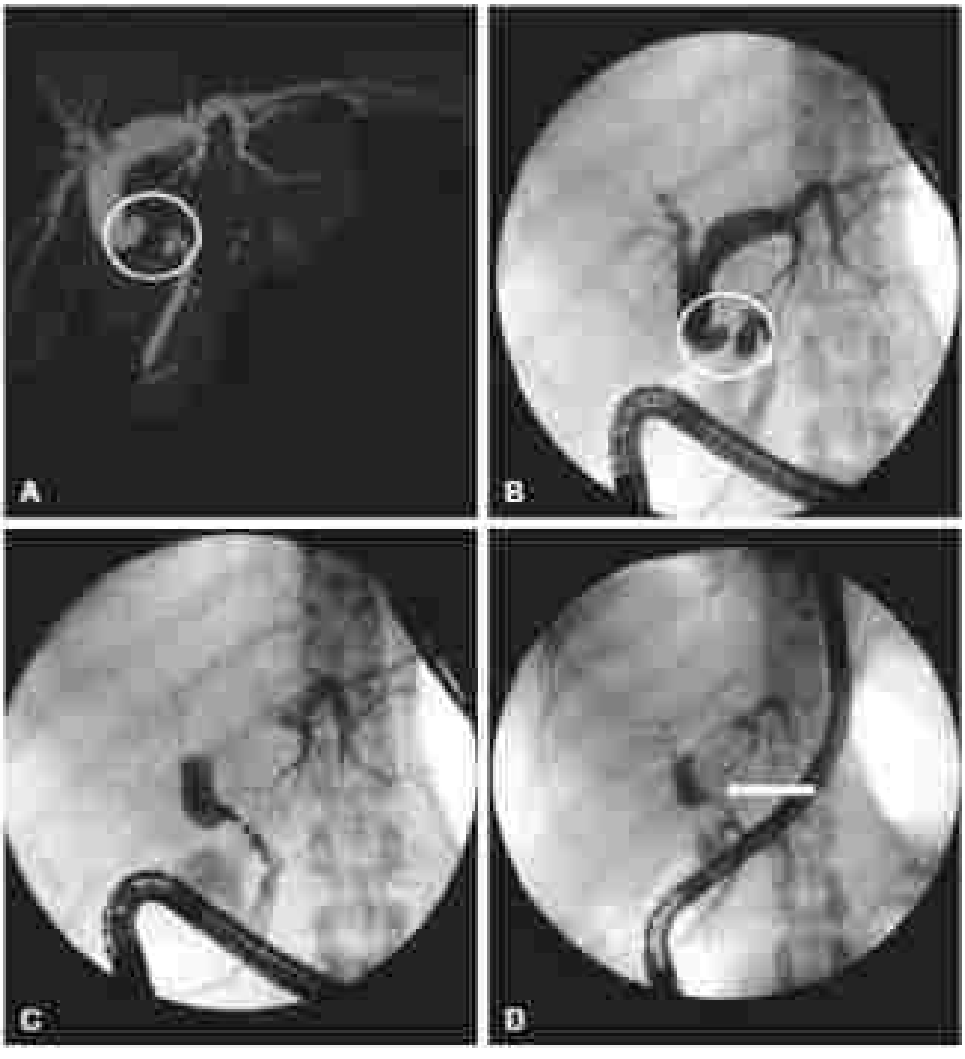


FIG. 12 Biliary stricture. Hepatic transverse cholangiopancreatogram (A) and endoscopic retrograde cholangiopancreatography (B) demonstrate high-grade anastomotic biliary stricture (arrow). Balloon dilation (C) and stent placement (D, arrow) ultimately resolved the stricture without surgical intervention.

TABLE 1 History of Living Donor Liver Transplantation

Date	Surgeons	Country	Liver Allograft	Notes
19[illegible]	S. Raia et al.	Brazil	Left lateral section	Mother to daughter with biliary atresia (unsuccessful)
19[illegible]	R. Strong et al.	Australia	Left lateral section	Mother to son with biliary atresia (successful)
19[illegible]	T. Hashikura et al.	Japan	Left hepatic lobe	Son to mother with primary biliary cholangitis
19[illegible]	C.M. Lo et al.	Hong Kong	Right hepatic lobe	Brother to brother with fulminant Wilson's disease
2001	S.G. Lee et al.	South Korea	Dual left hepatic lobes	To address donor graft recipient size insufficiency
2002	D. Cherqui et al.	France	Left lateral section	Completely laparoscopic procurement
2015	R. Samstein et al.	United States	Left hepatic lobe	Completely laparoscopic procurement
201[illegible]	O. Soubrane et al.	France	Right hepatic lobe	Completely laparoscopic procurement

BOX 2 Living Liver Donor Characteristics That Maximize Safety

Age >40 years
BMI <30 kg/m^2
Hepatic macrovesicular steatosis <10%
Remnant liver mass >30%

BMI, [illegible] by m.s, [illegible] al. x.

registration and initiate life in the donor. LDLT was born from the scarcity of organs for transplant and the need for size appropriate liver allografts in children. Because of cultural, religious, and societal beliefs that restrict transplant of organs from deceased donors, LDLT has flourished in Asia and the Middle East. In contrast, brain death laws and the national promotion and organization of deceased donors have helped support deceased donor liver transplant (DDLT) in Western countries. Worldwide, about 20% of liver transplants performed are from living donors; in the United States, about 4% to 5% of liver transplants are from living donors. South Korea performs the most LDLTs at 34 LDLT per million people versus 9 DDLT per million people in 2[illegible]. Comparatively, the United States performs about 1 LDLT per million people versus 23 DDLT per million people in 201[illegible]. Milestones in the history of LDLT are listed in Table[illegible] 1.

The selection of donors and recipients for LDLT involves comprehensive, multidisciplinary medical, surgical, and psychosocial evaluation. Donor safety is paramount, and the donor evaluation must ensure absolute health, voluntary donation without coercion, and fully informed consent. Characteristics that maximize donor safety are listed in Box 2. Although experienced centers safely and successfully push these limits. In general, for recipients in the United States, all pediatric patients should be considered candidates, whereas adult patients should meet select criteria including MELD score of 25 or less with significant complications of cirrhosis or cholestasis. Liver disease. Adult patients with hepatocellular carcinoma who meet transplant criteria but face prolonged wait times or cannot receive locoregional treatment for control of the tumor also may be candidates for LDLT.

Once a donor and recipient have been thoroughly evaluated, cross-sectional imaging of the donor is necessary to determine liver size and anatomy and plan the partial liver allograft for donation. Standard partial liver allografts include the left lateral section, right hemiliver with or without the middle hepatic vein, and left hemiliver with or without the caudate lobe. For an adult to child LDLT, the graft to recipient weight ratio should be between 1% and [illegible]% to avoid large-for-size syndrome, which is characterized by abdominal compartment syndrome, insufficient graft perfusion, and graft dysfunction. For an adult to adult LDLT, a graft to recipient weight ratio of 0.8% or greater avoids small-for-size syndrome, which is characterized by persistent hyperbilirubinemia, coagulopathy, and ascites in the absence of technical problems in the early posttransplant period.

The donor hepatectomy is designed with donor safety foremost and a complete liver allograft second to none. Principles of the donor operation include avoiding unnecessary dissection of the hepatic hilum with limited use of cautery to isolate the hepatic artery, portal vein, and hilar plate containing the bile duct. Intraoperative cholangiography can be performed to ensure proper division of the bile duct. After dissection of the hilar structures, the hepatic parenchyma is divided with care to ligate biliary radicals and preserve all accessory hepatic veins 0.5 cm or greater in diameter. A 70% hepatectomy at maximum can be performed on the donor. The majority of donors do not regain donation and report preoperation quality of life scores that meet or exceed the general population. Most donors also note improved relationships with recipients. The estimated risk of morbidity for the donor is about 40% with serious morbidity (defined as Clavien-Dindo grade III or higher) occurring in 1%. The estimated risk of mortality for the donor is between 0.3% and 0.5%, with the highest risk in the first "1" days. One third of donors report lingering physical symptoms, one-third report financial burdens such as lost wages or unreimbursed expenses, and one-quarter report exacerbation of depression or anxiety. These challenges require further advocacy and research on the national level to optimize safety and security for living liver donors.

LDLT can be planned electively when recipients have better functional and nutritional status, before significant deterioration of liver function. Principles of the recipient operation include piggyback dissection of the vena cava, high hilar dissection to preserve branches and length of vessels and bile ducts for reconstruction options, and minimal dissection of the hepatic artery bile duct complex to preserve optimal blood supply for the biliary reconstruction. Adequate hepatic venous outflow is essential for proper allograft function, which may require augmentation of both donor and recipient hepatic vein orifices as well as separate reconstruction of major segmental veins. Microvascular techniques are used to reconstruct the smaller caliber hepatic arteries and bile ducts that come with partial liver allografts. In the setting of significant portal hypertension, portal venous flow may need to be modulated by splenic artery ligation or creation of portosystemic shunts to avoid graft dysfunction or failure from excessive portal blood flow. Although there is increased short-term morbidity compared with recipients of DDLT, particularly with hepatic artery and biliary problems, the overall complications and time to resolution of these complications in LDLT are equivalent to DDLT.

OUTCOMES

With advances in the perioperative care of patients with decompensated cirrhosis and complications of portal hypertension, patient and graft survival after liver transplantation continue to improve despite the high acuity of many recipients. Five-year patient survival for adult recipients of LDLT is greater than 75%, whereas 5-year patient

survival for pediatric recipients of DIRT is greater than 80%. In highly selected adult and pediatric patients, DIRT offers significantly superior and durable survival with improved liver allograft and fly compared with DIRT. Future challenges include addressing the shortage of liver allografts, mitigating the side effects of immunosuppression, and ensuring long-term living donor and recipient survival with excellent quality of life.

Suggested Readings

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Endoscopic Therapy for Esophageal Variceal Hemorrhage

Anne Ag[illegible]

Varices are portosystemic venous collaterals that occur as a result of portal hypertension, most commonly in patients with cirrhosis. These collaterals protrude into the gastrointestinal lumen and their rupture with resultant hemorrhage is a complication with a high mortality rate (at least 20% at 6 weeks). Approximately 50% of patients with cirrhosis have varices and 8% of cirrhotic patients will develop them each year. Clinically significant varices are most commonly found in the distal esophagus and gastric cardia, which allows for easy detection and potential treatment with endoscopy.

MEDICAL MANAGEMENT

Patients who present with variceal hemorrhage will have signs of upper gastrointestinal bleeding (UGIB), such as hematemesis or melena. This may be accompanied by hemodynamic instability due to hemorrhagic shock or altered mental status. Variceal hemorrhage should be suspected in any patient with upper gastrointestinal hemorrhage and findings suggestive of portal hypertension or liver cirrhosis, including the presence of ascites, thrombocytopenia, elevated prothrombin time, or a history of cirrhosis.

The initial step in the assessment of any variceal bleed should be focused on ensuring adequate airway, breathing, and circulation in that order. Hematemesis can rapidly lead to aspiration of blood and respiratory failure, and so should prompt consideration of intubation to protect the airway. Patients with variceal hemorrhage are also at risk of developing encephalopathy due to shock or hyperammonemia, and so care should be given to ensure the patient is protecting their airway. If hypotension or the presence of shock physiology is present, attention must be paid to adequate resuscitation and consideration of vasopressor support to prevent hypoperfusion related end organ damage.

Care should be given to ensuring patients have adequate intravenous (IV) access, at least two large bore peripheral IVs or even large bore central access if necessary. Resuscitation via red blood cell transfusion is a necessity in almost all patients with variceal hemorrhage. Randomized control trials and a meta-analysis have demonstrated that a restrictive transfusion strategy with a transfusion threshold of 7 g/dL and a goal of 7 to 9 g/dL improves mortality and reduces rebleeding in patients with gastrointestinal ([illegible]) bleeding. Excessive transfusion and overload, by contrast, increases portal pressure and worsens bleeding. Notably, these studies typically exclude patients with massive exsanguinating hemorrhage—these patients may require blood transfusion at a rate that precludes waiting for confirmatory laboratory values. As cirrhotic patients often have a coagulopathy, patients may also require transfusion of platelets and fresh frozen plasma, particularly if they are receiving a large number of packed red blood cell transfusions. There is limited evidence to recommend a particular threshold for other platelets or the international normalized ratio (INR), particularly as INR is not a reliable indicator of coagulopathy in cirrhosis.

Broad-spectrum IV antibiotic prophylaxis should be administered as they have been shown to reduce mortality, rebleeding rates, and infections. Ceftriaxone is the most commonly used antibiotic and should be continued for prophylaxis for no more than 7 days. The use of vasoactive agents such as octreotide, vasopressin, somatostatin, or terlipressin has been shown to reduce 5-day all-cause mortality and lower transfusion requirements. Only one agent should be used. IV octreotide bolus and infusion is the only vasoactive agent available in the United States and should be continued for 2 to 5 days. Both antibiotic prophylaxis and a vasoactive agent should be started at the time of presentation and prior to endoscopic therapy.

The placement of a nasogastric tube for lavage is of limited utility in diagnosing variceal hemorrhage and has the theoretical risk of precipitating variceal rupture.

In patients for whom endoscopic therapy is delayed, balloon tamponade with a Sengstaken or Minnesota tube is highly effective at temporarily controlling bleeding. As it is associated with a high complication rate, including aspiration, migration, and necrosis/perforation of the esophagus, it should be used for no longer than 24 hours and as a bridge to definitive therapy.

Other nonendoscopic options to control acute variceal hemorrhage include the placement of a transjugular intrahepatic portosystemic shunt (TIPS) or, less commonly, a surgical portosystemic bypass. These techniques reduce the hepatic venous pressure gradient (HVPG) allowing for decompression of varices. TIPS placement involves the radiologically guided placement of a metal stent between the portal vein and hepatic vein by interventional radiology. Both these methods can be complicated by worsening hepatic

survival for pediatric recipients of DDLT to greater than 80%. In highly selected adult and pediatric patients, LDLT offers significantly superior and durable survival with improved liver allograft utility compared with DDLT. Future challenges include addressing the shortage of liver allografts, mitigating the side effects of immunosuppression, and ensuring long-term living donor and recipient survival with excellent quality of life.

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Endoscopic Therapy for Esophageal Variceal Hemorrhage

Amarit Agarwalla, MD, and Vikesh K. Singh, MD, MSc

Varices are portosystemic venous collaterals that occur as a result of portal hypertension, most commonly in patients with cirrhosis. These collaterals protrude into the gastrointestinal lumen and their rupture with resultant hemorrhage is a complication with a high mortality rate (as high as 20% at 6 weeks). Approximately 40% of patients with cirrhosis have varices and 8% of cirrhotic patients will develop them each year. Clinically significant varices are most commonly found in the distal esophagus and gastric cardia, which allows for easy detection and potential treatment with endoscopy.

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Care should be given to ensuring patients have adequate intravenous (IV) access, at least two large bore peripheral IVs or even large bore central access if necessary. Resuscitation via red blood cell transfusion is a necessity in almost all patients with variceal hemorrhage. Randomized control trials and a meta-analysis have demonstrated that a restrictive transfusion strategy with a transfusion threshold of 7 g/dL and a goal of 7 to 9 g/dL improves mortality and reduces rebleeding in patients with gastrointestinal (GI) bleeding. Excessive resuscitation and overload, by contrast, increases portal pressure and worsens bleeding. Notably, these studies typically exclude patients with massive exsanguinating hemorrhage—these patients may require blood transfusion at a rate that precludes waiting for confirmatory laboratory values. As cirrhotic patients often have a coagulopathy, patients may also require transfusion of platelets and fresh frozen plasma, particularly if they are receiving a large number of packed red blood cell transfusions. There is limited evidence to recommend a particular threshold for other platelets or the international normalized ratio (INR), particularly as INR is not a reliable indicator of coagulopathy in cirrhosis.

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Other nonendoscopic options to control acute variceal hemorrhage include the placement of a transjugular intrahepatic portosystemic shunt (TIPS) or, less commonly, a surgical portosystemic bypass. These techniques reduce the hepatic venous pressure gradient (HVPG) allowing for decompression of varices. TIPS placement involves the radiologically guided placement of a metal stent between the portal vein and hepatic vein by interventional radiology. Both these methods can be complicated by worsening hepatic

encephalopathy as well as prolonged in those patients with right-sided heart failure, and so patients need to be carefully selected for these therapies. Surgical portosystemic bypass, while effective, has been limited due to concerns regarding the safety of intra-abdominal surgery in patients with decompensated cirrhosis.

ENDOSCOPIC MANAGEMENT

Esophagogastroduodenoscopy (EGD) remains the central therapy for acute variceal hemorrhage. Though endoscopic evaluation is beneficial in primary and secondary prevention as well as risk stratification for variceal hemorrhage, this chapter focuses on the endoscopic management of acute hemorrhage. In situations where endoscopic management is unable to control bleeding, methods such as TIPS placement or surgical portosystemic bypass are also options.

Prior to endoscopy, consideration must be given to several factors that will affect post-endoscopic outcomes. Patients should be intubated prior to the procedure to prevent aspiration during endoscopy. Patients should be transferred to an intensive care unit where post-procedure monitoring can be continued. Patients should also be hemodynamically stable and adequately resuscitated, to a hemoglobin of 7 to 9 g/dL and a systolic blood pressure of 100 mm Hg. Though it is generally agreed that endoscopy should be performed, the appropriate timing remains unclear. Evidence remains conflicted; some studies have shown emergency endoscopy in patients with portal hypertension and hemodynamic improves endoscopic outcomes, while others have shown it can be delayed in patients with stable vital signs and the absence of active ongoing bleeding. Current guidelines recommend endoscopy within 12 hours of presentation for cirrhotics with acute UGIB. Patients who have demonstrated hemodynamic instability should undergo EGD as soon as possible once resuscitated and ready for endoscopy. In the absence of instability, recent evidence suggests no difference in outcomes within the first 24 hours of presentation. In all patients, pharmacologic therapy should be paired with endoscopic therapy; this improves initial hemostasis as well as 5-day rebleeding rates when compared to either therapy alone.

Endoscopically, varices appear as dilated and serpiginous blood vessels that protrude into the gastrointestinal lumen. They are most commonly seen in the distal esophagus or, less commonly, in the gastric fundus. Variceal hemorrhage can be diagnosed if there is active bleeding or the stigmata of recent or remote bleeding, including red wale sign, white nipple, cherry red spots, or overlying clot. The presence of fresh blood without another clear cause is also suggestive of varices as the source of bleeding. Often there is clotted blood preventing adequate visualization; several strategies, such as positional changes of the patient and/or use of endoscopes with a large accessory channel for increased suctioning can allow for adequate visualization of the lumen.

Endoscopic Band Ligation

Endoscopic variceal ligation (EVL) is the gold standard for the treatment of acute esophageal variceal (EV) bleeding. In EVL, a circular band ligator is applied over an esophageal varix, obliterating blood flow and decompressing the varix. Other modalities are used for treating gastric or ectopic varices or cases that are refractory to band ligation. To perform EVL, the endoscope is inserted into the patient and used to confirm the presence of variceal hemorrhage (▶ Fig. 1), with attention paid to the distal most location of the relevant varix. The endoscope is then removed, and a multiband ligator with a clear cap is attached to the distal end of the endoscope. This cap allows for visualization (▶ Fig. 2) and suction of the varix into the cap prior to placement of a band ligator. Many devices are available, and the endoscopist should be familiar with the setup and troubleshooting of the band ligator device. The endoscope is then advanced again under direct visualization to the previously noted distal most location of the varix. This is often at the gastroesophageal junction, where the esophageal mucosa is thin, predisposing to bleeding. The endoscope is positioned so the entire width of the target varix is within the walls of the cap, typically with the endoscope tip being placed orthogonal to the luminal wall. Suction is applied and maintained until the varix is completely sucked into the cap. The goal is to capture the entirety of the variceal wall within the cap otherwise the band can fall off and result in an ulcer over the vessel with catastrophic rebleeding. With continuous application of suction (which could precipitate hemorrhage), the band is deployed (▶ Fig. 3). This technique is then repeated in a clockwise fashion moving distal to proximal until all high risk varices have been ligated. Care should be taken not to traverse previously placed bands as this may dislodge them and precipitate hemorrhage.

Ligation is performed distal to proximal, as this is also the direction of blood flow in distal EV. Rarely, patients may develop "downhill" EV located in the proximal esophagus in the setting of superior vena cava obstruction, typically due to mediastinal etiologies. In these proximal varices, ligation should be performed cephalad to caudal, with care to take not to dislodge a previously placed band. Nasogastric or orogastric tube placement should also be avoided or done with care to prevent dislodgment of a band. However, no consensus exists on how long one should wait before placing nasogastric access after EVL.

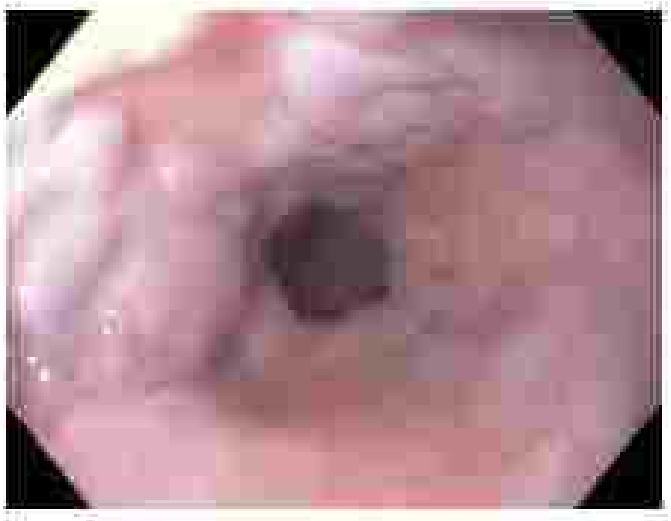

FIG. 1 Endoscopic view of esophageal varices.

FIG. 2 Visualization of the varix prior to placement of a band ligator.

FIG. 3 Placement of band ligator.

FIG. 4 Endoscopic view of a gastric varix.

EVL can be complicated by post banding ulcers that present with bleeding or chest pain. Patients should ideally undergo repeat banding to ensure complete eradication of esophageal varices, typically in 7- to 14-day intervals. Patients typically require 2 to 4 sessions to completely eradicate varices, after which they will require a repeat endoscopy in 3 to 6 months to evaluate for EV recurrence.

Endoscopic Injection Sclerotherapy

Prior to band ligation, endoscopic injection sclerotherapy (EIS) was the primary endoscopic management of acute EV hemorrhage. The advantages of EIS are its easy technique and high technical success. However, EIS appears to be associated with higher rates of complications, rebleeding, prolonged elevation in HVPG, and death. In general, EIS should not be used when EVL is available.

EIS is performed with ethanolamine, morrhuate sodium, or absolute alcohol, though no consensus exists on the ideal sclerosant or volume needed to inject. A 23- or 25-gauge endoscopic needle is inserted via the endoscope and injected into or between varices. Complications can include chest pain (seen in up to 40% of patients), or, less commonly, esophageal strictures or local necrosis.

Endoscopic Glue Injection

While EIS has generally fallen out of favor, endoscopic glue injection is increasingly used as a modality to treat gastric varices (Fig. 4). Cyanoacrylate, a liquid agent that polymerizes on contact with blood, is injected into the gastric varix with a similar technique as EIS. The procedure is often performed with the gastroscope in retroflexion to best visualize fundal varices. The needle is inserted into the varix orthogonal to the luminal wall, and 1 to 2 cc of cyanoacrylate are injected into the varix, followed by 1 cc of sterile water (Fig. 5). The needle should be withdrawn at the same plane as entry. The needle is retracted and a 1 cm length of catheter is left outside of the endoscope to avoid glue damage to the tip of the endoscope. Repeated injections may be necessary but increase complication rates, including the risk of embolization.

Glue injection may be enhanced by the guidance of endoscopic ultrasound (EUS). EUS can allow for identification of gastric varices and allow for antegrade injection. Coils can also be injected prior to glue injection to provide a structure for cyanoacrylate to polymerize, reducing the risk of embolization.

The most dreaded complication of glue injection is embolization, which can occur in 1% of patients. Other complications include transient fevers, chest or epigastric pain, or delayed onset bleeding due to ulceration at the injection site. In a poorly sedated patient, puncture

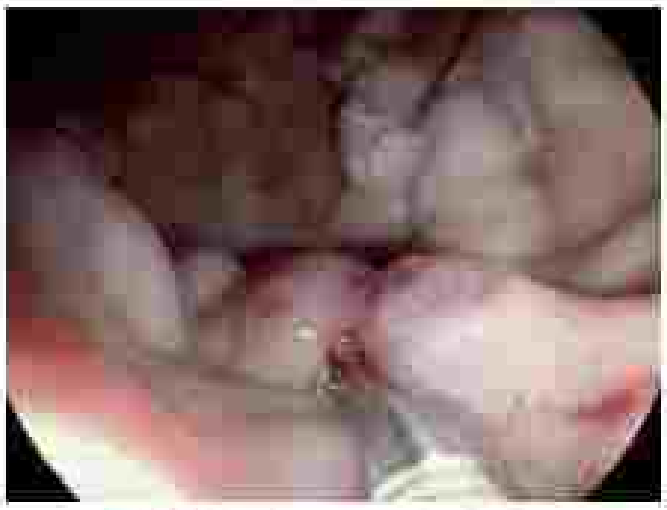

FIG. 5 Injection of cyanoacrylate into the varix.

of the gastric varix during treatment can also result in worsening hemorrhage.

Self-Expanding Metal Stent Placement

In patients with bleeding too rapid to allow for visualization and banding or for patients with bleeding that is refractory to EVL, the placement of a self-expandable metal stent (SEMS) can be used as a salvage therapy. A fully covered, removable esophageal SEMS, at least 25 mm in width, is deployed in the distal esophagus with or without the use of fluoroscopy. Successful placement provides tamponade and hemostasis. Once placed, these stents can remain in place for up to 7 days, allowing for resuscitation and plans for definitive therapy such as TIPS. One small trial comparing SEMS placement to balloon tamponade showed no difference in survival but did show SEMS had higher control of bleeding and fewer complications.

Gastric Varices

While the distal esophagus is the most common location of variceal hemorrhage, gastric varices are discussed in this chapter to highlight the similarities and differences in their treatment when compared to esophageal varices.

The location of gastric varices is important in determining the optimal treatment. Isolated gastric varices due to splenic

sion thrombosis should not be treated endoscopically as they rarely result in variceal hemorrhage. Varices that occur in both the esophagus and lesser curvature of the stomach (also known as GOVI) should be treated similarly to esophageal varices. Varices in the gastric fundus, however, rarely respond well to treatment with EVL, this is due to the difficulty in capturing the contralateral wall of the varix in the ligation cap, resulting in a high likelihood of band dislodgement, poor banding ulcer, and subsequent hemorrhage.

As mentioned above, the primary modalities for the treatment of acute gastric variceal hemorrhage is either the endoscopic injection of glue with or without coils, direct reduction in portal pressure with TIPS, balloon tamponade with a Sengstaken or Minnesota tube, or balloon occluded retrograde transvenous obliteration (BRTO). BRTO is transvenous obliteration performed by interventional radiology that instills sclerosants or embolic agents into a gastrorenal collateral through the left renal vein, aided by balloon occlusion. This requires the presence of an anatomic gastrorenal shunt, which is not present in all patients.

Ectopic Varices

Varices can occur anywhere in the GI tract, including in the duodenum, the remainder of the small bowel, colon, rectum, and enteric / colocutaneous stomas. The rates of bleeding from these ectopic locations is markedly lower than those from gastroesophageal varices, and so limited evidence is available as to which modality is optimal in their management. EIS, EVL, and glue injection have all been reported to be effective. Direct sutured ligation has also been reported for duodenal varices.

FUTURE DIRECTIONS

Two topical agents, Hemospray and Arkadia Hemostapler, have efficacy in early treatment in early gastric variceal hemorrhage as well as portal hypertensive gastropathy without the risk of embolization. However, the durability of hemostasis is unknown as these agents remain in the lumen for less than 24 hours, and their use is currently only approved for arterial bleeding and not for acute variceal hemorrhage.

SUMMARY

Esophageal variceal hemorrhage is a highly morbid complication of portal hypertension. The optimal management of variceal hemorrhage involves medical therapy with transfusion, vasoactive agents, antibiotics, as well as endoscopy, which remains the cornerstone of managing bleeding varices. Endoscopy allows for direct visualization, treatment, and risk stratification of patients with variceal hemorrhage. Endoscopic band ligation remains the gold standard therapy for esophageal varices, though other modalities including sclerotherapy, glue injection, and self-expandable fully covered metal stent placement remain part of the management toolbox. Endoscopy can be supplemented with other procedures, including TIPS, to treat acute hemorrhage or prevent rebleeding.

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Transjugular Intrahepatic Portosystemic Shunt

Robert R. Liddell, MD*

Cirrhosis is the most common cause of portal hypertension, which often causes variceal bleeding, therapy refractory ascites/hydrothorax, and hepatorenal syndrome. Since the first description of transjugular intrahepatic portosystemic shunt (TIPS) insertion in dogs by Rösch et al. in 1969, the first successful TIPS insertion in patients was reported by Rössle et al. in 1989. TIPS is now regarded as an established procedure in the treatment of the previously mentioned consequences of liver cirrhosis, resulting in significantly reduced portal pressure.

The techniques used in TIPS formation are well established, involving portal vein access via a hepatic vein approach, and subsequent placement of a stent between them, essentially unchanged from when it was first described 20 years ago. There have been a number of significant improvements made in imaging equipment and devices used in the successful creation of a TIPS.

INDICATIONS

The list for causes of portal hypertension is lengthy and are summarized in Table 1. Whatever the causative pathophysiology, TIPS can reduce or normalize the portal pressure and attenuate the associated symptoms. As the technique for placing a TIPS has become more refined and more safe, and the imaging and catheter technologies become more advanced, the indications for TIPS have gradually expanded. Table 2 shows the indications and contraindications for TIPS.

VARICEAL BLEEDING

Portal hypertension can cause varices along the entire gastrointestinal tract, including the small bowel and colon (hemorrhoids). Varices are present in 30% of compensated cirrhotic patients and 60% of decompensated cirrhotic patients. Varices are more apt to bleed through the mucosa of the gastroesophageal junction, where the coronary vein is particularly prone to dilatation. Mortality from acute variceal bleeding is said to be approximately 33% in patients with cirrhosis.

The primary treatment of bleeding gastroesophageal varices has traditionally been medical, and/or endoscopic management. Despite the high success rate of endoscopic management in variceal bleeding, the progressive nature of chronic liver disease leads to rebleeding in more than 50% of patients. Unlike medical or endoscopic management, shunting procedures such as TIPS address the portal hypertension which causes the variceal bleeding. Portosystemic shunting is the only definitive treatment for portal variceal bleeding. Meta-analysis of the literature has shown that TIPS has a lower rate of both variceal rebleeding and death resulting from rebleeding with a strong trend toward increased survival (at the expense of increased hepatic encephalopathy). Most of the studies included in these meta-analyses predate the era of polytetrafluoroethylene (PTFE)-covered TIPS stent grafts that have improved long-term patency over bare metal stents with a trend toward better overall survival. Head-to-head comparisons of TIPS created with stent grafts to endoscopic and medical management are lacking.

Currently, the primary indication for TIPS is to control portal variceal bleeding refractory to medical and endoscopic management; however, there is evidence supporting the early use of TIPS in selected patients with advanced cirrhosis (Child–Pugh class B and C) and acute esophageal variceal bleeding (early TIPS). Additional studies are needed to confirm this finding before TIPS can be accepted as a first line therapy for bleeding esophageal varices in patients with advanced liver disease.

ASCITES

Ascites is the most frequent complication of cirrhosis. In addition to the severe limitations in lifestyle that often accompanies the development of ascites, it also poses a risk for bacterial peritonitis and other infections, renal failure, and has been seen to increase mortality. No single cause for cirrhosis related ascites has been identified; however, it is likely that a combination of causes, including decreased plasma albumin levels, increased bowel permeability, and cirrhosis related hemodynamic changes—such as increased cardiac output, vasodilatation, and increased plasma volume—factor together in the formation of ascites.

Initial management consists of sodium restriction and administration of loop diuretics (furosemide) and aldosterone antagonists (spironolactone). In advanced stages, ascites becomes refractory to medical management, and TIPS may be indicated. TIPS is very effective in eliminating ascites. Because the root causes are humoral/hormone related, response to TIPS is often not immediate. It may take 2 to 4 weeks after TIPS for ascites to resolve, during which additional paracentheses may be necessary. Randomized controlled trials, meta-analyses, and systematic reviews of the literature have demonstrated that TIPS significantly improves transplant-free survival compared with repeated paracentesis.

HEPATIC HYDROTHORAX

Hepatic hydrothorax is defined as the accumulation of at least 500 mL of pleural fluid in a patient with cirrhosis without cardiopulmonary disease. Even though this definition is not 100% specific to hepatic hydrothorax, additional signs, such as reduced right-sided hydrothorax and concurrent ascites, help confirm the diagnosis. It occurs in less than 10% of patients with cirrhosis as peritoneal fluid permeates via small diaphragmatic communications. As with ascites resulting from portal hypertension, initial management is sodium restriction and diuretics. In nonresponsive patients, TIPS will eliminate hydrothorax in most and decrease the frequency of thoracocentesis in the rest.

HEPATORENAL SYNDROME

Hepatorenal syndrome portends a poor prognosis for the cirrhotic patient because it generally occurs during the late stages of cirrhosis. Hemodynamic changes related to portal hypertension lead to the release of vasoactive hormones, resulting in splanchnic vasodilation, renal arterial vasoconstriction, and the opening of small intrarenal arteriovenous communications. This initially results in renal hypoperfusion and can eventually lead to renal failure.

Two distinct forms of hepatorenal syndrome (HRS) have been identified: type 1, which is rapidly progressing, and type 2, which evolves slowly. Type 1 is precipitated by an event that incites acute intrahepatic liver failure, an exaggerated systemic inflammatory response, and kidney dysfunction as part of broader multiorgan failure. Targeting the precipitating event is the hallmark of treatment for type 1. Type 2 results to large part from a reduction in effective arterial blood volume created by shift of fluid from the intravascular compartment to the extravascular compartment (i.e., ascites). Studies suggest that

TABLE 1 Causes of Portal Hypertension

Presinusoidal	Perisinusoidal	Postsinusoidal
Portal, splenic, or superior mesenteric vein thrombosis	Cirrhosis	Budd-Chiari syndrome
Idiopathic portal hypertension	Congenital hepatic fibrosis	Venoocclusive disease (sinusoidal obstruction syndrome)
Mass effect (i.e., tumor)	Cystic liver disease	Chronic passive congestion
Schistosomiasis	Sarcoidosis	Mass effect (i.e., tumor)
Preterminal stage, primary biliary cirrhosis		
Alcoholic central sclerosis		
Arterioportovenous fistula (traumatic or Osler-Weber-Rendu)		
Endofibrosis (liver transplant, radiation injury)		
Hyperdynamic splenomegaly (infectious or myeloproliferative)		
Nodular regenerative hyperplasia		
Congenital extrahepatic portal vein occlusion		

TABLE 2 Indications and Contraindications for TIPS

Indications			Contraindications	
	Emerging Indications			
Standard of Care	Supported by Controlled Studies	Supported by Noncontrolled Studies and Case Series	Absolute	Relative
Portal variceal hemorrhage refractory to medical/endoscopic management	Cirrhotic portal vein thrombosis caused by slow hepatic flow to the portal vein	Hepatorenal syndrome (more so type II than type I)	Severely elevated right heart pressure	Hepatic vein thrombosis
Ascites refractory to medical management	Child-Pugh B and C with acute esophageal variceal bleeding (simultaneously treated with medical and/or endoscopic interventions)	Hepatopulmonary syndrome	Severe tricuspid regurgitation	"Noncirrhotic" portal vein thrombosis caused by hypercoagulability or tumor thrombus
Budd-Chiari syndrome not responsive to anticoagulation		Portal gastropathy refractory to β blockers	Severe pulmonary hypertension	Poor liver function scores
Hepatic hydrothorax refractory to diuretics and salt restriction		Hepatic venoocclusive disease	Severe congestive heart failure	Polycystic liver disease
			Severe encephalopathy	Central liver mass
			Uncorrectable bleeding diathesis	Caution; arterial variceal source
			Active sepsis or hepatic bacterial infection	
			Obstructive biliary obstruction	

the reduction of ascites post-TIPS can improve renal function in type 2. However, the use of TIPS in HRS should be undertaken after serious consideration because of the contrast load and acute hemodynamic changes it involves.

BUDD-CHIARI SYNDROME

Budd-Chiari syndrome is caused by mechanical obstruction of the hepatic venous outflow and gradually results in cirrhosis and portal hypertension. Excluding a focal hepatic venous web, which can often be successfully treated with simple balloon angioplasty, treatment for the fulminant form of Budd-Chiari syndrome is liver transplantation, although anticoagulation may help stave off disease progression. TIPS has proven to be a valuable tool to bridge such patients to transplantation.

In the fulminant form of Budd-Chiari syndrome, anticoagulation is first-line therapy. When anticoagulation fails, TIPS is a reasonable and accepted next step, or direct intrahepatic portosystemic shunt (IHPS) if access to hepatic veins is completely occluded. The use of TIPS in this patient population was reported in a large retrospective study that showed 1- and 10-year transplant-free survival that was much greater than expected. The American Association for the Study of Liver Diseases now recommends creation of a TIPS in patients with Budd-Chiari syndrome who fail to improve with anticoagulation.

Technique

Patient Preparation

In nonemergent situations, patients needing a TIPS should be seen in a clinic in advance of the procedure. This provides an opportunity to explain and discuss the pathophysiology of portal hypertension as it relates to the patient and how a TIPS addresses this. The potential risks, benefits, and alternatives to TIPS are also to be discussed during the clinic visit and allows the patient to make an informed decision as to whether to proceed with TIPS. Review of any cross-sectional imaging and laboratory findings that may be pertinent to the TIPS procedure are done during the clinic visit. If necessary, additional imaging and laboratory testing can be ordered before the TIPS procedure. A pre-TIPS echocardiogram is often performed to

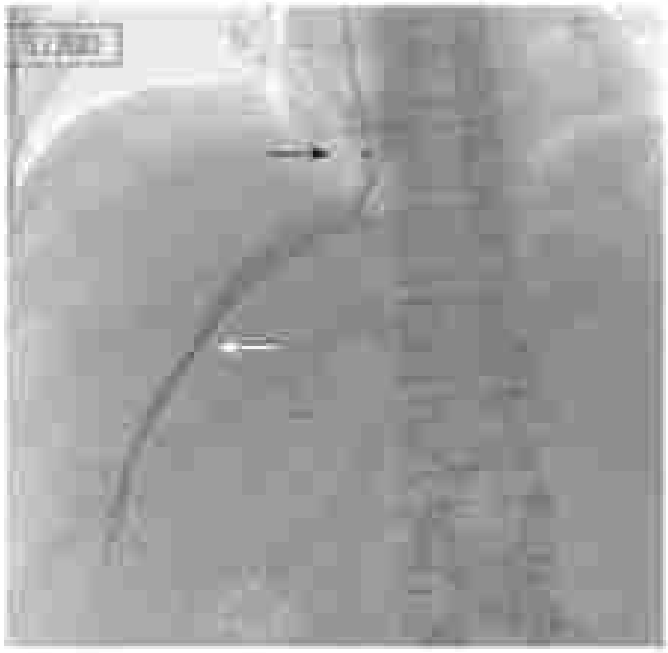

FIG. 1 Right hepatic venogram performed via a selective catheter (white arrow). The tip of the internal jugular sheath (black arrow) is below the diaphragm to avoid catheter/wire manipulations in the right atrium. The stages of transjugular intrahepatic portosystemic shunt insertion outlined in Figs. 1–9 are all from the same patient.

FIG. 2 Frontal digital subtraction views of a carbon dioxide (CO_2) hepatic venogram. CO_2 is injected via a balloon occlusion catheter to force the CO_2 retrograde into the portal system. The right portal vein and its intrahepatic branches, the left portal vein, and the main portal vein are easily visualized. The operator usually targets the right portal vein from the right hepatic vein with a long needle introduced via the right internal jugular sheath.

noninvasively evaluate cardiac function and exclude any evidence of right heart failure.

Many of the complications related to the placement of TIPS can be avoided by proper patient workup. Review of pertinent cross-sectional imaging will confirm a patent (nonthrombosed) portal vein, reveal the relative orientation and anatomic relationship of the hepatic and portal veins, and the presence or absence of varices. This minimizes the number of attempts to engage the portal vein and therefore decreases the associated bleeding risk. Good hydration will minimize the risk of acute renal failure, and initiation of metronidazole (Flagyl), rifaximin (Xifaxan), and/or lactulose mitigates the risk of encephalopathy. Type and cross of blood may prove lifesaving if a bleeding complication is encountered. Finally, all involved should be cognizant of related risks, especially the 30-day mortality, which ranges from less than 5% for elective procedures in well-compensated patients to 50% for emergent procedures in unstable patients with advanced liver disease.

Access

Access through the right internal jugular vein is preferred, although the left internal jugular vein can also be used. Access is maintained with a long, large vascular sheath positioned in the intrahepatic inferior vena cava to allow multiple catheter wire exchanges without recrossing the right atrium (Fig. 1).

Diagnostic Assessment

Optimizing TIPS outcomes requires not only a thorough anatomic assessment, but sometimes more importantly, a functional assessment of the patient's hemodynamic status. One of the contraindications to TIPS is an elevated right heart pressure. Unmasking the right atrial pressure is not severely elevated is mandatory before shunting the portal venous blood to an already overburdened right heart. Right atrial pressures below 15 mm Hg are generally safe, whereas pressures above 20 mm Hg predispose the patient to acute right heart failure. There are no specific guidelines, and sound clinical judgment is important. For example, a right atrial pressure of 16 mm Hg should not preclude creation of a TIPS in an unstable patient with ongoing variceal bleeding.

After selecting the right hepatic vein, free and wedged hepatic venous pressures are measured, which usually confirm portal hypertension. Normal corrected pressures should not necessarily terminate the procedure because these are not always accurate and are often inaccurate in cases of prehepatic portal hypertension (portal vein thrombosis, splenic vein thrombosis, primary biliary cirrhosis).

Delineation of the portal venous system is accomplished by injection of carbon dioxide (CO_2) via a catheter wedged into the hepatic vein. CO_2 is not nephrotoxic and can be given in virtually unlimited quantities. Frontal and lateral views show the anatomical relationships, so that the right portal vein can be targeted for access (Fig. 2).

In the vast majority of patients, the TIPS is placed from the right hepatic vein into the right portal vein as this is the shortest and most direct path for shunt creation. However, a recent randomized controlled trial found that using the left portal vein resulted in a significant reduction in the incidence of encephalopathy and rebleeding during 2 years of follow-up after TIPS creation. These data must be confirmed in additional studies before the standard approach of targeting the right portal vein is abandoned.

Shunt Placement

The next step in the cannulation of the right portal vein from the right hepatic vein. To accomplish this, a curved metallic sheath is advanced via the existing right internal jugular sheath in the right hepatic vein. The new catheter is rotated based on the anatomy revealed during CO_2 portography, so that it targets the right portal vein. When the operator judges the curved sheath to be directed toward the right portal vein, which is usually located anterior and inferior to the right hepatic vein, a long needle is advanced toward it. Aspiration of blood supports intravascular location, and contrast injection confirms the tip to be in the portal vein (Fig. 3). The use of ultrasound guidance during TIPS with intracardiac echocardiography is a new technique that may improve the technical success of portal vein access, decreasing procedure time and complications.

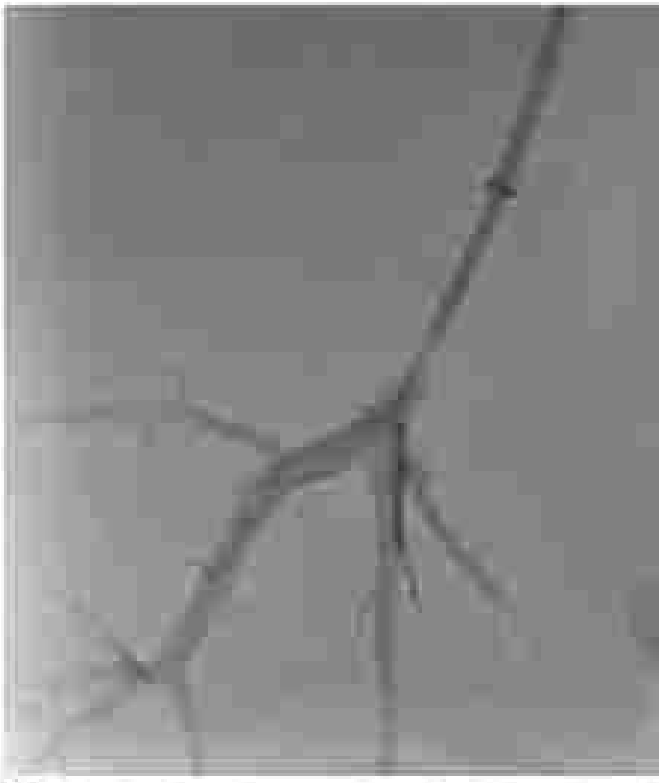

FIG. 3 Frontal unsubtracted venogram via a needle after it was advanced from the right hepatic vein through a catheter toward the right portal vein. Contrast dye injection of the right portal vein with hepatopetal blood flow.

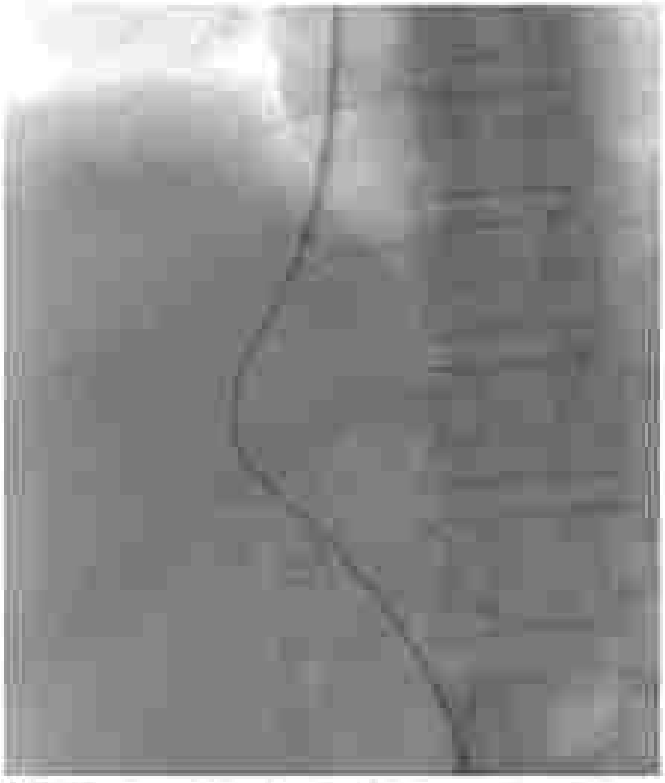

FIG. 4 After the needle is confirmed to be in the surgical portal vein branch, a wire is advanced through it into the portal vein. Note the location of the right internal jugular sheath. The wire crosses from the right hepatic vein, through a short segment of liver parenchyma, and into the right portal vein.

Once it is confirmed that the tip of the needle is in the right portal vein, an exchange length hydrophilic wire is passed distally through the main portal vein into the superior mesenteric vein or splenic vein for security (Fig. 4). In those patients with severe cirrhosis, the traversed liver parenchyma is often fibrotic and difficult to cross unless predilated. A small-caliber (4- to 6-mm diameter) balloon is used to predilate the liver parenchyma between the right hepatic and right portal vein created by the wire (Fig. 5). A marking catheter is then passed over the wire into the portal venous system. This allows for direct portal pressure measurement and a portal venogram. The venogram will be used to select the appropriate length stent to be placed (Fig. 6).

If the direct portal pressure and portosystemic gradient are within normal limits, TIPS creation is abandoned irrespective of the clinical picture. If a TIPS is not possible or is contraindicated, the gastroesophageal varices can be embolized via a catheter to stop the hemorrhage without placing a TIPS. Although this is very effective, it is nevertheless temporary. If present, the ongoing portal hypertension will likely cause new varices to form.

The stent is advanced through the larger sheath, which keeps it constrained and in position. The sheath is pulled back into the right atrium, uncovering the stent. The distal 2 cm of the stent is uncovered and flares out on withdrawal of the sheath. The rest of the stent is deployed once it is in the appropriate position (Fig. 7).

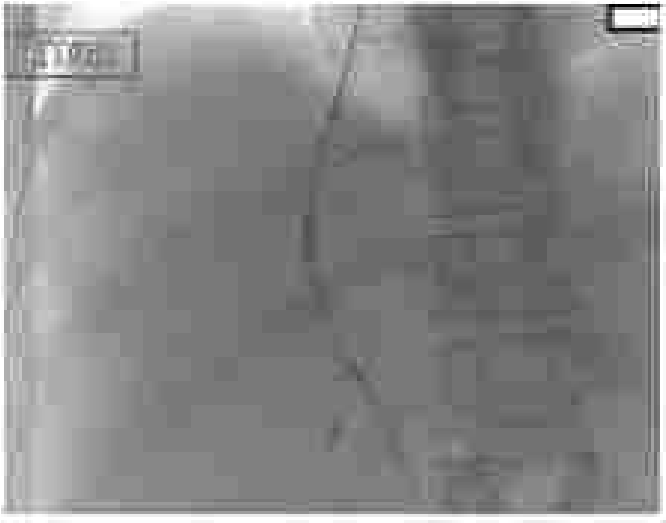

FIG. 5 Because cirrhotic liver is difficult to cross, it is predilated with a small balloon to facilitate the necessary shunt exchanges. The "waist" in the middle of the balloon reveals just how hard the liver parenchyma can be.

Shunt Evaluation

Usually, a 10-mm diameter stent is used and initially balloon dilated up to 8 mm in diameter. The direct portal pressure is measured again and, if it is not satisfactory, a 10-mm balloon is used to open the stent to capacity (Fig. 8). The smaller the stent diameter, the less the chance for encephalopathy postprocedure. A final portal venogram is performed to document flow and lack of variceal filling (Fig. 9). If at this point there are still varices present, coil embolization may be warranted.

Special Cases

Budd-Chiari Syndrome

The creation of a TIPS in a patient with Budd-Chiari syndrome is especially challenging because the hepatic veins are thrombosed. This shows as the classic spider vein appearance on a hepatic venogram (Fig. 10). Although it is true if the TIPS is placed from hepatic vein to portal vein, the lack of patent hepatic veins may necessitate an

FIG. 6 Frontal subtracted roadmap. Simultaneous manual injection via the right internal jugular sheath and marker catheter in the portal vein allows for calculation of the required length of the stent.

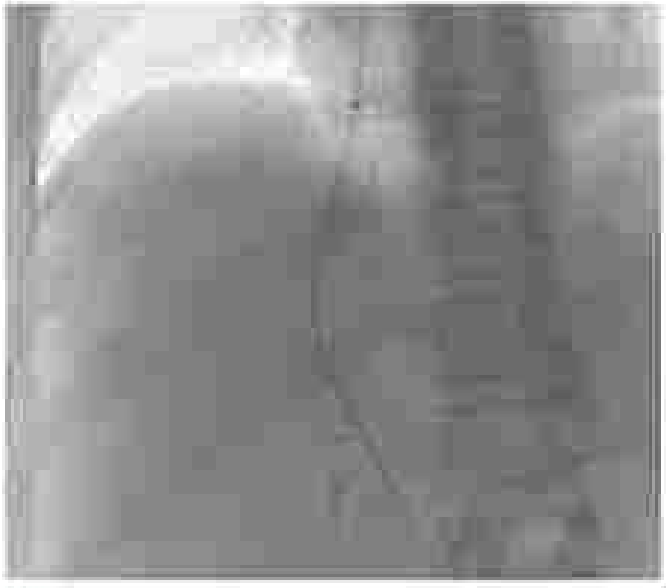

FIG. 7 Frontal view of the deployment sequence of a monojugular transhepatic portosystemic stent. The stent is first advanced via a sheath through the right hepatic vein, across the liver parenchyma, and into the portal vein. The stent's distal 2 cm are constrained only by the sheath and once the sheath is pulled back, a spotlight opens. The remainder of the stent remains unexpanded. The entire system is then gently withdrawn until the proximal end of the distal 2 cm lies the parenchymal tract. Once the operator judges the stent to be in proper position, the remainder of the stent is opened by pulling on the rip-cord.

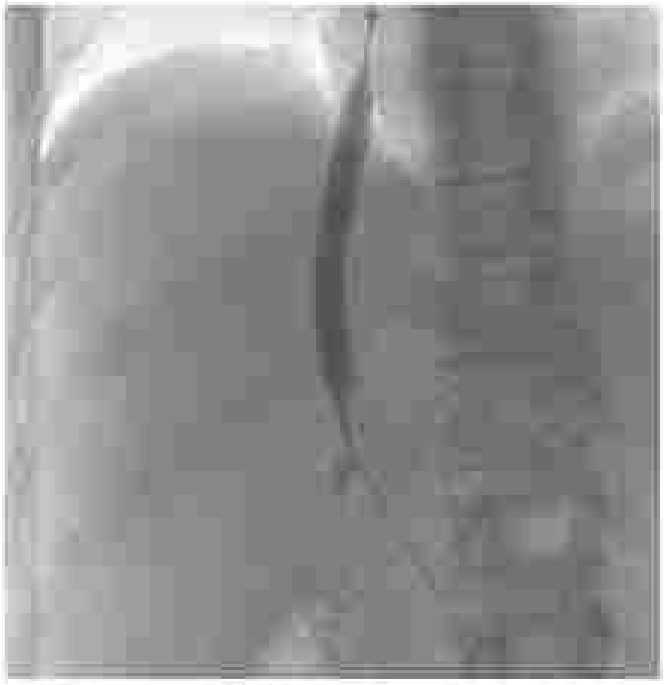

FIG. 8 After unwrapped monojugular transhepatic portosystemic shunt placement, a balloon is used to open the stent to the desired diameter. The objective is to open the stent to the minimum diameter required to reduce the portal pressure to the desired level.

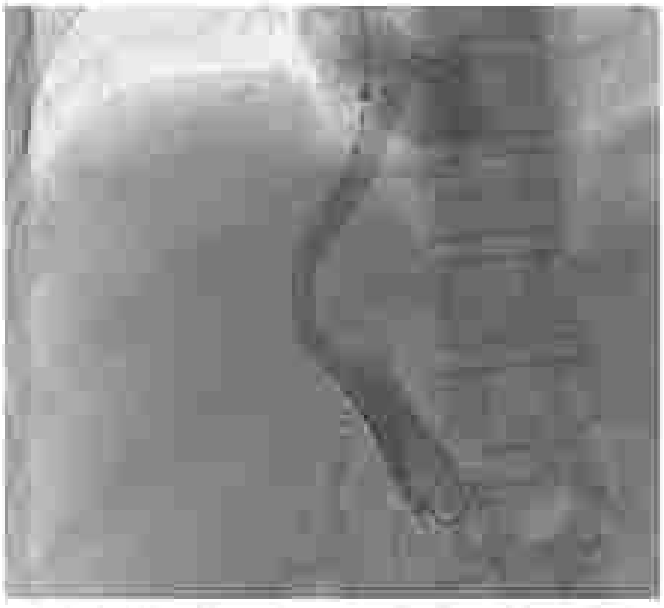

FIG. 9 Frontal view of a portal venogram via a catheter after monojugular transhepatic portosystemic shunt placement. Note the antegrade flow of contrast into the right atrium and no varices filling the varices and compare with Fig. 4.

inferior vena cava to portal vein TIPS through the caudate lobe, a so-called DIPS.

Parallel TIPS

Rarely, despite a previous TIPS, the patient's symptoms may not be completely alleviated. If portal hypertension and variceal bleeding are a persistent problem despite a TIPS, or if the first TIPS thrombooses, a second TIPS may be placed using the other hepatic and portal veins.

Transumbilical or Direct Portal Access

When access into the portal vein is challenging because of anatomy, the operator has two other options. First, access into the umbilical vein, which is usually dilated, provides a conduit into the left portal vein. A catheter then allows opacification of the portal venous system, which provides a better target for TIPS. Second, access through a

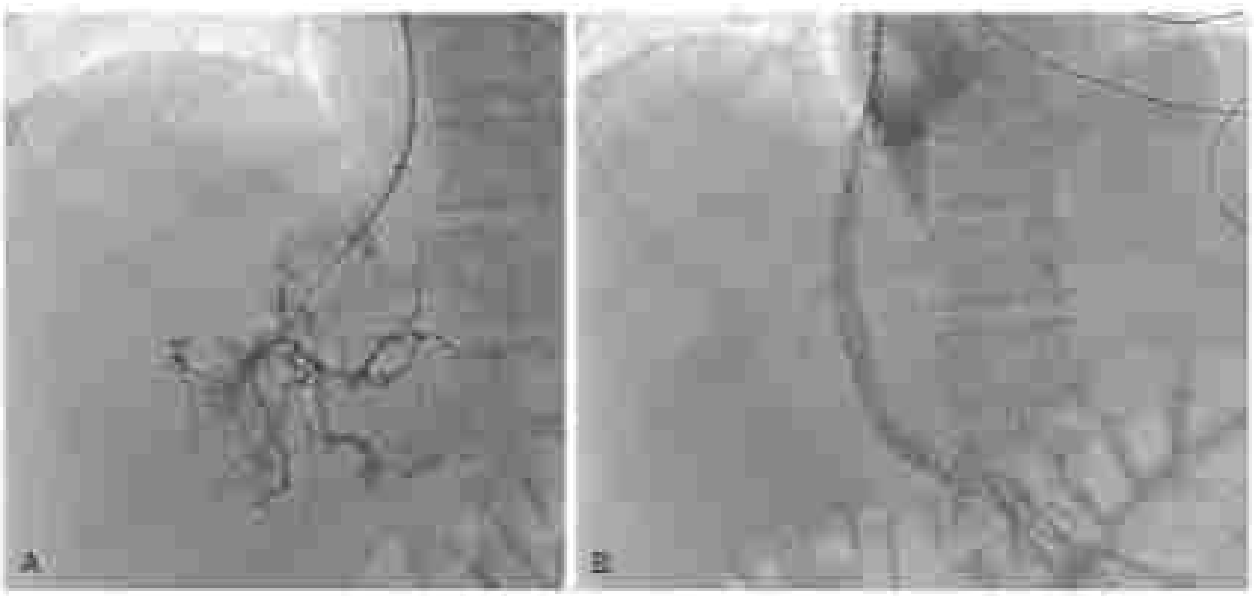

FIG. 16 (A) Frontal venous phase hepatic venogram in a patient with Budd–Chiari syndrome. Hepatic venogram shows the spiderlike appearance (arrow) of multiple small collateral draining veins. (B) Repeat unsubtracted portal venogram after placement of a direct intrahepatic portocaval shunt extending from the inferior vena cava to the right portal vein.

naturally occurring portosystemic shunt, such as a splenorenal shunt, can sometimes be used to gain access to the portal circulation. When the umbilical vein is not accessible and a natural portosystemic shunt does not exist, direct percutaneous access into the right or left portal vein can allow for contrast opacification and targeting.

TIPS Reversal/Revision

Occasionally, a TIPS reversal or revision is necessary. Limited liver reserve and/or overshunting may result in liver failure or intractable encephalopathy. In such cases, the interventionalist has the option to decrease the shunting or shut down the TIPS altogether. Several maneuvers exist to reduce shunting, including placing a stent within the TIPS, or two stents side by side, or even a "waisted" (hourglass-like) stent. If these interventions are not possible or are inadequate, then the entire TIPS can be shut down.

DIPS

DIPS is a recently developing modification to the TIPS procedure. Using intravascular ultrasound guidance, DIPS has been shown to decrease radiation dose and procedural time compared to TIPS. DIPS uses the caudate lobe as a parenchymal tract to create a side-to-side portocaval shunt, which alleviates the difficulties presented by significant hepatic vein stenosis. Portal access is accomplished by advancing a 21-gauge trocar needle through the caudate lobe into the main portal vein. After the inner trocar is removed, a guidewire (0.018-inch) can be advanced, followed by a 5Fr catheter. The needle and guidewire can then be removed, after which a 0.035-inch stiff guidewire can be advanced into the portal vein. Following portal vein access, a shunt can be created using a PTFE-covered stent graft (Fig. 18). In recent studies, DIPS creation was usually successful in entire patient cohorts and has produced higher patency and real-time imaging compared with TIPS. In some interventional radiology practices, DIPS has replaced TIPS as default procedure, especially in patients with occluded TIPS, challenging anatomy, calcification of the portal vein, or portal vein thrombosis resulting from hepatocellular carcinoma.

TIPS in Transplant Livers

TIPS has also been used to bridge liver transplants in patients in end-stage liver disease. Before transplant, TIPS is used to manage complications from portal hypertension and make sure that patients can remain transplant candidates. After transplantation, TIPS has a similar utility. The indications for TIPS in transplant livers are the same as those for pretransplant; studies have shown TIPS to be effective in addressing early complications such as portal vein thrombosis and delayed graft function. TIPS can be more complicated in liver transplant patients because of the altered anatomy of hepatic vessels. The piggyback technique for TIPS has been effective in addressing this challenge. In this technique, TIPS placement is done in the left intrahepatic portal vein rather than the right.

Results after TIPS in transplant patients are generally excellent but pose a different set of issues when compared with TIPS in non-transplant patients. Approximately 10% to 20% of stents in transplant patients require revision, whereas up to 70% do in nontransplant patients. Transplant patients undergoing TIPS have higher risks of infection, renal failure, and neurologic complications than nontransplant patients, however. For example, 30% to 50% of cases result in death by sepsis, the most common posttransplant TIPS complication. Interestingly, clinical success rate of TIPS in nontransplant patients is much higher than in transplant patients (93% vs 77%).

Balloon-Occluded Retrograde Transvenous Obliteration in Type I Gastric Varices

Isolated gastric varices often result from abnormal gastrorenal shunting of blood in response to portal hypertension. TIPS in these cases do not effectively address the splenorenal shunts that are the cause of the isolated gastric varices. Balloon-occluded retrograde transvenous obliteration (BRTO) was therefore developed and has been used to access the portosystemic gastrorenal shunt through the left renal vein via a transjugular or transfemoral approach. This procedure uses an occlusion balloon followed by injection of a sclerosing agent to control flow into the gastrorenal shunt and varices. BRTO has been reported to have excellent clinical success rates, ranging from 79% to 100%. Effectiveness of BRTO in controlling gastric varices ranges from 91% to 100%. The safety and efficacy of BRTO for managing varices has been established in many studies but is not as practiced in the United States as TIPS because of unfamiliarity of the procedure. Studies have shown BRTO to be as effective as TIPS and potentially more advantageous because it is less invasive. BRTO better supports portal blood flow, preserves liver function in patients with a poor hepatic functional reserve, and prevents encephalopathy.

TABLE 3 Complications Related to TIPS

Complication	Frequency	Predisposing Factors	Mitigating Factors
TIPS dysfunction	Occlusion/stenosis: 10%–70% Thrombosis: 10%–15%	Uncovered stents Smaller diameter stents Stent migration/suboptimal placement/positioning	Choice of stent Precise deployment Venography and/or ultrasound
Encephalopathy	In compensated liver disease: up to 12% In uncompensated liver disease: up to 50% Requiring TIPS reversal: 4%	History of encephalopathy High ammonia levels Limited reserve Increased age	Reduce or close the TIPS Metronidazole, rifaximin or lactulose
Bleeding	Hemolysis: <5% Intraperitoneal bleeding: 1%–2%	Difficult anatomy Abnormal coagulation profile	Correct coagulation profile
Sepsis	2%–10%	Active infection	Treat infection before TIPS
Renal failure	Highly variable	Elevated creatinine Dehydration Diabetes High contrast load	Hydrate Use carbon dioxide contrast
Liver failure/hepatic infarction	2%–4%	Limited reserve High filtration Overdiuresis	Reduce or close the TIPS

TIPS, Transjugular intrahepatic portosystemic shunt.

CLINICAL OUTCOMES

Clinical Response to TIPS

TIPS is the most effective option for treating gastroesophageal variceal bleeding. The rebleeding rate after TIPS placement is 4% per year, the lowest among all treatment options, including endoscopic management. TIPS is reserved after failure of endoscopic management only because of the greater risks associated with it, particularly encephalopathy. Cessation of bleeding is evident almost immediately after TIPS creation.

TIPS has also been shown to be very effective in treating ascites, and it reduces the risk of ascites by 50%–80% over the life of the patient. Additionally, TIPS has been shown to improve survival and transplant-free survival compared with other treatment options. Resolution of ascites may take up to 4 weeks after TIPS placement. TIPS improves renal function in 62% of patients with hepatorenal syndrome; however, it is occasionally difficult to distinguish noncirrhotic, related chronic renal insufficiency from hepatorenal syndrome.

Complications and Management

The complications related to TIPS are shown in Table 3. The most feared complication is liver failure, which usually results from excessive portosystemic venous shunting to a liver with limited baseline reserve. If patients with no liver reserve are appropriately excluded, the risk of liver failure is 2% to 4%.

Encephalopathy can be seen in up to 12% of patients with compensated liver disease and in up to 50% of patients with uncompensated liver disease. Metronidazole, rifaximin, and/or lactulose provide significant relief for such patients; however, a small percentage (~4%) will not respond and may require TIPS narrowing or occlusion.

Death from sepsis is rare (~4%) but very difficult to treat. Bacteremia results in TIPS stent seeding, which can be very challenging or impossible to treat. Broad-spectrum antibiotics may clear the bacteremia, but in some cases, it occurs after cessation of treatment because the seeded stent shields more bacteria. Active infection is an absolute contraindication to TIPS, and any infection must be cleared before intervention.

The overall post-TIPS 30-day mortality ranges from less than 10% to up to 40%. The higher mortality rate is seen in patients with poorly compensated liver disease who are having a TIPS created on an emergent basis, usually for life-threatening variceal bleeding. For patients with compensated liver disease who are having a TIPS created on an elective basis, mortality is less than 5%. It is therefore important to carefully select patients and refer for TIPS placement before it must be done on an emergency. Vasoactive drug therapy has been shown to reduce risk of mortality at 7 days, in addition to improving hemostasis and shorten length of stay.

The Model for End-Stage Liver Disease (MELD) score, routinely used to predict survival in patients with end-stage liver disease and allocate liver transplants, was initially developed to predict survival in patients after creation of a TIPS. The cutoff score for high-risk short-term mortality (expected survival less than 3 months after TIPS creation) in the initial MELD study was 18. The MELD-Na score, which incorporates serum sodium with the serum international normalized ratio, bilirubin, and creatinine of MELD, has been shown to be a more accurate predictor of risk post-TIPS. A MELD-Na score of 15 or greater is often associated with higher morbidity and mortality post-TIPS. Both versions of the MELD score are more accurate predictors of risk after TIPS than the Child-Pugh score.

Follow-up

TIPS follow-up is mostly based on clinical signs and symptoms. Ultrasound surveillance can be useful; however, false-positive reports (elevated velocities, occluded stent) can result if ultrasound is performed too soon after TIPS creation. The newly placed TIPS often has air trapped within it, which limits ultrasound penetration and can be mistaken for sonographic appearance of an occluded or narrowed TIPS. Waiting at least 2 weeks after TIPS for the air to be absorbed is generally adequate to avoid this problem. Recurrent variceal bleeding or ascites are very specific indicators of TIPS stenosis or occlusion and should prompt a diagnostic venogram and intervention if necessary. There is a 10% rate of reintervention for stenosed or occluded TIPS. The 1-year primary unassisted patency rate for expanded PTFE-covered stents is 80% to 90%. There is no role for the use of

uncovered bare metal stents because their restenosis rate after TIPS creation is unquestionably high.

SUMMARY

The most important determinant of clinical outcomes after TIPS placement is proper patient selection and preparation. Cirrhotic patients with portal hypertension should be evaluated by a hepatologist and should be referred for TIPS after conservative management fails, but before the complications of portal hypertension manifest into an emergency. This, along with optimal patient preparation, can help reduce the morbidity and mortality related to TIPS. Additionally, the introduction of expanded PTFE stents has improved the efficacy and patency rate of TIPS, and many patients survive with a TIPS for many years. The benefits of a TIPS include reduced drop in risk from the transplant list, improved lifestyle quality (i.e., resolution of ascites), as well as reduction in the many portal hypertension–related complications and future interventions to treat those complications. But most important, TIPS is often a lifesaving procedure for those with variceal hemorrhage.

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Management of Refractory Ascites

Robin Min, MD, and Yo-Hung C. Lin, MD

Ascites, the accumulation of fluid in the peritoneal cavity, is one of the major complications of cirrhosis. Approximately 50% of patients with a new diagnosis of cirrhosis will develop ascites within 10 years. It is a common reason for hospital admission and can lead to other complications such as hepatorenal syndrome and spontaneous bacterial peritonitis. The development of ascites in cirrhosis is an important marker in its natural history. One half of all cirrhotic patients with ascites die within 5 years without a liver transplant.

Refractory ascites is defined as fluid that cannot be mobilized despite a 2 g sodium–restricted diet and high-dose diuretic treatment (160 mg of furosemide and 400 mg of spironolactone) or fluid mobilization rapidly after therapeutic paracentesis. Signs of diuretic failure include lack of weight loss, inadequate sodium excretion in the urine (<78 mEq/day), and development of complications such as progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalances. Less than 10% of decompensated cirrhotic patients with ascites are refractory to standard medical treatment.

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Management of Refractory Ascites

Robin Min, MD, and Po-Hung Chan, MD

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URINARY ELECTROLYTE MEASUREMENT

Patients who gain weight on maximum diuretics but excrete less than 78 mEq of sodium per day from the urine are refractory to diuretics. To measure urinary sodium excretion, the 24-hour urinary collection is necessary as an inadequate collection can underestimate the true value; however, it can be difficult to obtain an accurate 24-hour urinary collection in a real life setting. A random urinary sodium/potassium ratio can quickly estimate urinary sodium excretion. Approximately 90% of patients with a urine sodium/potassium ratio greater than 1 excrete more than 78 mEq/day of sodium in a 24-hour collection.

MEDICAL TREATMENT CONSIDERATIONS IN REFRACTORY ASCITES

β-Blockers

Cessation of β-blockers should be considered in patients with refractory ascites. Cirrhotic patients often receive nonselective β-blockers for prevention of variceal hemorrhage. Although refractory ascites is not an absolute contraindication to β-blocker treatment, high doses greater than 160 mg/day of propranolol or 80 mg/day of nadolol should be avoided, particularly in those with signs of low perfusion such as arterial hypotension and acute kidney injury. There is an association between β-blocker use and poor survival in these patients. In a prospective observational study over an 8-month period, median survival was 6 months in patients on propranolol versus 20 months in those not on a β-blocker. We propose that the difference in survival was due to a postparacentesis circulatory dysfunction secondary to the limitation of increased cardiac output, which leads to decreased arterial pressure and low perfusion of the kidneys. β-Blockers may be reintroduced if circulatory function improves or refractory ascites reverses.

Midodrine

Oral midodrine 7.5 mg three times daily has been shown in a randomized trial to increase urinary volume, sodium excretion, and mean arterial pressure after 1 month. Given that caregivers and nursing staff may feel reluctant to administer diuretics to severely hypotensive patients, the addition of midodrine may alleviate some of these concerns. Midodrine may in a sense convert diuretic-resistant patients to diuretic-sensitive patients. Cessation of β-blocker may also contribute to an increase in mean arterial pressure, which may allow more aggressive diuresis.

SPONTANEOUS BACTERIAL PERITONITIS

Diagnosis

Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid in the absence of an intra-abdominal, surgically treatable source. The diagnosis is made in the presence of an elevated polymorphonuclear leukocyte (PMN) count of 250 cells/mm^3 or higher in the ascitic fluid. SBP is associated with significant in-hospital mortality, which has decreased over the past decade with prompt recognition and treatment. Because the presentations can vary from asymptomatic to mild abdominal pain to severe, a diagnostic paracentesis is often justified in hospitalized patients with cirrhosis and ascites.

Empiric Treatment

When the ascitic fluid PMN count is 250 cells/mm^3 or higher, empiric antibiotic therapy is indicated. Delaying treatment to wait for the fluid culture to grow bacteria is not recommended because an overwhelming infection can develop rapidly. Patients who meet the PMN criterion but have negative ascitic fluid cultures have been labeled with culture-negative neutrocytic ascites. These patients have the same symptoms and mortality as those with SBP and thus require the same treatment as SBP. Patients may also have fewer than 250 cells/mm^3 of PMN in their ascitic fluid yet have positive bacteria fluid culture. This is labeled monomicrobial bacterascites. It may represent an early stage SBP before there is neutrophil response versus bacterial colonization. Although colonization has been shown to resolve more than half of the time without treatment, empiric treatment is still recommended for the cirrhotic patient with monomicrobic bacterascites and any coexisting symptoms of infection, including sepsis, fever, abdominal pain, and encephalopathy.

Choice of Antibiotics

Broad-spectrum antibiotic therapy is warranted for the treatment of SBP. Specifically, the treatment of choice is cefotaxime or a similar third-generation cephalosporin because it provides coverage against 95% of the three most common bacterial species that cause SBP. Treatment may be narrowed based on sensitivities of cultured organisms. Cefotaxime 2 g every 8 hours has been shown to achieve adequate drug levels in ascitic fluid. Five days of treatment has been shown to be efficacious. Oral antibiotics may be an option as well; ofloxacin 400 mg twice per day may be as effective as cefotaxime in patients without shock. Patients who have received fluoroquinolone as prophylaxis against SBP should be treated with nonfluoroquinolone regimens because they may harbor resistant organisms.

Intravenous Albumin Infusion

Albumin infusion (1.5 g/kg body weight on day 1 followed by 1 g/kg on day 3) in addition to antibiotic treatment has been shown to decrease mortality in SBP. A randomized trial showed that albumin infusion plus cefotaxime versus cefotaxime alone decreased mortality from SBP from 29% to 10%. The benefit of albumin largely stems from increased renal perfusion and preservation of kidney function during SBP.

Follow-up Paracentesis

A repeat paracentesis to document resolution of SBP is generally not necessary. Most cirrhotic patients with SBP and typical ascitic fluid analysis will show clinical response on antibiotic treatment. However, if symptoms persist or worsen, atypical organisms grow in culture, or suspicion of secondary peritonitis arises, then a repeat paracentesis can be performed to evaluate possible ongoing infection.

INTERVENTIONAL METHODS IN THE TREATMENT OF REFRACTORY ASCITES

Liver Transplantation

Liver transplantation is the best therapy for cirrhotic patients with refractory ascites. The development of refractory ascites confers a poor prognosis, with approximately half of patients dying within 1 year without transplantation; therefore, suitable candidates should be referred to a liver transplant center.

Paracentesis and Albumin Replacement

Paracentesis can offer expedited relief for patients suffering symptoms of large-volume ascites, such as abdominal distention, pain, dyspnea, and early satiety. For volume removals of 5 L or more, an infusion of albumin (6–8 g/L of ascites removed) at or around the time of paracentesis may reduce mortality, electrolyte abnormalities, and renal dysfunction. Serial paracentesis is not an optimal long-term solution because it depletes proteins and worsens malnutrition; therefore, liver transplantation and other options to reduce portal hypertension should be considered in those who have refractory ascites.

The preferred site for needle entry is 3 cm medial and 3 cm superior to the anterosuperior iliac spine on the left lower quadrant of the abdomen. The right lower quadrant is less desirable because the

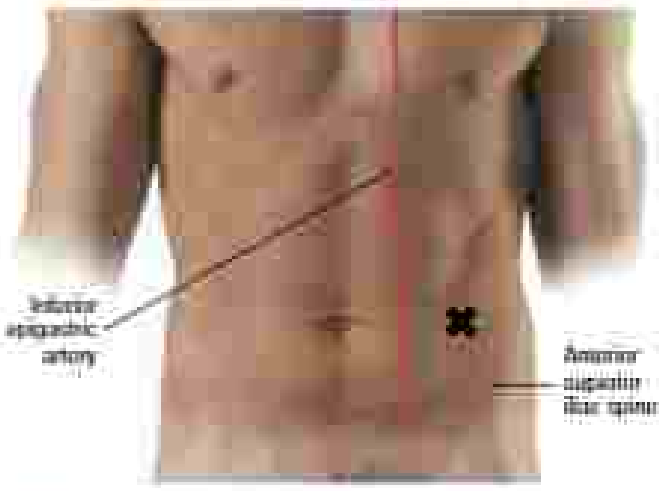

FIG. 1 Preferred needle entry site for paracentesis. (From Gilroy AM, Macpherson BR, Ross LM, et al. Atlas of Anatomy. Philadelphia: Thieme; 2016.)

cecum can become distended in patients who take lactulose. A distended cecum has a higher risk of perforation. The needle should avoid areas with cutaneous infection, abdominal wall hematomas, scars, or visibly engorged subcutaneous veins. Bedside ultrasound is useful in locating a safe site for needle entry away from vascular structures.

The paracentesis needle can be inserted with either the angular technique or the Z-track technique. In the angular technique, the needle is inserted obliquely from the cutaneous site into the peritoneum. In the Z-track technique, cutaneous tissues are pulled down and the needle is inserted straight into the peritoneum. These techniques ensure that cutaneous and peritoneal needle entry sites do not directly overlap each other, thereby minimizing postprocedure ascitic fluid leakage (Fig. 1).

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is an artificial communication between the portal vein and hepatic vein usually placed by an interventional radiologist (Fig. 2). The direct result of TIPS placement is a significant reduction in portal pressure through the creation of an alternative pathway for portal venous flow. Before and after TIPS placement, the proceduralist can quantify the degree of portal hypertension by measuring the portosystemic gradient. The benefit of TIPS is in lowering portal hypertension, the cause of many complications of cirrhosis. After successful TIPS procedure, ascites may completely resolve along with portosystemic shunts (e.g., esophageal varices).

Under fluoroscopic guidance, the interventional radiologist accesses the liver through the internal jugular vein in the neck. Once venous access is confirmed, the radiologist inserts a guidewire and introducer sheath that enables access to the hepatic vein by gaining the superior vena cava and the inferior vena cava. Once the catheter enters the hepatic vein, the radiologist injects contrast to locate the portal vein and advances a needle through the liver parenchyma to connect the two veins. An inflated angioplasty balloon creates the channel for the shunt along the needle tract. Last, the shunt forms by placing a polytetrafluoroethylene covered stent to maintain the tract. The covered stent has been a standard for many years. It has a higher patency interval compared with the older uncovered stent.

Absolute contraindications for TIPS include heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension. TIPS in the setting of these conditions can lead to severe cardiac volume overload because blood flow is diverted past the liver and into the right heart. Sepsis and biliary obstruction are other absolute contraindications to TIPS placement. The Model for End-Stage Liver Disease (MELD) score, now used to prioritize organ allocation in liver transplantation, was initially developed to predict the 3-month mortality after TIPS. A MELD score greater than 18 has been associated with poorer outcomes after TIPS. As procedural technology, including the stent itself improves, however, higher MELD scores may inform the decision for TIPS but are no longer absolute contraindications. Hepatic encephalopathy is a common occurrence after TIPS with an incidence of up to 45%. When mild, hepatic encephalopathy can be controlled through conservative medical management; however, severe baseline encephalopathy is another contraindication to TIPS.

Peritoneovenous Shunts

Peritoneovenous (shunt) drain ascitic fluid from the peritoneal cavity into systemic veins, such as the superior vena cava. The Denver shunt, popular in the 1970s, is the only peritoneovenous shunt still manufactured today. Although historically requiring an invasive approach, today it is placed percutaneously in a minimally invasive procedure through an internal jugular or subclavian route. The shunt is made of soft tubing connected to a pump chamber that lies subcutaneously over the lower ribs. Ascitic fluid flows spontaneously from the peritoneum to the superior vena cava, but manual pumping helps avoid buildup of proteinaceous material in the shunt. Nonetheless, because of poor long-term patency and complications such as coagulopathy, superior vena cava thrombosis, and sepsis, peritoneovenous shunts are infrequently used today.

Peritoneal Catheters

A peritoneal catheter (PleurX) inserted into the peritoneum can be an option for ascites removal in patients with the goal of palliation. Given the risk of introducing infection into the peritoneum, this option is typically reserved for patients who are near end of life. The catheter can be placed with minimal discomfort using a small incision. It is then tunneled in place to the skin and connected to a catheter bag. Patients may open the catheter to the bag at their convenience. This allows patients, who are likely less mobile, to avoid traveling to medical facilities for repeated paracenteses.

Experimental Options

Clonidine and Midodrine

Clonidine is an α_2-adrenergic receptor agonist that suppresses the renin-aldosterone system, which is activated in patients with refractory ascites. A randomized trial of 0.075 mg of oral clonidine twice daily versus placebo in cirrhotic patients with ascites showed faster mobilization of ascites with few complications. Midodrine is an oral vasopressor that acts through α_1-adrenergic activation. Midodrine (7.5 mg every 8 hours) or a combination of midodrine and clonidine (0.075 mg every 12 hours) plus standard medical therapy have been shown to be superior to standard medical therapy alone for the control of ascites.

Low-Flow Ascites Pump

European surgeons and radiologists have collaborated to develop a pump (AFEApump) that moves ascitic fluid from the peritoneal cavity into the urinary bladder. Several studies have shown a decrease in the need for large-volume paracenteses in those with refractory ascites, with most patients not requiring paracenteses after implantation of the pump system. The most commonly observed complications include blockage of the peritoneal catheter, infections, and bleeding. A multinational, randomized trial of the low-flow ascites pump versus TIPS versus therapeutic paracentesis is underway.

Endoscopic Ultrasound-Guided Placement of Gastric Stents

Gastric stents are placed under endoscopic ultrasound guidance into the stomach, creating a connection between the stomach lumen and

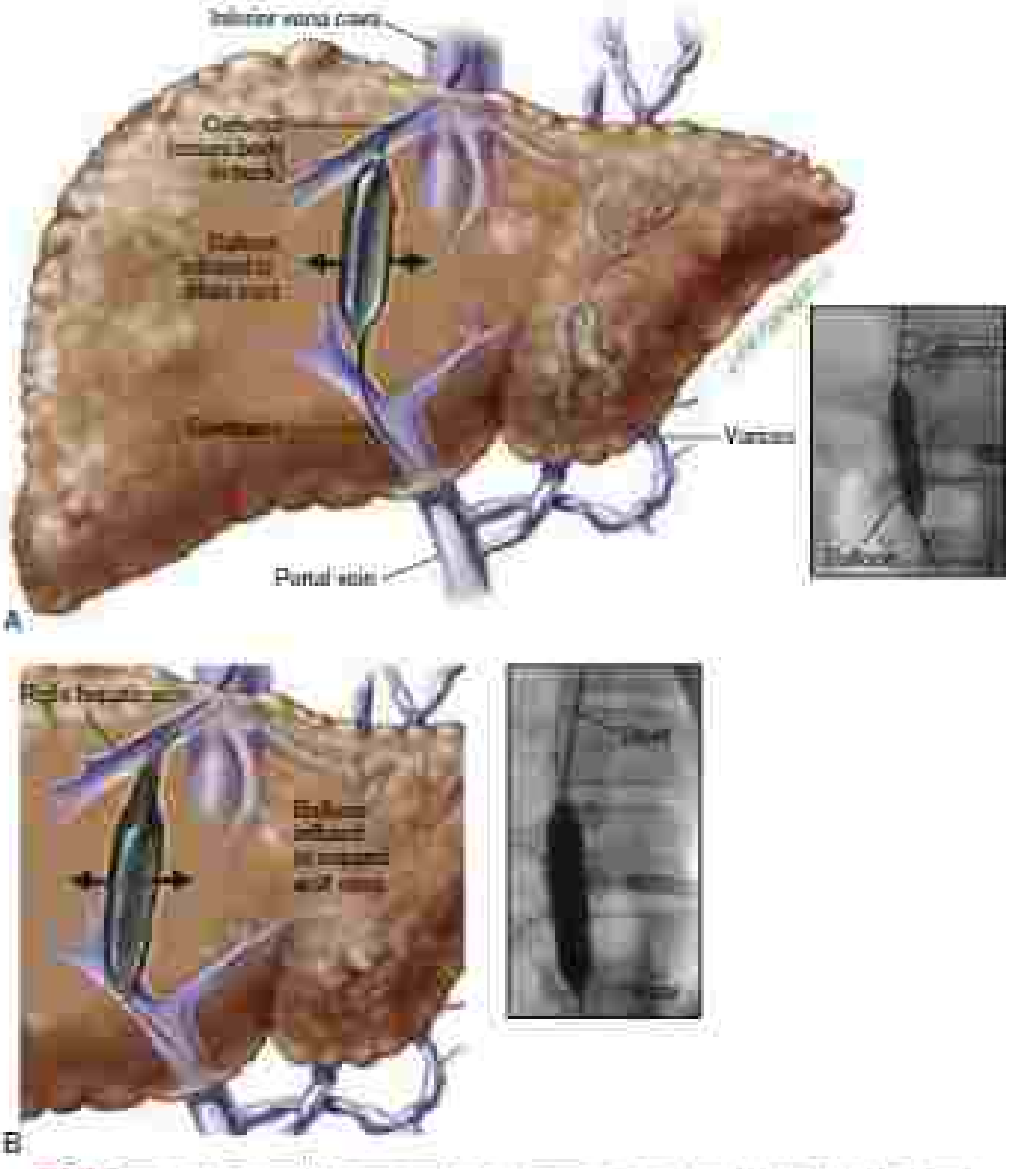

FIG. 2 Transjugular intrahepatic portosystemic shunt placement. (Courtesy Johns Hopkins Medical Institutions.)

the peritoneum. This is a relatively new method for controlling ascites that has two small case series. Complications included stent migration, stent occlusion by food, and leakage of gastric content into the peritoneum. The procedure has been studied only in malignant ascites. Symptomatic relief and technical success have been shown. By alleviating the need for paracentesis, patients may have improvement in their quality of life.

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Management of Hepatic Encephalopathy

Tanay Wooreta, MD, MPH, and Aarya Sharma, MD, M c

Hepatic encephalopathy (HE) is a life-threatening and potentially reversible complication of liver disease that can be seen in cirrhosis, acute liver failure, and in the setting of portal systemic bypass.

PATHOPHYSIOLOGY

The pathogenesis of HE is multifactorial and incompletely understood, but the prevailing theory centers around the neurotoxic effects of ammonia and other toxins that are inadequately cleared because of liver dysfunction. Ammonia is produced mainly in the gastrointestinal tract by the bacterial metabolism of dietary protein and other nitrogenous compounds and subsequently enters the portal circulation where it is converted to urea by hepatocytes under physiologic conditions. Additional sites of ammonia detoxification include the kidneys and skeletal muscle.

Ammonia accumulates in the systemic circulation resulting from portal hypertension and cirrhosis, or as a consequence of a portosystemic shunt, and traverses the blood-brain barrier. Astrocytes convert ammonia and the neurotransmitter glutamate into glutamine, which is an active osmole, thereby precipitating intracellular swelling and cerebral edema. Myriad additional factors are suspected to play a role in central nervous system dysfunction in HE, including excessive activation of the neuroinhibitory γ-aminobutyric acid–benzodiazepine system, dysregulated cerebral blood flow, derangements in the gut microbiome of cirrhotic patients, inflammatory cytokines, neurosteroids, manganese, and manganese deposition in the basal ganglia.

CLASSIFICATION AND DIAGNOSIS

HE manifests as a broad spectrum of neuropsychiatric and motor disturbances. The diagnosis of overt HE is clinical and made after excluding other causes of acute brain dysfunction in a patient with liver disease or portosystemic shunt. The West Haven Criteria is the gold standard classification system for HE (Table 1). Of note, covert HE is a practical entity comprising minimal HE (sometimes referred to as grade 0) and West Haven grade 1 HE. Patients with chronic liver disease affected by minimal HE typically have abnormalities that are only detected through specialized psychometric or neuropsychologic testing. The presence of minimal HE is associated with impaired driving ability, increased falls, reduced quality of life, and an increased risk of progression to overt HE.

Extrapyramidal signs common in HE include muscular rigidity, parkinsonian-like tremor, and hypokinesia. Various other neuromuscular findings can be observed such as an upgoing Babinski reflex, hyperreflexia, and hypertonia, although deep tendon reflexes may become attenuated with progression to coma. On physical examination, asterixis is a loss of postural tone that can be elicited as a bilateral, flapping tremor with dorsiflexion of the wrists, but may be observed elsewhere, such as the tongue. Of note, asterixis is a nonspecific feature of other metabolic encephalopathies independent of liver disease, such as uremic encephalopathy.

The finding of focal neurologic deficits on examination, new-onset seizures, or relevant history of falls or trauma merits neuroimaging to evaluate for intracranial hemorrhage or structural brain lesions.

Electroencephalography typically demonstrates triphasic wave changes in patients with HE but may be helpful in excluding subclinical seizures.

Elevated circulating ammonia levels are observed in the majority of patients with HE; however, in cirrhotic patients, ammonia levels are not recommended as a diagnostic or staging test for HE and do not have prognostic value for HE. Moreover, in patients with end-stage liver disease who do not have clinical signs of HE, an elevated serum ammonia level is not an indication to begin treatment. Young patients presenting acutely with fulminant hyperammonemia (>1000 μmol/L) in the absence of acute liver failure should be evaluated for a urea cycle defect or other inherited hyperammonemia syndromes by a metabolic genetics expert.

PRECIPITATING FACTORS

The majority of patients with cirrhosis who present with an episode of overt HE will have an underlying precipitating factor and management aimed at correcting the underlying cause will usually reverse encephalopathy (Table 2).

Each episode of HE requires a thorough evaluation for active infection and sepsis, including diagnostic paracentesis to exclude spontaneous bacterial peritonitis in patients with ascites, which may be primary or secondary. Typical considerations also include evaluation of urinary tract, pulmonary, and skin and soft tissue sources of

Perez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonascitic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-angiotensin system. Gastroenterology. 1983;84:961–968.

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TABLE 1 West Haven Criteria for Classification of Hepatic Encephalopathy

	Clinical Descriptors
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition Asterixis may be detectable
Grade 2	Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia
Grade 3	Somnolence to semistupor Confusion Disorientation for space and time Bizarre behavior Responsive to stimuli
Grade 4	Coma Unresponsiveness to painful stimuli

Modified from Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL. Copyright American Association for the Study of Liver Diseases.

TABLE 2 Common Causes of Hepatic Encephalopathy in Cirrhotic Patients

Infections (e.g., spontaneous bacterial peritonitis, urinary tract infection, pneumonia)	Drugs: sedatives (benzodiazepines, hypnotics), opiates, alcohol
Metabolic: hyponatremia, hypokalemia, metabolic alkalosis, hypovolemia	Portosystemic shunt (spontaneous or surgically or radiographically placed)
Constipation	Renal failure
Noncompliance with lactulose	Vascular (rare): portal vein thrombosis, hepatic vein thrombosis
Gastrointestinal bleeding	Hepatocellular carcinoma

infections. Empiric antibiotic therapy should be initiated promptly if there is high clinical suspicion for infection after collection of relevant cultures while awaiting results, in conjunction with initiation of lactulose therapy as outlined in the following section.

Gastrointestinal bleeding is a common precipitant of HE and may be suggested by an elevated blood urea nitrogen/creatinine ratio, presence of melena or hematochezia, and a known history of varices or portal hypertensive gastropathy. Gastrointestinal bleeding decreases perfusion to the key organs involved in ammonia clearance, the liver and kidneys, while concurrently depositing a large amount of protein substrate in the gut for formation of nitrogenous compounds.

Cirrhotic patients are vulnerable to electrolyte disturbances, particularly hypokalemia and hyponatremia, which can lead to decompensations of HE. The risk of hypokalemia is elevated in the setting of diuretic usage, lactulose therapy, and poor oral intake that worsens intravascular volume depletion. Rectifying hypokalemia is essential because this promotes renal ammonia production. Metabolic alkalosis and hypovolemia may be mediated by aggressive diuretics, nasogastric tube (NGT) suction, large volume paracentesis, or excessive diarrheal losses, which can be aggravated by lactulose therapy. The presence of a hypokalemic metabolic alkalosis further contributes to HE by facilitating ammonia transport through the blood brain barrier.

Hyponatremia is common in end stage liver disease because of impaired free water excretion, and the acuity and magnitude of the decrease in serum sodium relative to the patient's baseline must be carefully considered before invoking this as the main driver for HE.

Noncompliance with lactulose and resultant constipation is another common culprit. Sedative agents, in particular benzodiazepines, opiates, hypnotic agents, and alcohol, may precipitate HE. The sedative properties of valproic acid can cause an acute elevation in serum ammonia levels, although this agent is rarely used in end stage liver disease.

In parallel with the evaluation of precipitating factors for HE, it is important to initially consider a broad differential diagnosis in a patient presenting with an acute state of confusion, which can include complications related to diabetes such as hypoglycemia, ketoacidosis, or hyperosmolar state, drug or alcohol intoxication or withdrawal syndrome, Wernicke's encephalopathy, nonconvulsive seizures, or a primary psychiatric disorder. It is also prudent to maintain central nervous system sources of infection on the differential diagnosis for HE. Rarely, disseminated fungal infections such as cryptococcal meningitis may mimic HE in cirrhotic patients even in the absence of another cause of immunocompromise.

Finally, if the tempo of cognitive decline is more consistent with a subacute or chronic process, consideration of dementia due to a vascular or neurodegenerative disease, or another primary CNS process such as neoplasm or normal pressure hydrocephalus, may be appropriate.

TREATMENT

A central tenet of management of HE is the identification and reversal of any precipitating factors, particularly the treatment of underlying infection, correction of electrolyte abnormalities, and discontinuation of sedatives or opiate medications. In patients with chronic liver disease, pharmacologic therapies are aimed at lowering the blood ammonia level and reducing gut production of nitrogenous substances, irrespective of whether the serum ammonia level is indeed elevated (Table 3).

Nonabsorbable Disaccharides

Lactulose is considered first line therapy for the treatment of episodes of overt HE by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines. Lactulose is a nonabsorbable disaccharide metabolized to short chain fatty acids by colonic bacteria, thereby acidifying the bowel lumen, promoting the conversion of ammonia to ammonium, and stimulating fecal excretion of nitrogen containing compounds as a result of its osmotic laxative properties. Because of the relatively benign side effect profile, consisting of abdominal pain, flatulence, and diarrhea, we recommend maintaining a low threshold for the initiation of lactulose in patients with decompensated cirrhosis who exhibit early signs of HE.

Administration of lactulose to decompensated HE must be titrated to effect. Patients with clinically apparent HE should be initiated on scheduled lactulose 20 to 30 g (30–45 mL) every hour until defecation occurs, and the dose may be spaced to every 4 to 6 hours depending on clinical improvement. After the initial episode of HE, lactulose is recommended for prevention of recurrent episodes and titrated to achieve approximately two to three bowel movements per day. In patients unable to safely swallow (i.e., aspiration risk), obtain enteral access via NGT if appropriate for

TABLE 3 Treatment of Hepatic Encephalopathy

Initial Episode of Overt HE	
Lactulose	Oral: Start with 20–30 g (30–45 mL) every hour until defecation occurs. Reduce to 20 g (30 mL) every 4–6 hours until improvement. Maintenance: 20 g (30 mL) every 8–12 hours for goal 2–3 stools/day. Retention enema: Add 300 g (300 mL) of lactulose to 700 mL of tap water. Retain for 1 hour. Repeat every 4–6 hours.
Rifaximin[a]	Oral: 400 mg 3 times daily or 550 mg twice daily orally, up to 10 days.
Prevention of Recurrent Episodes of Overt HE	
Lactulose	Oral: 20 g (30 mL) titrated to goal 2–3 stools/day
Rifaximin	Oral: 550 mg orally twice daily
Second-line treatments for refractory cases	Supplementation with oral branched-chain amino acids. Evaluate and treat for zinc deficiency. Embolization of large portosystemic shunts.

[a]Consider adding if inadequate response to lactulose within 2–3 days.

lactulose administration. Alternatively, lactulose may be administered via retention enemas in patients with high grade HE who have contraindications to enteral access. Lactitol is a nonabsorbable disaccharide that may have comparable effectiveness to lactulose in the treatment of HE with fewer side effects; however, it is unavailable within the United States.

Polyethylene Glycol

The single-center Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350 Electrolyte Solution trial randomized patients to receive either lactulose or polyethylene glycol 3350 (PEG) electrolyte solution (GoLYTELY) and found a significantly faster improvement in HE within 24 hours among patients who received PEG compared with lactulose. The dose of PEG solution was 4 L orally or via NGT compared with three or more doses within 24 hours of lactulose 20 to 30 g orally or via NGT. In cirrhotic patients, PEG may be an effective alternative to lactulose therapy in the treatment of overt HE, presumably resulting from its potent cathartic effect on the colon; however, additional trials are needed before this treatment can be routinely recommended.

Low-Absorbable Antibiotics

Modulating the composition of gut flora to decrease ammonia production, which includes reducing the burden of urease-producing anaerobic bacteria, is the principle behind the use of poorly absorbed antibiotics in HE. Rifaximin, a semisynthetic nonaminoglycoside antibiotic, is recommended after the second episode of overt HE as secondary prophylaxis to prevent recurrences per AASLD and EASL guidelines. The prophylactic dose of rifaximin is 550 mg orally twice daily, and it cannot be administered via enema. Rifaximin can be initiated during the acute treatment of decompensated HE in patients with end-stage liver disease; however, it is not supported by the same strong recommendation as lactulose for this indication.

In one randomized trial, patients with overt HE receiving a short course (<10 days) of rifaximin 400 mg three times daily in addition to lactulose had significantly greater reversal of HE, decreased mortality, and length of stay compared with patients receiving lactulose alone. It is reasonable to add rifaximin in patients who have not improved despite lactulose monotherapy within 2 to 3 days of treatment. For limiting a recurrent episode of overt HE, secondary prophylaxis with a combination of lactulose and rifaximin is strongly recommended and may be continued indefinitely or until liver transplantation in select patients.

Neomycin, an aminoglycoside antibiotic, is no longer widely used in clinical practice for lowering of blood ammonia levels because of the adverse effects of ototoxicity and nephrotoxicity and unclear efficacy in clinical trials. Similarly, the use of metronidazole for the treatment of HE is currently limited because of the adverse effect profile and emergence of newer therapies.

Dietary Considerations

Although a high protein diet is associated with HE, cirrhotic patients have high rates of malnutrition and skeletal muscle catabolism, which further compromises extrahepatic ammonia detoxification. Cirrhotic patients with HE are recommended to receive 1.2 to 1.5 g/kg per day of protein intake and 35–40 kcal/kg (based on dry weight) according to the 2013 International Society for Hepatic Encephalopathy and Nitrogen Metabolism Guidelines. A standard nonprotein restricted diet is appropriate for most patients with mild to moderate HE that are able to take in nutrition orally.

ALTERNATIVE THERAPEUTIC OPTIONS IN REFRACTORY HE

A subset of patients with overt HE may prove refractory to conventional treatments for reasons that are incompletely understood. In this population, besides consideration of spontaneous portosystemic shunting as the etiology of intractable HE, there may be a benefit to attempting alternative therapies supported by varying degrees of evidence.

Supplementation with oral branched-chain amino acids (BCAA) is associated with a beneficial effect on HE but does not confer a survival benefit. Low levels of BCAA have been found in cirrhotic patients with sarcopenia; mechanistically, BCAA supplementation may promote ammonia detoxification by bolstering skeletal muscle anabolism. Per the 2014 AASLD/EASL practice guidelines, oral BCAA can be used as an alternative agent to treat patients unresponsive to conventional therapy.

Zinc, a cofactor for enzymes in the urea cycle, may facilitate ammonia clearance. We recommend evaluating for zinc deficiency, which is common in cirrhotic patients, and treating when indicated. A beneficial effect of empiric zinc supplementation in recurrent or chronic HE has not been established in large randomized trials; however, this is a relatively inexpensive and low-risk intervention.

L-ornithine is another supplement that may exert a modest benefit in HE, though robust data are lacking. In one randomized trial, acetyl-L-carnitine supplementation was associated with improvement in fatigue severity and other performance metrics in mild to moderate HE.

Administration of L-ornithine L-aspartate (LOLA) provides substrates to aid in the metabolism of ammonia and may have clinical benefit in overt HE on the basis of limited clinical trial data. Intravenous L-ornithine L-aspartate is currently not available in the United States.

The use of flumazenil, a benzodiazepine antagonist, has been associated with transient clinical improvement in HE in select patients in the absence of exogenous benzodiazepine exposure; however, it is not US Food and Drug Administration approved for the treatment of HE and rarely used for this purpose.

Probiotics, cultures of live microorganisms, may improve gut dysbiosis in cirrhosis and possibly improve recovery from overt HE and reduce recurrence relative to placebo or no intervention; however, current supporting data from clinical trials are low quality and insufficient to make a strong recommendation.

Glycerol phenylbutyrate and sodium phenylacetate are ammonia scavengers that may emerge as promising therapies to lower serum ammonia levels in patients with HE based on encouraging results from preliminary clinical trials.

Albumin infusion may be a useful adjunct to lactulose in the treatment of overt HE; however, supporting clinical trial data are very limited.

Fecal microbiota transplantation is another developing treatment that may be effective when combined with standard care to reduce HE recurrence; however, newer clinical trial data are needed. Ultimately, liver transplantation is the definitive therapy for end-stage liver disease associated with HE resistant to optimal medical therapy.

ADDITIONAL MANAGEMENT CONSIDERATIONS

Agitation may be a component of overt HE that is expected to improve with treatment. If patients are considered a hazard to themselves and caretakers, haloperidol is preferred over benzodiazepines because of the risk of accumulation of long-acting active metabolites with benzodiazepine therapy. If opiate therapy is required in the inpatient setting, we recommend avoiding hydromorphone for acute pain relief in cirrhotic patients because of the risk of accumulation of active metabolites in the setting of end-stage liver disease, in favor of judicious usage of fentanyl or oxycodone, resulting from the risk of precipitating or worsening preexisting HE.

Hepatic Encephalopathy Associated With Portosystemic Shunts

Cirrhotic patients who undergo a transjugular intrahepatic portosystemic shunt (TIPS) procedure for treatment of portal hypertensive complications are particularly vulnerable to the development of HE, with some studies estimating as high as 50% incidence of postprocedural encephalopathy. Routine prophylactic therapy with lactulose or rifaximin is not recommended for prevention of HE post-TIPS procedure on the basis of a randomized controlled clinical trial that failed to show benefit.

Management of HE post-TIPS involves similar principles of identifying and treating reversible precipitating causes, and initiating therapy with lactulose or combination lactulose and rifaximin. For the minority of patients who develop refractory HE post-TIPS, shunt diameter reduction, or even shunt closure, is an effective intervention to reverse HE in the majority of cases but may provoke complications related to increased portal hypertension and the original indication for TIPS placement.

Alternatively, the development of spontaneous portosystemic shunts, such as splenorenal shunts, may precipitate refractory HE in cirrhotic patients. In this circumstance, a radiographic procedure to identify and embolize the portosystemic collaterals may be indicated to facilitate resolution of HE in affected patients, although this strategy carries a potential risk of exacerbating portal hypertension.

Hepatic Encephalopathy Associated With Acute Liver Failure

The presence of HE is required for the diagnosis of acute liver failure (ALF) and the management is distinct compared with HE in patients with chronic liver disease. In patients with ALF, ammonia levels have a strong correlation with the presence and severity of HE, and the risk of cerebral herniation and death is highest with persistently elevated serum ammonia levels of 150 to 200 μmol/L or higher. Patients with ALF associated with grade 2 HE or higher benefit from close management in an intensive care unit and should be transferred to an institution with a liver transplant center. Patients with grade 3 HE or higher will require intubation for airway protection with neurologic checks performed every 1 to 2 hours to evaluate for signs of elevated intracranial pressure (ICP). A computed tomographic scan of the brain should be obtained in patients with ALF with a deterioration in neurologic examination to assess for cerebral edema. AASLD guidelines advocate maintaining a serum sodium between 140 and 145 mmol/L and the use of hypertonic saline infusion and intravenous mannitol boluses to reduce ICP. Additional measures include elevation of the head of the bed greater than 30 degrees, and maintenance of euglycemia and normothermia because mild hypothermia has not been shown to have a significant benefit in ALF. Using a ventilation strategy to lower partial pressure of carbon dioxide to 25 to 30 mm Hg may be desirable in the acute setting to promote cerebral vasoconstriction. Propofol is the preferred agent for sedation.

The use of invasive devices to monitor ICP is controversial and center dependent because ICP monitoring has not been shown to consistently improve outcomes in unselected patients with ALF and high-grade HE. Hemodynamically unstable patients should be empirically started on broad-spectrum antibiotics because of the high risk of sepsis in this population.

In patients with ALF and HE, there is not any specific pharmacologic treatment that has been clearly shown to improve overall outcomes. Lactulose may be attempted in the early stages of HE, although the benefit is unproven; rifaximin does not have a role in ALF management.

Preliminary clinical trial data have suggested a possible benefit of extracorporeal liver replacement devices, such as the *Molecular Absorbent and Recirculating System* in improving HE in patients with ALF. However, MARS and other bioartificial support systems do not appear to have a survival benefit and are not endorsed by guidelines.

SUGGESTED READINGS

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MANAGEMENT OF BUDD-CHIARI SYNDROME

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Initially noted by Carl Prosper von Baltzansky in 1842 and later formally described separately by the English physician George Budd in 1845 and the Austrian pathologist Hans Chiari in 1899, Budd-Chiari syndrome (BCS) remains a rare disease, a so-called orphan syndrome. As a result, most of the studies that deal with this condition have been small in numbers, often single institutional and retrospective in nature, and most of the recommendations regarding its management are from expert opinions and institutional biases rather than robust data. In this chapter, we summarize the most up-to-date information regarding the diagnosis and management of this disease.

Considered a form of splanchnic venous thrombosis, BCS is defined as hepatic venous outflow obstruction that can occur at any level from the small hepatic veins to the junction of the inferior vena cava (IVC) and the right atrium. Excluded from this definition are forms of outflow obstruction resulting from hepatic vein occlusive disease/sinusoidal obstruction syndrome (often from administration of toxic agents and seen almost exclusively in bone marrow transplantation) or cardiac disorders. BCS is a rare disease, occurring in roughly 4 patients per 1 million per year. Interestingly, the etiology of BCS often varies based on demography and geography; most Western patients suffer from venous outflow obstruction resulting from hepatic vein thrombosis, whereas Asian patients are more commonly found to have venous obstruction from a membranous web at the junction of the vena cava and hepatic veins. Considerable interest in associated hypercoagulability syndromes has led to the identification of a number of hematologic abnormalities associated with BCS, including myeloproliferative disorders (49%) or inherited thrombophilias (21%) such as Factor V Leiden (12%), protein C deficiency (9%), protein S deficiency (5%), G20210A prothrombin (3%) and antithrombin deficiency (3%). Acquired conditions such as antiphospholipid antibodies (25%), hyperhomocysteinemia (22%), paroxysmal nocturnal hemoglobinuria (19%), oral contraceptives (33%), pregnancy (6%), Behçet syndrome (2.5%) and sarcoidosis (1%) are also found in cohorts of patients with BCS. More than 80% of patients will be found to have at least one hematologic abnormality in BCS, and almost one half of patients will have multiple abnormalities.

Despite etiologic differences, there seems to be a common pathway in the downstream pathophysiology of BCS that involves liver congestion resulting from hepatic venous outflow obstruction, in turn leading to intrahepatic venous congestion with elevated sinusoidal pressure, erythrocyte extravasation in the hepatic parenchyma, and tissue hypoxia. This cascade ultimately leads to injury to surrounding perisinusoidal hepatocytes. Of note, the caudate lobe of the liver drains directly into the vena cava via multiple short veins that are usually spared in BCS. As a result, compensatory hypertrophy and hyperplasia in the unobstructed caudate lobe is manifest by caudate lobe enlargement, which is seen in most patients with BCS at the time of presentation. Without intervention, or if venous collateral systems do not develop early in the process, ongoing chronic tissue injury leads to the development of hepatic fibrosis, regenerative nodules, and possibly to cirrhosis.

CLINICAL PRESENTATION AND DIAGNOSIS

The dominant clinical feature of BCS is the development of ascites in an otherwise healthy person without preexisting liver disease or recognized risk factors for a liver disorder. Most patients with BCS present with ascites and/or abdominal pain, typically of less than 1 month's duration. Liver function is generally preserved, and liver function tests are normal or minimally deranged. A small fraction of BCS patients (<5%) develop fulminant hepatic failure with massive hepatocyte necrosis, rapidly progressive encephalopathy, and profound coagulopathy. In an equally small number of patients, hepatic vein occlusion is initially silent clinically, and BCS is identified only when an evaluation, including vascular imaging, is performed for a patient with cryptogenic cirrhosis. A prospective European study of 163 patients with BCS by Darwish Murad et al. identified esophageal varices in 58%, hepatic encephalopathy in 9%, portal vein occlusion on presentation in 18%, caudate hypertrophy in 77%, and involvement of all three hepatic veins in 75%. Histologically, 64% had sinusoidal congestion, 59% had fibrosis, 23% had hepatocellular necrosis, and 18% had cirrhosis.

Imaging continues to be the cornerstone of diagnosis and management of BCS and has three main roles: to establish the diagnosis; to plan care, especially endovascular intervention strategies; and to evaluate and distinguish commonly found benign regenerative liver nodules from rare primary liver malignancies. Initial evaluation with duplex ultrasonography of the liver is recommended and has a diagnostic sensitivity of greater than 85% in adults. In addition to ultrasound, triple-phase liver dedicated magnetic resonance imaging or rapid sequence computed tomography are ideal not only to establish the diagnosis of BCS, but also to assist the multidisciplinary team in therapeutic planning. Within the confines of multidisciplinary care, the inferior vena cavogram and hepatic venogram can add valuable information to the treatment planning by allowing the radiologist to measure venous pressures in the infrahepatic and suprahepatic vena cava, as well as in the right atrium.

Because of its high association, any patient with a known hematologic abnormality presenting with acute or chronic liver disease should be evaluated for presence of BCS. The converse is also true. Patients presenting with BCS should be thoroughly screened for hematologic abnormalities. History should include questions regarding use of oral contraceptives, personal and family history of hematologic abnormalities, and signs and symptoms of associated diseases. Laboratory workup should include evaluation for myeloproliferative neoplasia and several unique *JAK2* mutations, starting with *JAK2* V617F mutation. Discovered in 2005, the detection of *JAK2* V617F mutation will alleviate the need for bone marrow biopsy in up to 65% of patients who might otherwise require it to further delineate presence of myeloproliferative neoplasia. Other targets of investigation are continually being discovered, including *JAK2* exon 12 mutations, calreticulin, 5,10-methylenetetrahydrofolate reductase 2, and thrombopoietin receptor gene mutations. Because of the diversity and complexity of the various (and often rare) inherited thrombophilias and acquired conditions underlying BCS, inclusion of a hematologist in the multidisciplinary team is highly encouraged. Finally, a liver biopsy should generally be avoided as the initial presentation of the BCS patient, resulting from concerns for bleeding because anticoagulation is the mainstay of therapy at this stage. Furthermore, there does not appear to be a relationship between early liver pathology and survival in BCS.

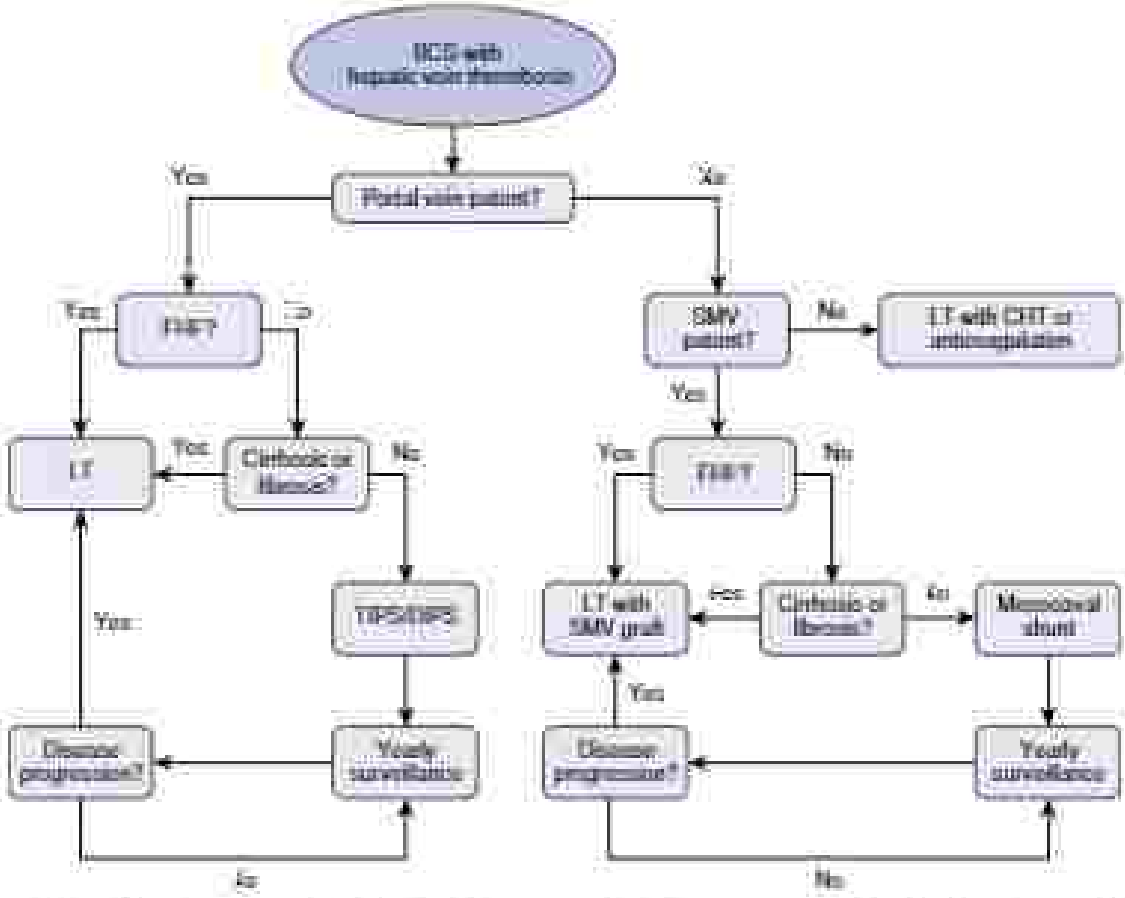

FIG. 1 Proposed algorithm for the management of Budd-Chiari Syndrome. CRT, Caval reconstruction; DIPS, direct intrahepatic portacaval shunting; FHF, fulminant hepatic failure; LT, liver transplantation; SMV, superior mesenteric vein; TIPS, transjugular portosystemic shunting.

TREATMENT

The natural history of untreated hepatic venous outflow obstruction is generally progressive hepatic fibrosis and cirrhotic changes. Cazenave and colleagues have demonstrated that persistent sinusoidal congestion leads to hepatocyte atrophy and impaired cellular regeneration. In fact, in a study reported by McCarthy and colleagues, 12 of 14 patients with BCS who were managed nonoperatively died within 6 months of diagnosis. An exception to this poor prognosis may be realized by the subset of patients determined to have incomplete hepatic venous obstruction. Preventing progressive liver dysfunction resulting from sinusoidal hypertension remains a central principle for managing BCS.

A multidisciplinary approach is key to the successful management of BCS. A stepwise strategy should focus on (1) preventing further venous occlusion; (2) managing the clinical sequelae of venous obstruction (such as ascites); and (3) portal decompression to prevent progression to cirrhosis. Anticoagulation is standard in BCS unless contraindicated by bleeding risk, but this serves only to prevent propagation of thrombosis and does not reverse established venous obstruction. Ascites and hepatic encephalopathy should be managed similar to other patients with end-stage liver disease with salt restriction, appropriate use of diuretics, and appropriate use of lactulose and rifaximin. Portal decompression is accomplished through implementation of one or more of the radiologic or surgical techniques discussed in the following section. A useful management algorithm for BCS is proposed in Fig. 1.

An important concept in the treatment of BCS that has evolved over the past decade is a stepwise approach to portal decompression. Liver transplantation (LT), which is the most radical solution for BCS, is rarely first-line therapy, and in recent years the use of portal decompressive surgery has waned and been replaced by minimally invasive interventional radiologic therapies. This strategy has led to overall survival rates of approximately 80% (Table 1). The primary goal of these interventional treatments for patients with BCS remains reduction of hepatic congestion and associated sequelae such as portal hypertension. In order of increasing invasiveness, the therapeutic options include pharmacologic agents such as diuretics and anticoagulants, thrombolysis, percutaneous transluminal angioplasty/stenting (PTAPS), transjugular intrahepatic portosystemic shunting (TIPS), direct intrahepatic portocaval shunting (DIPS), and the surgical options of portosystemic shunting and LT.

Anticoagulation should be viewed as a means to prevent clot progression or recurrent venous thrombosis, but it usually will not reverse established disease. Most patients with BCS will have to remain on anticoagulation therapy long term. In a follow-up to a large European study of patients with BCS (European Network for Vascular Disorders of the Liver [en-TAV-ble]) by Seijo and colleagues, about 40% of patients were treated with pharmacologic interventions only and did not undergo invasive treatments; 20 of the 69 patients treated without further intervention died within the 5-year follow-up. Because this represented 50% of the total mortality observed in the cohort, it begs the question of whether these patients should have had additional, and perhaps earlier, interventions for their BCS. Other studies have suggested that the percentage of patients with BCS that are well controlled on medical therapy alone are much lower. In more than one half of the cases of BCS in ex-USSR, the study continued to progress despite anticoagulation and required one or more interventions.

One option is to attempt thrombolytic therapy, angioplasty, and stenting. Thrombolysis and PTAPS seem to be more effective in the

Asian form of BCS compared with the Western form. This is likely related to the more frequent occurrence of hepatic venous web and venous stenosis in the former. Additionally, delivery of the thrombolytic agent "upstream" from the clotted hepatic veins is difficult or, in many cases, impossible. Nevertheless, thrombolysis and PTA/S can be an option in the rare patient who presents with BCS resulting from focal or short length segmental stenosis of a hepatic vein. In most reported series of the Western type of BCS, thrombolysis and PTA/S have played only a relatively minor role in the overall treatment of this disease.

TABLE 1 Comparison of Survival Outcomes for Endovascular vs Transplant Treatment of BCS

Study	N	Overall Survival	Need for Transplantation
TIPS			
Garcia-Pagan, 2008	124	79% 5 year OLT free	6.4% (8 of 124)
Senju, 2013	62	72% 5 year	4.3% (3 of 62)
Rössle, 2004	33	74% 5 year OLT free	6.1% (2 of 33)
TRANSPLANTATION			
Segev, 2007	510	80% 5 year (MELD era)	NA
Mentha, 2006	240	68% 10 year	NA
Singer, 1995	43	69% 10 year	NA
Uhlich, 2008	42	80% 10 year	NA

MELD, Model for End-Stage Liver Disease; NA, not available; OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunting.

ENDOVASCULAR VERSUS SURGICAL SHUNTING

Given the disease progression in most patients treated with medical management alone and the limited effectiveness of thrombolytic therapy and PTA/S in the management of the Western form of BCS, the next intervention in the treatment algorithm is endovascular shunting via TIPS or DIPS (Fig. 2). Accumulated worldwide experience in the performance of TIPS, coupled with stent technology advancements (e.g., polytetrafluoroethylene-covered self-expanding stents) has led to excellent outcomes. In a retrospective analysis of 54 patients who underwent TIPS for primary BCS from 2004 to 2014, Hayek and colleagues reported the primary and secondary technical success rates to be 93% and 98%, respectively. During this study's mean follow up of 56 months, 42% of patients required shunt revision, but the secondary patency rate was 100%. Procedure related mortality was zero, and the overall 5- and 10-year survival rates of the cohort were 83% and 74%, respectively.

These results appear to be significantly better than those reported for surgical shunts performed for BCS. In the initial 1983 report of surgical shunts in treatment of BCS, only 8 of the 42 patients who underwent surgical systemic-venous shunt placement survived to discharge from the hospital. An additional patient died from sequelae of shunt thrombosis. Another two patients developed recurrent ascites immediately after surgery again from shunt thrombosis. Overall, only three patients had patent shunts and did not require reoperation. Interestingly, follow up liver biopsies in these three patients showed normalization of liver histology over time, which has been the basis for early decompressive intervention in newly diagnosed BCS, even in the absence of symptoms. Unfortunately, newer series have not shown any better outcomes for surgical shunting in the setting of BCS, as can be seen in the in hospital death of five of six patients who underwent surgical shunt placement for BCS between 1996 and 2011 at a major academic center with excellent and internationally recognized experts in performance of surgical portosystemic shunts. Furthermore, four multicenter retrospective multivariate analysis studies failed to show survival benefit of surgical portosystemic shunting after adjusting for independent prognostic factors.

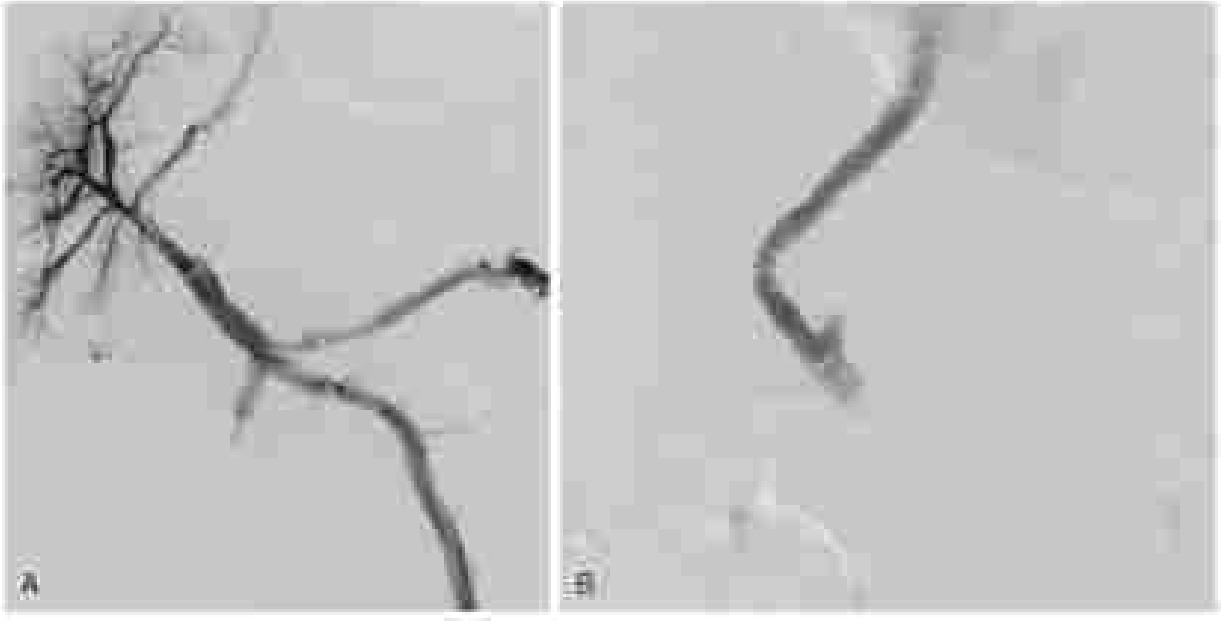

FIG. 2 Direct intrahepatic portosystemic shunt (DIPS) procedure. (A) Ultrasound-guided transhepatic portal venogram with guidewire ascending from splenic vein into portal vein, showing complete portal vein atresia/web with no evidence of hepatic vein runoff, consistent with BCS. (B) After placement of the metal stent, rapid flow through the stent into the vena cava is noted. No intrahepatic portal vein filling is noted because blood is shunted directly into the inferior vena cava from the main portal vein.

Given all these data, coupled with many of the diverse and declining technical expertise in portal systemic shunt surgery, routine use of surgical mesenteric-systemic or portal systemic shunting in the management of BCS cannot be recommended at this time. Surgical shunts should be reserved as an option in the uncommon situation where endovascular shunting is not possible (e.g., obstruction high in IVC not amenable to endovascular therapy).

The selection of which endovascular shunt approach is most appropriate in a BCS patient who progresses despite anticoagulation is driven largely by hepatic vein patency, the presence of which is required for performing a standard TIPS. In instances in which no adequately patent or suitable hepatic vein is present, recanalization of the vein may be attempted to allow subsequent TIPS. The development and evolution of TIPS provides an alternate endovascular approach to decompress the BCS liver. TIPS procedures involve creation of an endovascular shunt through the hepatic parenchyma which passes directly from IVC into the portal vein and does not require patency of the hepatic veins (Fig. 2). Successful TIPS has been greatly facilitated by intravascular ultrasound. Short- and long-term data on effectiveness of TIPS in management of BCS are limited, but the preliminary results are encouraging, with reported 100% technical success rate without complications and 83.3% overall clinical success rate, as reported by Hamdallah and colleagues. Several scoring systems have been proposed (e.g., Rotterdam classification III, Child, BCS-TIPS) as a way of predicting mortality in BCS and to determine urgency, and to some degree, the type of therapy to be used. Additional data are emerging but further validation is required. Of the patients in an FM Vic who received invasive therapies, up to 70% underwent TIPS. In that cohort, 22% received a liver transplant.

LIVER TRANSPLANTATION

For the rare patient who presents with fulminant hepatic failure secondary to BCS, LT is usually the only curative treatment option. In the 10% to 20% of patients who show progression of BCS despite all other therapies, LT is also the only remaining therapeutic option. In patients who develop hepatic venous thrombosis secondary to metabolic defects localized to the liver (e.g., antithrombin III deficiency, protein C deficiency), LT offers the singular benefit of being curative. The treatment options for patients with chronic hepatic venous outflow obstruction who have histologic evidence of cirrhosis are also limited to total hepatectomy and liver replacement because BCS patients with cirrhosis typically will do poorly with nontransplant treatment strategies. Newer advances in medicine such as use of the terminal complement inhibitor eculizumab have even opened the possibility for LT for paroxysmal nocturnal hemoglobinuria, once regarded as a definite contraindication to transplant because of high chance of recurrence in the liver allograft.

The first LT for BCS was performed in 1974. Over the next 15 years, 1- and 5-year posttransplant patient survival rates for BCS (~70% and 45%, respectively) were determined to be inferior to what was observed for adult liver recipients in general. The improved success reported in more recent series (5-year survival rates of 71%–89%) has been attributed to (1) a decreased interval between the onset of symptoms and initiation of therapy, (2) early institution of anticoagulants or antithrombotic therapy (or both) after transplantation, and (3) modern therapy of patients with a definable hypercoagulable state. Patients with BCS who undergo LT show survival rates and graft function that are equivalent to or better than those who undergo LT for most other reasons. Despite earlier concerns, BCS patients who undergo TIPS have not shown worse outcomes with LT; for this reason, endovascular shunting should not be considered a contraindication to LT.

Mentha and colleagues surveyed the European Liver Transplantation Registry between 1968 and 1999 and identified 205 patients transplanted for BCS. Complete follow-up data were obtained for 249 patients. The actuarial survival was 75.6%, 71.8%, and 68% at 1, 5, and 10 years posttransplant, respectively. Late mortality was low in this study; only 9 patients died after 1 year; however, 27 patients (11%) developed some form of venous thrombosis despite anticoagulation therapy. Six of these patients had recurrent hepatic venous thrombosis. In a more recent report by Segev and colleagues looking at 530 LTs that were done in the United States between 1987 and 2006, post-Model for End-Stage Liver Disease era graft and patient 3-year survival was found to be 81% and 83%, respectively.

Most series have suggested that early initiation of anticoagulation therapy has markedly reduced the incidence of recurrent BCS following LT. We would advocate for lifelong anticoagulation following LT for patients with BCS, even in the absence of an identifiable hypercoagulable state. This strategy is not without penalty. One series from Cambridge reported a 44% incidence of intestinal hemorrhage when a policy of early posttransplant anticoagulation was instituted. Nonetheless, there is evidence that complications secondary to bleeding are generally more amenable to treatment than are complications secondary to thrombosis. A European multicentre clinical series reported by Mentha and colleagues in 2006 identified risk of bleeding and thrombosis to both be around 11%, but the mortality from bleeding was 1%, whereas mortality after thrombosis was 40.2%.

LT poses specific technical challenges for patients with BCS. The obstructed liver is generally enlarged, firm, and difficult to mobilize during the hepatectomy. A diffuse fibrotic reaction to the retroperitoneum, perhaps related to the hepatic vein thrombotic process, increases the difficulty of identifying, mobilizing, and controlling the IVC. Because the caudate lobe is enlarged and the hepatic vein orifices are occluded, the "piggyback" technique of LT may be particularly challenging. Control of the vena cava may require incision of the diaphragm and isolation of the vena cava within the pericardial sac.

Not infrequently, BCS patients with hypercoagulable conditions present with thrombosis of other large vessels in their splanchnic circulation. Portal vein occlusion presents a particularly difficult problem because a plan for restoring portal venous inflow to the transplanted liver must be devised before proceeding with LT. If the portal vein is occluded but the superior mesenteric vein (SMV) is patent, preoperative transhepatic cannulation of the portal vein with thrombolysis and angioplasty has been shown to be successful in a small number of patients. Alternatively, direct thrombectomy of the SMV and portal vein can be used as a conduit from the recipient's SMV to the allograft portal vein. In cases in which both the portal vein and SMV are occluded, Ueda and colleagues have performed LT with cava bicavocaval anastomosis whereby the allograft portal vein is sewn end to side to the recipient's IVC. The IVC superior to this anastomosis is partially or totally ligated to preferentially direct systemic venous blood through the allograft portal vein. Patients treated with caval bicavocaval anastomosis have persistent portal hypertension as well as functional caval obstruction posttransplantation. Not surprisingly, morbidity and mortality are high in such patients, who arguably are best treated with anticoagulation alone with the hope that they will develop collateral splanchnic venous drainage and symptomatic improvement over time.

Despite a successful TIPS or less commonly a secondary systemic surgical shunt, persistent liver injury with histologic progression to fibrosis and cirrhosis has been documented in some patients. Shunt patency does not necessarily ensure complete decompression of the congested hepatic sinusoids. For this reason, lifelong follow-up and imaging of hepatic function is indicated in BCS patients treated with any form of portal venous decompression. The effect of radiologic therapies for BCS on a subsequent LT cannot be neglected. Intravascular stents become densely incorporated into their resident blood vessels. Should these stents migrate into the main portal vein, the suprahepatic IVC, or the right atrium, significant technical difficulties may be encountered during isolation of the hepatic vasculature and subsequent explantation of the liver.

There is little controversy that LT offers the most effective therapy for the minority of individuals with either fulminant hepatic failure or the chronic, cirrhotic form of BCS; however, most BCS patients present with acute or subacute manifestations of hepatic venous outflow obstruction. If long-term benefit were the sole benchmark by

which treatment was selected for these patients, who represent the majority of BCS patients, there is general agreement that, as a group, they will do best if given transplants. Unfortunately, from a practical standpoint, clinical outcomes alone cannot be used to determine whether LT is advisable for patients with BCS. A more restricted use of LT is mandated by (1) the widening gap between the number of patients who require a liver transplant and the static pool of donated organs, (2) the unpredictable availability of donor organs, (3) the need for and consequences of lifelong immunosuppression, and (4) the dramatically higher cost of transplant versus nontransplant therapies.

Suggested Readings

Darwish Murad S, Plessier A, Hernandez-Guerra M, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med. 2008;149:167–173.

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ASYMPTOMATIC GALLSTONES

Steven M. Strasberg, MD, FRCS(C), FACS, FRCS(Ed)

In the United States, 25% to [illegible] gallstones by age. More [illegible] people have gallstones [illegible] 80,000 patients [illegible] pregnancy [illegible] gallstones are found on routine [illegible] gallstones [illegible] gallstones are discovered when purposely searched for in asymptomatic persons with a strong family history of gallbladder cancer or in high gallbladder cancer endemic areas such as Chile and Alberta.

Clinical Stages of Cholelithiasis

Cholelithiasis has three clinical stages: the asymptomatic stage, the symptomatic stage, and the stage of complications. Complicated forms of cholecystolithiasis include acute cholecystitis and its complications, choledocholithiasis and its complications, gallstone ileus, and gallbladder cancer. Avoidance of these complications constitutes an important rationale for therapy in the symptomatic stage or under special circumstances in the asymptomatic stage.

Of importance in making recommendations about treatment is knowing the natural history of cholelithiasis, particularly the rate of conversion from the asymptomatic stage to the other stages. This information is necessary to weigh the risk of expectant management against the hazards of cholecystectomy. Historical series on the natural history of gallstones yielded controversial results, mainly because of the inclusion of patients with some biliary symptoms. This distorted the results toward a higher rate of symptomatic patients. Later, thinner studies with longer follow-up found that these gallstones most often remain silent or become symptomatic before causing complications and that expectant treatment of asymptomatic stones very rarely resulted in patient mortality. For these reasons, cholecystectomy is not recommended in asymptomatic patients with gallstones with some exceptions.

Types of Asymptomatic States

Asymptomatic gallstones may be identified in patients without any symptoms or in patients who have symptoms that are unconnected to the presence of gallstones. Although not usually made, this distinction is of practical importance.

Asymptomatic Gallstones in Asymptomatic Patients

Radiopaque gallstones, which make up about 15% of all gallstones, were commonly found on chest radiographs performed as part of an annual physical examination, but this is no longer a common practice. Another occasion for identifying a patient with asymptomatic gallstones is in the pregnant woman. Examination of the gallbladder is not part the standard obstetrical ultrasound examination, but stones may be identified on pregnant especially in the third trimester when the uterus enlarges into the upper abdomen. Based on the previously described natural history of gallstones, there is no indication for treatment of stones in this group of patients. However, there are some situations in which cholecystectomy may be indicated in asymptomatic patients.

Asymptomatic Gallstones in Symptomatic Patients

Several types of patient have symptoms at the time gallstones are discovered but whose symptoms are not connected to the presence of the gallstones. Some patients have symptoms clearly not of gastrointestinal origin. Common examples include those being investigated for symptoms based in nongastrointestinal organ systems (e.g., hematuria, cough). Although only a fraction of gallstones are radiopaque, computed tomography is so commonly used to diagnose chest and abdominal conditions that many patients are found to have gallstones by this route today. As previously stated based on the natural history of gallstones, there is no indication for treatment in such patients. Some patients have gastrointestinal symptoms but do not have abdominal pain. Bloating, belching, and nausea are common abdominal complaints. Such symptoms are no more frequent in patients with gallstones than in the general population, and their presence is not an indication for treatment of gallstones. Other patients have abdominal pain, which is the hallmark symptom of cholelithiasis, but their pain is not the result of gallstones. Decision making in this group of patients is more challenging because differentiating biliary from nonbiliary pain can be difficult. Understanding the characteristics of biliary pain and other gastrointestinal symptoms has been undertaken through the Rome Foundation, which has sponsored international conferences to define gastrointestinal function and dysfunction.

Rome Criteria for Biliary Pain

Pain of biliary origin in Rome I is defined as having the following characteristics:

1. Located in the epigastrium and/or right upper quadrant
2. Occurs at variable intervals (not daily)
3. Lasts at least ½ minutes
4. Severe enough to interrupt daily activities or lead to an emergency department visit
5. Builds up to a steady level
6. Is not significantly (<25%) relieved by bowel movements, postural changes, or acid suppression

Criteria supportive of biliary pain include pain that (1) is associated with nausea and vomiting, (2) radiates to the back and/or right infrascapular region, and (3) awakens the patient from sleep.

Gallstones are so common that it is not unusual for patients to have gallstones but another gastrointestinal problem actually responsible for the pain. Irritable bowel syndrome and peptic ulcer disease are examples of common problems in the differential diagnosis of abdominal pain in patients with gallstones. Both produce abdominal pain but usually have none or only one of the criteria of biliary pain. In some cases, the differentiation is straightforward. If the pain is in the lower abdomen and associated with constipation and/or diarrhea, irritable bowel syndrome is much more likely to be the diagnosis than symptomatic gallstone disease. Similarly, gnawing pain relieved by food and antacids will point to peptic ulcer disease. Cholecystectomy in these cases such as these is unlikely to improve symptoms. Conversely, persons with gallstones whose symptoms fit Rome IV criteria will need no further investigation to recommend cholecystectomy. It is an intermediate group that is more challenging because gallbladder pain may be atypical. For instance, the pain may be greatest in the left upper quadrant or in the back. It may be steady, especially when a stone is impacted. In this situation, when other Rome IV criteria are present, there is a definite possibility that the pain is of biliary origin. Once gallstones become symptomatic, the risk of conversion to complicated cholecystitis rises. If the pain is thought to be of biliary origin, cholecystectomy is advisable. Sometimes, when the pain is atypical, other diagnostic testing such as gastrointestinal endoscopy, abdominal computed tomography, chest radiograph, and cardiac evaluation should be considered before proceeding with cholecystectomy.

CHOLECYSTECTOMY FOR ASYMPTOMATIC GALLSTONES OR TO PREVENT STONE DEVELOPMENT

Cholecystectomy in Patients at an Increased Risk for Gallbladder Cancer

Porcelain Gallbladder

Porcelain gallbladder is believed to be due to heterotopic calcification of the gallbladder wall associated with chronic inflammation. There are two pathologic variations, focal calcium deposits in the mucosa of the gallbladder wall and diffuse infiltration of the muscularis of the gallbladder wall. Classically, porcelain gallbladder was an absolute indication for cholecystectomy because of purported high risk of development of gallbladder cancer. Rates as high as 60% were quoted. However, more recent data suggest that the incidence is much lower. There are no good studies of the natural history of the problem in part because it is quite uncommon. A modern estimate of the incidence of cancer and porcelain gallbladder is 6%. There is some evidence that the incidence of cancer is higher when the calcification is localized in the mucosa than when it is in the muscularis. Radiologically, when the calcification is in the muscularis, the gallbladder usually appears to be completely calcified (Fig. 1A), whereas when the calcification is in the mucosa it is incomplete (Fig. 1B) and often appears stippled. In considering whether to advise cholecystectomy, calcification type, patient age, comorbidities, and prior abdominal surgery need to be taken into account. Based on low-level evidence, it may be advised that younger healthier patients with mucosal type calcification should have cholecystectomy. Those who do not have cholecystectomy should probably be followed with serial imaging. Cholecystectomy in the presence of a porcelain gallbladder may be of increased difficulty. The gallbladder may be rigid from calcification and it may be a difficult to expose structures in the hepatocystic triangle because of the overhanging unyielding gallbladder. Laparoscopic cholecystectomy has been described in this disease but conversion to open surgery should be undertaken readily if there is operative difficulty displaying the anatomy.

Cholecystectomy in Populations With a High Risk of Gallbladder Cancer

Cholecystolithiasis is almost always present in patients who develop gallbladder cancer. However, in most populations in whom the incidence of gallbladder stones is high the incidence of gallbladder cancer is so low that as a public health strategy cholecystectomy in patients with stones is impractical. However, in Chile and India as well as northern India, gallbladder cancer is the most common form of gastrointestinal cancer, especially in women. The incidence is also high in Native (American) Indian women with gallstones. Although part of the explanation for the high incidence of gallbladder cancer in these populations may be a very high incidence of gallstones, the incidence of gallbladder cancer, which can reach 4% of gallstone-bearing women, exceeds that expected simply of the basis of the high incidence of gallstones.

Since 2006, the government of Chile has sponsored a program of prophylactic cholecystectomy for women with gallstones between the ages of 35 or 40 years. Approximately 40,000 patients had

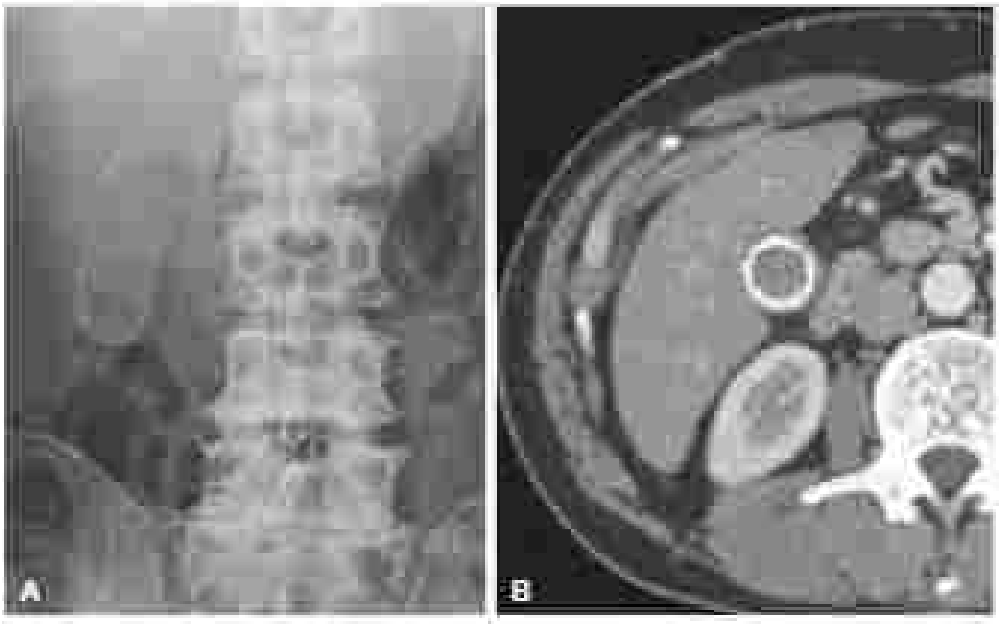

FIG. 1 [illegible] gallbladder wall.

cholecystectomy in the first 6 years of the program. It is too early to determine the overall effect on the incidence of gallbladder cancer, and the data are confounded by the fact that the incidence of gallbladder cancer overall in Chile has dropped in the past 10 years.

The risk of malignancy has been reported to be about 10 times greater in patients with stones larger than 3 cm than in those with stones of smaller than 1 cm and treatment may be indicated in this group of patients. However, the evidence is not as clear as it is in porcelain gallbladder, making a definitive recommendation impossible.

Occasionally a patient will be encountered who has a family history of gallbladder cancer and is asking for guidance, most simply when a close relative has recently been diagnosed with or has died of gallbladder cancer. Just such individuals have a fear of developing gallbladder cancer, which in some cases can be debilitating. Each one of these patients needs to be evaluated individually for the strength of the family history, presence of gallstones, and effect of the concern about developing cancer on the quality of life.

Cholecystectomy at the Time of Bariatric Surgery

Three questions are relevant to bariatric surgery and cholecystolithiasis: (1) What should be done at the time of bariatric surgery if the patient is symptomatic with cholecystolithiasis? (2) What should be done at the time of bariatric surgery if the patient has asymptomatic cholecystolithiasis? (3) Should cholecystectomy be done at the time of bariatric surgery in a patient with a normal gallbladder to avoid later formation of gallstones and the possibility of related problems?

Obesity is a major risk factor for the development of cholesterol gallstones; therefore, it is not surprising that many patients having bariatric surgery already have gallstones. There is general agreement that patients who have symptomatic gallstones should have a cholecystectomy at the time of bariatric surgery. This is not different from the recommendation for other patients with symptomatic gallstones. Although patients having Roux-en-Y gastric bypass are more likely to form gallstones in the postoperative period (see the following section), there is little evidence that patients with asymptomatic gallstones having bariatric surgery are more likely to develop symptoms postoperatively than other persons with asymptomatic gallstones. Consequently, prophylactic cholecystectomy is generally not recommended to patients with asymptomatic gallstones at the time of bariatric surgery. Another net-saving factor is that performing a cholecystectomy at the time of a laparoscopic gastric bypass is a significant addition to the duration of surgery and difficulty of cholecystectomy. The port placements for the typical laparoscopic gastric bypass are oriented toward the left upper quadrant and left abdomen and are not optimized for cholecystectomy; therefore, additional port placements may be needed. In addition, large liver weight and poor liver compliance make the cholecystectomy more difficult than that done in a lean individual or for a bariatric patient who is 3 months or more out from their procedure when liver fat is significantly reduced.

Rapid weight loss induced by Roux-en-Y gastric bypass is associated with a large increase in the amount of cholesterol excreted in bile with resultant increased gallbladder bile lithogenicity. Bariatric surgery may also interfere with gallbladder emptying, resulting in bile stasis in the gallbladder, which also is a risk factor for formation of gallstones. Gallstone formation rates of close to 60% within 6 months of Roux-en-Y gastric bypass have been reported. This problem can be largely avoided by treatment of patients with ursodeoxycholic acid for 6 months after surgery. As a result, prophylactic cholecystectomy in patients with normal gallbladders having Roux-en-Y gastric bypass is not recommended.

The preceding comments do not apply to the duodenal switch operation in which parts of the procedure are concentrated in the right upper quadrant very close to the gallbladder, making later surgery more difficult. This procedure induces the most rapid weight loss with consequent increase in gallstone formation. Therefore, the rationale for cholecystectomy in patients having this operation is stronger than in gastric bypass.

Cholecystectomy in Patients With Diabetes and Asymptomatic Gallstones

Controversy still exists about prophylactic treatment in patients with diabetes, in which those with asymptomatic stones do not seem more likely to become symptomatic than nondiabetic patients. It appears that once these patients become symptomatic, they are more likely to require emergency surgery for acute cholecystitis and surgery is attended by higher morbidity and mortality rates. On the other hand, the risk of elective surgery in patients with diabetes in the absence of other risk factors is similar to that in patients without diabetes. It therefore seems advisable to treat patients with diabetes with symptomatic gallstones but not to treat until symptoms develop.

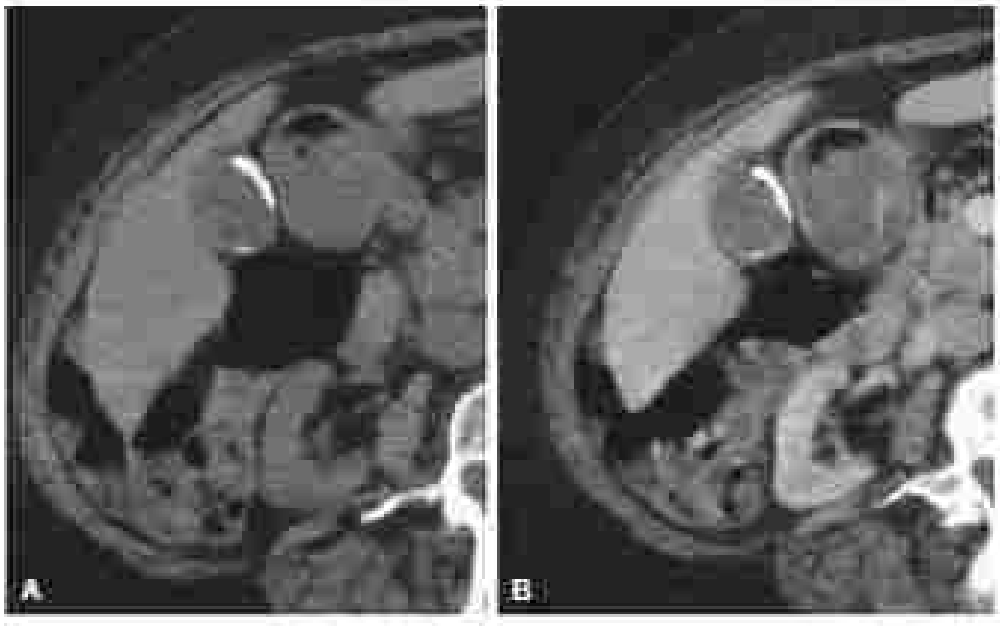

FIG. 4. Partial calcification of gallbladder wall. (A) Noncontrast computed tomogram. (B) Intravenous contrast computed tomography scan shown for comparison.

Cholecystectomy in Patients Having a Gastrectomy With and Without Asymptomatic Gallstones

The incidence of gallstones after gastrectomy is increased, especially gastrectomy for gastric cancer. Rates as high as 15% within 5 years have been reported. Formation of stones after gastrectomy has been associated with certain factors in different case series. These include total gastrectomy as opposed to partial gastrectomy, extensive lymph node dissection, and exclusion of the duodenum in the reconstruction. Obesity and male sex also have been reported as risk factors. Factors thought to be operative include rapid weight loss, gallbladder stasis from a lack of release of cholecystokinin and perhaps vagal denervation. Cholecystectomy has been advocated to avoid future gallstone formation after gastrectomy, but is not widely practiced.

There is a stronger argument for cholecystectomy in patients with gallstones already present at the time of gastrectomy because, similar to the situation with duodenal switch, cholecystectomy may be quite difficult following a prior gastrectomy especially after an N_2 node dissection.

Cholecystectomy in Patients With Hemolytic Anemias

Patients with sickle cell disease frequently form gallstones resulting from excessive excretion of bilirubin into bile. Gallstones are present in as many as 70% of adults with sickle cell disease. A key issue in this population is that sickle cell crisis may be very difficult to distinguish from biliary symptoms or biliary complications because these patients may have severe upper abdominal pain and leukocytosis. They may also become jaundiced. It has also been claimed that complications are more common after patients with sickle cell anemia become symptomatic. It seems reasonable to perform prophylactic cholecystectomy under circumstances in which it is not possible to distinguish between sickle crisis and biliary colic; however, the situation in other patients with asymptomatic gallstones is less clear. A large Jamaican study found that few patients with asymptomatic gallstones became symptomatic in follow-up. Patients with other types of hemolytic anemia such as spherocytosis and thalassemia may also develop symptomatic gallstones. Cholecystectomy in those groups is advocated only after the disease becomes symptomatic.

Cholecystectomy in Patients With Spinal Cord Injury

Patients with spinal cord injury are at increased risk of gallstone disease with an incidence of about 30%. In the great majority of patients with spinal cord injury, cholelithiasis presents with chronic pain rather than life-threatening complications. Presentation seems no more acute in patients with spinal cord injury than in the general population. Characteristic symptoms and signs are not necessarily obscured by spinal cord injury, regardless of the level. Expectant management should be the rule for patients with asymptomatic cholelithiasis. Cholecystectomy is indicated for patients with symptomatic gallstone disease.

Cholecystectomy in Short Bowel Syndrome

Patients with short gut syndrome are at increased risk of developing cholelithiasis if the intestinal remnant is smaller than 120 cm and particularly if the terminal ileum was resected and if the patient requires long periods of postoperative total parenteral nutrition. Long periods of fasting are associated with gallbladder stasis and the formation of sludge and gallstones. In a small series of five patients with short gut, all became symptomatic with acute cholecystitis or pancreatitis. Prophylactic cholecystectomy has been recommended in patients who have benign intestinal disease with short gut syndrome, especially when a laparotomy is being undertaken for another purpose.

Somatostatin interferes with gallbladder motility by interrupting the secretion of cholecystokinin. Consequently, its long-term use has been associated with the formation of gallstones. Asymptomatic gallstones form in about two-thirds of patients treated long term with somatostatin analogs. Seventeen percent of patients required cholecystectomy within 5 years of initiating treatment in one study; therefore, prophylactic cholecystectomy should be considered in these patients at the time that laparotomy is performed to remove the primary tumor.

Cholecystectomy in Transplant Patients

Expectant management is the preferred strategy for patients undergoing pancreas and/or kidney transplant with asymptomatic cholelithiasis based on a decision analysis. However, prophylactic posttransplantation cholecystectomy is favored for cardiac transplant recipients with asymptomatic cholelithiasis because in one study expectant treatment resulted in a mortality rate from complications of gallbladder disease of 44 in 1000 patients compared with 5 in 1000 for elective posttransplant cholecystectomy. Another study using the National In-Patient Sample database found that heart transplant patients are at an increased risk of inpatient mortality and morbidity after cholecystectomy compared with the general population. It was recommended that strong consideration be given to prophylactic cholecystectomy in such patients with asymptomatic gallstones.

Cholecystectomy in Patients With a Symptomatic Choledocholithiasis but Without Gallbladder Symptoms

Occasionally, patients will have stones pass into the bile ducts and become symptomatic with biliary pain, jaundice, or other consequences of choledocholithiasis without prior or concomitant symptoms from cholecystolithiasis. This situation may be described as asymptomatic cholecystolithiasis in the presence of symptomatic choledocholithiasis. There is good evidence that cholecystectomy should be performed in such patients, with the exception of very elderly or debilitated patients. For instance, in patients older than 75 years, once the bile duct stones are cleared by endoscopic means, it is unusual for patients to require a cholecystectomy for later symptoms arising from the gallbladder. However, it is advisable for such patients to have a protective endoscopic sphincterotomy at the time of stone clearance from the bile ducts by endoscopic retrograde cholangiopancreatography to prevent future symptoms arising from choledocholithiasis.

Cholecystectomy for Future Hostile Abdomen

As mentioned in regard to gastrectomy with extensive lymph node dissection and duodenal switch operation, cholecystectomy may be indicated for asymptomatic gallstones in circumstances in which a later cholecystectomy would encounter a hostile abdomen. In addition to the examples given, this situation would include operations on the head of the pancreas, duodenum, and certain liver operations.

Suggested Readings

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Management of Acute Cholecystitis

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Acute cholecystitis (AC) is acute inflammation of the gallbladder usually resulting from obstruction of the cystic duct with gallstones. Diagnosis is based on a combination of clinical signs and physical examination findings (most important, right upper quadrant abdominal pain and tenderness) and imaging showing cholelithiasis and/or gallbladder wall inflammation. Standard treatment is prompt laparoscopic cholecystectomy, although selected patients may be managed medically or with percutaneous cholecystostomy (PC) tube placement. Surgeons should be prepared to convert planned laparoscopic cholecystectomy to open cholecystectomy and be familiar with various options for the sometimes difficult cholecystectomy encountered in patients with AC.

CLINICAL PRESENTATION, EVALUATION, AND DIAGNOSIS

Patients with AC typically experience upper abdominal pain that localizes to the right upper quadrant and lasts for more than 6 hours. A history of prior similar episodes that were shorter in duration or less severe often can be elicited. Patients may have a known history of gallstones either identified during evaluation for prior episodes of abdominal pain or identified incidentally on imaging studies performed for other reasons. Nausea and vomiting are frequently present, fever less so. The most common physical examination finding is right upper quadrant abdominal tenderness, Murphy's sign, inspiratory arrest with palpation over the gallbladder, is the classic physical examination finding. All of these signs and symptoms may be muted or absent in patients who are obese, have diabetes, are on steroids or otherwise immunosuppressed, or have impaired sensorium.

The most important differential diagnosis is between AC and other biliary tract disease, such as biliary colic or choledocholithiasis. A number of other intraabdominal diseases, such as pancreatitis, peptic ulcer disease, mesenteric ischemia, hepatitis, and colitis, and extraabdominal diseases such as myocardial ischemia and pneumonia occasionally may resemble AC. History taking and physical examination should focus on narrowing this list to appropriately direct further laboratory and imaging tests.

There are no diagnostic laboratory studies. Mild leukocytosis is common. Liver function tests are typically normal or only mildly elevated and are helpful primarily in differentiating AC from other forms of complicated gallstone disease, such as choledocholithiasis and cholangitis, or medical liver illness such as acute hepatitis. Marked abnormalities in serum bilirubin, alkaline phosphatase, or transaminases should prompt consideration of an alternative diagnosis. Serum amylase and lipase should be sent to evaluate for acute pancreatitis.

The optimal choice of imaging test depends primarily on the pretest probability for AC relative to other forms of intraabdominal pathology. Ultrasonography, computed tomography (CT), cholescintigraphy (HIDA scan), and magnetic resonance imaging are capable of identifying AC with variable sensitivity and specificity and have different levels of cost and availability. Using them correctly depends on the clinical scenario. For patients with a typical presentation and a high clinical suspicion for AC, transabdominal ultrasound is the current diagnostic test of choice. It is inexpensive, requires no ionizing radiation, is widely available, and is more than 90% accurate for detection of cholelithiasis. Signs of AC on ultrasound include pericholecystic fluid, gallbladder wall thickness greater than 4 mm, gallbladder distension, a gallstone lodged in the neck of the gallbladder, and a sonographic Murphy's sign. However, ultrasound, although very sensitive for the detection of gallstones, is only about 60% to 70% sensitive for detecting these "objective" signs of AC. Thus the scenario in which a patient has a convincing clinical presentation for AC, followed by an ultrasound showing gallstones, but no objective ultrasonographic signs of cholecystitis is a common one. In this scenario, for surgically low risk patients, we recommend proceeding to cholecystectomy, confident that the patient either has AC (as diagnosed clinically) or at least significantly symptomatic gallstone disease that merits cholecystectomy.

Scenarios frequently arise in which the orderly progression from history, to physical examination, to laboratory evaluation, to ultrasonography, to a diagnosis of AC does not occur. It is very common for surgeons to be consulted in patients who come to the emergency department with abdominal pain and after initial evaluation undergo CT scanning as the first radiologic test. When the CT scan shows evidence of AC, is a subsequent ultrasound necessary? We would argue rarely or never. Although not the first line test for AC and poorly sensitive for cholelithiasis, CT is actually more sensitive than ultrasound for detecting objective signs of AC, such as pericholecystic fluid or inflammation and gallbladder wall thickening (Fig. 1). It is also the most versatile test for evaluating the other entities usually considered in the differential diagnosis of AC. If a CT scan shows AC and no other diagnosis is suggested strongly by the clinical presentation or CT scan, there is little to no utility to performing ultrasonography just to demonstrate stones in the gallbladder.

Another common scenario is the patient with an atypical clinical presentation for AC, in whom ultrasonography demonstrates stones but no clear evidence of AC. Are these incidentally found stones in a patient with some other pathology, or are they the true source of the problem? After reviewing the patient and clinical data, the surgeon must decide whether there is a significant risk of intra-abdominal pathology not related to the biliary tract. If there is significant concern for other intraabdominal pathology as the source of the patient's symptoms, we usually perform abdominal CT scanning with intravenous contrast. It is the test most likely to either confirm the diagnosis of AC and rule out an alternative diagnosis or to provide an alternative explanation for the patient's symptoms. The other commonly used test to evaluate for AC when the diagnosis is unclear after clinical evaluation and ultrasonography is HIDA. Although HIDA is highly sensitive and specific for cholecystitis, it is not as widely available as CT and if negative for AC, it provides no useful information regarding other possible diagnoses. Thus we use it very selectively.

MANAGEMENT

Cholecystectomy is the standard treatment for AC and has the advantage of not only treating the current episode but also removing the risk of subsequent bouts of AC and other biliary tract complications related to gallstones. All patients diagnosed with AC should receive appropriate antibiotics. The decision regarding which of the following treatment options to use depends on the overall medical condition of the patient and the severity and duration of symptoms. Patients with minimal medical comorbidities presenting early in their disease generally should be managed surgically, those with significant comorbidities but mild AC may merit a trial of medical therapy, and those who are critically ill or have severe medical comorbidities and severe AC are managed best with PC.

Cholecystectomy

Cholecystectomy is standard treatment for patients with AC and should be performed within 72 hours of onset of symptoms, the sooner the better. Alternatives to cholecystectomy and when to apply

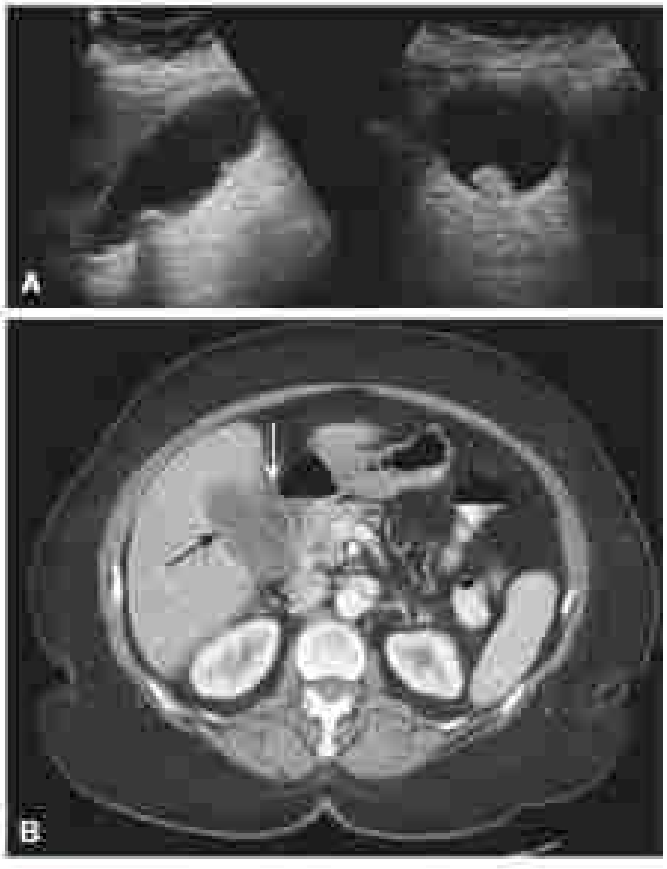

FIG. 1 Computed tomographic scan and its annotated image of a patient with acute cholecystitis. (A) Ultrasonic image. (B) Computed tomographic scan. The gallbladder is distended, with wall thickening and pericholecystic fluid. The gallbladder wall is thickened and edematous, and pathologic findings were consistent with acute cholecystitis.

them are discussed later. Once the decision to operate is made to operate, there is nothing to be gained by waiting, and prompt surgery provides quicker relief to the patient, limits overall hospital stay, and avoids peripheral inflammation that can worsen as days pass and make dissection more difficult. Laparoscopic cholecystectomy is the procedure of choice, but surgeons must be familiar with both laparoscopic and open techniques because the conversion rate in AC is 10% to 30%.

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy is the approach of choice to AC because multiple studies have demonstrated low morbidity, shorter hospital stays, less time until return to normal function, and lower costs with the laparoscopic approach. The technique of laparoscopic cholecystectomy for AC is fundamentally the same as for elective cholecystectomy—for other indications, the procedures are simply more difficult. The basic steps of patient positioning, equipment, abdominal access, exposure of the gallbladder and cystic structures, dissection of the cystic structures until a critical view of safety is obtained, and indications and use of cholangiography when needed to define the anatomy are the same and are described in detail elsewhere in this book. We discuss a few factors specific to cholecystectomy for AC.

Simply grasping an inflamed gallbladder may be problematic, and this often can be aided by decompression. Occasionally decompression can be accomplished with a purpose-made laparoscopic needle aspirator, but this is often too small to achieve effective decompression in AC. A 14-gauge angiocatheter needle placed through a tiny stab incision has a better chance of success. If this does not achieve adequate decompression, a 5-mm laparoscopic trocar can be thrust directly into the fundus of the gallbladder and a suction aspirator used to evacuate the gallbladder. If this technique is used, an endoloop can be used to close the cholecystotomy to prevent more spillage. Standard laparoscopic graspers may not be able to effectively grasp the thickened and edematous gallbladder wall in AC. This is not a minor nuisance, it is an actual danger because ineffective gallbladder retraction, especially laterally, is a risk factor for bile duct injury. Tripod graspers or large claw graspers may be able to effectively grasp an inflamed gallbladder when standard 5-mm toothed graspers cannot. It is worth identifying a piece of equipment at your home institution that is effective for this purpose.

Once the gallbladder is rendered graspable, the dissection begins. Adjacent structures, usually omentum, duodenum, and sometimes transverse colon or mesocolon, must be packed off the gallbladder. This is best done by identifying the plane where the structure meets the gallbladder and pushing bluntly downward parallel to the gallbladder wall rather than pulling outward. Adhesions to the adjacent liver capsule may be tougher than the capsule itself and so should be divided with scissors or electrocautery before this blunt dissection to avoid bleeding from a capsular tear. Once the gallbladder is exposed, the cystic dissection begins. As with any laparoscopic cholecystectomy, the peritoneum and fatty tissue surrounding the cystic structures must be cleared. Inflammation may pull the gallbladder in close to the porta hepatis, and so we often begin in cases of AC by retaining the gallbladder medially and bluntly stripping the peritoneum and tissue lateral to the cystic structures. This is a relatively safe area to work in initially because it is away from the portal structures, and relaxing this lateral peritoneum often improves the amount of lateral retraction that is possible when dissecting in Calot's triangle. Because of edema, electrocautery may be less effective in some cases of AC than in more elective cholecystectomies, and thus blunt dissection may be more useful. The suction irrigator or a laparoscopic probe dissector can be used for this. Some small capillary oozing may be seen in cases of AC, and this usually can be swept away bluntly as the dissection continues. It is critical to maintain the same standards of visualization as during an elective cholecystectomy. Although it may be harder to obtain the critical view of safety, the same standards of anatomic definition must be applied in cases of AC. Some authors have advocated a top-down laparoscopic dissection, beginning at the gallbladder fundus, when inflammation impairs the initial cystic dissection. We are not advocates of this technique unless it is used regularly in elective cases because it leaves the surgeon using an unfamiliar technique to only the hardest cases.

Occasionally the cystic duct may be foreshortened and/or thickened because of acute and chronic inflammation. If it is not safe to safely clip with standard clips, an endoloop or laparoscopic stapler may be used. In either case, when a duct appears too large to clip, the surgeon must be absolutely sure, either by dissection or cholangiography, that it is in fact the cystic duct. Once that is clear, the endoloop or stapler should be applied so as not to narrow the common bile duct. If stapling, we usually use a 30 mm long linear cutting stapler with 2.5 mm staples. Once the cystic structures are divided safely, the gallbladder must be removed from the liver bed. This is a commonly underdiscussed portion of the operation that can still result in problems if not done correctly. A significant portion of bile leaks after laparoscopic cholecystectomy are related to subvesical ducts, most of which course through the liver parenchyma just deep to the gallbladder fossa. Maintaining adequate tension with the retracting instruments and staying in the correct anatomic plane of dissection minimizes this complication and bleeding from the liver parenchyma.

Finally, although we have attempted to provide a few tips relevant to accomplishing laparoscopic cholecystectomy in cases of AC, when the anatomy cannot be defined clearly because of inflammation or other factors, there should be no hesitation to convert to an open procedure (described later). Although morbidity is increased somewhat

be an open approach, this small increase is nothing compared with the morbidity of a major bile duct or vascular injury, which may occur when persisting laparoscopically with inadequate exposure or dissection. It is very hard to find a surgeon who regrets converting a laparoscopic cholecystectomy to open, but there is no shortage of surgeons who regret persisting laparoscopically in cases of unclear anatomy with sometimes disastrous results.

Open Cholecystectomy

Because laparoscopic cholecystectomy is the standard procedure in cases of AC, most open cholecystectomies in this setting occur as a conversion from a laparoscopic procedure. There are very few conditions that mandate open cholecystectomy with no attempt at laparoscopy, but there are a number of risk factors for conversion to open cholecystectomy, including obesity, long duration of symptoms, cirrhosis, and male sex. Keeping in mind these risk factors, there are some theoretical advantages to performing planned open cholecystectomy rather than converting from a laparoscopic approach. Operating time and equipment costs can be reduced and planning for postoperative analgesia, including regional anesthesia, can be performed preoperatively. In some series, the highest complication rates are in cholecystectomies converted to laparoscopic to open, often after laparoscopic misadventure. It is possible that correctly identifying these difficult cases and starting with an open approach could limit some of these complications.

Both upper midline and right subcostal incisions provide excellent exposure for open cholecystectomy. We prefer a fundus-down technique, in which the fundus is grasped and separated from the liver edge with electrocautery. The medial and lateral peritoneal leaves overlying the gallbladder are incised with cautery, and the hepatic attachments are dissected either with cautery or bluntly with fingers or a suction catheter. When the infundibulum is reached, lateral retraction helps expose the cystic duct and artery, which are ligated.

Bailout Options

Even experienced surgeons will encounter gallbladders that cannot be removed safely. Options depend on when this is recognized. Ideally it will be recognized preoperatively, and patients will be treated nonoperatively as described later. If difficulties are recognized while the gallbladder is relatively intact or if the patient has medical instability early in the procedure, cholecystostomy tube is an excellent option. If the problem is that the gallbladder is fused to the liver and efforts to separate it result in repeated injury to the hepatic parenchyma with bleeding and associated risk of bile leak, then the back wall of the gallbladder abutting the liver can be wholly or partially left in place and the mucosa cauterized to reduce the risk of mucocele. If the cystic structures cannot be dissected safely out from a hostile porta hepatis, then subtotal cholecystectomy is acceptable and far preferable to risking significant injury to adjacent structures. If subtotal cholecystectomy is performed, we remove all stones from the gallbladder and then either oversew a small remaining cuff of infundibulum attached to the cystic duct, or if that is not possible because of poor tissue quality, we attempt to identify the cystic duct orifice from within the lumen of the gallbladder and oversew it from within. After performing any of these bailout maneuvers, we leave a closed suction drain.

Complications and Postoperative Care

Major bile duct injury is the most discussed, feared, and morbid complication of cholecystectomy, and is discussed at length in different sections of this book. We only can reiterate that the key to prevention is complete dissection of the cystic structures with judicious use of cholangiography as needed to help define the anatomy. If injury does occur, the key is to recognize it. Partially visualized clipping to control bleeding should be avoided and, if performed, should be followed by a careful postclipping analysis of the anatomy. The source of any bile leakage in the field should be identified clearly. If it is unknown from a small grasper-related tear in the gallbladder fundus, there is no cause for worry, but that should be ascertained clearly rather than assumed. After completion of the cholecystectomy, the area should be surveyed actively for any bile leakage and the source identified. Techniques for repair of bile duct injury are discussed elsewhere, but note: if the operating surgeon is not comfortable performing these, early identification, drainage, and transfer to a center of expertise for definitive management can limit morbidity.

Most bile leaks after cholecystectomy are not related to undiagnosed major bile duct injuries, but to leakage from the cystic duct stump or small subhepatic ducts. When the surgeon perceives a higher than average risk of this, closed suction drainage should be left. This can include cases in which the gallbladder was exceptionally adherent to the liver parenchyma so that subhepatic ducts may be at risk, cases with poor cystic duct tissue quality, or cases in which bailout maneuvers described earlier were used. Leaks in these scenarios may not be immediately apparent in the operating room. Because most patients undergoing such difficult cholecystectomies for AC will at least spend the night in the hospital, we remove these drains immediately before discharge if there is no evidence for bile leak. If a small leak is present, it usually will heal with drainage alone. If patients have biloma because of an unanticipated leak in an unplanned case, percutaneous radiologically guided drainage should be used. Once a bile leak is drained, the next decision is usually whether to perform endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and/or common bile duct stent placement to decompress the biliary tree. The advantages of ERCP in this setting are that it can identify the source of the leak, reduce the volume of bile leakage, and reduce the time to healing and drain removal. The disadvantage is that it is yet another procedure with its own risks of complications. In general, we tend to avoid immediate ERCP if we have an anticipated low volume bile leak, that is adequately drained, such as may occur after any of the bailout maneuvers described earlier. If we have an unanticipated or high volume bile leak, then we tend to use ERCP to define the anatomy and decompress the biliary system.

Bile and gallstone spillage are common during cholecystectomy for AC. Bile should be irrigated and aspirated, and an effort should be made to retrieve any dropped gallstones. Sludge and small stones may be difficult to retrieve, but also pose the lowest risk of postoperative complication. Larger stones can result in abscess formation and a more extensive effort to retrieve them should be made. Postoperative drainage should be used infrequently, generally in cases in which there is significant concern for postoperative bile leak. Postoperative antibiotics should similarly be used very rarely, typically only in cases with ongoing systemic inflammatory response syndrome or sepsis. Pulmonary complications including pneumonia and retentions are not uncommon after open cholecystectomy. Strong consideration should be given to regional anesthesia with transversus abdominis plane block, paravertebral block, or epidural anesthesia both for patient comfort and to limit the risk of serious pulmonary complications.

Medical Management

As discussed earlier, medical therapy generally should be used for patients with moderate to severe medical comorbidities and mild AC. Antibiotics are the cornerstone of medical management for AC. Although only about half of patients with AC will have positive bile cultures, there is no reliable method for identifying who these patients are, and there is no other medical therapy specific for the disease. The most common organisms are enteric gram-negatives (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.), anaerobes (*Bacteroides fragilis*, *Clostridium* spp.), enterococci, and streptococci; antibiotic therapy should cover these all empirically. A number of antibiotic regimens can provide needed coverage. A typical duration of coverage is 7 to 14 days, although there are very few data regarding the optimal duration of treatment. As noted earlier in patients undergoing surgery, antibiotics generally should be discontinued postoperatively. Analgesia with

acetaminophen, nonsteroidal antiinflammatories, and opiates should be used until pain resolves and supportive intravenous fluids until adequate oral intake is tolerated. If patients do not improve clinically within 72 hours, strong consideration should be given to using percutaneous or surgical treatment. Studies report a greater than 85% response rate for medical therapy with most patients unimpeded by recurrent biliary events over short-term follow-up (1 to 3 years).

Percutaneous Drainage

PC should be used in patients who do not respond to medical therapy, have contraindications or are high risk for general anesthesia, have severe AC particularly with local complications such as adjacent liver abscess, or have a prolonged duration of symptoms (>3 to 4 days), which may increase the risk of cholecystectomy and the possibility of open conversion. PC is approximately 90% effective in relieving symptoms. It is usually performed under local anesthesia or light sedation with ultrasound guidance. Minor complications, such as catheter dislodgement or blockage, occur in approximately 15% of cases, more serious complications such as bleeding or bile leakage occur in fewer than 1% of cases.

We usually perform contrast injection of the tube at 4 to 6 weeks. If the cystic duct is patent, then the tube can be removed. The risk of recurrent AC or other biliary complications after PC is poorly defined, and reports range from 10% to 50%. How the decision about whether to perform interval cholecystectomy can be individualized on the basis of patient age and surgical risk. If the cystic duct remains occluded, we leave the tube in place until the time of cholecystectomy.

Endoscopic Therapy

Endoscopic therapy for AC can consist of transpapillary stenting or transmural drainage. Transpapillary stenting uses ERCP to place a stent into the gallbladder via the cystic duct. This is usually left to internally drain into the duodenum and eventually is removed endoscopically. Transpapillary stenting is technically successful in 80% to 90% of cases and is as effective (about 90%) as PC in resolving symptoms. The technique requires sphincterotomy and so incurs small risks of postsphincterotomy bleeding, perforation, and pancreatitis. Transmural drainage involves puncturing the gallbladder under endoscopic ultrasound guidance, dilation of the tract, and placement of a stent. Newer lumen-apposing covered stents may provide long-term internal drainage.

Special Situations

Pregnancy

The differential diagnosis of AC in pregnant patients includes all the entities mentioned earlier and several pregnancy-specific entities, such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) and acute fatty liver of pregnancy. The traditional teaching that cholecystectomy should be avoided in the first and third trimesters of pregnancy is challenged by actual evidence suggesting that laparoscopic cholecystectomy is at least as safe as nonoperative management in all trimesters. Nonetheless, data less specific to cholecystectomy suggest that fetal organogenesis may be affected by laparoscopic surgery in the first trimester and that surgery during the third trimester may precipitate preterm labor. We typically pursue semi-elective cholecystectomy during the second trimester in low-risk patients (short duration of symptoms, medically low risk). In the first and third trimesters, we usually attempt medical management followed by PC if needed as a bridge to cholecystectomy in the second trimester or postpartum period, respectively.

Acalculous Cholecystitis

Acalculous cholecystitis is an inflammatory condition of the gallbladder not resulting from gallstones. It results from gallbladder stasis and ischemia, often leading to secondary infection, and typically occurs in critically ill patients. Treatment options are the same as for calculous AC. Because of the usually poor medical condition of patients with acalculous cholecystitis, and the fact that they are not at risk for recurrent complications of gallstones, PC is a much better option as "destination therapy" in acalculous than in calculous disease. We usually reserve cholecystectomy for patients who have evidence for perforation or who fail to improve after PC, which may be due to gallbladder necrosis.

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Proper Use of Cholecystostomy Tubes

Amanda K. Arrington, MD, and Taylor S. Riall, MD, PhD

Cholecystostomy tubes have traditionally been considered for the treatment of acute cholecystitis (calculous or acalculous) when definitive treatment (cholecystectomy) is contraindicated secondary to high morbidity or mortality risk. This risk can be related to the severity of the underlying gallbladder pathology and/or comorbid conditions with decompensation. The Tokyo guidelines for the management of acute cholecystitis recommend cholecystostomy tubes in two specific situations. The data from multiple US reports indicate however that current practice patterns are not adherent to the Tokyo guidelines, with only a minority of patients receiving cholecystostomy tube placement. Though the Tokyo guidelines were revised in 2018 (TG18), and now factor in patient comorbidities and physiologic status, controversy still exists regarding the indications for placement of cholecystostomy tubes.

Once placed, the recommended management of cholecystostomy tubes based on TG18 is cholecystectomy within 3 months of initial tube placement. Cholecystectomy following cholecystostomy tube placement occurs rarely despite TG18 guidelines, leading to multiple tube-related complications and recurrent gallbladder pathology. Recommendations for management after cholecystostomy tube placement are not standard and primarily focus on the patency of the cystic duct and the patient's surgical risk. Clear indications for the use of cholecystostomy tubes and their subsequent management are imperative. This chapter reviews the current literature on cholecystostomy tube placement and provides recommendations based on the best current evidence.

INTRODUCTION

Gallstone disease is one of the most common gastrointestinal diseases encountered by general surgeons. Surgeons are increasingly presented with older patients with severe cholecystitis and associated

acetaminophen, nonsteroidal antiinflammatories, and opiates should be used until pain resolves and supportive intravenous fluids until adequate oral intake is tolerated. If patients do not improve clinically within 72 hours, strong consideration should be given to using percutaneous or surgical treatment. Studies report a greater than 85% response rate for medical therapy with most patients untroubled by recurrent biliary events over short-term follow-up (1 to 3 years).

Percutaneous Drainage

PC should be used in patients who do not respond to medical therapy, have contraindications or are high risk for general anesthesia, have severe AC particularly with local complications such as adjacent liver abscess, or have a prolonged duration of symptoms (>3 to 5 days), which may increase the risk of cholecystectomy and the possibility of open conversion. PC is approximately 90% effective in relieving symptoms. It is usually performed under local anesthesia or light sedation with ultrasound guidance. Minor complications, such as catheter dislodgement or blockage, occur in approximately 12% of cases; more serious complications such as bleeding or bile leakage occur in fewer than 1% of cases.

We usually perform contrast injection of the tube at 4 to 6 weeks. If the cystic duct is patent, then the tube can be removed. The risk of recurrent AC or other biliary complications after PC is poorly defined, and reports range from 10% to 50%. Thus the decision about whether to perform interval cholecystectomy can be individualized on the basis of patient age and surgical risk. If the cystic duct remains occluded, we leave the tube in place until the time of cholecystectomy.

Endoscopic Therapy

Endoscopic therapy for AC can consist of transpapillary stenting or transmural drainage. Transpapillary stenting uses ERCP to place a stent into the gallbladder via the cystic duct. This is usually left to internally drain into the duodenum and eventually is removed endoscopically. Transpapillary stenting is technically successful in 80% to 90% of cases and is as effective (about 90%) as PC in resolving symptoms. The technique requires sphincterotomy and so incurs small risks of postsphincterotomy bleeding, perforation, and pancreatitis. Transmural drainage involves puncturing the gallbladder under endoscopic ultrasound guidance, dilation of the tract, and placement of a stent. Newer lumen-apposing covered stents may provide long-term internal drainage.

Special Situations

Pregnancy

The differential diagnosis of AC in pregnant patients includes all the entities mentioned earlier and several pregnancy-specific entities, such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) and acute fatty liver of pregnancy. The traditional teaching that cholecystectomy should be avoided in the first and third trimesters of pregnancy is challenged by actual evidence suggesting that laparoscopic cholecystectomy is at least as safe as nonoperative management in all trimesters. Nonetheless, data less specific to cholecystectomy suggest that fetal organogenesis may be affected by laparoscopic surgery in the first trimester and that surgery during the third trimester may precipitate preterm labor. We typically pursue same-admission cholecystectomy during the second trimester in low-risk patients (short duration of symptoms, medically low risk). In the first and third trimesters, we usually attempt medical management followed by PC if needed as a bridge to cholecystectomy in the second trimester or postpartum period, respectively.

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Suggested Readings

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TABLE 1 Tokyo Guidelines Definition of Acute Cholecystitis Based on Disease Severity

Grade	Definition
I (mild)	• No findings of organ dysfunction and acute cholecystitis (does not meet criteria for grade II, III) • Clear [illegible] and no earlier risk and case • [illegible] duration of symptoms [illegible] 72 hours
II (moderate)	• Degree of [illegible] with operative difficulty if cholecystectomy is to be undertaken • [illegible] one of the following • Elevated white blood cell count (> 18,000/mm³) • A palpable tender mass in the right upper quadrant • Symptoms > 72 hours • Marked local inflammation (e.g., gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
III (severe)	• Cholecystitis associated with organ dysfunction to include any of the following • Cardiovascular dysfunction (hypotension requiring treatment with dopamine ≥ 5 μg/kg/min, or any dose of norepinephrine) • Neurological dysfunction (decreased level of consciousness) • Respiratory failure (partial pressure of oxygen to arterial blood/fraction of inspired oxygen ratio < 300) • Renal failure (oliguria, creatinine > 2.0 mg/dL) • Hepatic failure (international normalized ratio > 1.5) • Hematologic dysfunction (platelet count < 100,000/mm³)

physiologic decompensation resulting from both underlying medical comorbidities and potential coexisting gallbladder pathology such as cancer. The preferred definitive treatment in patients with acute cholecystitis is laparoscopic cholecystectomy; however, when the cholecystitis leads to sepsis and hemodynamic instability, when baseline underlying comorbid conditions put the patient at high risk for surgery (e.g., severe cardiac disease, metastatic abdominal malignancy), or when cholecystitis has caused acute decompensation of otherwise stable comorbid illness, an emergent cholecystectomy is not always feasible as first-line treatment. In these cases, a cholecystostomy tube should be considered as a minimally invasive technique that avoids general anesthesia and controls the source of infection. The first ultrasound-guided cholecystostomy tube was performed and later described by Radder on a 54-year-old patient with gallbladder empyema.

The establishment of the Tokyo guidelines for cholecystitis and cholangitis in 2007 (TG07) and subsequent revisions in 2013 (TG13) and TG18 were developed to provide consensus regarding the diagnosis and management of cholecystitis. The TG07 and TG13 provide guidelines for the classification of the severity of cholecystitis, yet they did not account for a patient's medical comorbidities (Table 1). The Tokyo guidelines exclusively many cases based on a US study evaluating the sensitivity, specificity, and accuracy. Based on the grading classification defined in TG07 and TG13, an algorithm for cholecystostomy tube placement has been derived. The guidelines specifically recommend the use of cholecystostomy tubes in patients with grade II cholecystitis with symptoms lasting more than 72 hours who do not respond to antibiotic therapy or with grade III cholecystitis (Fig. 1).

The TG13 guidelines were revised in 2018 and now take into account patients' comorbidities in the form of Charlson Morbidity Index (CCI) and the American Society of Anesthesiologists (ASA) physical status classification system. TG18 guidelines recommend percutaneous cholecystostomy tube placement in grade II and III cholecystitis in those high surgical risk patients in whom antibiotics and supportive care fails (Fig. 1).

Although the use of cholecystostomy tubes in the United States has increased 2.5 -fold from 1998 to 2010 (2.8% to 9.2%) in grade III cholecystitis, the majority of patients with grade II disease are appropriately undergoing immediate cholecystectomy based on data regarding safety in this setting. Recent data reporting on Medicare beneficiaries with a diagnosis gallstone disease between 1998 and 2011 found only 6.4% of patients with a diagnosis of grade III cholecystitis and only 3% of those patients actually underwent a cholecystostomy tube.

Despite the move toward early cholecystectomy in all patients presenting with acute cholecystitis, there remains a subset of patients who present with a high surgical risk secondary to the severity of their cholecystitis, the complexity of their comorbid conditions, or both. It is in this subset of patients that cholecystostomy tube placement may be indicated; however, there remains controversy regarding indications, which may be addressed by the new TG18 guidelines.

KEY POINTS

- The TG18, adapted from the TG13, takes into account patient comorbidities and disease severity in the management of acute cholecystitis and placement of cholecystostomy tubes.
- Current practice in the United States is more aligned with TG18 treatment of grade II and III cholecystitis.
- After a cholecystostomy tube is placed, its subsequent management remains variable in literature, with multiple algorithms proposed.
- Cholecystostomy tubes have both short- and long-term complications; once placed, patients should undergo interval cholecystectomy if their underlying medical conditions can be optimized and cholecystectomy safely performed.

INDICATIONS FOR CHOLECYSTOSTOMY TUBE PLACEMENT

It is important to understand that cholecystostomy tube placement is driven by two main components: gallbladder pathology and patient-related factors. Gallbladder pathology primarily refers to the presence or absence of stones (calculous or acalculous cholecystitis), the severity of the inflammatory process, underlying malignancy, presence of sepsis or hemodynamic instability, and the duration of symptoms. The patient-related factors are more subjective and less well defined, typically based on physician judgment. Patient-related factors can include underlying cardiac, respiratory, renal, and other systemic disease that increase surgical risk. Such comorbid conditions in the setting of acute cholecystitis may lead to physiologic decompensation in the setting of manageable inflammation from the surgical standpoint. In the United States, cholecystostomy tube placement is performed in critically ill, debilitated, and/or high surgical risk with cholecystitis.

The TG18 guidelines attempt to define the group of patients at high risk for early operative intervention by including the CCI and ASA classifications. In TG18, for grade II disease, cholecystostomy tube is recommended in patients who have a CCI of 6 or greater or are ASA class III or greater in whom supportive care with antibiotics have failed.

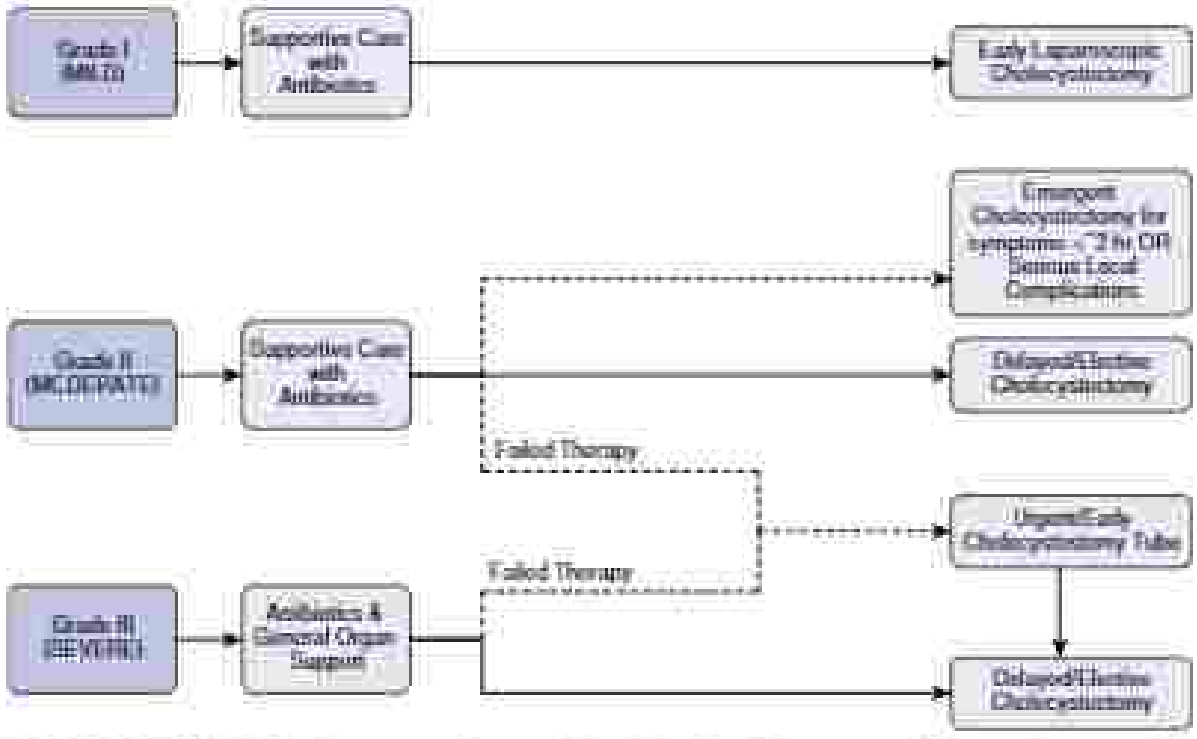

FIG. 1 Tokyo Guidelines 2013 algorithm for the management of acute calculous cholecystitis. Cholecystostomy tube placement is recommended in grade II and III disease when antibiotics and supportive care do not give the source control. Delayed elective cholecystectomy is recommended after tube placement. (From Mayumi T, Okamoto K, Takada T, et al. Diagnostic criteria for the diagnosis and treatment of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Surg. 2007;14:27–34.)

to control local inflammation. For grade III disease, a cholecystostomy tube is recommended in patients who fail supportive care with antibiotics, who are jaundiced and have neurologic or respiratory dysfunction, and whose associated organ system failure is not rapidly reversible with therapy. A cholecystostomy tube is also recommended in grade III disease, in which antibiotics and supportive care is effective, cardiovascular and renal organ system failure is reversed, but the patient has a poor performance status (ECOG >4 and ASA class V) (Fig. 2).

Acute Calculous Cholecystitis

Acute cholecystitis is most often related to gallstones. Complications from gallstones include acute calculous cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis. The pathophysiology of acute cholecystitis is obstruction of the cystic duct by an affected gallstone, which then leads to transmural edema and inflammation with potential necrosis. Cholecystostomy tube placement allows for gallbladder decompression in the setting of cystic duct obstruction without requiring a major anesthetic because the procedure can be done under ultrasound guidance, with local anesthetic and sedation. Decompression of the gallbladder reduces the inflammatory process allowing the patient to recover from the infectious process and any underlying systemic inflammatory response. Further, cholecystostomy tube placement provides a bridge to definitive therapy with an interval cholecystectomy.

Multiple studies in the United States have looked at the use of cholecystostomy tube decompression in the setting of acute calculous cholecystitis (Table 2). These studies indicate that the primary indications for tube placement are patient related and rather independent of the severity of cholecystitis, mostly including patient comorbidities making the risk of anesthesia and surgery prohibitive (Table 2). Some studies are nonspecific, simply recommending cholecystostomy tube in "poor surgical candidates" without clear definitions. Other studies report specific patient related factors as indications for cholecystostomy tube placement. In 2017, Hanks et al. reported in a retrospective analysis of 424 cholecystostomy tube patients that it was at the attending surgeons discretion whether a patient was considered a high risk surgical candidate; review of the data identified five risk factors for cholecystostomy tube placement: cardiac surgery within 3 months of symptom onset, pulmonary infection, end stage liver disease with cirrhosis, new diagnosis of pulmonary embolism, use of systemic anticoagulation, or hemodynamic instability. Other retrospective reviews have reported cholecystostomy tube indications such as stage IV terminal cancer and coronary artery disease.

Acalculous Cholecystitis

Other studies have reported cholecystostomy tube placement in patients with acalculous cholecystitis (Table). Acalculous cholecystitis primarily occurs in patients who are critically ill who cannot tolerate surgical intervention. Given the lack of cholelithiasis, this is not considered an obstructive process. One of the larger retrospective studies on acalculous cholecystitis found lower morbidity in the cholecystostomy tube group compared with the cholecystectomy group but mortality was similar. Mortality rates in those with acalculous cholecystitis and percutaneous cholecystostomy tubes remain relatively high according to the data, 30-day and in-hospital mortality ranges from 9% to 21%. Even though these data propose cholecystostomy tubes as definitive treatment for those with acalculous cholecystitis who cannot tolerate cholecystectomy, one-third of patients eventually undergoes definitive treatment with a cholecystectomy (Table).

Underlying Malignancy Precluding Definitive Surgery

A small subset of patients develop acalculous cholecystitis from an obstructive process secondary to underlying malignancy, as in the

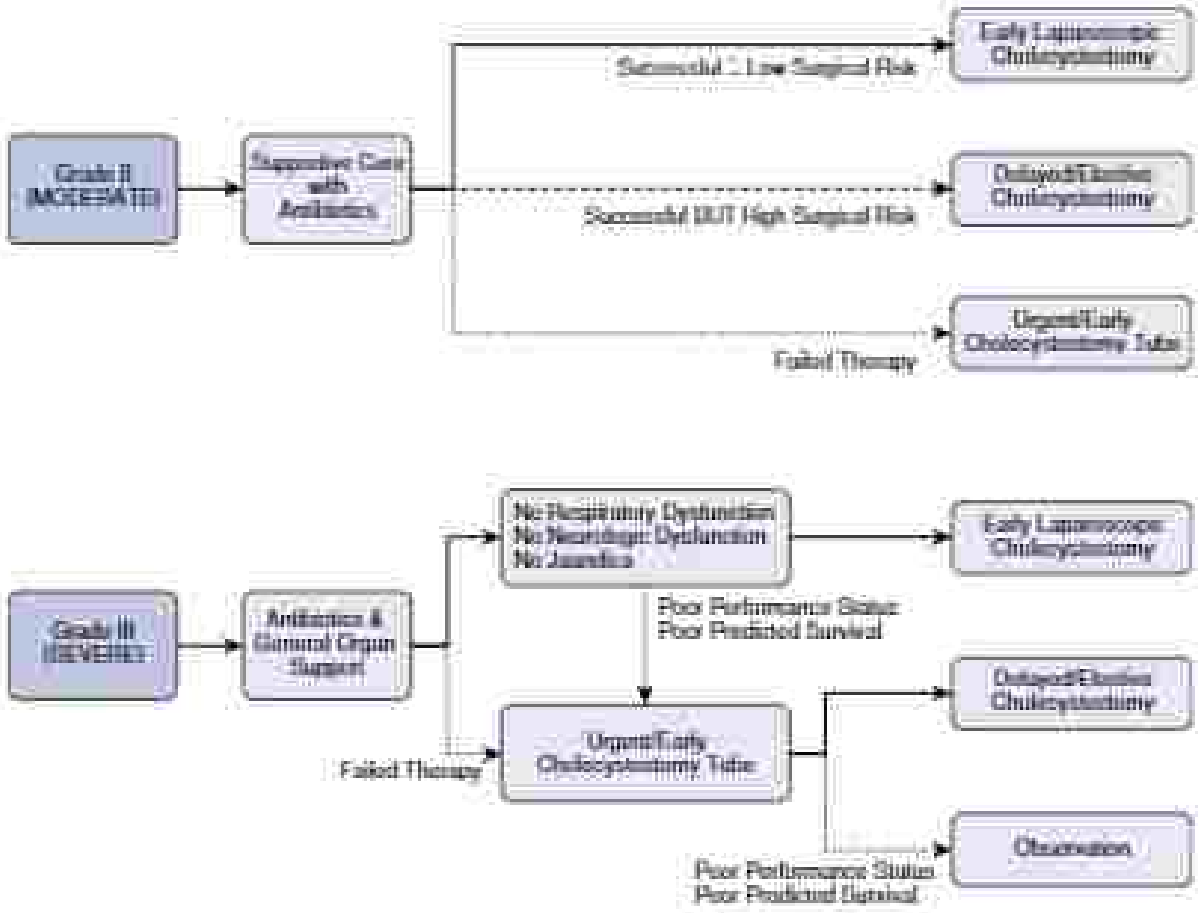

FIG. 2 Tokyo Guidelines 2018 algorithm for the management of patients with acute calculous cholecystitis. Cholecystostomy tube is now recommended in patients with grade II disease only if they fail antibiotics and supportive care and are not candidates for cholecystectomy based on poor performance status as measured by a Charlson Comorbidity Index >4 or American Society of Anesthesiologists class >3. In grade III disease, cholecystostomy is recommended in patients who (1) do not respond to antibiotics and supportive care, (2) have respiratory and/or neurologic dysfunction, and (3) do not rapidly resolve their cardiovascular and renal dysfunction. After cholecystostomy tube placement, cholecystectomy is recommended unless the Charlson Comorbidity Index is >4 and life expectancy is short, in which case patients can be observed. These management protocols assume advanced clinical centers with intensive care unit care, appropriate surgical expertise, and advanced endoscopy. [Adapted from Yokoe M, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci. 2012;19(6):578–585.]

TABLE 2 Studies Reporting Various Indications for Cholecystostomy Tube Placement

Study	Sample Size	Study Design	Reported Indications
Joseph (2018)	962	Retrospective	Patient's general condition, comorbidities, and fitness for anesthesia, rather than the grading and acute disease process itself
Kim (2018)	114	Retrospective	No specific indications except for decision for tube placement was a "multidisciplinary manner"
Rankin (2017)	286	Retrospective	Cardiac surgery within 3 months of symptom onset Pulmonary infection End stage liver disease New diagnosis of pulmonary embolism Use of systemic anticoagulation Hemodynamic instability
Pang (2016)	71	Retrospective	Declined surgery Severe sepsis/shock Gallbladder perforation Multiple comorbidities
Wang (2016)	229	Retrospective	Patient preference Failure to respond to initial medical management Impending rupture of severely distended gallbladder Severe sepsis/septic shock

Continued

TABLE 2 Studies Reporting Various Indications for Cholecystostomy Tube Placement—cont'd

Study	Sample Size	Study Design	Reported Indications
Ruda (2015)	257	Retrospective	Physician discretion and either the presence of comorbid conditions and/or lack of clinical improvement with antibiotic therapy alone
Daun (2015)	278	Retrospective	High burden of comorbidity Prolonged symptom duration reported as >5 days
Khasawneh (2015)	295	Retrospective	Calculous cholecystitis Acalculous cholecystitis Sepsis likely from a biliary source
Cha (2014)	82	Retrospective	Patient comorbidities
Chang (2014)	68	Retrospective	Failure to respond to initial medical treatment in patients with high perioperative risk Impending rupture of a severely distended gallbladder that may cause clinical deterioration Suspected gallbladder necrosis or perforation in patients with severe comorbidities and no other treatments available
Hsieh (2013)	166	Retrospective	Septic shock/severe sepsis Gallbladder rupture Failed conservative treatment after 48 hr
Yeung (2012)	186	Retrospective	Poor surgical candidates
McKay (2012)	68	Retrospective	Surgeon discretion
Kortram (2011)	27	Retrospective	A component of one or more of the following: Age • ASA • APACHE Comorbidity
Nassar (2011)	62	Retrospective	ASA grade III/IV Significant sepsis resulting in hemodynamic instability Patients deemed moderate or high risk for general anesthesia
Saeed (2010)	43	Observational case series	Calculous cholecystitis Acalculous cholecystitis Gallbladder perforation and/or empyema
Parra (2006)	54	Prospective	Poor surgical candidate secondary to comorbidities and/or symptoms >72 hr
Bateman (2005)	118	Retrospective	Medical comorbidity including terminal cancer, uncontrolled hypertension and diabetes, CAD, HTN, CHF, ARF
Byrne (2004)	116	Retrospective	Medical comorbidities including cardiovascular disease and malignancy
Hatzidakis (2002)	63	Prospective	Randomized to cholecystostomy tube group, but patients were referred to surgical team for possible tube placement
Spira (2002)	76	Retrospective	Biliary sepsis Septic shock Severe comorbidities
Barbor (2000)	17	Retrospective	High risk for general anesthesia secondary to comorbidities and/or chronic illness Inflammation too severe during attempted laparoscopic cholecystectomy

APACHE, Acute Physiology and Chronic Health Evaluation II; ARF, acute renal failure; ASA, American Society of Anesthesiologists; CAD, coronary artery disease; CHF, congestive heart failure; HTN, hypertension.

case of pancreatic cancer and cholangiocarcinoma. In this population, the malignancy itself can obstruct the cystic duct leading to cholecystitis or the intervention such as stenting of the bile duct to relieve a common bile duct obstruction can occlude the cystic duct. In both cases, the underlying malignancy may preclude a safe cholecystectomy and, in our opinion, a cholecystostomy tube is indicated. Multiple case reports and one retrospective study have shown that the use of a cholecystostomy tube in these instances decompresses the gallbladder and allows patients to recover and potentially proceed to treatment of their malignancy. In the case of resectable disease, the gallbladder can be addressed at the time of definitive therapy. In these cases, close tube management in a multidisciplinary team effort as patients will not be able to undergo definitive interval cholecystectomy.

TABLE 3 Studies Primarily Reporting Outcomes in Patients With AAC Who Undergo PC Placement

Study	Total AC (N)	Study Design	Outcomes
Hara (2015)	278	Retrospective	30 day mortality was 4.7%–54.7% of patients were definitively treated with PC with a follow up of 5 yr. 23.0% of patients were readmitted for recurrent cholecystitis; 29% underwent an LC at some point in the study period.
Kirkegard (2015)	56	Observational	30 day mortality was 16.7% with 80.4% being definitively treated with PC; 9% underwent LC at some point in the study period.
Anderson (2014)	8329	Retrospective	Decreased mortality in patients undergoing cholecystostomy vs PC (hazard ratio, 0.78; $P < .001$).
Simone (2013)	704	Retrospective	Compared with LC and OC, those who underwent PC had decreased LOS, mortality, ICU stay, and cost. No difference in mortality.
Chang (2012)	57	Retrospective	In-hospital mortality was 23% and 0% were managed nonoperatively; 19% underwent cholecystectomy; 2% had recurrent cholecystitis.

AAC, acalculous cholecystitis; ICU, intensive care unit; LC, laparoscopic cholecystectomy; PC, percutaneous cholecystostomy; OC, open cholecystectomy.

TABLE 4 Tube-Related Complications, Readmission, and Cholecystectomy Rates Associated With Cholecystostomy Tube Placement

Study	Total (N)	Tube-Related Complications (%)	Readmission Rates (%)	Recurrent Cholecystitis (%)	Cholecystectomy (%)
Kim (2017)	144	21.4	NR	9.2	22.9
Papis (2017)	39	8	15.4	15.4	30.7
Bruhin (2016)	380	9[a]	5.7	NR	32.9
Pang (2016)	71	28	NR	NR	45
Wang (2016)	279	NR	NR	9.2	33
Rafa (2015)	257	31	15	NR	63.8
Jang (2015)	93	3.2	NR	16.3	33
Khasawneh (2015)	245	NR	NR	NR	83
Cha (2014)	82	NR	0	0	14.8
Chang (2014)	60	5.8	NR	11.7	5
Al-Issaiti (2013)	30	0	NR	NR	36.7
Horn (2014)	238	35.3	23.5	23.5	28.4
Habib (2013)	166	16.9	NR	15.8	32.9
Joseph (2012)	106	5	NR	NR	37
McKay (2012)	60	18.7	0	0	30
Kortram (2011)	37	5.7	NR	18.7	16
Nasim (2011)	62	1.6	NR	9.5	37
Sarwal (2010)	41	22	NR	NR	22
Winstanley (2010)	86	21	NR	NR	14.6
Pairan (2006)	54	33	19[a]	NR	51.8
Bassetti (2009)	18	5.6	NR	NR	42.8
Byrne (2005)	65	2	NR	NR	37.8
Hatanaka (2003)	63	5	NR	NR	25
Spira (2003)	55	14	19.2	18.7	54.4
Barber (2000)	15	13	NR	NR	80[a]

[a]Percent of patients who had PC and never underwent surgery because showed mild.
[b]Unknown discrimination.
NR, not reported.

TECHNIQUE OF CHOLECYSTOSTOMY TUBE PLACEMENT

In 2018, the majority of cholecystostomy tubes are placed via a percutaneous approach. However, these tubes can also be surgically placed via an open or laparoscopic approach. Success rates of tube placement exceed 90% in most studies. Percutaneous cholecystostomy is most often performed by interventional radiologists in tertiary centers but can be done by a trained surgeon or physician. After localization by computed tomography (CT)/ultrasound (Figs. 1 and 4), the gallbladder is accessed percutaneously with radiologic guidance via either a transhepatic or transperitoneal approach. Traditionally, the transhepatic approach is preferred especially if it is possible to go through the liver area of a gallbladder to prevent the possibility of peritoneal spillage. This approach prevents bile leakage, especially in the setting of severe cholecystitis and a potentially necrotic gallbladder wall. In practice, however, there is the possibility of hepatic abscess and transient bacteremia with the transhepatic approach due to the direct connection with hepatic sinusoids. The transperitoneal approach is an alternative method which works best when the gallbladder wall is extremely inflamed and thickened because it is more likely to stick, and also more likely to contain a cutting wire without rupturing.

A long, hollow Yueh sheathed needle is placed to access the gallbladder through the liver and bile is aspirated (Fig. 3C, D). In many cases, the cystic duct is obstructed and this fluid will be clear secondary to the resolution hydrops. Once the gallbladder is accessed, a wire (short 35 cm Amplatz or Rosen curved tip wire) is placed into the gallbladder through the needle (Fig. 3C–D). A dilator is placed over the wire and an 8Fr pigtail catheter is then advanced and coiled in the gallbladder lumen (Fig. 3E and Fig. 4E, F). At the end of the procedure a CT and/or ultrasound are used to confirm the position (Fig. 4D, F). The drain is secured to the skin by a suture or proprietary adhesive device.

A cholecystostomy tube can also be placed surgically via a laparoscopic or open approach. This option should be kept in mind when the surgeon operates with the intent of performing cholecystectomy but finds inflammation so severe he or she feels dissection is unsafe for the patient to undertake and thus is aborted. In either approach, the gallbladder is directly visualized by the surgeon and the tube is can be placed under direct vision through a small cholecholecystostomy or transhepatically using the Seldinger technique. If placed directly into the gallbladder, the drain can be secured to the gallbladder wall to prevent bile leakage around the tube or slippage of the tube. If the gallbladder wall is necrotic, a frustrating partial cholecystectomy, removal of stones, and wide drainage may be a better option if cholecystectomy is not feasible.

Complications of Cholecystostomy Tube Placement

Although cholecystostomy tube placement is often not difficult and can avoid operation in poor surgical candidates, both immediate and long-term complications can occur. Immediate complications from cholecystostomy placement include failure of resolution/progression of acute cholecystitis, biliary peritonitis, sepsis, and tube dislodgement. Data on complications are largely derived from small, single institution retrospective studies. Although actual placement of the cholecystostomy tubes is 98% to 100% in most studies, some patients will not resolve their cholecystitis after placement of a cholecystostomy tube as measured by ongoing sepsis, leukocytosis, and/or right upper quadrant (RUQ) pain. In a study by Joseph et al., 32% of critically ill patients who had a cholecystostomy tube placed did not improve or declined clinically after cholecystostomy tube placement. Cha and colleagues reported a technical success rate was 100% in 82 patients undergoing cholecystostomy tube placement, with a clinical success rate of 98%, with one patient dying of cholecystitis-related complications. Across studies, 5% to 63% of patients underwent subsequent cholecystectomy; the timing of cholecystectomy is not clearly described, but most are delayed cholecystectomy for definitive management and not for failure to resolve immediate symptoms.

Overall complications specifically related to cholecystostomy tube placement ranged from 0% to 33% across studies and are primarily related to bleeding, or bile leakage/tube dislodgement. To prevent bleeding, especially in a transhepatic approach, the surgeon and/or interventional radiologist should ensure that any coagulopathy is corrected before tube placement. Bile leakage can occur if the tube is dislodged or the gallbladder wall is necrotic and the bile leaks around the tube itself. This can lead to sepsis, diffuse biliary peritonitis, or a biloma/abscess in the RUQ if the leakage is contained and

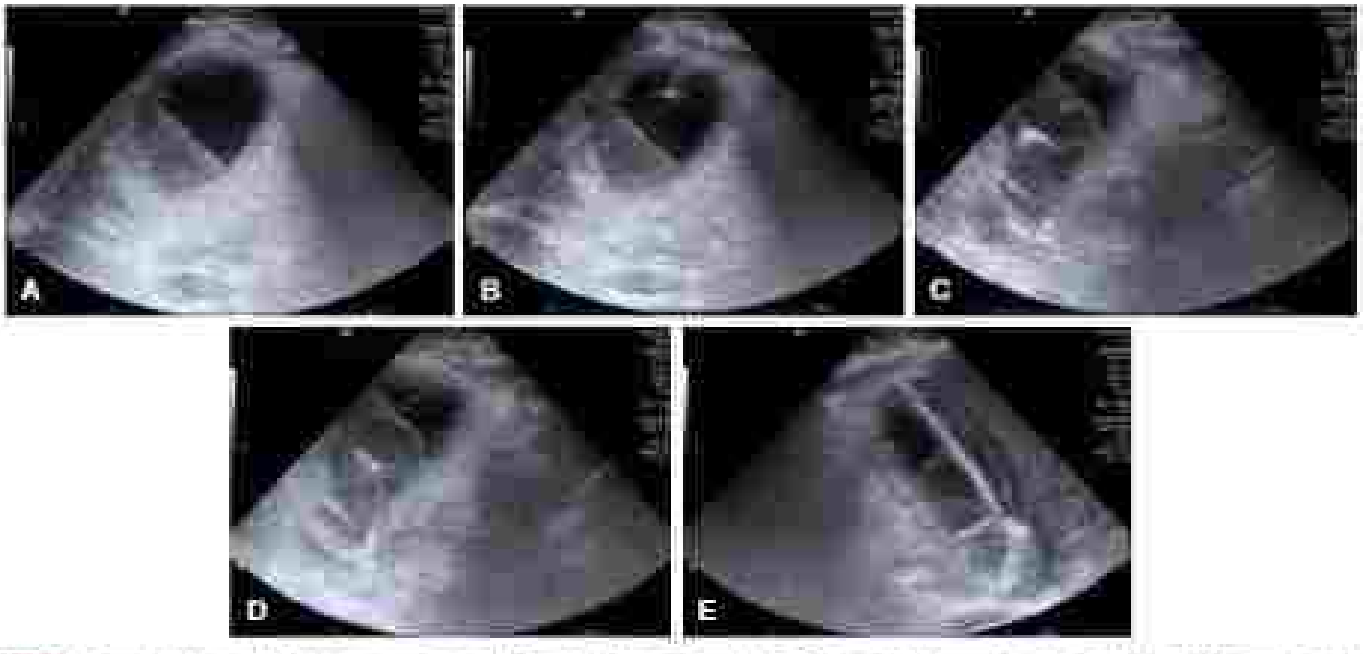

FIG. 3 Ultrasound placement of cholecystostomy tube. (A) Gallbladder is visualized. (B, C) Gallbladder is accessed with a thin needle. (D, E) Pigtail catheter is placed into the gallbladder lumen.

localized. This should be suspected when leukocytosis worsens or does not improve after tube placement or signs and symptoms initially improve and the patient subsequently develops sepsis, hemodynamic instability, fever, worsening leukocytosis, or worsening RUQ or abdominal pain.

In the long term, both readmission to the hospital and recurrence of acute cholecystitis are common after cholecystostomy tube placement if delayed definitive therapy with cholecystectomy is not performed. There is significant cost associated with frequent hospital visits, radiologic interventions, and overall increased hospital days, stressing the importance of definitive cholecystectomy when at all possible. Recurrence of acute cholecystitis after cholecystostomy tube placement ranges from 9% to 41% in small series and readmissions occur up to 41% of the time in some studies. Readmissions are most commonly related to inadvertent tube dislodgement or removal, tube occlusion, recurrent cholecystitis, or catheter site related pain.

In a study of long term outcomes in Medicare beneficiaries with grade III cholecystitis, 30-day, 90-day, and 1-year survival was significantly lower in patients who underwent cholecystostomy tube placement compared to propensity matched controls. Specifically, 1-year survival was 39% versus 61% in those with a tube compared to those without, respectively.

Long-Term Management of Cholecystostomy Tubes

Cholecystostomy Tube removal

The management of cholecystostomy tubes after initial treatment remains controversial. There are no published guidelines regarding tube management; however, the TG2018 clearly recommend delayed cholecystectomy after tube placement, regardless of initial grade of the cholecystitis. In the literature, several authors propose different algorithms for the management of cholecystostomy tubes, many of which involve cholangiography to assess the patency of the cystic duct and biliary tree. The duration of recommended tube drainage, the need for definitive cholecystectomy, the timing of tube removal, and the timing of cholecystectomy if performed remain topics of debate. The reported median length of time that the tube remained varies widely in the literature and depends on whether definitive cholecystectomy was performed. Times ranged up to 70 days if patients did not undergo definitive treatment with a cholecystectomy compared with only 10 days in those who eventually underwent cholecystectomy. Most studies recommend drainage for 3 to 6 weeks because this allows a tract to develop. Others recommend earlier removal and early definitive cholecystectomy, whereas others recommend a longer period of tube drainage in patients with uncontrolled diabetes, persistent infection, malnutrition, and those on steroids. Such conditions may hinder the healing process and tube drainage is recommended for a longer period.

In a study by Cha and colleagues, patients underwent a cholangiogram through the cholecystostomy tube to evaluate for patency of the cystic duct and biliary tract once their symptoms and clinical status improved. This was done during the index hospitalization. If patency was demonstrated via contrast emptying into the duodenum, the catheter was clamped. If, after clamping, patients developed recurrent cholecystitis, worsening laboratory values, or worsening symptoms the catheter placed back to external drainage for 7 days at which time patients were reassessed. If the patient tolerated clamping and had continued clinical improvement, the cholecystostomy tube was removed during the initial admission. If the cystic duct was not patent, patients were discharged with the cholecystostomy tube and draining externally.

Zamir and colleagues reviewed outcomes of 119 patients who underwent cholecystostomy tube placement for acute cholecystitis. In their study, all patients who underwent tube placement were discharged with the tube in place and draining externally. Follow-up cholangiogram 2 to 3 weeks later, if the duct was patent and the patient was deemed an appropriate surgical candidate the tube was clamped, left in place, and the patient subsequently underwent

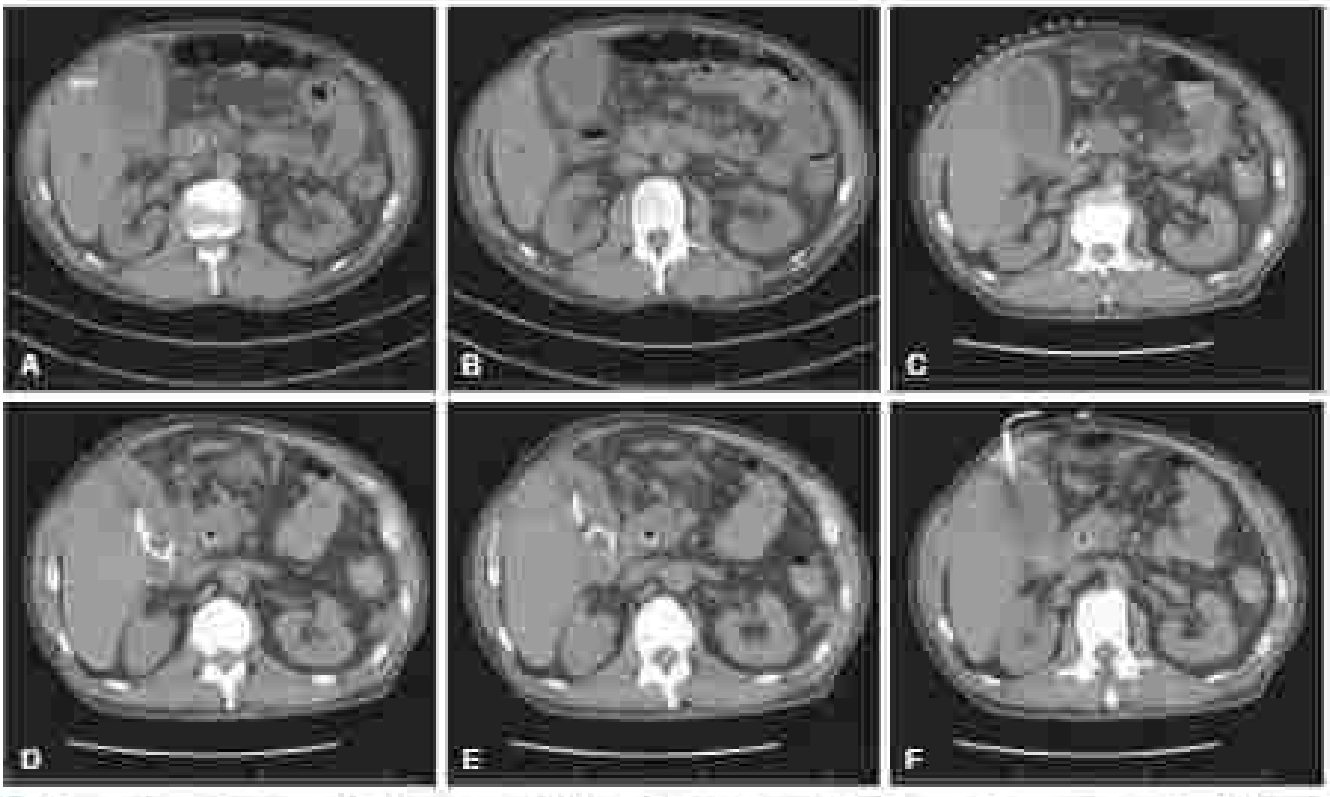

FIG. 4 Computed tomography placement of cholecystostomy tube. (*A–E*) Gallbladder is decompressed. (*C*) Computed tomography markers placed on abdominal skin on right upper quadrant to help with guidance. (*D–F*) Infiltration of pigtail catheter placement in gallbladder lumen.

cholecystectomy. In patients who were not deemed to be had biliary tract patency, the tube was removed.

Ultimately, tube removal is dependent upon resolution of the patient's symptoms, the presence or absence of cystic duct obstruction, and whether the patient is a candidate for cholecystectomy. This is done through evaluation of laboratory values, abdominal examination, and patient's report of resolved abdominal pain. In our opinion, if the patient's acute cholecystitis has resolved and he or she is a candidate for cholecystectomy, tube evaluation is not necessary. Cholecystectomy should be scheduled as soon as possible and the tube should be left in situ and draining externally until surgery is performed. This can be done laparoscopically or open, though conversion rates in this setting are higher than normal should not be unexpected. If the patient's clinical status improves and he or she is not a candidate for cholecystectomy, the patient should undergo a tube cholangiogram. Specifically, there must be patency of the patient's cystic duct or tube removal should not be considered as the likelihood of recurrent episodes of cholecystitis is extremely high. The timeline in which a cholangiogram is done in these patients varies in the literature, but we recommend 3 to 4 weeks to allow for a good track to form before tube removal. If cholangiogram demonstrates a patent cystic duct, the next step is clamping of the cholecystostomy tube, with removal in the absence of recurring symptoms after clamping.

Of note, the criterion of cystic duct patency does not necessarily apply to those with acalculous cholecystitis as the pathophysiology is different, but patients should at least undergo clamping trials before removal to reduce the risk of patient's having recurrent symptoms after tube removal and requiring an additional procedure.

Definitive Treatment With Cholecystectomy

Cholecystectomy remains the only definitive treatment for patients with acute cholecystitis. In patients who undergo cholecystostomy tube placement, the TG18 recommend delayed interval cholecystectomy after tube placement (Figs. 1 and 2), except for patients with initial grade III disease, poor performance status, and limited predicted life expectancy. These recommendations apply to those with calculous cholecystitis, but other reports on patients with acalculous cholecystitis agree that cholecystectomy may not be necessary. The recurrence of acute cholecystitis in those who do not undergo definitive therapy ranges from 11% to 41%; therefore, definitive therapy should be sought after if the patient's clinical status allows.

Despite the Tokyo guidelines and recommendation for cholecystectomy, cholecystectomy rates vary widely, with 15% to 80% of patients undergoing cholecystectomy after cholecystostomy tube placement across small retrospective series. Ideally, cholecystectomy should be done in the elective setting after the patient's clinical status has improved. Cholecystectomy may be required more urgently if cholecystostomy tube placement fails to control local inflammation and systemic sepsis or recurs acutely. Data published in Medicare beneficiaries undergoing cholecystostomy tube placement for grade III cholecystitis demonstrate that only one third of these patients undergo definitive treatment with a delayed cholecystectomy.

PROPOSED ALGORITHM FOR CHOLECYSTOSTOMY TUBE PLACEMENT AND MANAGEMENT

The proper use of cholecystostomy tubes includes temporary treatment for patients with cholecystitis, calculous or acalculous, who cannot tolerate surgery according to the TG18 guidelines. The severity of cholecystitis or the duration of symptoms are not absolute contraindications for cholecystectomy and do not mandate cholecystostomy tube placement. Potential reasons for a patient's inability to tolerate surgery includes severe systemic disease including cardiovascular disease, underlying malignancy, and any condition that precludes general anesthesia.

The TG18 algorithm for management of patients with acute cholecystitis is shown in Fig. 2. Initial evaluation should include assessment of patients' clinical status and severity of their gallbladder disease. If patients are hemodynamically stable and able to tolerate a general anesthetic, cholecystectomy should be performed as soon as possible during the index admission regardless of the Tokyo grade. Cholecystostomy tubes should be reserved for patients who do not rapidly respond to antibiotics and supportive care and are not candidates for cholecystectomy due to underlying comorbidity and/or physiologic decompensation resulting from acute illness. In cases of grade III disease, if a patient improves with antibiotics and organ support, reevaluation should be undertaken during his or her index hospitalization for possible cholecystectomy. If not performed on the index admission, then delayed or elective cholecystectomy should be done should on patients who have a life expectancy of greater than a year as recurrence rates are high. Incorporating models that predict patient survival into the treatment algorithms for patients with grade II and III cholecystitis may help guide decision making. Regardless, as with all interventions, there are risks and benefits, therefore, physicians must consider the risks and benefits of this intervention and its long-term consequences.

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Management of Common Bile Duct Stones

Cecilia T. Ong, MD, and Theodore N. Pappas, MD, FACS

Choledocholithiasis refers to the presence of gallstones in the common bile duct. If choledocholithiasis is suspected preoperatively, it is usually managed via endoscopic retrograde cholangiopancreatography (ERCP) to prevent complications such as cholangitis, obstructive jaundice, and pancreatitis. Because common duct stones can often go unrecognized before surgery however, it is imperative for surgeons, especially those who routinely perform laparoscopic cholecystectomy, to know the surgical approaches to cholangiography and common bile duct exploration for stone extraction.

EPIDEMIOLOGY AND PRESENTATION

Most cases of choledocholithiasis are clinically asymptomatic and thus, the true incidence of disease is unknown. Choledocholithiasis may be identified in 10% of cholangiograms routinely performed at the time of cholecystectomy. Retained stones are also discovered following 1% to 2% of cholecystectomies despite normal preoperative liver function tests. When not clinically silent, common duct stones may present as right upper quadrant pain that is more prolonged than typical episodes of biliary colic; as symptoms of obstructive jaundice such as dark urine, acholic stools, or as ascending cholangitis. Charcot's triad, the constellation of fever, right upper quadrant pain, and jaundice, is considered pathognomonic for cholangitis; however, the full triad is only present in approximately 15% to 20% of patients with the condition. Progression to hypotension and mental status changes which comprise Reynold's pentad indicates shock from a biliary source and requires emergent biliary decompression.

Pathophysiology

Common duct stones are classified by their point of origin. Primary stones arise in the bile duct and comprise a precipitate of bile pigments and cholesterol. These so called brown pigment stones are more common in Asian populations and are associated with bacterial infection of the bile duct and/or biliary stasis. Secondary stones travel from the gallbladder and lodge in the common bile duct and are the major etiology of calculous biliary disease in the United States.

Diagnosis

Patients with symptomatic cholelithiasis routinely undergo liver function tests and transabdominal ultrasonography; these can suggest the potential for choledocholithiasis or other variants of biliary disease. Elevated liver function tests and common bile duct dilation warrant further evaluation for choledocholithiasis.

Abnormalities in the hepatic function panel indicating a cholestatic picture include elevated total bilirubin, alkaline phosphatase, and amylase. Though these are commonly present in choledocholithiasis and can help differentiate this condition from uncomplicated gallstone disease, functional gallbladder disorders, or acute cholecystitis, such enzymatic derangements are neither sensitive nor specific for choledocholithiasis.

Ultrasound is the initial imaging study of choice for a diverse array of suspected biliary issues due to its noninvasive nature and low cost. It may demonstrate the presence of common duct stones. In the absence of visualized stones, though, biliary ductal dilation (>6–8 mm) in the setting of right upper quadrant pain, gallstones, and/or jaundice is highly suggestive of choledocholithiasis. Transabdominal ultrasound has poor sensitivity for stones in the distal common bile duct as views can be obscured by overlying bowel gas. Findings on ultrasound can assist in the decision to pursue further imaging or management of suspected choledocholithiasis.

ERCP offers an opportunity for diagnosis and management of common duct stones. It is a highly sensitive and specific method of diagnosis and, when paired with sphincterotomy or balloon dilation and stone extraction, is an effective method of treatment for choledocholithiasis. ERCP is currently used in more than 90% of cases of common duct stones and can provide therapeutic clearance of stones in 75% of patients at the first procedure, and in 90% if a repeat procedure is required. This modality is preferred for patients with high risk or suspicion of choledocholithiasis, ascending cholangitis, biliary pancreatitis, limited surgeon/center experience, and patients with multiple medical comorbidities and/or contraindications to surgery. ERCP can also be pursued postoperatively when incidentally discovered choledocholithiasis cannot be managed by common duct exploration or for retained stones. ERCP can fail, however, when stones are large, intrahepatic, multiple, or impacted, or if there is altered gastric or duodenal anatomy or duodenal diverticula. Failure of ERCP necessitates operative intervention. Furthermore, as it is an invasive procedure, ERCP is not without complications including pancreatitis, bleeding, and perforation.

Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) are both highly sensitive and specific methods of imaging the biliary tree which have replaced ERCP as the diagnostic modalities of choice in patients at intermediate risk for choledocholithiasis. When EUS demonstrates stone disease, the endoscopist can proceed immediately to therapeutic ERCP. When the EUS is negative, the potential risks of post-ERCP complications, including pancreatitis, can be avoided. MRCP is an attractive noninvasive option but has the potential to miss biliary sludge and stones smaller than 4 mm.

Percutaneous transhepatic cholangiogram similarly offers a route of diagnosis and management of choledocholithiasis. It has similar complication rates to ERCP and is most effective in patients with a dilated biliary system.

General Considerations in the Management of Choledocholithiasis

If choledocholithiasis is determined preoperatively, postoperatively, or in patients with symptoms of cholangitis, every attempt should be made for endoscopic sphincterotomy and stone extraction. Successful ERCP with stone extraction does not eliminate the risk of recurrent biliary stone disease, however, and 30% will have recurrence of symptoms after successful ERCP. Thus, in good surgical candidates, interval cholecystectomy with intraoperative cholangiogram is generally recommended following ERCP duct clearance.

Patients who failed endoscopic therapy or who are determined to have choledocholithiasis intraoperatively can receive intraoperative ERCP, intraoperative common bile duct exploration (discussed later), or postoperative ERCP. The choice between these approaches largely depends on equipment availability and surgeon comfort with intraoperative exploration.

Patients at intermediate risk for choledocholithiasis, such as those with dilated common bile duct without visualized stone or clinical gallstone pancreatitis, can undergo EUS- or MRCP or can proceed to laparoscopic cholecystectomy with intraoperative cholangiogram.

Endoscopic Common Bile Duct Clearance

The endoscopic methods for bile duct clearance include sphincterotomy, balloon dilation of the ampulla, and basket or balloon extraction techniques. Sphincterotomy involves severing the deep muscle layers of the sphincter of Oddi with electrocautery to relieve the anatomic barrier to stone passage and to facilitate stone extraction.

sphincterotomy is the procedure of choice for patients with dilated common bile ducts. A sphincterotomy of adequate length to completely unroof the papilla decreases the risk of papillary stenosis. Balloon dilation can be used if the patient has contraindications to sphincterotomy such as anticoagulant or antiplatelet use. It can also aid in the removal of large stones if the sphincterotomy cannot be extended; however, it does increase the risk of post-ERCP pancreatitis relative to sphincterotomy.

Following sphincterotomy or balloon dilation, stones smaller than 1 cm can pass spontaneously. Larger stones can be extracted using balloon or basket retrieval devices. Basket devices are helpful with a dilated duct or when multiple stones are present. The successful extraction of multiple or large stones can be improved with mechanical lithotripsy. Balloons, commonly can be used in normal-sized ducts or single-free floating stones.

Short-term complications of ERCP with sphincterotomy include pancreatitis, perforation of the duodenum or bile duct, bleeding, and infection and occur in fewer than 10% of patients. Long-term, stone recurrence is the most commonly cited complication, hence the recommendation for cholecystectomy in appropriate surgical candidates. Surgery is recommended within 2 weeks after the endoscopic clearance to decrease the risk of recurrent biliary events and conversion to open cholecystectomy. Other long-term but infrequent complications of sphincterotomy include papillary stenosis and cholangitis.

Young patients or those at a high risk of bleeding have an increased risk of developing such long-term complications. They are thus candidates for endoscopic methods that do not require sphincterotomy such as balloon dilation of the ampulla with stone extraction.

Intraoperative Cholangiography

Intraoperative cholangiography (IOC) should be performed before any attempt at laparoscopic common bile duct exploration. The equipment and setup required for IOC can include a 0.035-inch guidewire, 30- or 50-cc biliary Fogarty's catheters, wire baskets, balloons (8-mm outer diameter) or mechanical (7Fr–12Fr) dilators, 3- to 5-mm choledochoscope with 1.1 mm or larger working channel, loop ligatures, and T tubes. Additional cholangioscopic equipment and support includes a separate light source, an adapter to allow simultaneous irrigation via the biopsy channel, a second camera and monitor, picture-in-picture display with video switcher, C-arm, and fluoroscopy support. The C-arm is brought in from the patient's left side and its position should be taken into account when positioning video monitors, the operating surgeon, and the assistant.

To perform laparoscopic IOC, the critical view of safety is obtained as in a standard laparoscopic cholecystectomy. An additional 5-mm port can be placed in the right midclavicular line to facilitate access to the cystic duct. The gallbladder is left in situ to provide liver retraction and countertraction on the cystic duct. The critical view is obtained, and before opening the cystic duct, a clip is applied across the cystic duct–infundibulum junction above the site of the planned ductotomy. This prevents contrast passage into the gallbladder and further translocation of stones. A transverse ductotomy is created, and the contents of the duct are milked toward the incision. A 14-gauge transhepatic angiocatheter is placed in the right upper quadrant, through which a 4Fr–5Fr cholangiogram catheter with a reinforced tip is introduced. The cholangiogram catheter is guided laparoscopically into the cystic duct and secured using clips, cholangiogram clamps, or other devices. Water-soluble contrast is injected and fluoroscopy is used to evaluate the biliary anatomy including the junction of the cystic and common bile ducts and the size of the common duct, and filling defects impeding contrast flow into the duodenum or into the liver (Fig. 1).

If routine contrast administration does not adequately visualize the proximal or distal ductal system, pharmacological adjuncts can be employed. Visualizing the proximal bile ducts including the intrahepatic system can be aided by intravenous morphine to contract the sphincter of Oddi, directly occluding the distal bile duct, or repositioning the patient in Trendelenburg. To visualize the distal duct and confirm contrast passage into the duodenum, intravenous glucagon can be used to relax the sphincter of Oddi. Dilated ducts, filling defects, or failure of contrast flow into the duodenum can suggest the presence and position of choledocholithiasis. The successful and accurate completion of cholangiography is highly operator dependent and may be unfeasible in patients with a severely inflamed gallbladder or a small or inflamed cystic duct.

Laparoscopic Common Bile Duct Exploration

Despite the widespread adoption and performance of laparoscopic cholecystectomy, surgeon experience with laparoscopic common bile duct exploration is much more infrequent. However, for surgeons comfortable with the approach, it offers an attractive option to manage biliary stone impaction and prevent future recurrence of choledocholithiasis in one procedure. Access to the common duct is achieved through either the transcystic approach or directly through a choledochotomy.

Transcystic Approach

A transcystic approach is generally performed in patients with stones smaller than 1 cm, common duct diameter less than 8 mm, stone location distal to the junction of the cystic and common duct, and cystic duct diameter larger than 4 mm. It is contraindicated if the stones are in the common hepatic duct, numerous (>8), or large (>1 cm), or if the patient has a small friable cystic duct not amenable to instrumentation.

Following cholangiography, the duct is cannulated with a wire. The ductotomy already made for the cholangiogram can be used, or an incision closer to the junction with the common bile duct in a less tortuous segment of the duct can be made. If the patient has a narrow cystic duct, a flexible dilator or balloon catheter is passed over the wire via the Seldinger technique to dilate the duct (Fig. 2).

The initial maneuver to clear the duct is to flush the distal common bile duct with saline. Flushing of the proximal duct should be avoided; if stones are pushed into an intrahepatic location, they may be irretrievable. If the stone cannot be flushed through the duct, a balloon catheter is the next step in stone retrieval. A 3Fr–5Fr Fogarty balloon catheter is advanced through the ductotomy into the duodenum. Positioning of the catheter in the duodenum is confirmed

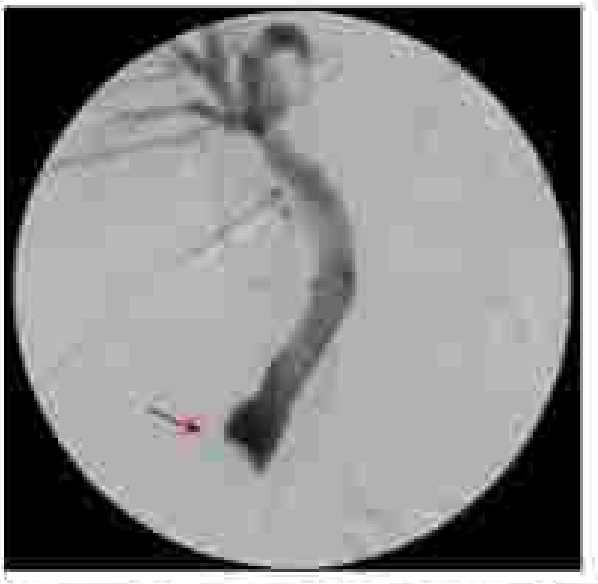

FIG. 1 Intraoperative cholangiogram shows obstruction of biliary drainage distally with a characteristic meniscus sign (arrow) indicating the presence of an obstructing common bile duct stone.

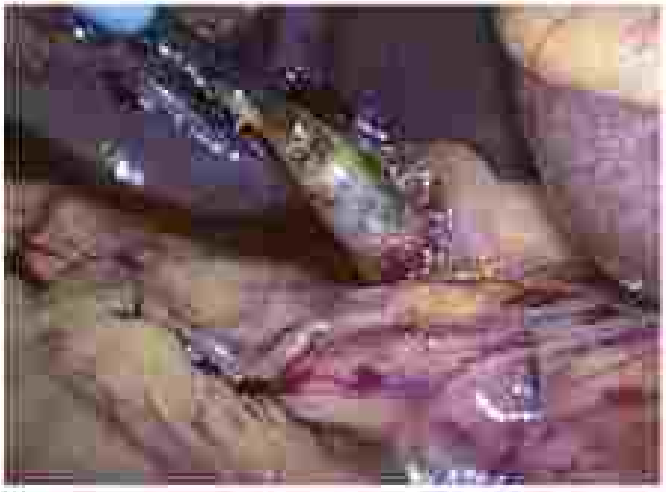

FIG. 2. Transcystic common bile duct exploration and stone extraction can be facilitated by balloon dilation of the duct, as explored here. The balloon catheter is advanced over a guidewire, which has been advanced from the cystic duct into the duodenum.

fluoroscopically then by inflating the balloon and withdrawing the catheter until the resistance of the ampulla is met. The balloon is deflated, withdrawn slightly, and inflated again. These steps are repeated until the stones are pulled retrograde through the ductotomy. Care should be taken to withdraw the catheter superiorly along the axis of the common duct, to increase the tension on the ductotomy. This procedure is generally effective but carries the risk of propagating stones into the common hepatic duct. If balloon catheter retrieval is unsuccessful, wire basket retrieval through a cholangiogram catheter is performed. The choledochoscope aids in visualization of the stone and reduces the trauma to the common bile duct, although it does require dilation of the cystic duct to accommodate the scope. A wire basket is advanced through the working channel of the scope, and once the stones are extracted, the basket is usually withdrawn together with the choledochoscope.

Following stone removal through the transcystic approach, the duct is irrigated again with saline and completion cholangiography performed to ensure duct clearance. The cholecystectomy is completed, paying particular attention to closure of the cystic duct stump to avoid bile leakage. This can be performed by clip or loop ligature; however, the latter is preferred due to the trauma of cystic duct dilation and instrumentation.

Direct Choledochotomy

Laparoscopic direct choledochotomy is indicated in the event of failure of the transcystic approach, in a narrow or tortuous cystic duct, in a dilated common duct (> 10 mm), large (>10 mm) or multiple stones, or stones located proximal to the cystic/common bile duct junction. Compared with the transcystic approach, choledochotomy has equivalent stone clearance rates but longer operative time and hospital length of stay. There are reports of lower postoperative bile leak rates following the transcystic approach, likely resulting from the additional laparoscopic suture applied to the cystic duct stump and lack of direct violation of the common duct wall.

To perform a direct choledochotomy, the gallbladder is again left in situ and the cystic duct is dissected down to the level of the common duct junction. The tissue overlying the anterior common duct is cleared, taking care to avoid excessive dissection which could compromise the peritubular blood supply and impair healing. Two stay sutures are placed on either side of the planned incision. A 1-cm incision into the common bile duct is made below the cystic duct takeoff. The orientation of the ductotomy is dependent on the planned method of closure: if T tube drainage is planned, the incision should be oriented longitudinally, whereas if a primary repair is planned, the incision is best oriented transversely. The stone can be directly extracted if its location is amenable; otherwise, similar techniques including saline flush, balloon, or wire basket capture can be performed as described previously.

At the completion of exploration, the common ductotomy can be closed with monofilament absorbable suture in a continuous or interrupted fashion primarily or around a 12Fr 14Fr T tube. Permanent suture should be avoided as this can promote further stone formation. Historically, routine T-tube drainage was performed after choledochotomy to provide biliary decompression while edema or spasm of the sphincter resolved, and to provide postoperative access to the bile duct for cholangiography or further intervention for retained stones; however, T tubes increase the risk of biliary leak, duct obstruction, and infection. Primary closure has been found to be feasible and safe with equivalent bile leak rates, shorter operative times, and hospital length of stay. The posterior attachments of the common bile duct preclude the mobilization necessary to close a longitudinal ductotomy transversely; thus, transverse closure of a transverse choledochotomy minimizes narrowing of the duct.

Open Common Bile Duct Exploration

Although the frequency of open common bile duct exploration has decreased with the greater utilization of endoscopic and laparoscopic approaches, the open approach is still required when these other measures have failed or are not possible, as in the case of previous gastric bypass, or when biliary drainage is required; thus, surgeons who perform laparoscopic cholecystectomy should be prepared to convert to open common bile duct exploration if needed. Open exploration is indicated in patients who have failed laparoscopic exploration, those with choledocholithiasis who have other indications for open cholecystectomy, and those with severe inflammation of the triangle of Calot that precludes dissection. The critical view of safety required in a laparoscopic approach is often unattainable when the open procedure is required. Thus, the gallbladder is usually dissected in a dome-down fashion to facilitate access to the cystic and common bile ducts.

Choledochotomy

To gain access for an open direct choledochotomy, a midline or right upper quadrant subcostal incision is made. The liver is retracted superiorly using a broad-bladed, curved retractor. The duodenum is retracted inferiorly, and the omentum and stomach to the patient's left to facilitate visualization. A Kocher maneuver is performed to expose the distal common bile duct. Gentle palpation of the duct can localize the stone and milk it back from the ampulla toward the eventual extraction point. After placement of stay sutures, a longitudinal, 1.5-cm choledochotomy in the distal common bile duct is made (Fig. 3). Stones can be milked to the incision and extracted manually, or balloon catheters can be used to clear the proximal then distal duct. Care must be taken to avoid crush injuries to the duct. If a flexible choledochoscope is available, it may be useful in extracting stones that are otherwise difficult to retrieve from the distal common bile duct.

Postclearance cholangiography via an 18Fr T tube is performed before duct closure. The ends are trimmed obliquely so the proximal limb does not obstruct the hepatic ducts and the distal limb terminates before the ampulla. The posterior wall of the T tube is excised to improve its flexibility and aid in eventual removal. The T tube is brought out through the skin of the abdominal wall under the costal margin and secured. Completion cholangiogram through the T tube is performed to confirm proper tube position and to verify there are no residual stones. The T tube can be removed about 2 weeks postoperatively after repeat T-tube cholangiography demonstrates patent distal flow. If a T tube is placed, a closed suction drain should also be placed next to the common duct; it can be removed in the first 2 days after surgery if a cholangiogram demonstrates a patent biliary system without biliary leakage around the T tube.

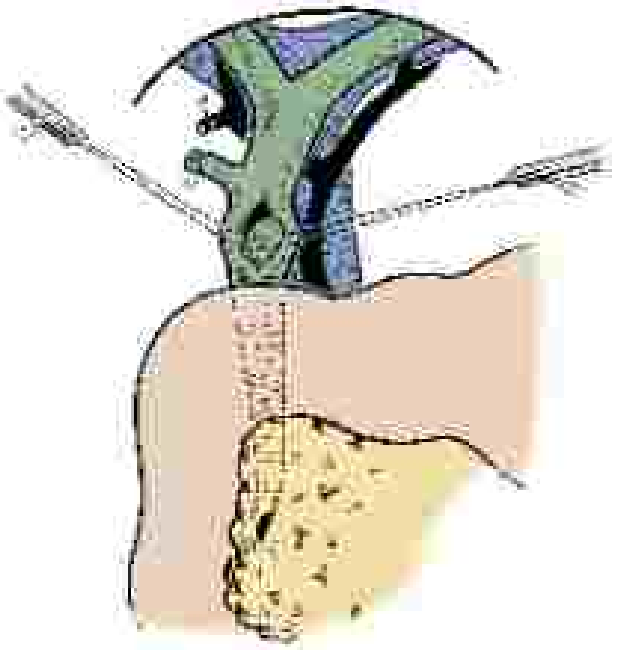

FIG. 3 Stay sutures are applied to either side of the planned choledochotomy to elevate the common bile duct and minimize the risk of injury to the posterior wall of the duct. From Jarnagin WR, Blumgart LH. Surgery of the bile ducts and the liver. In: Blumgart LH, ed. Surgery of the Liver, Biliary Tract and Pancreas. 4th ed. Philadelphia, PA: Elsevier; 2007.

Transduodenal Sphincteroplasty

A transduodenal sphincteroplasty may be necessary to provide drainage for patients with a nondilated biliary tree and stones impacted at the ampulla. This is contraindicated if there is a long supraphincteric stricture or severe periampullary inflammation. This procedure can be performed open or laparoscopically, although the latter should only be attempted by the most skilled laparoscopic surgeons. Lower linear placement than that for routine cholecystectomy suffices placing an additional port in the right lower quadrant can assist in the visualization of the ampullary reconstruction.

After Kocherization of the pancreas and duodenum, a longitudinal incision in the lateral aspect of the second part of the duodenum is made using electrocautery. The longitudinal orientation of the incision, when closed transversely, decreases the likelihood of stricture and potential duodenal obstruction. The papilla is then located and a 4Fr–5Fr flexible catheter, such as a Nélaton probe, is introduced into the ampulla. This provides a guide for the sphincterotomy, which is made using electrocautery to the 11 o'clock position to avoid injury to the pancreatic duct. Fine absorbable sutures are then placed between the duodenal wall and the common bile duct to suture open the sphincteroplasty. The total length of the sphincteroplasty should be approximately 10–12 mm to open the entire length of the common duct of the sphincter of Oddi. Adequate sphincterotomy allows the passage of angled Randall's forceps and stone extraction using these forceps, Fogarty's catheter, or wire baskets. Following successful stone removal, the longitudinal duodenotomy is closed transversely with absorbable sutures such as Vicryl or Maxon.

Biliary-Enteric Drainage

Certain patients should be considered for biliary-enteric drainage such as those with stones not amenable to endoscopic or surgical removal, or to prevent future recurrence of choledocholithiasis. Such procedures are indicated in elderly patients, those at risk for primary stone formation, or those with multiple, large duct stones, dilated ducts, intrahepatic stones, or benign distal bile duct stricture.

Choledochoduodenostomy

Choledochoduodenostomy is the most physiologic reconstruction and allows endoscopic access to the entire biliary tree; however, it may not be possible if the duodenum is inflamed or cannot be completely mobilized. In the laparoscopic approach, trocar placement is similar to that for transduodenal sphincterotomy as is the initial Kocherization and exposure of the distal common duct. A complete circumferential dissection of the duct is required if planning an end-to-side anastomosis. A 1.5 cm longitudinal supraduodenal choledochotomy is made in the anterior wall of the duct. A 1 cm longitudinal duodenotomy is made in the adjacent duodenum and is made shorter as the choledochotomy will stretch. The choledochoduodenostomy is then sewn in a side-to-side fashion with absorbable suture in a single layer, interrupted fashion.

Potential complications include sump syndrome, or emetic reflux into the common duct causing inflammation and recurrent cholangitis. This complication is seen more frequently in diabetic patients with side-to-side anastomoses as the bile duct distal to the anastomosis does not drain well and thus collects debris which could obstruct the anastomosis.

Roux-en-Y Choledochojejunostomy

The Roux-en-Y choledochojejunostomy is the most common surgical reconstruction for biliary obstruction. It provides superior drainage of the biliary tree but does not allow for postoperative endoscopic evaluation of the hepatic duct.

The jejunum is mobilized and divided with a stapler approximately 20 cm distal to the ligament of Treitz to create a 50- to 70-cm Roux limb. Enough mesentery is divided to allow the reach of the limb to the duct with care taken not to devitalize the limb. The Roux limb can be passed retrocolic or antecolic. The anastomosis can be created in an end-to-side or side-to-side fashion. For an end-to-side anastomosis, the bile duct segment is transected, and the stump is sutured with 3-0 absorbable sutures. A jejunotomy is created on the antimesenteric side of the bowel approximately 2 cm from the staple line. The anastomosis is constructed in a single layer with interrupted sutures of 4-0 absorbable sutures. A side-to-side anastomosis has a lower risk of bile duct devascularization. The anterior surface of the duct is exposed and a 2.0 cm ductotomy is created and the anastomosis to the jejunum is made as previously described. Finally, the jejunojejunostomy is created 40 cm distal to the choledochojejunostomy.

Approach to a Patient With Prior Cholecystectomy

Choledocholithiasis can occur following cholecystectomy resulting from a dropped stone at the time of cholecystectomy or to de novo stone formation within the duct. Retained stones are usually found within 2 years of cholecystectomy. Stones found longer than 2 years from cholecystectomy are attributed to primary stone formation. These brown pigment stones are more commonly seen in Asian countries, likely resulting from recurrent pyogenic cholangitis. However, primary choledocholithiasis can also occur in conditions associated with biliary stasis such as strictures, cysts, fibrosis, periampullary diverticuli, parasitic infections, choledochal cysts, or sclerosing cholangitis.

Transabdominal ultrasound is less helpful in diagnosing choledocholithiasis following cholecystectomy as postcholecystectomy patients can have physiologic dilatation of the duct up to 10 mm. In such patients, EUS or MRCP can confirm the presence of stones or, alternatively, in the absence of stones, may suggest sphincter of Oddi dysfunction. In either circumstance, ERCP is still indicated although, in the latter circumstance, additional measures such as biliary stents may prevent recurrence of symptoms.

Suggested Readings

Freitas ML, Bell RL, Duffy AJ. Choledocholithiasis: evolving standards for diagnosis and management. *World J Gastrointest Surg*. 2006;1(1):11–21. [162].

Maple JT, Ikenberry SO, Anderson MA, et al. The role of endoscopy in the management of choledocholithiasis. *Gastrointest Endosc*. 2011;74(4):731–744.

Rio-Tamayo G, Armijo-Alonso D, Lopez-Cano M, et al. Transcystic common bile duct exploration in the management of patients with choledocholithiasis. *J Gastrointest Surg*. 2003;7(5):622–626.

Management of Acute Cholangitis

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Acute cholangitis, most commonly presenting as fever and right upper quadrant pain, results from either obstruction of the common bile duct (CBD), leading to bile stasis with the development of infection or from iatrogenic introduction of bacteria through biliary intervention. Severity of the disease can range from mild to severe and even life threatening when the infection becomes systemic and is not promptly diagnosed and treated appropriately.

EPIDEMIOLOGY

The most common cause of acute cholangitis is choledocholithiasis (30%–70%) usually secondary to cholelithiasis. Other etiologies of acute cholangitis in patients without prior intervention are benign stricture (5%–30%) or malignancy (10%–30%). Patients with prior intervention either from biliary stents, indwelling drains, or postoperative complications from biliary reconstruction are also at risk for acute cholangitis. In the recent era, this is an increasing cause of cholangitis. Although endoscopic retrograde cholangiopancreatography (ERCP) is the primary technique of biliary drainage for treatment of acute cholangitis, the procedure itself can result in cholangitis in up to 3% of patients undergoing therapeutic ERCP procedures. In addition, as many as 20% of patients are bacteremic postintervention of biliary endoscopy without developing symptoms of sepsis or cholangitis. Acute cholangitis occurs most commonly in patients aged 50 to 70 years and with equal prevalence in men and women. Risk factors include prior medical or surgical intervention on the biliary tree and the presence of choledocholithiasis; thus, risk factors for choledocholithiasis are also related to risks for acute cholangitis.

Relevant Anatomy/Pathogenesis

Acute cholangitis results from obstruction of the common bile duct. Bile is inherently sterile due to the continuous flow of bile, immunoglobulin A secreted in the biliary tree, and bile salts, which contain a bactericidal mechanism. Biliary stasis results in development of infection when bacteria enter the biliary tree through the sphincter of Oddi (ascending cholangitis) and proliferate often with the presence of a stone or stent to act as the nidus for infection. Systemic spread causing bacteremia and sepsis occurs via translocation into the portal vein into the systemic blood supply. Direct inoculation of the biliary tree via intervention and placement of biliary stents can also lead to acute cholangitis. Finally, an increasing occurrence occurs when existing stents or drains become malpositioned or develop partial or complete obstruction resulting from sludge or tumor ingrowth leading to biliary stasis and subsequent cholangitis.

Although the bacterial profile in acute cholangitis is polymicrobial, gram-negative rods are the most prominent bacteria present in acute cholangitis (Table 1). *Escherichia coli* is present in 25% to 50% of cases. Initial empiric antibiotic treatment should cover gram-positive and gram-negative bacteria as well as anaerobes. After culture sensitivities are determined, the antibiotic regimen can be narrowed to appropriate coverage. Patients should be treated 7 to 14 days with at least 2 weeks of treatment for patients with bacteremia and sepsis.

The obstruction can be intrinsic (stone, stricture, polyp, tumor, blood clot, infectious parasite, food impaction) or result from external compression on the duct. Similarly, causes can be benign or malignant. Benign structure can be inflammatory (from chronic pancreatitis or Mirizzi syndrome with compression by a stone filled gallbladder) or iatrogenic resulting from ischemia or injury. Benign iatrogenic strictures can develop following prior surgery without biliary reconstruction (most commonly cholecystectomy) or with biliary reconstruction following pancreaticoduodenectomy, liver transplant, or Roux-en-Y or other forms of biliary bypass. Malignant obstruction can be intrinsic to the common bile duct such as cholangiocarcinoma, or extrinsic from any malignancy causing compression of the common bile duct such as pancreatic, ampullary, gallbladder, or duodenal adenocarcinoma; however, malignant obstruction alone does not often result in cholangitis, and most patients with malignancy develop acute cholangitis only following prior intervention and manipulation of the biliary tree.

Biliary obstruction of the common bile duct can be at all levels but most commonly occurs distally resulting from a stone lodged at the sphincter. Obstruction from stricture or cancer leading to cholangitis can occur at any location from proximally at the right and/or left hepatic ducts duct to distally at the ampulla. The location of the obstruction along the CBD traditionally has affected treatment strategy; although currently nonoperative techniques are successful for managing obstructions at any location. Patients with biliary obstruction and previously placed stents will have infection proximal to the level of the stent and require exchange of the stent to reestablish free biliary drainage.

CLINICAL PRESENTATION

Fever and right upper quadrant pain are the most common symptoms, occurring in more than 80% of patients with acute cholangitis. Less than 20% of patients have all three symptoms of Charcot's triad: right upper quadrant pain, fever, and jaundice. Addition of altered mental status and hypotension (Reynold's pentad) are seen in patients with severe cholangitis. Immunocompromised and elderly patients may present with hypotension or altered mental status only. Severe acute cholangitis can progress to sepsis and multisystem organ failure, requiring admission to the intensive care unit.

Charcot's triad of symptoms are commonly seen in patients presenting with acute cholangitis but are not sensitive or specific enough for definitive diagnosis. In 2006, an International Consensus Meeting was held in Tokyo to better define diagnostic criteria for acute cholangitis. Since then, multiple iterations of the Tokyo Guidelines have been published, most recently in 2018. The Tokyo Guidelines classify patients as having three different grades of acute cholangitis and give recommendations to adjust treatment guidelines according to severity of illness.

Diagnosis

The differential diagnoses for patients presenting with acute cholangitis includes acute cholecystitis, Mirizzi syndrome, liver abscesses, right lower lobe pneumonia, or empyema.

Examination

Patients presenting with acute cholangitis range from mildly ill with mild right upper quadrant pain to severe tenderness on examination. Almost 60% of patients present with jaundice. Some patients may have high fever, hypotension, tachycardia, and altered mental status consistent with sepsis.

Laboratory Values

Most commonly, patients have elevated white blood cell count consistent with infection and elevated bilirubin (conjugated more than unconjugated) with associated elevations in alkaline phosphatase and transaminases. The tumor marker Ca 19-9 can be elevated because of the biliary obstruction but does not necessarily indicate the presence

TABLE 1 Most Commonly Isolated Bacteria From Bile and Blood Cultures in Acute Cholangitis

Organism	Bile Culture Isolates (%)	Blood Culture Isolates (%)	
		Community Acquired	Healthcare Associated
GRAM-NEGATIVE BACTERIA			
Escherichia coli	31–44	35–42	23
Klebsiella species	8–28	12–28	16
Pseudomonas species	0.5–19	4–14	17
Enterobacter species	5–8	2–7	7
Serratia species	—	1	7
Citrobacter species	—	2–6	5
GRAM-POSITIVE BACTERIA			
Enterococcus species	3–14	19–23	28
Streptococcus species	2–10	6–8	5
Staphylococcus species	0	2	4
Anaerobes (usually associated with polymicrobial infections)	8–20	1	2
Other (fungal, worms, flukes)	—	17	11

From Gomi H, Solomkin JS, Takada T, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2013;20(1):35–46.

of malignancy. Ca 19-9 should be ordered in patients with malignant obstruction once the bilirubin normalizes and the obstruction is resolved. Bile cultures are positive in approximately 60% to 90% of cases, although they are not obtained in all cases of acute cholangitis and reported rates of positive blood cultures in acute cholangitis have ranged from 20% to 70%.

Imaging

Noninvasive imaging is necessary to distinguish cholangitis from other differential diagnoses and identify the underlying etiology of obstruction for therapeutic intervention guidance. Invasive imaging techniques, such as endoscopic ultrasound (EUS), often have better success at identifying common bile duct stones and the level of the obstruction along the biliary tree, but these studies are often not the best first test to perform in the setting of acute infection. If suspicion is very high for acute cholangitis, some may proceed with urgent ERCP if available so as not delay treatment. Patients with prior biliary tree interventions, especially with stents or drains, may proceed directly to repeat ERCP or interventional radiology as appropriate.

Abdominal Ultrasound

The first imaging test that should be obtained after stabilizing the critically ill patient and initiating broad-spectrum antibiotics is an abdominal ultrasound. Findings on ultrasound commonly show biliary dilation (can be isolated intrahepatic or both intra- and extrahepatic depending on the level of obstruction). Cholelithiasis and gallbladder sludge are a common finding in cholangitis, but the presence of gallbladder stones alone is not sufficient for diagnosis of cholangitis. Choledocholithiasis is often not appreciated even when biliary dilation is appreciated and can be diagnosed on ultrasound in only 30% of cases.

Cross-Sectional Imaging

Computed tomography (CT) scans document biliary dilation and even the location of the obstruction, but similar to ultrasound, CT is often not effective in identifying the source of obstruction (stricture vs stone vs mass). CT is only effective in identifying stones in the CBD in 40% of cases. MRCP is the best test for characterizing biliary structure and the underlying etiology. MRCP is about 80% accurate in diagnosing choledocholithiasis with stones greater than 6 mm. For smaller stones, MRCP is not as accurate in identifying the presence of stones but is still the best noninvasive test for demonstrating the location and nature of biliary stricture.

TREATMENT ALGORITHM

The primary treatment for acute cholangitis is urgent biliary drainage with appropriate antibiotic coverage followed by definitive surgical management to address the underlying etiology of the cause of obstruction (Fig. 1). Treatment of acute cholangitis requires a multidisciplinary team approach often involving interventional endoscopists and radiologists, and intensivists as well as infectious disease specialists if necessary. All patients should be promptly started on appropriate empiric antibiotic coverage. Single agent options for treatment include carbapenems or piperacillin-tazobactam. Metronidazole with the addition of cephalosporins or fluoroquinolones are options for dual therapy. For severe or hospital-associated cholangitis, vancomycin should be added and fungal coverage considered. Appropriate definitive antibiotic coverage is dependent on drug resistance patterns, patient allergies and comorbidities, and final culture data from blood and bile cultures (Box 1).

Patients with severe acute cholangitis should be admitted to an intensive care unit with fluid resuscitation, broad-spectrum antibiotics, correction of any electrolyte abnormalities, critical care monitoring, and any support necessary such as pressors or intubation. Patients with prior biliary intervention with external drains should have those drains placed to gravity drainage and have any obstructed drains flushed or exchanged if necessary. Those with indwelling stents will require urgent endoscopic intervention to potentially relieve any stent obstruction and/or exchange the obstructed prosthesis.

Seventy-two patients with symptoms of sepsis should undergo biliary drainage as soon as they are adequately resuscitated and stabilized. Moderate acute cholangitis requires biliary drainage, although with less urgency than severe disease. Patients with mild disease may respond to antibiotics and not require biliary drainage (Box 2). Recent literature indicates less urgency is required for biliary drainage in severe cholangitis than formerly recommended;

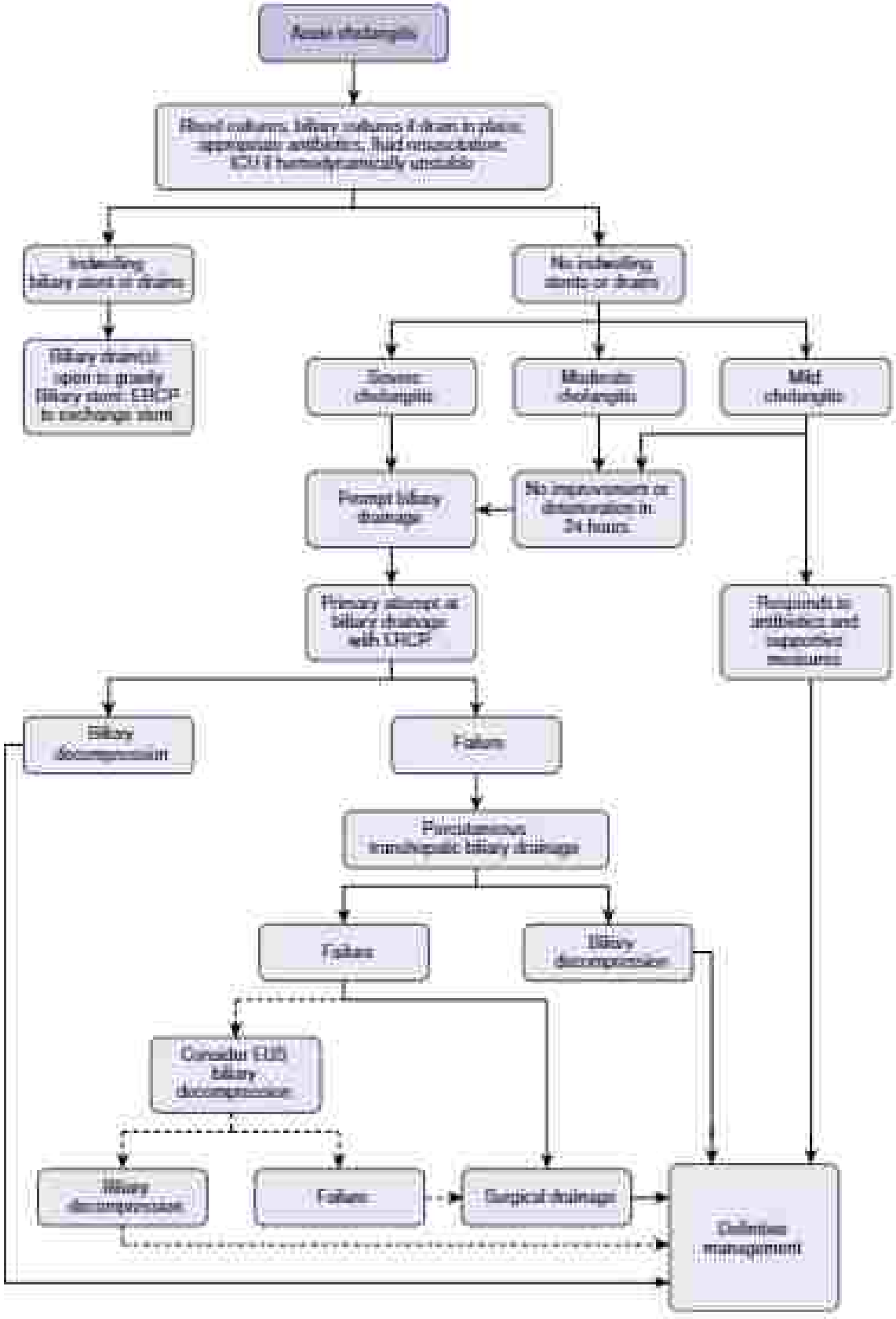

FIG. 1 Management algorithm for patients with acute cholangitis. Dotted lines represent optional progression to EUS biliary decompression, however the priority is prompt biliary drainage and some patients may require surgical drainage without attempted EUS biliary decompression. ERCP, endoscopic retrograde cholangiopancreatography; C.T, endoscopic ultrasound.

BOX 1 Options for Antibiotic Regimens*

Single Agent

- Carbapenem
- Ertapenem (mild or moderate)
- Meropenem (consider for severe hospital associated)
- Piperacillin/tazobactam
- Ampicillin/sulbactam (>20% resistance rate)

Combination Therapy

- Metronidazole, PLUS one of the following:
  - Cephalosporin (moderate to severe or hospital associated, use fourth generation)
  - Fluoroquinolone (mild or moderate)
- For hospital associated infection, severe cholangitis additional coverage with:
  - Vancomycin (daptomycin if vancomycin resistant enterococcus cultured)
  - Consider fungal coverage

*Antibiotic coverage depends on severity of acute cholangitis and history of prior biliary tract medical or surgical interventions.

Modified from Gomi H, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2018;25(1):3–16.

however, timely drainage is still indicated as a function of source control.

Nonoperative Approaches

First-line preferred biliary drainage is via ERCP. ERCP is both diagnostic and therapeutic, but at the time of initial procedure, particularly in patients with systemic sepsis, decompression of the obstructed biliary tree is the top priority. Nasobiliary tube drainage effectively decompresses the biliary tree but the tube is prone to dislodgement and its use has gone out of practice. Other diagnostic or therapeutic interventions can follow when sepsis is controlled. Ultimately, transoral endoscopists can remove any obstructing stone or sludge, perform a sphincterotomy, if appropriate, to allow future stones to pass, and place a stent for drainage. Additionally, for benign structures and potential malignant disease, a cholangiogram can be performed to better elucidate the extent of disease. Brushings can be performed if a structure is suspicious for cancer and sent for cytology and pathology. ERCP is successful in treating distal bile duct obstructions in 90% to 95% of cases. Complications of ERCP occur in 5% to 15% of cases and include bleeding from the sphincterotomy in coagulopathic patients, intestinal perforation, pancreatitis and infecting or worsening cholangitis; thus, supporting a conservative approach at any initial procedure in septic patients is advisable.

Some patients may not be able to have an ERCP because of their anatomy, such as those with prior surgical reconstruction (Roux-en-Y hepaticojejunostomy, Roux-en-Y gastric bypass, pancreaticoduodenectomy, or gastrectomy), difficult access to the ampulla, or duodenal obstruction. Severe pancreatitis may also limit endoscopic biliary drainage secondary to external compression. If patients have intrahepatic biliary dilation, an alternative approach to biliary drainage is percutaneous transhepatic cholangiography (PTC) and percutaneous transhepatic biliary drainage (PTBD). Similar to ERCP, PTC is diagnostic, providing images and details about the location of the obstruction as well as giving a way to perform brushings if malignancy is a concern. As with ERCP, the goal of any initial procedure is to establish biliary drainage, not full diagnostic or therapeutic procedures. PTBD is successful about 90% of the time and is contraindicated in ascites and can be difficult in patients with intrahepatic strictures where multiple drainage catheters may have to be placed.

BOX 2 Tokyo Guidelines 2018: Grades of Acute Cholangitis 2018 and Recommended Treatment

Grade I (Mild)

Definition: not meeting criteria for moderate (grade II) or severe (grade III) cholangitis

Treatment: allow empiric antibiotics and supportive care. Only requires biliary drainage if inadequate response to resuscitation and antibiotics.

Grade II (Moderate)

Definition: At least 2 of the following 7 criteria:
- WBC >12,000/mm³ (or <4000/mm³)
- Temperature >39°C
- Age ≥75 years
- Total bilirubin ≥5 mg/dL
- Albumin less than the lower limit of normal value (<0.73 g/dL)

Treatment: antibiotics, supportive care plus endoscopic or percutaneous drainage in >48 hours

Grade III (Severe)

Definition: cholangitis as above + sepsis and organ damage in cholangitis and one of the following markers of end organ damage:
- Cardiovascular dysfunction (requiring the use of dopamine >5 mg/kg/min or norepinephrine)
- Altered mental status with decreased consciousness
- Respiratory dysfunction (partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio <300)
- Renal dysfunction (oliguria or serum creatinine >2.0 mg/dL)
- Hepatic dysfunction (prothrombin time international normalized ratio >1.5 or platelet count <100 ($\times 10^9$/L)
- Hematologic dysfunction: platelet count <100,000/mm³

Treatment: intensive care unit admission, appropriate support for interventions (e.g., intubation, pressors), prompt initiation of broad-spectrum antibiotics, and urgent biliary drainage via endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography when able.

Surgical intervention in the management of acute cholangitis is rare, but definitive surgical management of the underlying etiology of biliary obstruction to allow necessary once the acute episode has resolved.

WBC, White blood cells.

Modified from Miura F, Okamoto K, Takada T, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. *J Hepatobiliary Pancreat Sci*. 2018;25(1):31–40.

Complications of PTBD include biliary fistulas, bleeding, recurrent cholangitis, and hepatic abscesses.

In select cases when ERCP has failed and there is not significant intrahepatic biliary dilation to perform PTBD, an alternative is EUS-guided biliary drainage (EUS-BD). A covered metal stent can be placed via EUS-guided choledochoduodenostomy or hepaticogastrostomy in an urgent setting. This has been a successful strategy for nonoperative biliary drainage, even in patients with ascites and hilar strictures. When compared with patients undergoing operative management with biliary drainage resulting from ERCP and PTBD failure, some studies have shown similar long-term survival, but fewer complication rates and better quality of life for EUS-BD. Similarly, when comparing EUS-BD to PTBD following ERCP failure, some report fewer adverse events and reintervention in patients undergoing EUS-BD. One limitation of this technique is that it requires advanced endoscopic skills often limited to tertiary centers. This intervention may also complicate definitive operative strategies for underlying etiologies of cholangitis and therefore is most often used in unresectable malignancy.

Finally, placement of a percutaneous cholecystostomy tube may be beneficial if all other nonoperative techniques have failed and the patient is a poor surgical candidate or there is concern for simultaneous cholecystitis, which is rare. For a percutaneous cholecystostomy tube to be successful, the cystic duct must be patent and the obstruction must be distal to where the cystic duct joins the CBD. We emphasize that the sole priority in any management algorithm for acute cholangitis, especially in the setting of sepsis, is urgent biliary drainage.

Surgical Options

Urgent surgical intervention has been the traditional method of treatment for obstructive jaundice since the days of Halsted; however, therapeutic options have changed with ERCP now that the optimal treatment and preferred management of acute cholangitis, followed by PTBD if ERCP is not technically possible. Surgery is now a last option because it is associated with high morbidity and mortality for patients with severe acute cholangitis. Surgical management, however, must still be considered if the patient's condition is deteriorating without a nonoperative means of biliary decompression.

If all other biliary drainage options have failed, and the patient is sick enough to require surgical intervention, the primary goal of this operation is simple, uncomplicated biliary drainage, with definitive management strategies being pursued later. In mild and moderate cholangitis that resolves with antibiotics, after resolution of acute illness, definitive management at the time of initial presentation can be considered. In severe acute cholangitis, we recommend complete resolution of the cholangitis before attempting definitive management of the underlying etiology of disease.

The best operative intervention to achieve safe and efficient surgical biliary decompression in severe disease is limited common bile duct exploration (CBDE) via choledochotomy, stone removal if easy to accomplish, and T tube placement. If the gallbladder has stones, a straightforward cholecystectomy can be performed if the patient is stable. Skilled laparoscopic surgeons may perform the CBDE laparoscopically, but the open approach remains safe and appropriate. In all cases, the experience level and comfort of the surgeon must be considered when the best approach is discussed.

For laparoscopic CBD exploration, stone retrieval, and T tube placement, laparoscopic port sites are placed in similar positions as for laparoscopic cholecystectomy. For small stones or sludge, some may consider the transcystic approach, but because that approach would necessitate cholecystectomy, this option is best reserved for stable patients with mild to moderate cholangitis. In patients with severe illness, the best approach would be directly via choledochotomy as long as the duct is at least greater than 6 mm in diameter to prevent future stricture. The technique involves an approximately 1-cm longitudinal choledochotomy made in the middle of the anterior surface of the common bile duct. A choledochoscope can then be advanced into the distal common bile duct. A stone seen via direct visualization through the choledochoscope can be retrieved using a wire basket passed through the operating channel of the choledochoscope. Once the stone is removed, a 12F–14Fr T tube can be placed through the choledochotomy and the duct closed with 4-0 or 5-0 monofilament absorbable suture.

Recent literature advocates for primary closure of the common bile duct after elective CBDE because of complications from T tube placement; that is, patients with cholangitis, placement of a T tube is necessary for biliary decompression and allows easy access for future cholangiograms if the obstruction does not resolve. T tube drainage has been associated with bile leak and requires externalization of the tube for several days until postoperative cholangiography demonstrates resolution of obstruction. Primary closure can lead to stricture and bile leak and result in no direct access to the biliary tree for future investigations.

To perform the open common bile duct exploration, the anterior surface of the common bile duct is exposed and stay sutures are placed in the 2 and 10 o'clock positions of the CBD (avoiding the blood supply at 3 and 9 o'clock). A 1 to 1.5 cm longitudinal choledochotomy is made between the stay sutures, and a sterile four French biliary Fogarty balloon catheter is passed into the distal common bile duct. Small stones or sludge may be cleared from the duct by direct flushing. Administration of glucagon will relax the sphincter of Oddi. A choledochoscope can also be used through this open approach to directly visualize and clear the stone. Similar to the laparoscopic approach, a T tube should be placed, and the choledochotomy is closed transversely with 4-0 or 5-0 absorbable monofilament sutures (Fig. 2). A closed suction drain should be left to place near the choledochotomy. A cholangiogram should be obtained 4 to 5 days postoperatively through the T tube to show patency of the CBD prior to capping the tube and then again 4 to 6 weeks later before T tube removal.

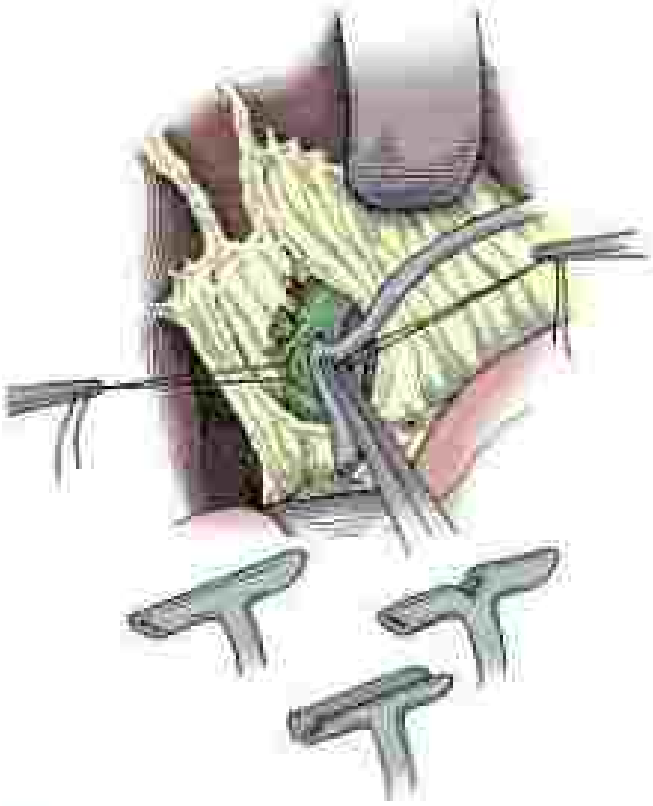

FIG. 2 Insertion of a T tube in the common bile duct with subsequent closure using absorbable monofilament suture (4-0 or 5-0). The T tube is prepared in one of the ways shown. (From Aldrete JM, Johnson DG, Shorvon PJ, et al. Operative Endoscopy and Ultrasound of the Biliary Tract and Pancreas. 2nd ed. New York: Taylor & Francis; 2007.)

The best acute surgical management for an impacted stone at the ampulla in the setting of acute cholangitis is T tube drainage, decompression of the biliary tree, and treatment of infection. If further endoscopic attempts including lithotripsy are not successful at clearing the stone from the ampulla, definitive surgical management with transduodenal sphincteroplasty can be pursued after resolution of the acute cholangitis. Complications from transduodenal sphincteroplasty include duodenal leak and recurrent pancreatitis.

Other surgical interventions such as formal biliary enteric bypass, liver resection, transduodenal sphincteroplasty, and pancreaticoduodenectomy are all definitive treatment options depending on the etiology of the biliary obstruction causing acute cholangitis. Such procedures should be performed following resolution of the acute infection and illness. The most common biliary enteric anastomosis used for a bypass of proximal biliary obstruction resulting from benign strictures is a Roux-en-Y hepaticojejunostomy.

Choledochoduodenostomy, another biliary bypass option, requires an anastomosis involving the duodenum and results in the biliary system being in continuity with the gastrointestinal tract. This eventually can lead to recurrent cholangitis through ascending, when a dysfunctional sphincter of Oddi results in bile and stone stasis in the distal common bile duct; therefore this procedure is not considered the ideal operative bypass strategy by the authors.

Because manipulation and flushing of the biliary system for either the nonoperative or operative approaches may lead to increased biliary pressure and lead to translocation of more bacteria systemically, it is not uncommon for even patients who were stable before intervention to show signs of sepsis or even systemic inflammatory response syndrome postoperatively. Broad antibiotic coverage should continue for at least 48 to 72 hours following the intervention, narrowing the antibiotic selection once sensitivities are available, and some patients may even require transfer to an intensive care unit.

OUTCOMES

Most cases of acute cholangitis resolve with antibiotics and nonsurgical biliary drainage (~ 85%); however, morbidity and mortality can be high when patients are immunocompromised or elderly. Reported overall mortality remains at 2% to 10%, with higher mortalities in patients with advanced unresectable malignancy often on chemotherapy. Overall, with better nonsurgical drainage techniques and fewer cases requiring operative intervention, the mortality rate has decreased significantly in the past 30 years. The primary treatment goal is early broad-spectrum antibiotic coverage, adequate resuscitation, and appropriate biliary drainage. After resolution of the acute episode, underlying disease must be addressed. If the severity of the acute cholangitis is mild or moderate, definitive management with cholecystectomy or biliary bypass may be considered during the same admission, but the priority is resolution of infection.

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MANAGEMENT OF BENIGN BILIARY STRICTURES

Irada Ibrahim-zada, MD, PhD, and Steven A. Ahrendt, MD

Benign biliary strictures are most commonly caused iatrogenically, usually after cholecystectomy, or after liver resection or transplantation. Benign biliary strictures also occur in a wide variety of conditions, including chronic pancreatitis, primary sclerosing cholangitis, acute cholangitis, several autoimmune diseases, or following either blunt or penetrating abdominal trauma. Most injuries are recognized either intraoperatively or in the early postoperative period, and with appropriate management the long-term results are acceptable. However, with unrecognized or inappropriately managed biliary strictures, recurrent cholangitis, secondary biliary cirrhosis, and portal hypertension may eventually develop.

IATROGENIC BILIARY INJURIES

Biliary Injury at Laparoscopic Cholecystectomy

Mechanism of Injury/Risk Factors

Before the widespread use of laparoscopic cholecystectomy, bile duct injuries were relatively infrequent, occurring in about 1 in 200 open cholecystectomies. The rate of bile duct injury with laparoscopic cholecystectomy is greater than with open cholecystectomy. Several large studies have estimated the rate of injuries at about 0.3%. The incidence of major bile duct injuries is about 0.2% and the incidence of bile leaks or minor injuries is 0.3%.

Several factors have been implicated in the occurrence of bile duct injury during laparoscopic cholecystectomy. Local operative factors can increase the difficulty of the procedure and, therefore, the risk of injury. The bile duct injury rate is increased in patients with complications of gallstones including acute cholecystitis. Significant inflammation obscures normal anatomical relationships and is more likely to be present when symptoms have been present for more than 3 days, when the white blood cell count is higher than 10,000, and with a palpable gallbladder. Additional factors associated with injury include obesity, poor exposure, and bleeding obscuring the operative field. Furthermore, increased patient age, male gender, a long period of symptoms before cholecystectomy, and number of attacks all are associated with increased difficulty of the procedure.

Aberrant biliary anatomy is also often cited as a factor in biliary injuries. A common anomaly that increases the risk of bile duct injury is an aberrant right hepatic duct coursing through the triangle of Calot and entering the common hepatic duct. Occasionally the cystic duct enters a small aberrant right hepatic duct, which is mistaken for the cystic duct and ligated and/or divided.

Intraoperatively, several factors have been implicated and biliary injuries. The classic laparoscopic injury involves the misidentification of the common duct for the cystic duct (Fig. 1). This injury occurs from excessive cephalad retraction of the gallbladder fundus or inadequate lateral retraction on the infundibulum. The common bile duct is mistaken for the cystic duct, with subsequent clipping and transection. As the dissection proceeds cephalad, the common hepatic duct is divided a variable distance from the hilus, and often the right hepatic artery is injured as well. Other intraoperative factors implicated in bile duct injury include excessive traction on the cystic duct, which can lead to clip placement on the common bile duct; dissecting too deep in the liver parenchyma, which can injure intrahepatic ducts; poor clip placement on the cystic duct; or injudicious use of cautery.

Biliary injuries can occur in combination with vascular injuries. The right hepatic artery may be erroneously misidentified as the cystic artery and lead to the most common type of injury. Arterial injuries usually happen most commonly from transection, followed by occlusion by clips, and thrombosis of the vessel. The vessel is often damaged while attempting to control bleeding during the dissection; hence, it is important to address hemorrhage with tamponade rather than by blind application of clips or considering conversion to open operation. Finally, vessel occlusion may occur due to biliary peritonitis.

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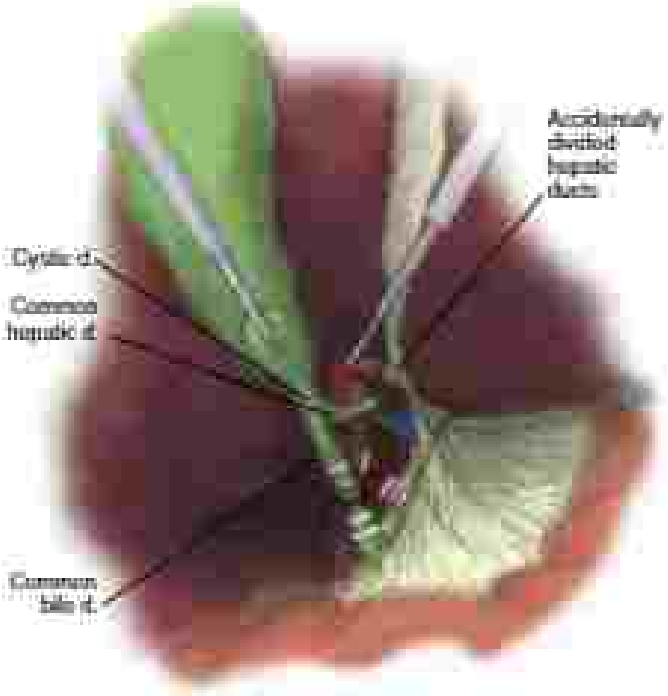

FIG. 1 Classic laparoscopic misinterpretation of bile duct injury. The cystic duct and common bile duct are aligned by traction on the gallbladder. The common bile duct is mistaken for the cystic duct leading to ligation of the common bile and common hepatic ducts at duct. (From Strasberg S, Hertl M, Soper N. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg*. 180:101–125, 1995.)

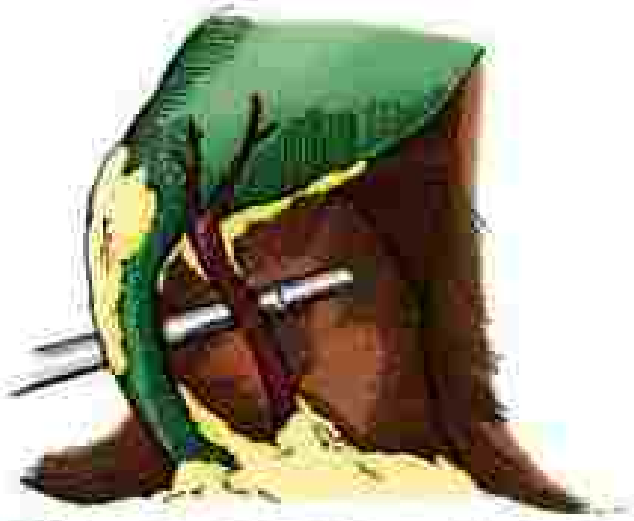

FIG. 2 The critical view to safety: (1) the hepatocystic triangle was dissected free of all tissue except for putative cystic duct and artery; (2) the lower one-third of the gallbladder was dissected off the cystic plate; and (3) two (and only two) structures are seen to be attached to the gallbladder. (From Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg*. 180(1):101–125, 1995.)

Additional factors also implicated in the occurrence of bile duct injuries include surgeon training. The number of surgeon cases and the learning curve were recognized as factors in early reports of laparoscopic bile duct injuries. Single incision cholecystectomy has also been reported to be associated with a higher rate of common bile duct injury.

Several strategies have been advocated for lowering the risk of bile duct injury. Routine intraoperative cholangiography may define the biliary anatomy, increase the intraoperative recognition of bile duct injury, and limit the extent of biliary injury; however, its use has not been conclusively demonstrated to lower the overall risk of bile duct injury. Obtaining the critical view of safety is an important step described by Soper and Strasberg in the 1990s. It allows the surgeon to proceed safely with the clipping and transection once it is achieved. The critical view (Fig. 2) includes (*1*) the hepatocystic triangle is dissected free of all tissue except for putative cystic duct and artery; (2) the lower one-third of the gallbladder has been dissected off the cystic plate; and (3), two (and only two) structures are seen to be attached to the gallbladder.

Anatomic Classification

The appropriate management of biliary tract injuries depends on the type, extent, and level of injury. The most common anatomical classification in use currently was developed by Strasberg et al., adapting the Bismuth classification for commonly seen laparoscopic injuries (Fig. 3). This system classifies bile duct injuries based on the most distal level at which healthy biliary mucosa at the proximal site of the injury or stricture is available for anastomosis. It has been created to assist in choosing the appropriate technique for repair and has a good correlation with the final outcome. Type A injuries are cystic duct leaks or leaks from small ducts in the liver bed. Types B and C injuries involve aberrant right hepatic ducts. Type D injuries are lateral injuries to major bile ducts. Type E injuries are strictures in the hepatic ducts and are further defined by proximal extent. Type E_1, common hepatic duct division, is more than 2 cm from bifurcation. Type E_2, common hepatic duct division, is less than 2 cm from bifurcation. Type E_3 is a common bile duct division at bifurcation. Type E_4, bile stricture, includes involvement of confluence and loss of communication between right and left hepatic duct. Type E_5 is involvement of aberrant right hepatic duct with concomitant stricture of the common hepatic duct.

Presentation

Intraoperative

Patients with bile duct injuries can present intraoperatively, in the early postoperative period, or may present months or years after the initial injury. Only a minority of cases of biliary duct injuries (8%–15%) are recognized immediately during laparoscopic cholecystectomy. An injury is usually suspected from ongoing biliary drainage or late recognition of the anatomy. An intraoperative cholangiogram is imperative once biliary injury is suspected and helps to delineate the biliary anatomy and to avoid any additional dissection. Once an injury is confirmed, the surgeon must decide whether to repair the injury or refer the patient to a specialized hepatobiliary center. An intraoperative consultation with an experienced biliary surgeon may be helpful in making this decision. Immediate repair should only be attempted if the reconstruction involves techniques commonly used by the operating surgeon. If the patient is to be referred to a tertiary care center, a closed suction drain should be placed laparoscopically in the subhepatic space. If immediate repair is selected, the procedure should be converted to an open laparotomy.

If an experienced surgeon is available, then primary repair or reconstruction will be based on the type of injury. Lateral bile duct (type D) injuries recognized at the time of cholecystectomy should be managed with placement of a T-tube. A T-tube can be placed at the site of the injury if it is similar in size to a choledochotomy. If the biliary defect is more extensive, the injury is repaired primarily and stented with a T-tube placed through a proximal or distal choledochotomy. If a significant thermal injury is present, a hepaticojejunostomy may be necessary. Isolated hepatic ducts smaller than 3 mm and draining a single hepatic segment can be safely ligated. Ducts larger

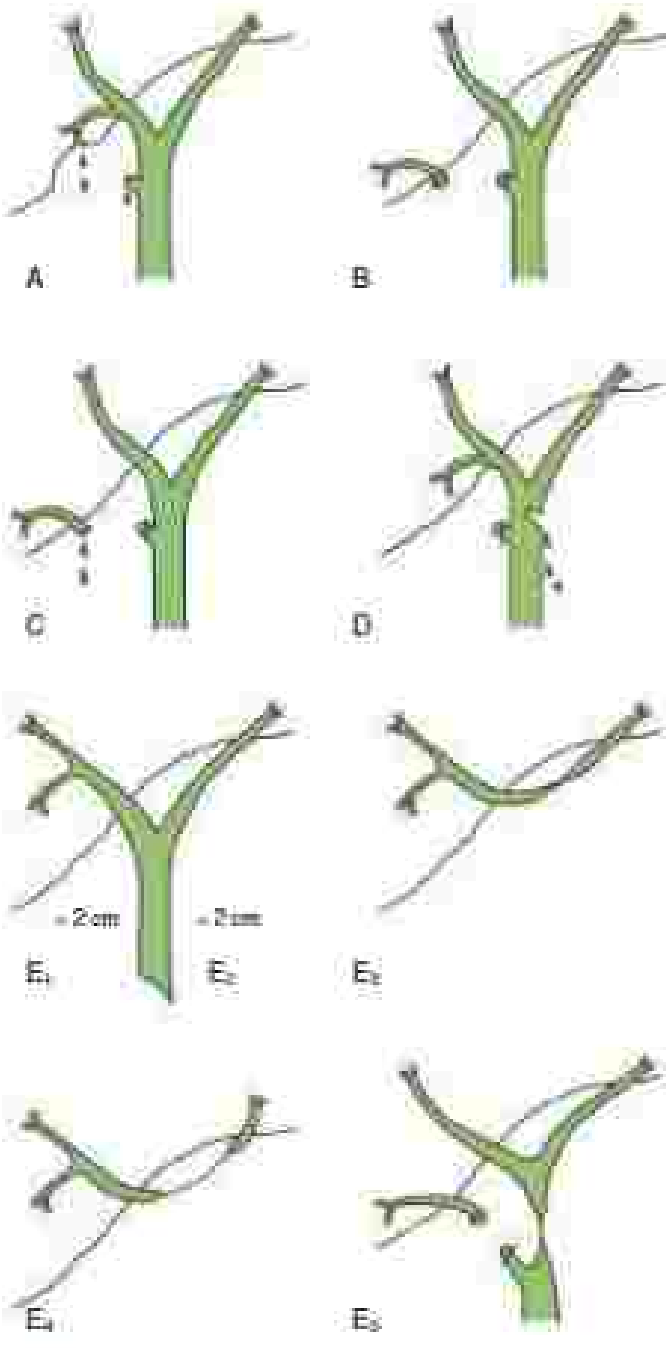

FIG. 1 Strasberg-Bismuth classification of laparoscopic bile duct injuries. Type A injuries are cystic duct leaks or leaks from small ducts in the liver bed. Type B and C injuries involve aberrant right hepatic ducts. Type D injuries are lateral injuries to major bile ducts. Type E injuries are strictures to the hepatic ducts and are further defined by proximal extent. Type E_1, common hepatic duct division, are >2 cm from bifurcation. Type E_2, common hepatic duct division, are <2 cm from bifurcation. Type E_3 is a common bile duct division at bifurcation. Type E_4, hilar stricture, involves confluence and loss of communication between right and left hepatic duct. Type E involves aberrant right hepatic duct with concomitant stricture of the common hepatic duct. (From Strasberg SM, Hertl M, Soper NJ, et al: An analysis of the problem of biliary injury during laparoscopic cholecystectomy, *J Am Coll Surg* 180:101, 1995.)

than 3 mm are more likely to drain several segments or an entire lobe and need to be reimplanted. Bile duct connections should be reconstructed with a Roux-en-Y hepaticojejunostomy. Primary repair with a choledochocholedochostomy is rarely feasible because of the loss of bile duct length from thermal injury, excision and/or devascularization, and associated with a high rate of postoperative stricture.

Postoperative

Approximately 75% of injuries are diagnosed at some point in the postoperative period. Patients usually present with a stricture diagnosed on imaging, with deranged liver function tests or recurrent bouts of cholangitis. In some cases, patients present with secondary biliary cirrhosis, which has been reported on average at about 4 months after the biliary injury. It has been reported to occur on average at about 8 months.

Clinical Presentation

Patients can present with a variety of symptoms based on the anatomy of the injury. Patients with a bile leak from the cystic duct stump, a connected aberrant right hepatic duct, or a lateral injury to the main bile duct usually present within 2 weeks of cholecystectomy with pain, fever, and/or bilious hypersalivation from a biloma or bile peritonitis. The degree of pain and physical findings may be quite subtle initially. Occasionally, bile begins leaking externally through a drain or surgical incision. Type E injuries involve occlusion of the common hepatic or bile duct without an intraperitoneal bile leak. With these injuries, jaundice with or without abdominal pain is the common mode of presentation. A persistent increase in bilirubin or alkaline phosphatase after cholecystectomy should prompt the assessment of a bile duct injury.

Evaluation

For patients with a suspected bile leak, an abdominal computed tomography (CT) scan or ultrasound identifies peritoneal fluid, a biloma or abscess. A CT has higher sensitivity (96% vs. 70%) in detecting fluid collections. Perihepatic or other intraabdominal fluid collections should be drained percutaneously. Ongoing biliary drainage through a percutaneous catheter establishes an active bile leak. The anatomy of the bile leak can be established with a cinegram through an existing drain if a fibrous tract has been established. An endoscopic retrograde cholangiogram (ERC) can also define the location of the injury and can often treat the leak effectively by placement of a biliary endoprosthesis.

For patients presenting with jaundice, the evaluation proceeds somewhat differently. A magnetic resonance cholangiogram is useful to evaluate for intrahepatic bile duct dilatation, level of injury, any cholangitic liver abscesses and liver atrophy. In addition, it can provide information on associated fluid collections. The postoperative common bile duct (CBD) should measure minimally 12 mm, and taper slowly. If a dilated or ligated hepatic or CBD is present, intrahepatic biliary ductal dilation will extend to the level of the occlusion with an abrupt cutoff. An ERC is often limited in defining the proximal biliary anatomy if the duct is occluded. In these patients a percutaneous transhepatic cholangiogram should be obtained and a catheter placed to decompress the intrahepatic biliary tract. The cholangiogram should define the proximal extent of the injury, which is critical in defining treatment. It is important to confirm integrity of all ductal bile ducts. For patients with E_3, E_4 injuries, more than one transhepatic catheter may be necessary. There is no role for diagnostic exploratory laparotomy or laparoscopy to delineate biliary anatomy.

All patients with a bile duct injury should undergo either a magnetic resonance or CT angiography to identify the presence of a concomitant arterial or portal venous system injury. The most common finding is represented by the nonenhancement of the right lobe during the arterial phase. Duplex ultrasound is less reliable method but useful for intraoperative assessment.

Management

The appropriate management of bile duct injuries depends on the time of diagnosis following the initial laparoscopic cholecystectomy.

the level and extent of injury, and the patient's general condition. A leak from the cystic duct or bile duct, a lateral injury, or a minor confluential stricture (type A and D injuries) can be diagnosed and managed by endoscopic retrograde cholangiography. Endoscopic treatment includes placement of a biliary endoprosthesis across the ampulla and proximal to the cystic duct or lateral injury site. The stent increases transpapillary flow, reduces the pressure gradient across the injury and, hence, reduces the extravasation out of the biliary tract. The bile leak and symptoms usually resolve fairly promptly. Stents are removed 4 to 6 weeks later. Endoscopic stents are quite effective in management of cystic duct leaks and minor main duct lacerations (<25% of the circumference). The presence of a bile leak in the peritoneal cavity may provoke a severe systemic response and all biliomas should be drained percutaneously. Percutaneous drainage and endoscopy have about 90% success rate for minor bile leaks.

Patients with strictures of the common bile or common hepatic duct with an intact duct may be amenable to endoscopic therapy. These injuries usually follow partial transections, partial clip placement, or thermal injury. Strictures are managed with serial dilations and multiple simultaneous biliary stents until the stricture is no longer present. The success rate of endoscopic therapy approaches 75% in this setting, with approximately 25% of patients developing recurrent strictures requiring surgical intervention.

Surgical intervention will be necessary in patients with a transected or occluded bile duct. Preoperative preparation is essential to maximize the chance of success. The goals for adequate preoperative preparation in these patients are to decompress the obstructed biliary tract with transhepatic catheters, define the anatomical extent of the injury, control sepsis by adequately draining any perihepatic fluid collections, and restore homeostasis by correcting any fluid and electrolyte abnormalities and optimizing nutritional status. CT imaging and cholangiograms must be reviewed together to ensure that all hepatic segmental ducts are defined so that all hepatic segments are included in the repair. Patients referred within days of the injury with good drainage and without any physiologic derangements may be able to proceed with surgery once the preoperative evaluation is complete. Patients referred weeks to months after the initial injury may benefit from decompression and drainage for several months while the acute inflammatory changes in the subhepatic space improve.

The goal of surgical repair is a tension-free anastomosis to ensure duct-enteric anastomosis. A Roux-en-Y hepaticojejunostomy using a 40 cm Roux limb will provide a tension-free repair and is superior to a choledochojejunostomy. In patients with E_1 and E_2 injuries (intact hepatic duct confluence) an end-to-side repair is constructed with interrupted 4-0 absorbable sutures. If inadequate length of the common hepatic duct remains for reconstruction, the left hepatic duct can be opened anteriorly and a side-to-side anastomosis fashioned to the proximal end of the Roux limb. In E_3 injuries with a partially intact confluence, a wide anastomosis is constructed including both left and right hepatic ducts. For more proximal injuries, separate hepaticojejunostomies may be required. Transhepatic catheters placed preoperatively are useful technical aids to identify the hepatic ducts particularly with more proximal strictures and are placed across the anastomosis and left in postoperatively for several months to stent the anastomosis and provide access for imaging.

Results

The morbidity and mortality from bile duct leaks and injuries is substantial. Patients with a bile duct leak or injury at laparoscopic cholecystectomy are more likely to die than patients without an injury. This risk is greatest in patients older than 50 years who have a greater than twofold increase in mortality. The morbidity and mortality occur both after the initial injury when the risk of sepsis and multisystem organ failure is high and following repair of the injury. In most large series of operative repair of bile duct injury, more than 90% of patients are free of jaundice and cholangitis with short-term follow-up. Operative mortality is low (<1%) and significant complications occur in about 30% of patients. Recurrent strictures develop in 10% to 15% of patients with long-term (>10 years) follow-up. Two-thirds of these will develop within 2 years of the initial repair. The majority of recurrent strictures following hepaticojejunostomy can be successfully managed with percutaneous dilating and dilation. Factors contributing to recurrent strictures include proximal injury, multiple repairs, and male gender.

After Liver Transplant Strictures

Several biliary complications may arise following orthotopic liver transplant (OLT), including the formation of strictures, bile leaks, and biliary filling defects. Benign biliary strictures may present anytime from days to years after the original OLT. Early strictures (<30 days after OLT) may be the result of ischemic anastomosis between donor and recipient and are often located at the anastomosis. Hepaticojejunostomies are more prone to early strictures than duct-to-duct anastomoses. Late strictures (>30 days after OLT) are most often associated with ischemic injury and mandate longer and more aggressive management which can often lead to retransplantation or revision.

Posttransplant strictures are classified into anastomotic strictures and nonanastomotic strictures. Anastomotic strictures comprise about 80% of all post-OLT strictures. Anastomotic strictures present with a single, short segment in the middle portion of the CBD. It usually develops within the first 1 to 2 months after OLT and is managed with endoscopic dilation and stent placement. The late presentation often requires stent exchange every 3 months to ensure a durable response to therapy.

Nonanastomotic strictures usually are numerous, diffuse, and proximal to the anastomosis involving the hilum and intrahepatic biliary ducts. These strictures are often associated with donor-recipient ABO blood type incompatibility or prolonged ischemic time. The patients at the highest risk are the recipients of the liver from donor after cardiac death (37% at 3 years of follow-up vs. 12% in patients after brain death). The presence of nonanastomotic strictures should prompt an evaluation of hepatic artery flow by Doppler ultrasound and/or CT angiography. They typically present later than anastomotic strictures (a mean time of 10 months) and are less responsive to endoscopic therapy. Biliary dilation and stenting are recommended and is often a bridge to retransplantation. Twenty-five to 50% of patients with nonanastomotic strictures undergo retransplantation.

Biliary-Enteric Strictures

Biliary-enteric strictures can occur after Roux-en-Y hepaticojejunostomy, partial liver resection, or pancreaticoduodenectomy (Whipple's procedure). The incidence of benign bile duct strictures following pancreaticoduodenectomy is about 4% and is more common in patients with a small caliber (<3 mm), thin-walled bile duct. Endoscopic management of this strictures can be more challenging due to modified anatomy; however, most (75%) of these strictures can be managed successfully with endoscopic stenting.

OTHER BENIGN BILIARY STRICTURES

Chronic Pancreatitis

Biliary strictures may develop in 3% to 23% of patients with severe chronic pancreatitis secondary to fibrosis of the intrapancreatic portion of the common bile duct or due to compression from a pseudocyst. In addition, up to 40% of cases, patients with autoimmune pancreatitis develop biliary strictures. Patients most commonly present with jaundice, abdominal pain, and acute cholangitis and less frequently secondary biliary cirrhosis. Benign biliary strictures from chronic pancreatitis are usually smooth, tapered and 2 to 4 cm in length. Both a pancreas protocol CT scan and an endoscopic retrograde cholangiopancreatography (ERCP) provide useful information in selecting the appropriate management. The CT scan can identify a pseudocyst, which may be contributing to the biliary obstruction.

Relief of the pancreatic compression with internal drainage may lead to resolution of the biliary stricture. The CT scan can also identify a mass or other features suspicious for malignancy. Further evaluation with ERCP and/or endoscopic ultrasound–guided fine needle aspiration or core biopsies and serum CA19-9 levels can help differentiate between benign and malignant strictures. Furthermore, the presence of numerous immunoglobulin G4–positive plasma cells confirms the diagnosis of autoimmune pancreatitis.

The clinical presentation guides the selection of therapy. In patients without significant pain and with a low suspicion of malignancy, endoscopic therapy is appropriate. For most distal strictures, placement of either multiple, side-by-side plastic biliary stents or a covered self-expandable metallic stent have produced excellent results. Both treatments have led to resolution of the biliary stricture in about 90% of patients after 1 year of stenting. Two-year stricture-free rates of 90% have been reported. Fewer ERCPs are needed with the use of the covered self-expandable metallic stent. Surgical therapy with a Roux-en-Y hepaticojejunostomy is reserved for patients with persistent or recurrent strictures following endoscopic management.

In patients with significant pain, management of the biliary stricture is part of a more extensive procedure to relieve pain. The Frey procedure may relieve compression on the obstructed distal bile duct or can be combined with a hepaticojejunostomy. A pancreaticoduodenectomy will also relieve the biliary obstruction and is the preferred procedure if malignancy cannot be excluded.

Strictures From Gallstone Disease

Mirizzi's syndrome results from obstruction of the common hepatic duct by a gallstone impacted within the gallbladder infundibulum or cystic duct. Inflammation from the impacted stone can lead to fibrosis, ulceration, and erode into the common hepatic duct. Most patients with Mirizzi's syndrome present with pain and jaundice. The diagnosis can be made by CT or magnetic resonance cholangiopancreatography and confirmed by ERCP. Open cholecystectomy is warranted with careful dissection of the gallbladder infundibulum from the common hepatic duct or a small portion of the gallbladder wall can be left in place to avoid injury to the duct. If a fistula to the common hepatic duct is present, a Roux-en-Y hepaticojejunostomy may be necessary.

Ortneal cholangiohepatitis results from chronic, parasitic infections. *Clonorchis sinensis* and *Opisthorchis viverrini* that lead to inflammatory and fibrotic changes in the bile duct walls that eventually result in stricturing, bile stasis, and stone formation. The disease is characterized by the presence of intra and extrahepatic lesions and black pigment stones and recurrent attacks of pyogenic cholangitis. The goal of treatment is to prevent or minimize the long-term consequences of the disease such as biliary cirrhosis and cholangiocarcinoma. Key aspects of management include treatment of the parasitic infection, stone removal and biliary drainage. ERCP is effective for extrahepatic biliary tree. However, surgical resection is an option in patients with limited left-sided intrahepatic disease. In high-risk patients with extensive stone disease, percutaneous transhepatic drainage and stone removal is often effective. Long-term outcomes of recurrent pyogenic cholangitis include progression to secondary biliary cirrhosis (7%–10%) and development of cholangiocarcinoma (2%–10%).

Strictures From Noniatrogenic Bile Duct Injuries

Noniatrogenic injuries to the bile ducts from penetrating or blunt abdominal trauma are rare but can be a source of significant morbidity. Penetrating injuries are often accompanied by injuries to the hepatic artery or portal vein, resulting in significant hemorrhage and devascularization of the bile duct. Biliary tract injuries in blunt trauma can be challenging and complicated because of multiple associated injuries and are often overlooked. The evaluation and management of these injuries is similar to iatrogenic injuries.

Benign Inflammatory Pseudotumors

Biliary inflammatory pseudotumors (IPTs) represent an exceptional benign cause of obstructive jaundice. IPTs are rare, idiopathic, benign mass lesions composed of fibrous tissue with marked nonspecific inflammatory infiltrate, mainly consisting of spindle cells, plasma cells, lymphocytes, eosinophils, and macrophages. Patients with IPT usually present with painless jaundice. Their clinical presentation and imaging features are nonspecific and are indistinguishable from those of cholangiocarcinoma, making their preoperative diagnosis extremely difficult. Most IPTs involve the proximal intrahepatic biliary tree. These lesions are often mistaken for cholangiocarcinoma and are treated with major resections, because their final diagnosis can be achieved only after formal pathologic examination of the resected specimens.

Suggested Readings

Strasberg SM, Helton WS. An analysis of the problem of laparoscopic bile duct injury. *Am J Surg* 2011;201:466–472.

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Management of Cystic Disorders of the Bile Ducts

Sudeep Ramarjan, MD, MAS, Bryan Clary, MD, MBA, and Jason K. Sicklick*, MD, FACS

Choledochal cyst is a rare dilatation of the extrahepatic and/or intrahepatic biliary tree. Although choledochal cysts usually develop during infancy and childhood, the disease is commonly diagnosed in adults.

Epidemiology

The incidence of choledochal cyst ranges from 1 to 15 per 100,000 people in Western countries, but their incidence is as high as 1 in 1000 in select East Asian countries. Furthermore, choledochal cysts are four times more common in women than men. Although the exact incidence remains unknown, choledochal cysts predispose individuals to developing cholangiocarcinoma.

Etiology

The frequent presentation of choledochal cysts in infancy supports a congenital origin. An anomalous pancreaticobiliary ductal junction (APBJU) is one purported mechanism for the development of choledochal cysts. In APBJU, the pancreatic duct joins the common bile

Relief of the pancreatic compression with internal drainage may lead to resolution of the biliary stricture. The CT scan can also identify a mass or other features suspicious for malignancy. Further evaluation with ERCP and/or endoscopic ultrasound–guided fine needle aspiration or core biopsies and serum CA19-9 levels can help differentiate between benign and malignant strictures. Furthermore, the presence of numerous immunoglobulin G4–positive plasma cells confirms the diagnosis of autoimmune pancreatitis.

The clinical presentation guides the selection of therapy. In patients without significant pain and with a low suspicion of malignancy, endoscopic therapy is appropriate. For most distal strictures, placement of either multiple, side-by-side plastic biliary stents or a covered self-expandable metallic stent have produced excellent results. Both treatments have led to resolution of the biliary stricture in about 90% of patients after 1 year of stenting. Two-year stricture-free rates of 90% have been reported. Fewer ERCPs are needed with the use of the covered self-expandable metallic stent. Surgical therapy with a Roux-en-Y hepaticojejunostomy is reserved for patients with persistent or recurrent strictures following endoscopic management.

In patients with significant pain, management of the biliary stricture is part of a more extensive procedure to relieve pain. The Frey procedure may relieve compression on the obstructed distal bile duct or can be combined with a hepaticojejunostomy. A pancreaticoduodenectomy will also relieve the biliary obstruction and is the preferred procedure if malignancy cannot be excluded.

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Etiology

The frequent presentation of choledochal cysts in infancy supports a congenital origin. An anomalous pancreaticobiliary ductal junction (APBJU) is one purported mechanism for the development of choledochal cysts. In APBJU, the pancreatic duct joins the common bile

duct more than 15 mm proximal to the ampulla, resulting in a long common channel with free reflux of pancreatic secretions into the biliary tract. In turn, this reflux of pancreatic juice results in increased biliary pressure and inflammatory changes within the biliary epithelium. Ultimately, it is hypothesized that these effects are related to the formation of choledochal cysts. Initial studies cited APBJD rates as high as 100% in patients with choledochal cysts, whereas more recent series identify only 25%. This wide range suggests that multiple etiologies likely underlie the pathogenesis of these lesions.

Classification

The current classification of choledochal cysts was initially proposed by Alonso Lej (1959) and subsequently modified by Todani (1977) (Fig. 1). Type I cysts (i.e., dilations of the extrahepatic biliary tract) are the most common and comprise 70% of choledochal cysts. Type I cysts are more prevalent in children (80%) than adults (65%) and further subdivide into cysts (Ia) (Fig. 2), focal (Ib), and fusiform (Ic) subtypes. Type IV cysts (i.e., cystic dilation of both the intrahepatic and the extrahepatic biliary tract) are the second most common (20% of patients) and are more frequently diagnosed in adults (30%) than children (12%). They further subdivide into the common case of multiple intrahepatic cysts and a single extrahepatic cyst (IVa) (Fig. 3) or, more rarely, as only multiple extrahepatic cysts (IVb). Type II (i.e., saccular diverticulum of the extrahepatic bile duct), type III (i.e., bile duct dilation within the duodenal wall [also known as a choledochocele]), and type V cysts (i.e., intrahepatic cysts [also known as Caroli's disease]) are much less common, with each type being diagnosed in 1% to 3% of choledochal cyst patients.

Clinical Presentation

The clinical presentation differs somewhat among children and adults. The classic clinical triad includes right upper quadrant pain, jaundice, and an abdominal mass; however, this presentation occurs very rarely. In both children and adults, abdominal pain is the most common symptom with frequencies of 41% and 72%, respectively. Children also present with jaundice (32%), pancreatitis (24%), and/or early satiety (11%). Adults may also develop symptomatic cholelithiasis (18%), pancreatitis (16%), and/or jaundice (12%). Less common symptoms or clinical findings include early satiety (11%), cholangitis (10%), or a palpable abdominal mass (1%). Prior biliary surgery is common in adults with choledochal cysts, with 32% having undergone cholecystectomy and 8% having undergone common bile duct resection. Finally, asymptomatic or incidental diagnoses account for 10% of pediatric and 18% of adult presentations.

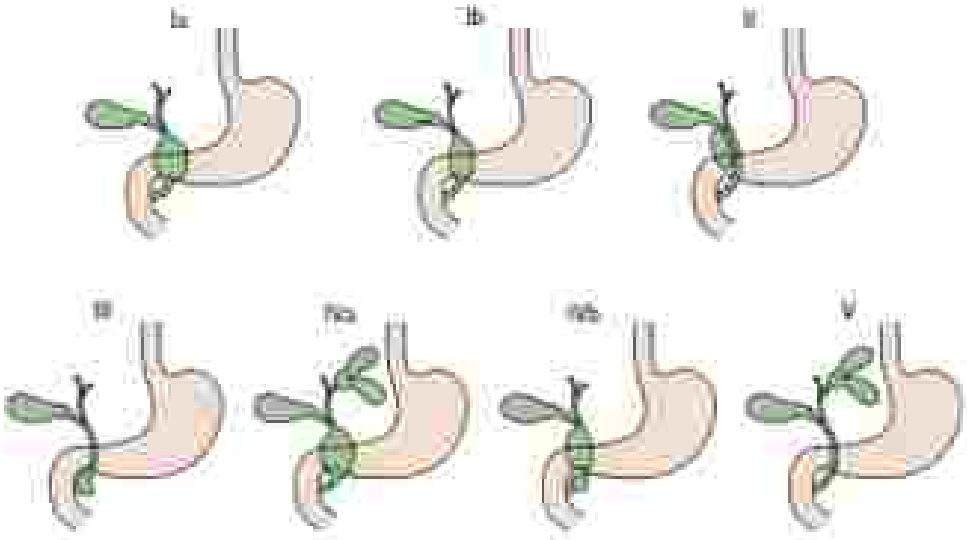

FIG. 1 Choledochal cysts: Alonso-Lej classification of choledochal cysts. Type Ia, choledochal cyst; type Ib, segmental choledochal dilation; type II, extrahepatic duct diverticulum; type III, choledochocele; type IVa, multiple intrahepatic and extrahepatic duct cyst; type IVb, multiple extrahepatic duct cysts; type V, intrahepatic duct cyst (Caroli's disease). (From Sanjai A, et al. Video article: Laparoscopic excision of choledochal cysts. *Surg Endosc*. 2008.)

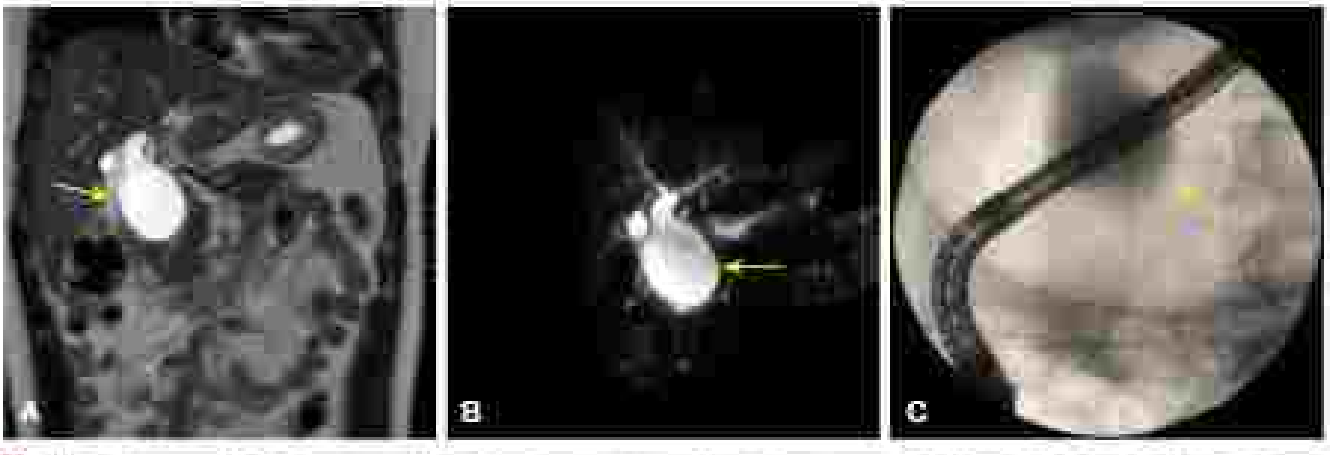

FIG. 2 Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography of a type Ia choledochal cyst (arrow) demonstrating intrahepatic biliary dilation immediately distal to the hepatic duct confluence. (A) Coronal magnetic resonance image. (B) Magnetic resonance image with three-dimensional reconstruction. C: Cholangiogram.

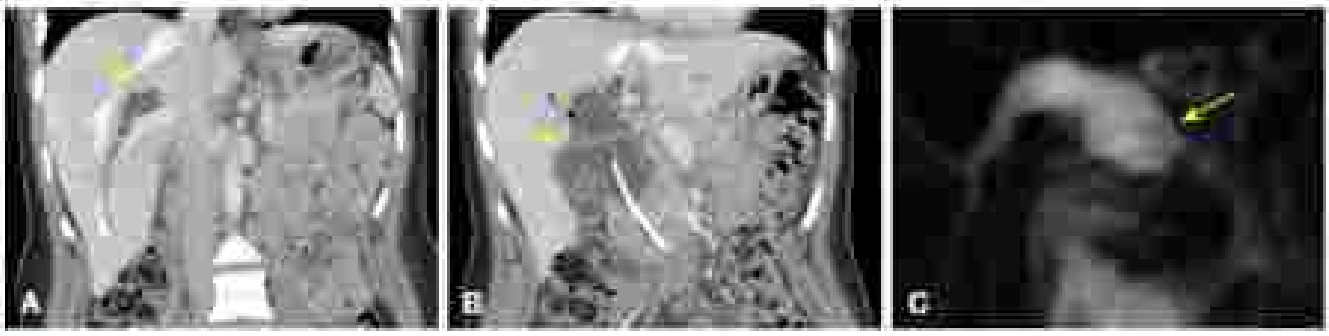

FIG. 1 Computed tomography (CT) and magnetic resonance cholangiopancreatography of a type IVb choledochal cyst (arrow). (A) Coronal CT demonstrates extrahepatic cystic component. (B) Coronal CT demonstrates extrahepatic cystic component. (C) Magnetic resonance cholangiopancreatography.

Diagnosis

Laboratory evaluation most frequently demonstrates normal levels of transaminases, amylase, prothrombin time and tumor markers, including CA 19-9 and carcinoembryonic antigen. The most common imaging modalities used for diagnosis include ultrasound (US, 42%), computed tomography (CT, 57%), magnetic resonance imaging (MRI, 13%) and magnetic resonance cholangiopancreatography (MRCP, 58%). In the pediatric population, US is historically the preferred diagnostic modality and remains a commonly used imaging modality. US therefore remains a commonly used imaging modality. Moreover, there are well established criteria for suspicion of choledochal pathology. A common bile duct diameter exceeding 1 cm in an adult suggests a distal obstruction from a stone, periampullary neoplasm, or the presence of cystic dilation of the biliary tract. The presence of a right upper quadrant cyst distinct from the gallbladder is also suggestive of a choledochal cyst. MRCP is equally becoming the preferred technique given its high sensitivity (76%–100%) and specificity (90%–100%), as well as avoidance of radiation associated with CT. Likewise, with improved experience and technologies, MRCP is becoming more commonly used in children. Although more invasive, endoscopic retrograde cholangiography (ERCP) and percutaneous transhepatic cholangiography are the most sensitive techniques, allowing for clear visualization of both intra- and extrahepatic biliary cysts with the added benefit of potential for therapeutic interventions such as biliary drainage or biopsy. Importantly, APBUD is not readily identified using US, whereas both MRCP and ERCP are accurate in defining this anatomic finding. Preoperative interventions (i.e., ERCP, percutaneous transhepatic cholangiography) are common in adults (45%) and children (31%). Modern protocols that reduce radiation exposure and contrast agent volume permit more frequent usage in the pediatric population.

Management

The indication for definitive surgical management of choledochal cysts is based on an observed increase in the risk of cholangitis and pancreatitis, as well as malignant degeneration into cholangiocarcinoma. Historically, choledochal cysts were managed with internal drainage procedures (e.g., cystoenterostomy) and cholecystectomy; however, this approach led to persistent biliary stasis and a high rate of cholangitis, pancreatitis, recurrent strictures, and liver fibrosis. More significantly, the risk of cholangiocarcinoma in the remaining biliary cyst was unacceptably high (range, 12%–16%). The current-day approach includes cholecystectomy, complete resection of the choledochal cyst whenever possible to minimize the risk of malignant transformation, and a biliary enteric anastomosis to prevent further reflux of pancreatic juice into the biliary tract. Patients initially managed with cystoenterostomy should undergo resection as outlined in the following sections because of the increased risk of malignancy.

TYPE I: EXTRAHEPATIC BILE DUCT CYST

Treatment of type I choledochal cysts, the most common type of choledochal cyst, centers around resection of the common hepatic duct, common bile duct, and the gallbladder. Following cholecystectomy, a Kocher maneuver should be performed. The anterior wall of the choledochal cyst can then be dissected distally until it narrows at the tubular portion of the cyst. The distal CBD is then ligated at this level and divided, taking care not to injure the pancreatic duct. The cyst is then reflected anteriorly to allow dissection off of the portal vein. The cyst is mobilized to the level of the confluence of the left and right hepatic ducts. The common hepatic duct is divided just distal to hepatic duct confluence. Frozen sections of the proximal and distal bile duct margins should be obtained to exclude the presence of cholangiocarcinoma at the margin. Biliary enteric continuity is restored with an end-to-side Roux-en-Y hepaticojejunostomy. This type of reconstruction is preferred to hepaticoduodenostomy, which has a higher risk of postoperative bile reflux, gastritis, and gastric cancer. In cases in which the cyst extends to the head of the pancreas, pancreaticoduodenectomy should be performed. Laparoscopic resection with biliary enteric anastomosis has been shown to have equivalent success rates in experienced centers and is frequently the preferred approach in the pediatric population.

TYPE II: EXTRAHEPATIC BILIARY DIVERTICULUM

Type II cysts usually can be managed by simple diverticulectomy with closure of the common bile duct at the cyst neck. These cysts are typically not associated with an APBUD and do not have a high risk of malignant transformation.

TYPE III: CHOLEDOCHOCELE

The majority of choledochoceles are small and can be managed with endoscopic sphincterotomy. These cysts also do not carry an elevated risk of cholangiocarcinoma. Larger cysts have been managed successfully with transduodenal excision.

TYPE IV: INTRAHEPATIC AND EXTRAHEPATIC BILE DUCT CYST

The management of type IV choledochal cysts, the second most common type of choledochal cyst, is challenging. Diffuse involvement of the intrahepatic bile ducts can make complete excision impossible. The extrahepatic component is treated with cyst excision and biliary enteric reconstruction, similar to type I choledochal cysts. Partial hepatectomy is recommended when only one lobe is involved, and when technically and clinically feasible. Importantly, subtotal resection is associated with high rates of biliary complications; therefore, confidence in complete surgical resection is paramount. Patients with

bilobar disease should be aggressively surveilled for malignant degeneration with serial imaging and serum CA 19-9. The development of complicated bilobar disease should prompt evaluation for orthotopic liver transplantation.

TYPE V: CAROLI'S DISEASE

Treatment of Caroli's disease is predicated on management of cholangitis with antibiotics, biliary drainage procedures, and stone extraction. Asymptomatic patients with uni- or bilobar disease should undergo aggressive biochemical and imaging surveillance for cholangiocarcinoma. Patients developing symptoms from unilobar disease, or those with localized intrahepatic cysts are best managed with hepatic resection. Patients with complicated bilobar disease (despite maximal medical therapy), portal hypertension, or suspicion of early cholangiocarcinoma may be candidates for orthotopic liver transplantation.

SHORT-TERM AND LONG-TERM MORBIDITY

Perioperative morbidity and mortality in patients undergoing choledochal cyst resection are comparable to other major hepatobiliary procedures. Common morbidities include hepatobiliary complications (e.g., bile leak, peritonitis, abscess, cholangitis; 17%), wound infection (11%), and gastrointestinal complications (e.g., bowel obstruction, pancreatitis, ileus; 11%). Long-term complications are common, with 29% of patients requiring readmission within 2 years of surgery. Reasons for readmission include anastomotic stricture, cholangitis, and cholangiocarcinoma. The management of complications requires biliary procedures in 17% of cases and a second operation in 15% of cases. Despite resection, choledochal cysts can recur in 3% of patients, and 82% (i.e., 5.7% of all patients) present with recurrent symptoms.

PROGNOSIS

The rate of cholangiocarcinoma at the time of surgical resection is approximately 11%, with a median age of 42 years at diagnosis. Overall, the 5-year survival rate of patients with choledochal cysts managed with resection and biliary reconstruction is 96%, however, those patients with incidental cholangiocarcinoma have a far worse prognosis, with a median survival of 29 months. Finally, across all subtypes, the risk of cholangiocarcinoma remains elevated after choledochal cyst resection with 11% of patients developing cancer after 10 years therefore, patients with resected choledochal cysts should undergo long-term surveillance. In summary, these operations are often done for risk reduction, although in a small subset of cases, they may be curative. Given the poor prognosis of cholangiocarcinoma and risk of recurrent disease, aggressive surgical management remains warranted.

Suggested Readings

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Management of Primary Sclerosing Cholangitis

Nazeen Ghanekar, MD, and Steven C. Cunningham, MD, FACS

Primary sclerosing cholangitis (PSC) is a chronic idiopathic inflammatory disease affecting the intrahepatic (IHB) or extrahepatic (EHB) biliary tree or both (75%), which causes chronic cholestasis and eventual liver failure. The etiology of PSC is unknown but is believed to be due to a combination of genetic and environmental factors that cause chronic inflammation of the bile ducts resulting in stricture formation and upstream dilatation. It is a rare disease with a prevalence between 0.22 to 14.2 per 100,000 persons, with increased prevalence in northern European countries compared with the United States. It affects males more than females, usually in the fourth to fifth decade of life, and progresses to end-stage liver disease with a median survival of 12 to 18 years after diagnosis.

It is essential to distinguish PSC from secondary sclerosing cholangitis because many of the primary causes of secondary sclerosing cholangitis, including infectious, obstructive, immunologic, ischemic, and congenital etiologies may respond to specific therapies to which PSC does not respond. Similarly, it is important to recognize that an overlap syndrome exists between autoimmune hepatitis and PSC in 35% of pediatric and 9% of adult patients because these patients may respond well to systemic steroids.

PSC has strong associations with inflammatory bowel disease (IBD) especially ulcerative colitis, which develops in 68% to 75% of PSC patients, whereas Crohn's disease develops in only 5% to 10%. Although a majority of patients with PSC have IBD, only 3% to 5% of patients with IBD have PSC. Other autoimmune diseases commonly associated with PSC include celiac disease, diabetes mellitus type 1, hypothyroidism, ankylosing spondylitis, and autoimmune hepatitis.

PSC is a major risk factor for the development of cholangiocarcinoma (CCa), which occurs in 10% to 20% of PSC patients and is the second leading cause of death. In addition, CCa is found incidentally in up to 10% of explanted livers at the time of transplantation for PSC and up to 40% of PSC patients at autopsy.

PRESENTATION AND DIAGNOSIS

PSC has an indolent course, and the majority of patients are diagnosed while asymptomatic, generally during the evaluation of an abnormal liver panel, particularly with elevated alkaline phosphatase, although bilirubin and transaminase may also be elevated less commonly. A large variety of autoantibodies have been detected in PSC patients, but specificity is generally low. One of the most prevalent is perinuclear antineutrophil cytoplasmic antibody, present in 26% to 94% of cases. In symptomatic patients, pruritus, abdominal pain, diarrhea, jaundice, fatigue, and fever are common. Delayed presentations may be in the form of decompensated liver failure with manifestations of portal hypertension such as ascites, variceal bleeding, jaundice, and splenomegaly. Dominant biliary strictures may occur anywhere but commonly affect the hepatic confluence, usually presenting with recurrent cholangitis, and raising suspicion for CCa.

Cholangiography with endoscopic retrograde cholangiopancreatography (ERCP) has been considered the gold standard for diagnosing PSC but has been largely replaced by magnetic resonance

bilobar disease should be aggressively surveilled for malignant degeneration with serial imaging and serum CA 19-9. The development of complicated bilobar disease should prompt evaluation for orthotopic liver transplantation.

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Primary sclerosing cholangitis (PSC) is a chronic idiopathic inflammatory disease affecting the intrahepatic (IHB) or extrahepatic (EHB) biliary tree or both (3%), which causes chronic cholestasis and eventual liver failure. The etiology of PSC is unknown but is believed to be due to a combination of genetic and environmental factors that cause chronic inflammation of the bile ducts resulting in stricture formation and upstream dilatation. It is a rare disease with a prevalence between 0.22 to 14.2 per 100,000 persons, with increased prevalence in northern European countries compared with the United States. It affects males more than females, usually in the fourth to fifth decade of life, and progresses to end-stage liver disease with a median survival of 12 to 18 years after diagnosis.

It is essential to distinguish PSC from secondary sclerosing cholangitis because many of the primary causes of secondary sclerosing cholangitis, including infectious, obstructive, immunologic, ischemic, and congenital etiologies may respond to specific therapies to which PSC does not respond. Similarly, it is important to recognize that an overlap syndrome exists between autoimmune hepatitis and PSC in 35% of pediatric and 9% of adult patients because these patients may respond well to systemic steroids.

PSC has strong associations with inflammatory bowel disease (IBD) especially ulcerative colitis, which develops in 68% to 75% of PSC patients, whereas Crohn's disease develops in only 5% to 10%. Although a majority of patients with PSC have IBD, only 3% to 5% of patients with IBD have PSC. Other autoimmune diseases commonly associated with PSC include celiac disease, diabetes mellitus type 1, hypothyroidism, ankylosing spondylitis, and autoimmune hepatitis.

PSC is a major risk factor for the development of cholangiocarcinoma (CCa), which occurs in 10% to 20% of PSC patients and is the second leading cause of death. In addition, CCa is found incidentally in up to 10% of explanted livers at the time of transplantation for PSC and up to 40% of PSC patients at autopsy.

PRESENTATION AND DIAGNOSIS

PSC has an indolent course, and the majority of patients are diagnosed while asymptomatic, generally during the evaluation of an abnormal liver panel, particularly with elevated alkaline phosphatase, although bilirubin and transaminase may also be elevated less commonly. A large variety of autoantibodies have been detected in PSC patients, but specificity is generally low. One of the most prevalent is perinuclear antineutrophil cytoplasmic antibody, present in 26% to 94% of cases. In symptomatic patients, pruritus, abdominal pain, diarrhea, jaundice, fatigue, and fever are common. Delayed presentations may be in the form of decompensated liver failure with manifestations of portal hypertension such as ascites, variceal bleeding, jaundice, and splenomegaly. Dominant biliary strictures may occur anywhere but commonly affect the hepatic confluence, usually presenting with recurrent cholangitis, and raising suspicion for CCa.

Cholangiography with endoscopic retrograde cholangiopancreatography (ERCP) has been considered the gold standard for diagnosing PSC but has been largely replaced by magnetic resonance

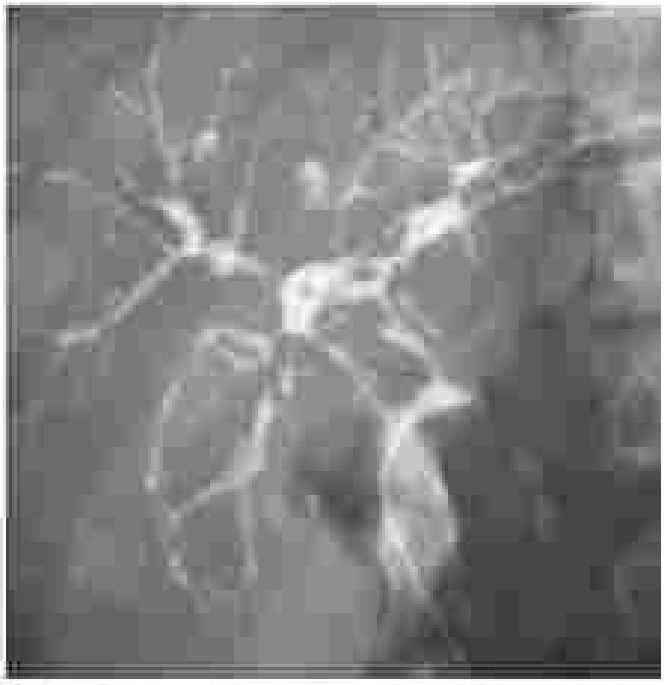

FIG. 1 Typical characteristic primary sclerosing cholangitis on cholangiography showing stricturing and beading.

cholangiopancreatography (MRCP) (Fig. 1). ERCP, however, retains the advantage of being not only diagnostic for both PSC and for CCa, but also potentially therapeutic. Any patient with a typical picture of dominant strictures and/or persistently elevated CA 19-9 should be considered for ERCP with brushings or directed biopsy to assess for CCa, ideally in a high volume center with access to and expertise in cholangioscopy. Although the diagnostic yield of endobiliary brushings is unfortunately low, newer brushes recently available have increased the sensitivity of brushed specimens. Benign strictures may be treated at ERCP with balloon dilatation, with or without placement of stents.

Other imaging modalities include abdominal ultrasound, contrast-enhanced computed tomography, and magnetic resonance imaging to detect masses concerning for malignancy. Liver biopsy is indicated in appropriate patients to quantify the degree of fibrosis, as this impacts future decisions for resection versus transplantation, and may also show cholestasis, recurrent cholangitis, and ductular proliferation.

MANAGEMENT

There are several different but overlapping aspects of PSC that warrant specific management considerations, including dominant strictures, CCa, gallbladder disease, liver failure, hepatocellular cancer, related systemic symptoms and diseases (such as pruritus, vitamin malabsorption, and hepatic osteodystrophy), and IBD and the attendant risk of colorectal cancer, as delineated in the following section. An algorithm for the management of the primary manifestations of PSC is shown in Fig. 2. Medical therapy, although shown to normalize laboratory values, is largely ineffective at retarding disease progression or extending survival and is therefore first reserved for clinical trials.

Recurrent Cholangitis and Dominant Strictures

Dominant strictures are defined by a diameter of 1.5 mm or less in the common bile duct or 1.0 mm or less in the common hepatic duct and are concerning for their propensity to cause recurrent cholangitis and to harbor or develop CCa.

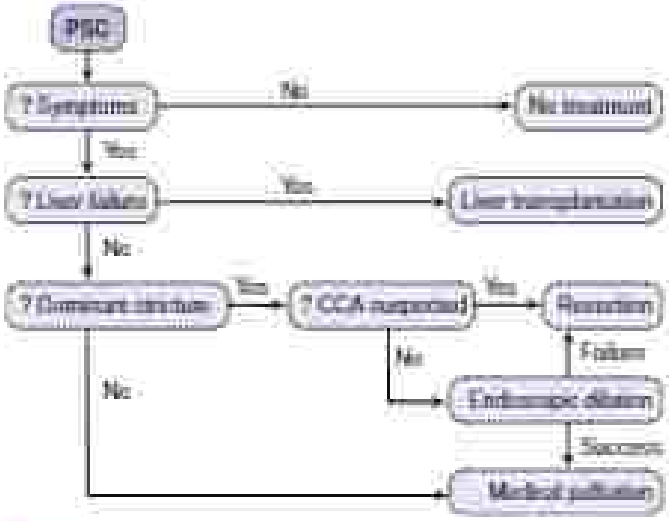

FIG. 2 Management algorithm for primary sclerosing cholangitis. CCA, cholangiocarcinoma.

Multiple modalities have been described for treating patients with biliary strictures, including percutaneous, endoscopic, and surgical modalities. ERCP is currently the most useful in managing strictures with balloon dilatations and stents. Endobiliary stents are typically reserved for patients who fail balloon dilatation. Not uncommonly, repeat ERCP is needed for recurrent strictures. Percutaneous interventions are also available but are falling out of favor given advancements in ERCP. Nevertheless, percutaneous transhepatic drainage remains a useful intervention in cases where endoscopic therapy is not available or technically feasible. Perprocedural antibiotic coverage is very important in PSC patients, especially in those previously instrumented or with recurrent cholangitis. Some patients who continue to suffer from recurrent cholangitis despite successful treatment of strictures benefit from rotating antibiotics to mitigate recurrent cholangitis episodes.

Resection for dominant extrahepatic or hilar strictures often durable results, delays the development of cirrhosis, and offers an opportunity to exclude CCa, ideally in high volume centers for selected patients with preserved liver function and no or only early fibrosis or compensated cirrhosis. Resection in these patients typically includes the entire extrahepatic biliary tree with a Roux-en-Y hepaticojejunostomy reconstruction over transhepatic stents. Preoperative placement of percutaneous bilateral transhepatic stents not only aids in dissection of the biliary confluence but also allows creation of a hepaticojejunostomy over stents, which are often left in place significantly longer than in non-PSC patients.

The operation may be performed through an upper midline or right subcostal incision. After entry in the abdomen, careful examination of the peritoneal cavity, liver, and porta hepatis is performed to identify any metastatic disease. Intraoperative ultrasound is used to examine the intrahepatic stones. A wide Kocher maneuver is performed to expose the distal common bile duct, which is transected, biopsied by frozen section, ligated as close to the pancreas as possible, and then reflected cephalad and anterior to facilitate dissection of the bile duct from the portal vein(s) and hepatic artery(ies) (Fig. 3). The right and left hepatic ducts are transected and biopsied by frozen section. The transhepatic stents are exchanged in a retrograde fashion with fiberoptic guidance and the hepaticojejunostomy performed using 2-0 PDS in a running or interrupted fashion to a Roux limb of jejunum, which is brought through the base area of the transverse mesocolon just to the right of the middle colic artery. The Silastic drains are brought through the abdominal wall in the right upper quadrant, taking care to avoid kinking. Closed suction drains are placed around the hepaticojejunostomy.

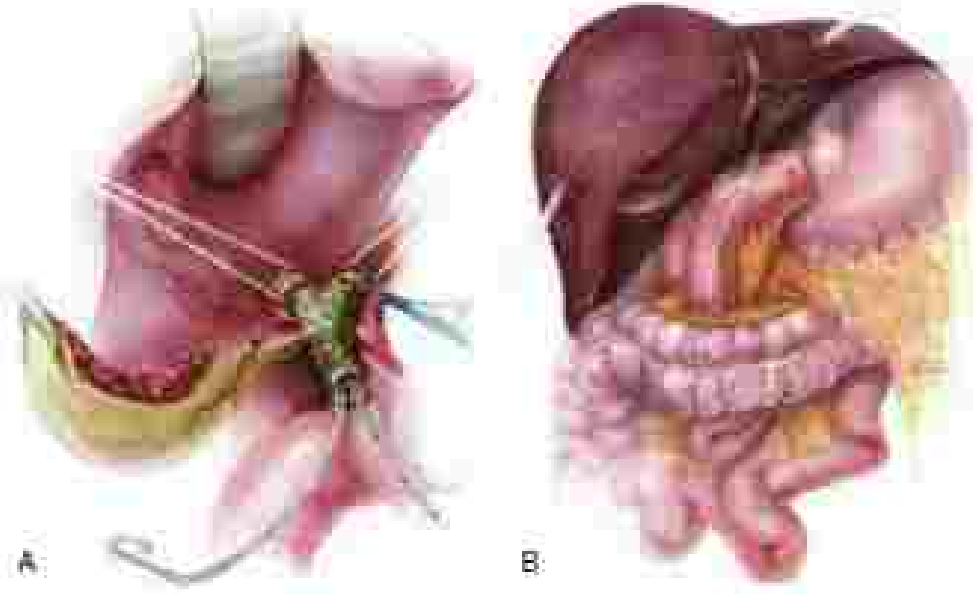

FIG. 3 (A) Resection of extrahepatic biliary tree with (B) reconstruction by Roux-en-Y hepaticojejunostomy over endoprosthesis biliary stents. (Courtesy Carlos Galdino, Mark Clements, Lecture C. Atlas of Gastrointestinal Surgery, 2nd Ed. [2]. Hamilton, Ontario: BC Decker Inc.)

In selected patients, this surgical approach offers good long-term results as compared to endoscopic or percutaneous modalities with a 5-year survival of 85%, similar to liver transplantation (Figs. 4 and 5). In the presence of cirrhosis, however, liver transplantation is the preferred treatment modality. Following liver transplantation for PSC, however, recurrent biliary strictures are more common than after transplantation for other diseases. Nonanastomotic recurrent biliary strictures have been diagnosed in up to 25% of patients after transplant (median follow-up, 5–10 years) and are more common in males than females, and in the presence of IBD, especially with an ileostomy. Other transplant considerations specific to PSC patients are discussed below.

Cholangiocarcinoma

Diagnosing CCa in patients with PSC is challenging because it is difficult to differentiate from inflammatory strictures, even with a biopsy. Patients with suspicious strictures on magnetic resonance cholangiopancreatography or elevated CA19-9 should undergo ERCP with brushings or biopsy of dominant strictures. Although the sensitivity of brush biopsies is traditionally very low, the addition of fluorescence in situ hybridization of brush cytology looking for polysomy increases the sensitivity. Cholangioscopy with directed biopsies has also been shown to increase sensitivity compared to traditional cytology brushings.

Surgical resection for CCa in the setting of PSC is ill-advised in patients with advanced cirrhosis or poor liver function because it is usually associated with prohibitively high postoperative mortality. In patients with findings suspicious for CCa or diagnosed CCa in the absence of extrahepatic disease or metastatic spread liver transplant after neoadjuvant chemoradiation is increasingly recommended. This approach has shown good outcomes with a 5-year survival of 70% (Fig. 6). Patients with suspicious looking strictures should be followed closely with repeat imaging and referral to a transplant center.

Gallbladder Disease

Given that PSC has been associated with an increased risk for developing both benign and malignant gallbladder disease, special consideration of the gallbladder is warranted in PSC patients. For example, not only is the threshold for cholecystectomy for gallbladder polyps lower in PSC than in non-PSC patients because the observation of gallbladder adenocarcinoma in even polyps smaller than 1 cm, but also some experts recommend that patients with PSC undergo annual ultrasound screening to look for gallbladder polyps and masses, and that cholecystectomy be considered in any patient with gallbladder

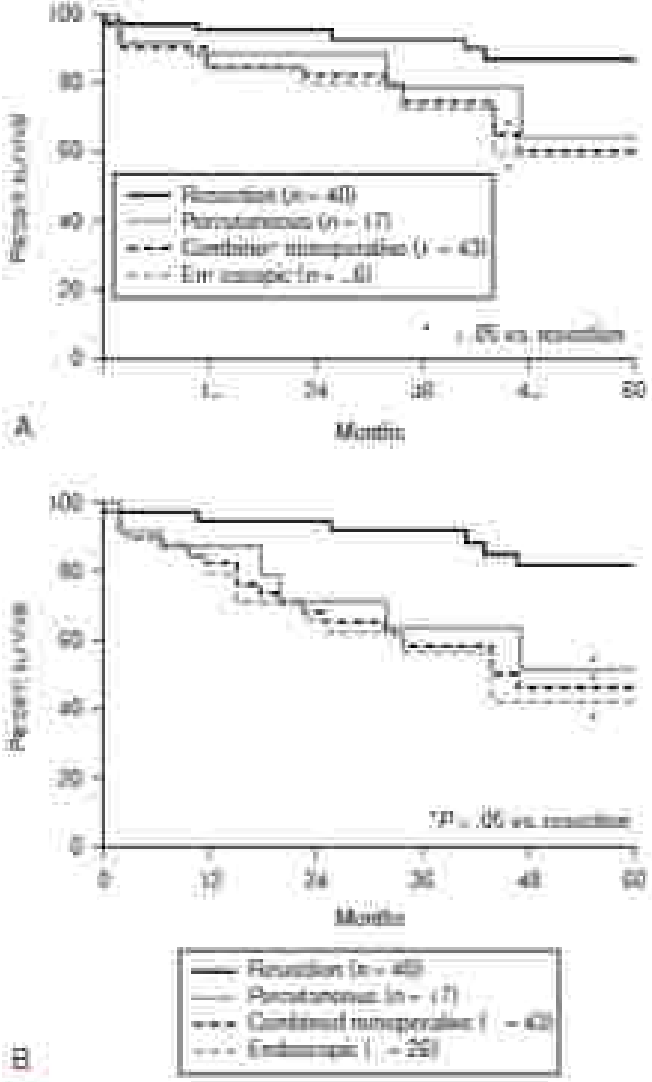

FIG. 4 (A) Overall and (B) transplant-free survival curves for nonoperative patients undergoing resection, endoscopic and percutaneous treatment for dominant biliary strictures. (From Rerknimitr R, Fogel EL, Kalayci AG, et al. Primary sclerosing cholangitis in adults: an evolving spectrum. Am J Gastroenterol 2004;99:1798–807 [3].)

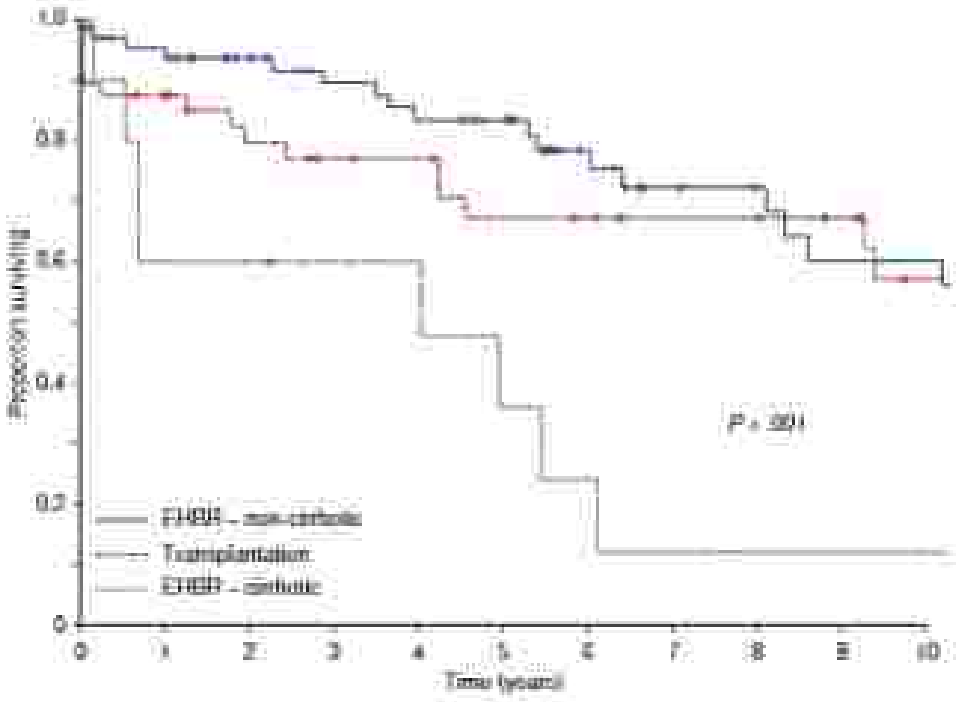

FIG. 5 Survival rates for noncirrhotic primary sclerosing cholangitis patients treated with extrahepatic biliary resection (EHBR) were similar to those treated with transplantation, whereas cirrhotic patients treated with EHBR had significantly worse survival. (From Overby DW, Odorico JS, Markmann JF, et al: Extrahepatic biliary resection for primary sclerosing cholangitis. Am J Surg 2006;192:430.)

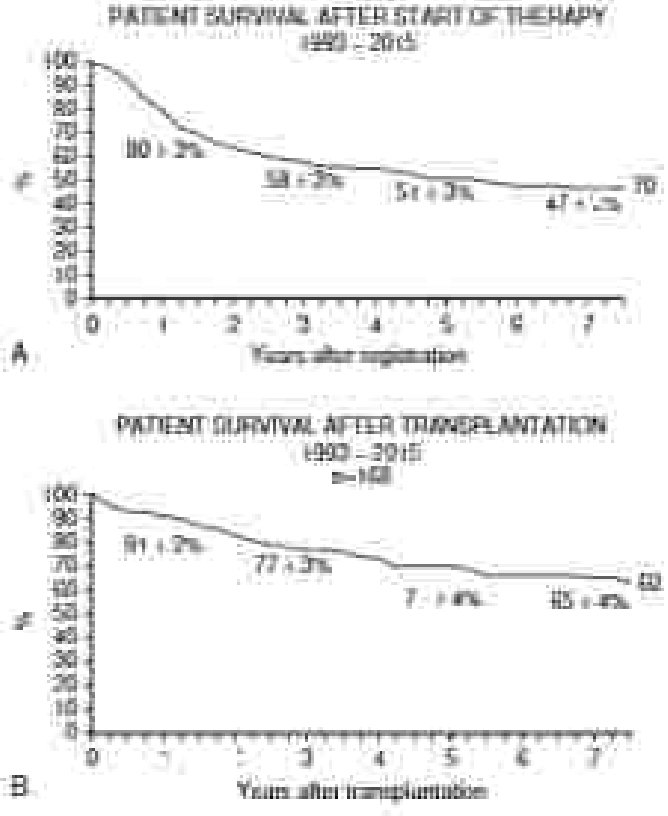

FIG. 6 Survival after start of medical therapy (A) and survival following transplantation (B). (From Lerner MR, Hochwald SN, Hochwald SN, et al: Surgery of the bile ducts and pancreas. Adv Surg 2010;44:193–210.)

polyps (~3% of patients with PSC). Patients with PSC are also at a higher risk (25%) of developing benign gallstone disease and are at increased risk to develop acalculous cholecystitis resulting from diffuse lymphoplasmacytic infiltration of the gallbladder, in which cases cholecystectomy may be indicated.

Liver Failure and Hepatocellular Carcinoma

PSC is the fifth most common indication for liver transplant in the United States and the most common indication for transplant in Scandinavia. As with other diseases warranting transplantation, the indication for liver transplant in PSC with liver cirrhosis is based on the model for end-stage liver disease (MELD) score. Patients with PSC usually have lower MELD scores because of preserved liver function but suffer from complications related to the disease from recurrent cholangitis to lifestyle limiting pruritus. These patients may get additional exception MELD points after evaluation by regional review board.

Hepatocellular carcinoma is observed in 2% to 6% of cholangiocytes in the setting of PSC. Abdominal ultrasound screening for hepatocellular carcinoma, typically every 6 months, with or without alpha fetoprotein should be performed for patients with PSC and evidence of liver cirrhosis.

During liver explant, excision of the entire biliary tree should be performed down to the head of the pancreas. Biliary reconstruction is then performed as a Roux en Y choledochojejunostomy. Following liver transplant, survival in patients with PSC is similar to liver transplant for other indications with 1- and 5-year survival rates of 83% and 87.3%, respectively, and graft survival rates of 87% and 79.2% at 1 and 5 years, respectively.

Post-transplant, PSC patients are at risk for disease recurrence, acute rejection, and chronic rejection. It is difficult to differentiate between ischemic strictures versus recurrence of disease versus chronic rejection. Recurrence of PSC is observed in 20% to 25% of patients following liver transplant, and male patients with IBD and an intact colon are at greatest risk of PSC recurrence.

Pruritus, Vitamin Malabsorption, and Hepatic Osteodystrophy

Pruritus is a common symptom that develops in patients with cholestatic liver disease. Dilatation of dominant strictures usually leads to relief of symptoms but some patients continue to suffer from severe pruritus despite resolution of jaundice. Several medications have been used for management of pruritus, including antihistamines, ursodeoxycholic acid, rifampicin, cholestyramine, naltrexone, and sertraline reuptake inhibitors. Patients with severe and refractory symptoms may receive MELD exception points after approval by a regional review board.

Patients with cholestasis also suffer from malabsorption of fat-soluble vitamins (A, D, E and K), putting them at risk to develop associated diseases such as osteoporosis and coagulopathy. Supplementation with fat soluble vitamins should therefore be offered to appropriate PSC patients.

IBD and Colon Cancer

As discussed previously, PSC is strongly associated with IBD. In most cases, the diagnosis of IBD precedes the diagnosis of PSC, but IBD can be diagnosed at any point during the course of PSC. Given that risk of colon cancer in PSC patients appears to be even higher after liver transplantation, patients with an intact colon should undergo screening colonoscopy during transplant evaluation and an aggressive screening regimen should be continued after transplantation.

SUMMARY

PSC is a progressive cholestatic disease that eventually results in liver failure. It is strongly associated with IBD. No medical therapy has shown evidence to alter the natural history of the disease. Endoscopic and percutaneous interventions are the main modalities in managing patients with dominant biliary strictures. In very selected patients with preserved liver function, intrahepatic bile duct resection with hepaticojejunostomy reconstruction over transhepatic stents offers good long-term results and prolonged survival. Patients with evidence of liver disease should be referred to a transplant center. Patients diagnosed with or suspected to have CCA should be offered a multimodality therapy including preoperative chemoradiation and possible liver transplant.

Suggested Readings

Chapman RA, Pitt HA, Keller AM, et al. Primary sclerosing cholangitis: onset, illness, or homeland? Ann Surg. 1998;227:612–623.

Clavien PA, Harder RW, Sterling HF, et al. Sclerosing cholangitis: biliary resection with Roux-limb transhepatic stents. Surgery. 1989;106:324–330.

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Pawlik TM, Ribeiro VA, Pitt HA, et al. Primary sclerosing cholangitis: role of intrahepatic biliary resection. J Am Coll Surg. 2006;203:822–830.

Rabl S, Pawlik TM. Primary sclerosing cholangitis: the role of intrahepatic bile duct resection. Adv Surg. 2009;43:175–188.

Management of Intrahepatic, Hilar, and Distal Cholangiocarcinomas

Michele M. Gage, MD, Mohammad Al Efishat, MD, and Richard A. Burkhart, MD

Cholangiocarcinoma, or bile duct cancer, originates from the epithelial lining of the biliary tree, and accounts for approximately 3% of all gastrointestinal tumors. They are the second most common primary liver tumor after hepatocellular carcinoma (HCC). The overall incidence of cholangiocarcinoma has been rising, though incidence varies by geographical location resulting from environmental and genetic differences. Incidences range from 113 per 100,000 person-years in Thailand, where liver flukes are endemic, to 0.5 to 1.5 per 100,000 person-years in the Western Hemisphere. The best chance for long-term survival and cure is surgical resection with a negative margin; however, cholangiocarcinoma is often diagnosed late, and only one-third of patients qualify for curative resection at diagnosis. Even after surgical resection, disease recurrence is common and the 5-year survival can range from 10% to 50% or more depending on disease stage.

Cholangiocarcinoma typically affects patients in the sixth or seventh decade of life and has a slightly higher predominance in men than women. Most cholangiocarcinomas in the Western population are likely sporadic in nature. There have been several risk factors recognized across populations, including biliary tract disorders (such as primary sclerosing cholangitis), parasitic infections (such as liver flukes Opisthorchis viverrini and Clonorchis sinensis endemic in Southeast Asia), hepatic toxins, and hepatitis B and C. Genetic polymorphisms, inflammatory bowel disease, choledochal cysts, cirrhosis, diabetes, obesity, hepatolithiasis, cholecholithiasis, and alcohol abuse have also all been linked to cholangiocarcinoma.

Cholangiocarcinoma is a diverse disease that is clinically grouped according to anatomical location within the biliary tree: intrahepatic, hilar (also known as Klatskin tumors), or distal. Intrahepatic tumors arise within the liver parenchyma and account for less than 10% of all cholangiocarcinomas. Hilar tumors are located in the extrahepatic biliary tree above the cystic duct and are the most commonly seen disease (60%–70%). Distal tumors are those that are centered in the extrahepatic biliary tree below the cystic duct takeoff and account for 20% to 30% of all cholangiocarcinomas. Cholangiocarcinomas commonly propagate longitudinally along the bile ducts resulting in disease that can overlap these anatomic landmarks.

The dominant histopathology is adenocarcinoma, and there are three classical subtypes of disease on microscopy: sclerosing, nodular, and papillary. The most common subtype is sclerosing cholangiocarcinoma, which is thought to extend in a subepithelial plane and cause thickening of the duct without a significant obstructing intraluminal mass. These are often detected clinically only after significant growth, and in many cases, discovered at a stage of disease that precludes resection. Nodular cholangiocarcinomas also result in thickening of the duct, but the radial growth pattern can clinically result in early biliary obstruction allowing for earlier diagnosis in some patients. Papillary cholangiocarcinomas consist of approximately 10% of all cholangiocarcinomas and typically arise in the distal bile duct. Papillary tumors are typically polypoid and expand the lumen of the duct. In all subtypes, perineural and lymphovascular invasion of the hepatoduodenal structures are also frequently seen.

INTRAHEPATIC BILE DUCT CANCER

Presentation and Preoperative Evaluation

Similar to many intrahepatic tumors, intrahepatic cholangiocarcinoma (ICCA) is often discovered incidentally on imaging obtained for an unrelated reason. When symptomatic, patients can present with a variety of symptoms including abdominal pain, fatigue, weight loss, poor appetite, and fever. Physical examination findings range from an asymptomatic patient to jaundice and signs of chronic liver disease. Rarely, patients may develop paraneoplastic dermatologic syndromes such as Sweet's syndrome, erythema multiforme, or porphyria cutanea tarda. Laboratory evaluation includes a liver chemistry panel, which may reveal an elevation in liver enzymes with an obstructive (direct) hyperbilirubinemia and an elevated alkaline phosphatase. Cancer antigen 19-9 (CA19-9) is the most likely tumor marker to be elevated (>129 units/mL) but it is neither highly specific nor sensitive for cholangiocarcinoma and can be falsely elevated in cholangitis or cholestasis. Workup should also include tumor markers

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that are associated with primary liver and gastrointestinal tumors such as alpha-fetoprotein in HCC, carcinoembryonic antigen (CEA) in colorectal liver metastasis, chromogranin A in carcinoid tumors, and immunoglobulin profiling in patients with findings suspicious for autoimmune disease.

Cross-sectional imaging with a liver-protocol multiphase, contrast-enhanced magnetic resonance imaging (MRI) or multiphasic contrast-enhanced multidetector computed tomography (CT) is a mainstay of the diagnostic evaluation and can aid in differentiating intrahepatic cholangiocarcinoma from HCC or focal nodular hyperplasia. It is also useful for operative planning by identifying aberrant ductal anatomy. Radiographic features of intrahepatic cholangiocarcinoma vary depending on tumor type: mass-forming, periductal infiltrating with intrahepatic ductal dilation, or annular type. On multiphasic contrast-enhanced multidetector CT, intrahepatic cholangiocarcinoma usually appears as a well-defined or infiltrative hypodense lesion with biliary dilatation, often with capsular retraction, and exhibits rim enhancement throughout both arterial and venous phases. On liver-protocol multiphase, contrast-enhanced MRI, it appears as a hypointense lesion on T1-weighted images and heterogeneously hyperintense on T2-weighted images. Primary liver cancer can arise with a histologic subtype of mixed HCC-ICC. These often appear as an irregular mass with rim enhancement on gadoxetic acid–enhanced MRI, whereas mass-forming ICCA appear as lobulated lesions with a weak rim and a target appearance. Of note, these mixed tumors are staged as ICCA rather than HCC.

Classic findings on history, physical examination, and cross-sectional imaging can often obviate the need for biopsy. When doubt about the underlying etiology of disease exists, metastatic disease from another primary malignancy should be kept in mind. In these instances, a search for a primary tumor can be sought with upper and lower endoscopy, chest CT, and mammography in female patients. For ICCA presenting with typical imaging characteristics and high-quality data, positron emission tomography scan is infrequently used. In patients with resectable disease, many surgeons advocate for a staging laparoscopy during the workup to evaluate for occult peritoneal dissemination.

Surgical resection is the primary treatment modality in localized disease as summarized by guidelines summarized by the National Comprehensive Cancer Network. Characteristics of disease that preclude resection include metastatic disease on preoperative staging and lymph node metastasis beyond the porta hepatis. Although disease spread to locoregional (portal) lymph nodes is not a contraindication to resection, the prognosis of patients with gross disease in this location is generally poor. Multifocal hepatic disease is a strong indicator of systemic disease spread and, although not an absolute contraindication to resection, patients presenting with this pattern of disease are poor candidates for a surgery first approach to management. Additional poor prognostic factors include the presence of small localized satellite lesions and portal hypertension. Technical resectability is defined as the ability to completely remove the disease while leaving an adequate future liver remnant (FLR). Unresectable local disease is most commonly noted for tumors that involve either inflow or outflow bilaterally. Other technical resectability can only be determined by intraoperative exploration and attempt at extirpation.

An assessment of liver volumes and function should be performed as part of preoperative planning. The volume of the FLR should, at the least, be estimated from cross-sectional imaging. When major hepatectomy is planned, CT volumetrics can assist with preoperative risk assessment. An FLR of at least 20% to 40% of normal hepatic parenchyma (two contiguous Couinaud's segments) should be maintained postresection with an intact arterial and portal inflow, hepatic venous outflow, and biliary enteric drainage. If cirrhosis is present or suspected, the FLR needed is increased, with most surgeons targeting 40% to 50%. The Child-Turcotte-Pugh score and the Model for End-Stage Liver Disease score are commonly used to indirectly assess liver function and degree of cirrhosis. Other hepatic functional assessment using a variety of techniques, including indocyanine green kinetics, is also selectively used when considering major hepatectomy.

In preparing for surgical resection, preoperative global functional assessment is ideal given the morbidity (30%–50%) and mortality (5%–10%) of major hepatic resections in this patient population. Common tools used for functional assessment include Eastern Cooperative Oncology Group performance status (range, 0–5), G8 geriatric screening tool (range, 0–17, with a score of 14 or less identifying at-risk individuals), and the American College of Surgeons Surgical Risk Calculator (http://riskcalculator.facs.org).

Staging

Historically, staging guidelines for ICCA were identical to those used for HCC. In 2010, however, the seventh edition of American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system introduced a unique staging system for ICCA. Though prognosis was better stratified in the context of this unique system, long-term survival was not different in patients with stage II and stage III disease. The AJCC eighth edition revised guidelines were published in 2017 (Table 1) and have incrementally improved prognostic capacity, particularly in the ability to separate survival between T1b2 disease and T3 disease. This is a result of the T1 category being divided to reflect the prognostic importance of tumor size, and the T2 category now takes into account the prognostic values of vascular invasion and tumor multifocality. Despite the improvements in the staging of T stage, it is important to note that survival differences across several of the clinical stages remain small (stage IIa, II, and IIIa, for example, have similar rates of 5-year overall survival).

Management

Resection

Liver resection achieving negative margins offers the only chance for cure and should be attempted in the cohort of patients who are otherwise healthy and share goals of care that are in line with early, aggressive surgical management. Historically, curative resection with tumor-negative margins can be achieved in less than 30% of patients. This number appears to be improving as advances in intraoperative ultrasound imaging and resection techniques continue to evolve. Portal lymphadenectomy is recommended, and these lymph nodes are positive in approximately one-third of patients. The benefit of lymphadenectomy is controversial and likely limited to prognostic value. Positive resection margins and positive nodes are associated with worse prognosis. Adjuvant gemcitabine-based chemotherapy and fluoropyrimidine-based chemoradiation may be beneficial, although high-quality data are lacking. Extent of resection depends on tumor size and the expected residual volume of the liver, which could range from nonanatomic wedge resection for small tumors to formal anatomic resections, such as extended hepatectomy, for large tumors. If the FLR is too small, preoperative unilateral portal vein embolization can result in contralateral hypertrophy of the FLR and help to define, and at times mitigate, the risk of postoperative liver failure. Major liver resection combined with portal and/or caval resection and reconstruction has been performed safely in highly selected patients who are otherwise healthy, but these operations should only be performed in high-volume or liver transplant centers.

In an open operative approach, a right subcostal incision, which can be extended bilaterally to a chevron incision with or without a vertical midline extension, provides excellent exposure. A midline incision may be used for selected lesions, or when a liver resection is combined with curative abdominal surgery. Based on suspicion from preoperative imaging, diagnostic laparoscopy may precede open operation to assess for carcinomatosis or assess the extent of multifocal disease if suspected. Increasingly complex hepatectomies for malignant disease are successfully performed laparoscopically or robotically, and the decision on an open versus minimally invasive approach is surgeon dependent. The safety of minimally invasive

TABLE 1 Tumor-Node-Metastasis Staging System for Intrahepatic Cholangiocarcinoma, Eighth Edition

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
REGIONAL LYMPH NODES (N)	
NX	Cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis present

PROGNOSTIC STAGE			
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

From Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. ©American College of Surgeons.

surgery in hepatic resections is increasingly demonstrated by high volume surgeons in the literature.

Surgery typically begins with exploration, often laparoscopically, to rule out metastatic disease in the abdomen. For a hemihepatectomy or extended hepatectomy, the liver is mobilized by incising the coronary, triangular, and falciform ligaments. Intraoperative ultrasound is helpful in localizing the tumor, ruling out occult liver lesions, and delineating the parenchymal anatomy. A cholecystectomy is typically performed. Inflow is controlled in the hilum, and venous outflow is controlled by isolating the corresponding hepatic vein(s), generally extrahepatically, before parenchymal transection. In selected cases, the vein can be transected before parenchymal dissection to decrease blood loss. A flamed tourniquet can be positioned around the hilar vasculature in preparation for a Pringle's maneuver, should it become necessary. When used, Pringle's inflow occlusion can vary between surgeons. One common strategy is to maintain occlusion for periods of 15 minutes with 5 minute periods of reperfusion. Parenchymal transection is also surgeon dependent with the more commonly used techniques being the clamp crush technique, stapled hepatic resection, and transection with ultrasonic dissection or energy devices. Practically, a combination of the above is used as the situation demands with ties, titanium clips, and cautery used for hemostasis and biliary ligation. Direct pressure, Prolene suture, and topical hemostatic agents can also be used to control bleeding from the raw surface of the liver. The use of drainage catheters following major liver resection is surgeon dependent and our use is largely confined to patients requiring multivisceral resections, biliary-enteric reconstruction, or diaphragmatic repair.

Other Treatments

Unfortunately, many patients with intrahepatic cholangiocarcinoma present with unresectable disease, and even for those who undergo surgical resection, many recur either locally in the liver (25%–70%) or outside the liver (10%–30%) and are thus managed with palliative intent. Survival rates for resected patients are generally between 20% and 50% at 5 years (depending on stage). Patients who underwent R0 resections with node negative tumors can have 5 year survival rates that exceed 60% in some series. Adjuvant chemotherapy using a gemcitabine/cisplatin (per the ABC trial) or capecitabine/gemcitabine followed by FU based chemoradiotherapy (per the adjuvant Southwestern Oncology Group 50800 trial) should be considered in high risk patients with R0 resection. These adjuvant therapies are strongly recommended in R1 resection or positive lymph nodes, as these patients are managed similar to those with unresectable disease. Stereotactic body radiotherapy is an alternative to FU based chemoradiotherapy and is starting to gain favor in high volume centers.

Liver transplantation has yet to become widely accepted for ICCA and is most commonly considered in those with HCC or perihilar cholangiocarcinoma, however, transplantation may be considered in the context of a clinical trial for highly selected patients with severe liver disease or primary sclerosing cholangitis with ICCA, usually following neoadjuvant chemoradiation. Survival data suffer from selection bias and the inclusion of perihilar cholangiocarcinoma, with some experienced centers reporting 5 year survival of up to 53% following liver transplantation in ICCA.

Patients with unresectable tumors because of poor functional status, inadequate FLR, or locally advanced disease, may still be candidates for external beam radiotherapy, transarterial chemoembolization (TACE), transarterial radioembolization, or ablation. TACE and selective radioembolization with radioactive isotopes (e.g., iodine 131 labeled lipiodol or yttrium 90 tagged glass or resin microspheres) are appealing options given that most of the tumor blood supply is derived from the hepatic artery rather than the portal vein. Large unresectable tumors can sometimes be converted to resectable disease following TACE or radioembolization. Ablative techniques for ICCA include radiofrequency ablation, microwave ablation, irreversible electroporation, and photodynamic therapy (PDT). Several limited studies have demonstrated the safety and efficacy of these local therapies, but there are no high quality data to support the use of one approach over another in ICCA.

HILAR CHOLANGIOCARCINOMA

Presentation and Preoperative Evaluation

Early diagnosis of hilar cholangiocarcinoma most commonly presents with symptoms of jaundice and pruritus, which is present in up to 90% of patients. Other symptoms are relatively nonspecific and include abdominal pain, fatigue, weight loss, and anorexia. The diagnosis can also be made following work up of abnormalities on routine laboratory tests, or imaging obtained to diagnose vague symptoms. Despite a relatively early presentation commonly driven by clinically apparent symptoms, in comparison to ICCA, the proximity of the hilum to critical structures does raise the specter of involvement of critical vascular structures that can preclude resection.

Once hilar cholangiocarcinoma is suspected, a thorough evaluation is recommended. This typically includes high-quality cross-sectional imaging with CT of the chest, abdomen, and pelvis. MRI is a commonly used modality for imaging of the liver in this setting and anatomic delineation of the disease can be clarified by formal magnetic resonance cholangiopancreatography. In the absence of need for decompression of biliary biopsy, magnetic resonance cholangiopancreatography has been shown to be equivalent to endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of hilar cholangiocarcinoma. The chest imaging is used to rule out metastatic disease, whereas abdominal imaging assists in evaluating the degree of local and distant invasion, particularly vascular invasion, portal lymphadenopathy, hepatic atrophy, and biliary dilatation. Invasion of the right hepatic artery is more commonly observed than the left because of the right hepatic artery's proximity to the ductal confluence. Laboratory profiling should include, at a minimum, liver function tests and tumor markers CA19-9 and CEA. Sensitivity and specificity of CA19-9 and CEA vary widely, and these values should not be used to a diagnostic capacity in the setting of jaundice and biliary mass. Tissue diagnosis is often difficult to obtain and is not necessary if laboratory and imaging findings are pathognomonic for disease.

The approach to disease in the hilum mimics that for HCC with resection as a primary modality when technically achievable. Criteria for unresectable disease include main portal vein involvement, bilateral spread to secondary biliary radicals, bilateral hepatic artery and/or portal venous branch involvement, unilateral hepatic artery involvement with contralateral ductal spread, and/or presence of distal metastases (Box 1). Clinical staging paradigms, as discussed further in this chapter, have been developed to assist surgeons in patient selection.

The preparation of a patient for resection in hilar cholangiocarcinoma requires careful preoperative planning. The underlying principle of resection is an attempt to achieve R0 resection. As historical data have demonstrated that rates of R0 resection are improved in the setting of concomitant hepatectomy, the standard of care dictates a major hepatectomy in conjunction with extrahepatic biliary resection and reconstruction. For patients with obstructive jaundice and cholestasis, preoperative biliary drainage has been associated with decreased postoperative complications and mortality. There is currently not a standard optimal preoperative bilirubin level, though cutoffs of 5 to 10 mg/dL are frequently used to trigger biliary intervention. Both endobiliary prosthesis and percutaneous biliary drainage catheters can be used to relieve hepatic congestion, and the debate about an ideal approach is ongoing.

Before surgery, all patients should undergo a thorough review of general functional and medical status, particularly in regards to their likelihood of tolerating a major liver resection. Due to frequent intrahepatic or vascular involvement in hilar cholangiocarcinoma, major hepatectomy is the standard of care, and the ability of the patient to tolerate this procedure and the remaining FLR should be carefully assessed. Portal vein embolization, as described for intrahepatic cancers above, should be considered for patients who are estimated to have less than 25% to 30% FLR.

BOX 1 Local Tumor-Related Criteria for Unresectability

- Hepatic duct involvement up to secondary biliary radicals bilaterally
- Encasement or occlusion of the main portal vein proximal to its bifurcation*
- Atrophy of one hepatic lobe with contralateral encasement of portal vein branch
- Atrophy of one hepatic lobe with contralateral involvement of secondary biliary radicals
- Unilateral tumor extension to secondary biliary radicles with contralateral vein branch encasement or occlusion

Modified from Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507.

*Relative criterion. Portal vein resection and reconstruction may be possible.

Staging

The three most commonly used staging systems for hilar cholangiocarcinoma are the Bismuth Corlette, AJCC TNM, and the Blumgart staging system. Bismuth and Corlette published one of the first anatomical classification systems for hilar cholangiocarcinomas. Based on tumor location and ductal infiltration, tumors are classified into four categories (Fig. 1). This system is useful for stratifying patients based on the degree of involvement through the biliary tree but does not provide information regarding resectability or survival since vascular, lymphatic, and hepatic parenchymal findings are not noted. The AJCC TNM system (Table 2) is one of the most commonly used, and considers size, presence of the tumor, regional nodal involvement, and metastases. This staging system, commonly used in the preoperative period, has limitations in both the assessment of technical resectability and in prognostic stratification (sharing many of the same concerns as the BCLC system described previously). The Blumgart system expands on the Bismuth Corlette system by classifying patients into three T stages based on longitudinal and radial extent of the tumor, as well as vascular involvement, and liver atrophy (Table 3). Increased T stage has been associated with decreased likelihood of R0 resection and associated worse survival (Table 3 and Box 1). The unique characteristics of the Blumgart system have resulted in a facile tool for surgical patient selection.

Management

Surgical Resection

Surgical resection is the best chance of cure and long-term survival. Resection is often challenging and options include hepatectomy, pancreaticoduodenectomy, or liver transplantation in attempts to achieve R0 resection. As many as 80% of patients are found to have metastatic or unresectable disease at time of exploration, and some surgeons use exploratory laparoscopy before laparotomy as a matter of routine. A right subcostal incision, often with midline extension, is commonly

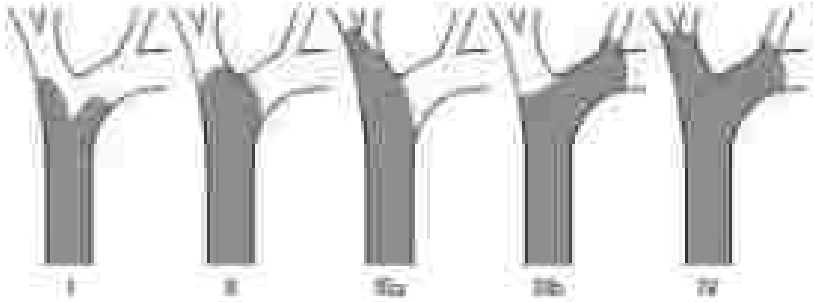

FIG. 1 Bismuth-Corlette classification of hilar bile duct cancers. Type I, tumors located distal to hepatic confluence. Type II, tumors involving the confluence. Type IIIa, tumors involving the confluence and right hepatic duct. Type IIIb, tumors involving the confluence and the left hepatic duct. Type IV, tumors involving both right and left hepatic ducts. (From Jarnagin WR, Schwartz M. Surgical staging, clinical presentation, and outcome of cholangiocarcinoma of the liver hilum. In: Blumgart LH, Fong Y, eds. Surgery of the liver and biliary tract. 4th ed. London: WB Saunders; 2007:1317.)

TABLE 2 Tumor-Node-Metastasis Staging System for Perihilar Cholangiocarcinoma, Eighth Edition

PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1-3 positive lymph nodes typically involving the bile, cystic duct, common bile duct, hepatic artery, portal vein, pancreaticoduodenal, and portal vein lymph nodes
N2	4 or more positive lymph nodes from the sites described for N1
DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis present

PROGNOSTIC STAGE			
0	Tis	N0	M0
I	T1	N0	M0
II	T2a-b	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IVA	Any T	N2	M0
IVB	Any T	Any N	M1

From Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. © Society American College of Surgeons.

and the exposure. Other options for selected tumors include a chevron, Mercedes, or midline laparotomy. The steps of the operation can vary according to surgeon preference and patient disease. One common approach is outlined briefly herein.

The hepatoduodenal ligament is dissected and the portal triad is skeletonized in keeping with the principles of a formal lymphadenectomy. Tumor tissues are often left intact with the main specimen during the course of the early dissection. The bile duct is transected distally and a margin is sent for frozen section. This assists in operative planning because it determines if a pancreaticoduodenectomy is necessary for a negative margin. Next, the bile duct is reflected anteriorly and the portal vein and hepatic artery are dissected free and assessed for tumor involvement. The gallbladder may be removed at this time or maintained for use as retraction. Resectability is assessed by evaluating local tumor invasion to the surrounding vasculature. Cases are deemed unresectable in the event of unreconstructible main portal vein involvement, bilateral hepatic artery involvement, involvement of the artery or vein on the contralateral side in relation to apparent involvement of the biliary tree, or a positive margin at the common bile duct along its entry into the pancreas in a patient who would not tolerate concomitant pancreaticoduodenectomy with their resection. Here, preoperative risk stratification and judgment on surgical risk assumed by more advanced technical maneuvers are required of the operating surgeon. Practically, involvement of bilateral biliary secondary radicals is often unknown until division of the ducts and committing to operative extirpation.

If the tumor is deemed unresectable, local excision of the bile duct should be completed at this time (if feasible) with creation of a Roux-en-Y hepaticojejunostomy for palliation. If resectable, proceeding with hilar resection in the context of hepatectomy is appropriate. The choice of hepatectomy (right vs. left, standard vs. extended) is dictated by intraoperative findings and informed by preoperative staging as discussed previously. Caudate resection is typically performed for all patients with hilar disease. Commonly, transection of the hepatic artery and portal vein supplying the specimen side of the liver is completed as the next step. The hepatic vein to the corresponding liver can then be transected and hepatectomy is performed. The transection of the hepatic ducts is often the last maneuver to be undertaken, as this margin would dictate R (resection) status of the surgery. The proximal margin should also be assessed by frozen section analysis and a positive result should prompt a further dissection of the biliary tree, if possible, in attempt to reach a negative margin. There are reports of extrahepatic biliary tree resection without hepatectomy in the absence of vascular involvement and relatively low lying tumors without preoperative evidence of disease extending into the second-order biliary radicals. If this approach is to be taken, both the right and left hepatic ducts should be assessed for local involvement of disease prior to leaving the operating room. In the context of historical data demonstrating increased rates of R1 resection, caution should be used before adopting this approach.

Following resection, a Roux-en-Y hepaticojejunostomy is commonly performed for reconstruction. Commonly, more than one biliary radical is found that requires anastomosis. In these cases, it may be considered to join two adjacent lumens with sutures to make a

TABLE 3 Blumgart Clinical Tumor Staging for Hilar Cholangiocarcinoma

T1	Tumor involving the biliary confluence + unilateral extension into second-order biliary radicles
T2	Tumor involving biliary confluence + unilateral extension to second-order biliary radicles and unilateral portal vein involvement + unilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence with bilateral extension to second-order biliary radicles, or unilateral extension to second-order biliary radicles with contralateral portal vein involvement, or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy, or main or bilateral portal venous involvement

From Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234(4):507-517.

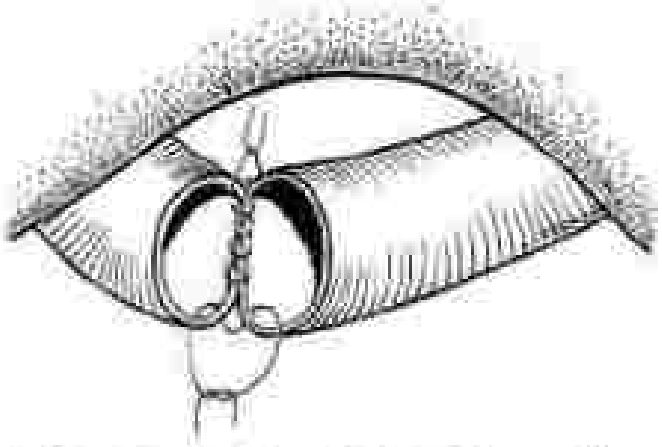

FIG. 2 Vascular anatomy of adjacent hepatic anatomy. (From Jarnagin WR, Blumgart's Surgery of the Liver, Pancreas, and Biliary Tract, 5th ed. Philadelphia: Elsevier; 2012.)

common wall, enabling creation of a single enteric anastomosis (Fig. 2). Drains are universally used in our practice for combined hepatectomy with bile duct reconstructions.

Additional Treatments

Chemotherapy and radiation are typically offered to patients with unresectable disease, postoperative patients as adjuvant therapy, or preoperative patients as neoadjuvant therapy. While studies are limited, gemcitabine-based combination chemotherapies have demonstrated prolonged overall survival when used as adjuvant therapy. Routine chemoradiotherapy is also being studied with prospective trials under way. There is an expanding experience with transplant in hilar cholangiocarcinoma after neoadjuvant chemoradiation. Initial data demonstrate that long-term survival is possible in this highly selected cohort. PDT is also being explored as a palliative modality in unresectable cases of hilar cholangiocarcinoma but is not routinely performed in all high-volume centers. This involves intravenous administration of a photosensitizing agent, such as porphyrin, which accumulates in cancer cells. Phototherapy is then delivered, intraluminally by cholangioscopy, generating oxygen free radicals and tumor cell death. There is some evidence PDT may increase survival by up to 3 months compared with biliary stenting alone.

DISTAL CHOLANGIOCARCINOMA

Presentation and Preoperative Evaluation

Distal cholangiocarcinoma, or cholangiocarcinoma arising between the cystic duct and the ampulla of Vater, commonly presents with painless jaundice and other nonspecific abdominal symptoms including nausea, anorexia, fatigue, and weight loss. Liver enzymes are typically elevated, with a bilirubin elevated more than 10 mg/dL being highly suggestive of a malignant process. Initial ultrasound performed for jaundice will typically reveal both intrahepatic and extrahepatic biliary ductal dilatation, compared with only intrahepatic dilatation in hilar cholangiocarcinoma. High-quality imaging with CT or MRI of the chest, abdomen, and pelvis is helpful in assessing invasion of surrounding structures, anatomical abnormalities, and regional or distant metastases. Pancreatic atrophy or pancreatic ductal dilatation may be present based on location of the tumor. These tumors can be very small and difficult to characterize on imaging. Preoperative laboratory values and tumor markers (CA19-9 and CEA) should also be evaluated.

Though not always necessary, invasive studies such as ERCP with EUS may be utilized to further characterize the tumor and obtain a tissue diagnosis. In cases of cholangitis or severe hepatic congestion, ERCP and stent placement can also provide therapeutic drainage; however, routine ERCP with stenting is not recommended unless necessary because it increases the risk of postoperative infection resulting from colonization of the biliary tree. Relief of jaundice is not as critical as in hilar cholangiocarcinomas because hepatectomy is rarely necessary in distal cholangiocarcinomas. Preoperative assessment should similarly evaluate the patient's ability to tolerate local excision of the biliary tree and/or a pancreaticoduodenectomy.

TABLE 4 Tumor-Node-Metastasis Staging System for Distal Cholangiocarcinoma, Eighth Edition

PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed
T0	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth <5 mm
T2	Tumor invades the bile duct wall with a depth of 5–12 mm
T3	Tumor invades the bile duct wall with a depth >12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to 1–3 regional lymph nodes
N2	Metastasis to ≥4 regional lymph nodes
DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis present

PROGNOSTIC STAGE

0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIA	T2	N0	M0
IIB	T2	N1	M0
IIB	T3	N0–1	M0
IIIA	T1–3	N2	M0
IIIB	T4	Any N	M0
IV	Any T	Any N	M1

From Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual, 8th ed. New York: Springer; 2017. Courtesy American College of Surgeons.

Staging

Distal cholangiocarcinoma is most often staged by the AJCC TNM system (Table 4). The TNM staging shares some similarities with the system for proximal bile duct cancers. For example, T1 and T2 are confined (T1) or invade through (T2) the bile duct wall, whereas T3 includes invasion of adjacent organs and T4 includes invasion of adjacent vasculature. The nodal staging system differs, however, with two classifications (N1, N2) as opposed to three (N1, N2, N3) for perihilar bile duct cancers. The nodal staging is performed at the time of surgery with the sampling of at least 12 nodes, analogous to the management of pancreatic cancer.

Management

Surgical Resection

The goals of resection are as follows: remove the tumor, relieve obstruction, and provide accurate staging information to direct selection of further therapies. Resection of distal cholangiocarcinomas requires pancreaticoduodenectomy in the majority of cases. Resectability is assessed intraoperatively by confirming the absence of distant metastatic disease and evaluating for unresectable vascular invasion. The procedure may be performed open, laparoscopically, or robotically. In proceeding with open resection, an upper midline incision provides excellent visualization. Unlike hilar cholangiocarcinomas, distal cholangiocarcinomas are frequently identified relatively early in their disease course and metastatic disease not identified on CT is less likely (5%–10%). For this reason, many surgeons forego routine staging laparoscopy and opt to begin with a multidisciplinary.

As discussed by several chapters, there is variation in the order of maneuvers done for pancreaticoduodenectomy. One common approach is as follows. After exploration for metastatic disease, the duodenum, head, and uncinate process of the pancreas are mobilized out of the retroperitoneum with wide lymphadenectomy. The course of the superior mesenteric artery is assessed. The superior mesenteric vein is identified along the inferior border of the pancreatic neck and the portal vein is inspected in the porta hepatis. Also, in and around the porta, the common hepatic artery, gastroduodenal artery, and proper hepatic artery are inspected for resectability. The gastroduodenal artery is identified, dissected free, and ligated. A permissive pulse in the porta hepatis should be verified. At this point, if all critical structures are verified to be free of tumor involvement the case may proceed. Venous involvement of the tumor may not preclude resection so long as the operative team is prepared and experienced with vascular resection and reconstruction. Arterial resection and reconstruction remain controversial in the setting of periampullary malignancy.

The stomach is transected with a linear cutting stapler approximately 4 to 6 cm proximal to the pylorus. Alternatively, a pylorus-preserving pancreaticoduodenectomy spares the pylorus. The gastroduodenal artery is then transected with silk ties, and the common stump is reinforced with Prolene suture. The common bile duct is then transected with electrocautery, and a bulldog clamp is used to control bile spillage. A frozen section of the duct is sent to ensure a negative margin. A Penrose drain is placed through the previously established tunnel behind the pancreas, and the neck of the pancreas is divided with electrocautery or scalpel. Next, the transverse mesocolon is elevated and the ligament of Treitz (LOT) is identified. The LOT is incised and the first portion of the jejunum is mobilized. The jejunum is then transected with linear cutting stapler approximately 10 to 20 cm from the LOT. The proximal jejunum is separated from the mesentery and passed into the right upper quadrant through the LOC. Last, the dissection is completed by separating the head and uncinate process of the pancreas from the portal vein, superior mesenteric vein, and superior mesenteric artery using a combination of sharp dissection, silk ties, and energy devices. This from the Whipple specimen to be sent off as specimen.

For reconstruction, a pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy are performed. First, the LOT defect is closed with running Prolene suture. The cut surface of the jejunum is then passed through a defect created in a bare area of the transverse mesocolon to the right of the middle colic artery. The staple line of the jejunum is removed and laid onto the pancreas without tension. An end-to-side pancreaticojejunostomy (PJ) is created in two layers. There are myriad techniques to construct the PJ with few demonstrating superiority. In our center, we commonly use a two-layer duct-to-mucosa technique. Next, for the hepaticojejunostomy, an end-to-side hepaticojejunostomy is created with absorbable suture. The jejunum is tacked to the transverse mesocolon at the point of passage through the transverse colon mesentery to secure the afferent limb and close this defect. The jejunum is then traced approximately 40 cm to a point where it may easily approximate the stomach. An antecolic gastrojejunostomy (or duodenojejunostomy if a pylorus preserving pancreaticoduodenectomy was performed) is then constructed. Similar to the PJ, a variety of techniques have been demonstrated to function well for these anastomoses. At creation of the operative, closed suction drainage is employed routinely after a Whipple operation in our practice.

Other Treatments

Similar to hilar cholangiocarcinoma, chemotherapy and radiation are typically offered to patients with unresectable disease or perioperative patients as adjuvant therapy. Because of the rarity of disease, the role of adjuvant chemotherapy and chemoradiotherapy in patients with resected distal cholangiocarcinomas is poorly defined. Many studies investigating adjuvant therapy in cholangiocarcinoma have combined distal and hilar cholangiocarcinomas as one entity, extrahepatic disease, and at times have often included gallbladder cancers. As such, the true benefit of adjuvant disease is difficult to ascertain. Most adjuvant chemotherapy and chemoradiation regimens demonstrating benefit have been fluoropyrimidine or gemcitabine based. However, there is limited clinical trial data to define a standard regimen. In the metastatic setting, a 2010 randomized, controlled, phase III trial (ABC-02 study) demonstrated improved overall survival of gemcitabine and cisplatin combination therapy compared to gemcitabine alone. More recent studies have demonstrated similar findings, and combination gemcitabine-cisplatin is considered first line chemotherapy for patients with advanced or metastatic biliary tract cancers. PDT may also be considered as a palliative modality in unresectable cases of distal cholangiocarcinoma.

SUMMARY

Cholangiocarcinomas are a diverse group of tumors with evaluation and initial management considerations based largely on location in the biliary tree and the extent of local disease or evidence of dissemination. Surgical resection is the cornerstone of treatment in a curative paradigm. Thorough preoperative evaluation for resectability, operative candidacy, and likelihood of R0 resection are required in all cases. For patients requiring liver resection, the estimated FLR should be carefully evaluated before surgery and consideration for biliary decompression should be assessed. The best chance of survival is R0 resection, and frozen sections should be used liberally in the operating room. Though the use of adjuvant therapies is common, definitive evidence of benefit from adjuvant chemotherapy and chemoradiation is mixed at this time. Unfortunately, many cases are diagnosed late, and palliation of symptoms, chemotherapy, and chemoradiation are commonly utilized in these cases. As with all complex oncologic care, management of these cases can often be optimized by multidisciplinary input at high volume centers.

Suggested Readings

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MANAGEMENT OF GALLBLADDER CANCER

Akhil Chawla, MD, and Cristina R. Ferrone, MD

Gallbladder cancer is one of the rarest and most aggressive gastrointestinal malignancies. Surgical resection offers the best chance at long-term survival. Patients generally have a poor prognosis, except those with early stage disease, which is most often found incidentally. The current available systemic therapy is not effective in the majority of patients with high rates of distant metastases. In the United States, patients are often diagnosed after elective cholecystectomy for cholelithiasis–related disease. Alternatively, patients may present after imaging findings suspicious for malignancy are found during workup for symptomatic gallstone disease. In patients found to have disease amenable to resection, only a select group of patients will benefit from an aggressive operation. The surgeon is most often the diagnostician of this rare malignancy. Therefore, an in-depth knowledge of the appropriate workup and management of such patients is mandatory. This chapter focuses on the staging, appropriate evaluation, workup, and treatment of patients with gallbladder cancer.

EPIDEMIOLOGY AND PATHOGENESIS

There is strong variability in the incidence of gallbladder adenocarcinoma that parallels the geographic prevalence of cholelithiasis. The highest rates of malignancy are seen in South American countries including Chile, Bolivia, and Ecuador as well as South Asian and Southeast Asian countries including India, Pakistan, Japan, and Korea, with rates of gallbladder adenocarcinoma in excess than 10 of every 100,000 people. In the United States, gallbladder cancer is rare, with an incidence of just over 2 per 100,000 people.

The median age of diagnosis is 72 years, with a female to male predominance of 2:1 to 4:1. Increasing age as well as the presence of cholelithiasis are both independent predictors of malignancy. These data support the rationale that chronic mucosal inflammation may lead to dysplastic changes and eventual malignant transformation. Further supporting this hypothesis are data which demonstrate metaplasia in nearly one half of examined gallbladder specimens found to have gallstone disease. The adenoma to carcinoma progression seen in various gastrointestinal malignancies may also play a role in the pathogenesis given the increased incidence of adenocarcinoma in gallbladder polyps greater than 10 mm, particularly if solitary.

STAGING AND SURVIVAL

TNM Staging

The eighth edition of the American Joint Committee for Cancer (AJCC) TNM Cancer Staging system for gallbladder adenocarcinoma is shown in Table 1. The T stage, which describes the depth of invasion, has importantly been changed in the latest AJCC staging system. There are strong data demonstrating poorer prognosis of tumors that are located on the hepatic interface of the gallbladder as opposed to the peritoneal side. Tumors invading the perimuscular tissue on the hepatic side, without any extension into the liver parenchyma are now designated as T2b. T2b tumors demonstrate an increase in intrahepatic as well as nodal recurrence after curative radical resection compared with T2a tumors, and therefore portend a worse prognosis. In addition to these changes, the newest edition of the AJCC staging system reclassifies N stage based on the number of nodes involved, rather than the anatomic location of involved nodes. The eighth edition of the AJCC for gallbladder cancer has been validated using the National Cancer Database (Lee et al.) (Fig. 1).

Survival

Historically, the median survival time for patients with gallbladder adenocarcinoma was less than 6 months. There has been an increase in median overall survival to 12 months for all cancers in recent years. This can be attributed to improved surgical technique, lower perioperative morbidity, and the key understanding that improvement in survival is particularly dependent on the final margin status. Incidentally found gallbladder cancers have a far better survival rate than those that are symptomatic. The 5-year survival in patients who are found to have malignancy on final pathology after routine cholecystectomy is 50%. This is more than twice the 5-year survival of unincidentally identified cancers, which are often a more advanced stage of disease at diagnosis. Similar to other cancers, nodal metastases are also an independent predictor of survival. The 5-year survival rate is 65% for patients with early-stage disease (stages I and II) and drops to 20% for patients with stages III and IV disease.

Benefit of an Operation

The true survival benefit of performing a curative minor resection for gallbladder cancer is strongly contingent on the pathologic stage of the tumor. Those with carcinoma in situ tumors (Tis) or tumors invading the lamina propria (T1a) derive no additional benefit from extended cholecystectomy over simple cholecystectomy. Therefore, patients who have incidentally found Tis or T1a malignancies after routine cholecystectomy should not undergo a more aggressive operation. However, it is imperative that such cases are reviewed by an expert pathologist to ensure proper staging.

Depth of invasion (T stage) is an independent predictor of survival in patients with gallbladder adenocarcinoma; therefore, T3 and T4 tumors should be approached with caution, as these cancers have been shown in numerous series to carry a significantly worse prognosis with a marginal benefit from an aggressive operation. T3 and T4 cancers have an increased rate of nodal metastasis and distant metastasis. Historical series do not demonstrate any benefit in resection of these tumors; however, contemporary data indicate a potential benefit for the fit and properly staged patient with a T3 adenocarcinoma. Improved surgical outcomes and modern chemotherapy may account for this discrepancy.

The involvement of nodal disease signifies a significantly worse prognosis. Only 8% of such patients will survive 5 years. Appropriate surgical staging involves portal lymphadenectomy inclusive of recovering at least six lymph nodes, evaluation of the anatomical nodal basin, as well as recovery of any suspicious regional nodal tissue. Patients who are found to have nodal involvement of the aortocaval, celiac, or superior mesenteric artery nodes do not seem to benefit from an operation because they already have disseminated disease disease.

Taken together, patients with a noninvasive malignancy with clinical findings suggestive of locally advanced disease (T3, T4, or N+) should be evaluated by a multidisciplinary team with a strong consideration for neoadjuvant therapy.

PRESENTATION

Incidentally Discovered Gallbladder Cancer

Incidental gallbladder adenocarcinomas are most often identified during or after routine cholecystectomy for gallstone disease. The rate of gallbladder carcinoma after cholecystectomy is less than 0.2%. Outcomes of patients with incidentally identified gallbladder cancers are superior to those in which adenocarcinoma was diagnosed nonincidentally, provided appropriate staging and resection is performed.

Patients who have undergone open cholecystectomy are 17 times more likely to harbor a malignancy than those who underwent laparoscopic cholecystectomy. This is most likely because of the increased difficulty of the operation resulting from the cancer.

TABLE 1 Staging of Gallbladder Cancer

Definition of Primary Tumor (T)	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or muscular layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Definition of Regional Lymph Node (N)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in one to three regional lymph nodes
N2	Metastases in four or more regional lymph nodes

Definition of Distant Metastasis (M)	
M Category	**M Criteria**
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups			
When T is...	**And N is...**	**And M is...**	**Then the Stage Group is...**
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1–3	N1	M0	IIIB
T4	N0–1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVC

From Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Noninicidentally Discovered Gallbladder Cancer

Patients may present with symptomology similar to those with biliary colic, or with unintentional weight loss or vague abdominal pain. Rarely jaundice can be the presenting symptom which portends an extremely poor prognosis, as this a sign of biliary tree involvement. The presence of jaundice is an indicator of increased risk for a margin positive resection and aggressive disease with a disease specific survival of only 6 months. Therefore, for these patients an operation should not be considered, but rather a strategy involving neoadjuvant chemotherapy to treat tumor biology, followed by diagnostic laparoscopy before attempt at curative intent resection.

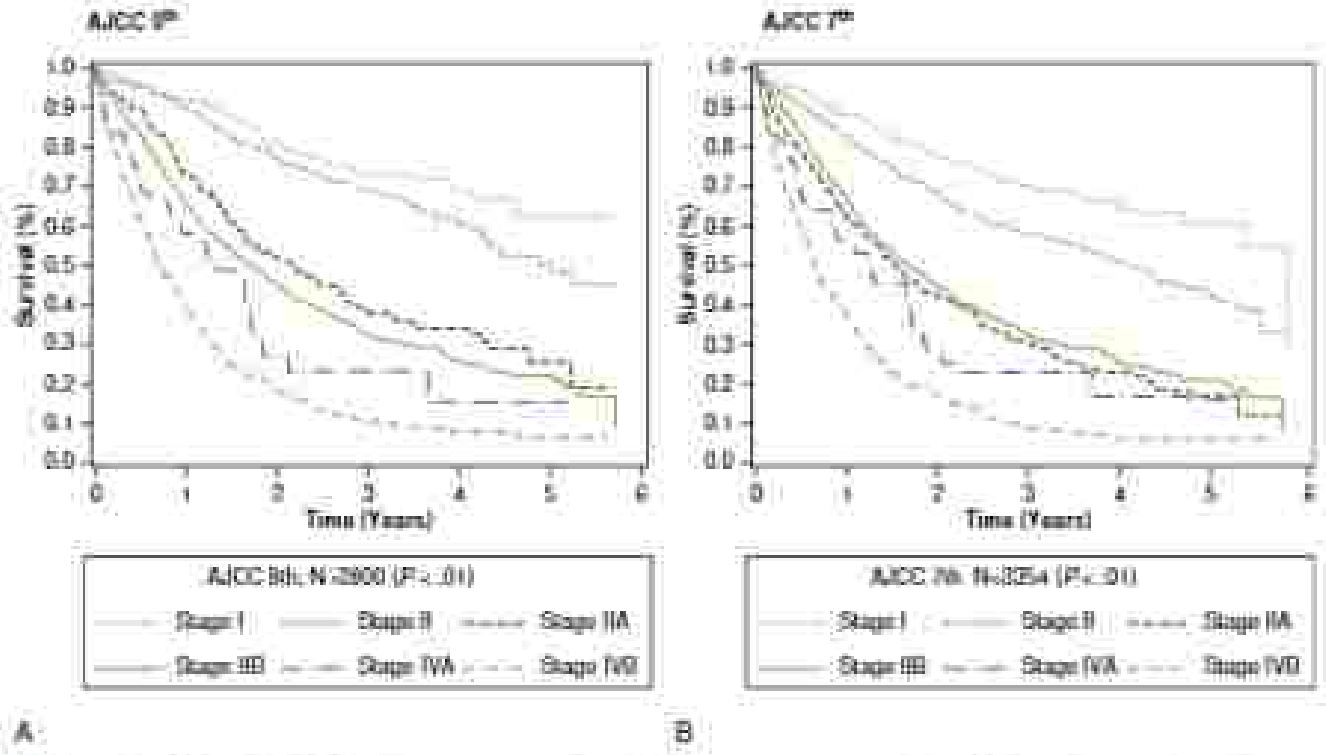

FIG. 1 Comparison of American Joint Committee on Cancer seventh and eighth edition staging system. Although both staging systems have similar c-statistics overall, when evaluated with patients compared, American Joint Committee on Cancer eighth edition was superior to separation of higher stages. (From [A] Chang JS, Tsai CR, Chen LT, et al. Validation of American Joint Committee on Cancer eighth staging system for gallbladder cancer and its prognostication patterns. J Surg Res. 2016;202(2):493–499.e1.)

WORKUP

Patients should have a detailed workup involving tumor markers including carcinoembryonic antigen and CA19-9, as well as expert review of pathology if malignancy is incidentally discovered. In addition, high-resolution cross-sectional imaging is mandatory.

Ultrasonography is the most frequent modality used to image the gallbladder; therefore, it is important to understand the imaging characteristics that increase the probability of a malignancy. High-risk ultrasonography findings that should be further evaluated with cross-sectional imaging include a mass greater than 1 cm, a gallbladder wall with irregular thickening, imaging suggestive of direct extension of the soft tissue in the pericholecystic space or within the liver, biliary obstruction with ductal dilation, lymphadenopathy, as well as nearby liver lesions.

Magnetic resonance imaging (MRI) with gadolinium enhancement allows for enhanced visualization of the biliary anatomy, as well as better definition of small liver lesions, especially in patients with steatosis or cirrhosis. Contrast-enhanced computed tomography (CT) of the abdomen allows excellent visualization of the post-operative resection bed, potential gross margin status from a previous operation, local vascular invasion, lymphadenopathy, variant vascular anatomy for preoperative planning, and evaluation of distant peritoneal or intrahepatic metastases. Both CT and MRI are useful to evaluate for lymphadenopathy with a detection rate of nodal disease in nearly a quarter of patients.

The role of 18-FDG positron emission tomography (PET)-CT continues to be elucidated. If there is a high suspicion of a gallbladder malignancy in the setting of a suspicious gallbladder mass, the sensitivity of a PET scan to detect occult peritoneal, omental, and nodal metastases is only 50%. PET-CT is most useful in those patients with a high risk of distant disease based on initial cross-sectional imaging, as well as in those patients who have a mass incidentally discovered malignancy. PET-MRI is a modern imaging modality that has the advantages of delivering higher spatial resolution in combination with enhanced functional information. Its role in gastrointestinal and biliary tract malignancies continues to be investigated. In our practice, we use PET-MRI to characterize suspicious lymph nodes or intrahepatic nodules that may indicate unresectable disease.

MANAGEMENT

Incidentally Discovered Gallbladder Cancer

Incidentally discovered malignancy may be found either intraoperatively or on postoperative pathology after cholecystectomy. Intraoperative discovery of a gallbladder malignancy during laparoscopic or open cholecystectomy should prompt closure and, if needed, subsequent referral to a hepatobiliary center. This allows for complete staging, a full discussion with the patient and family, pathologic evaluation with regard to depth of tumor invasion, as well preoperative planning for oncologic resection. Patients who undergo a suboptimal positive margin resection fare from shorter to numerous series to have a far worse survival in comparison to those who undergo an oncologically sound margin-negative resection. There is no oncologic detriment to returning to the operating room at a later time.

Cases that are incidentally found to be gallbladder cancer on final pathology after routine cholecystectomy should undergo review by an experienced pathologist (Fig. 1). In our practice, all patients after any diagnosis of gallbladder cancer undergo either staging CT scan or MRI, if not already performed. No additional operation, other than cholecystectomy, is necessary for Tis and T1a lesions. Those with T1b to T3 lesions should be evaluated further for a radical re-resection. T3 lesions with imaging suggestive of nodal involvement or T4 cancers should selectively be offered radical resection based on tumor biology and functional status after consideration of neoadjuvant therapy. T1b and above lesions should be appropriately staged with CT scan of the chest,

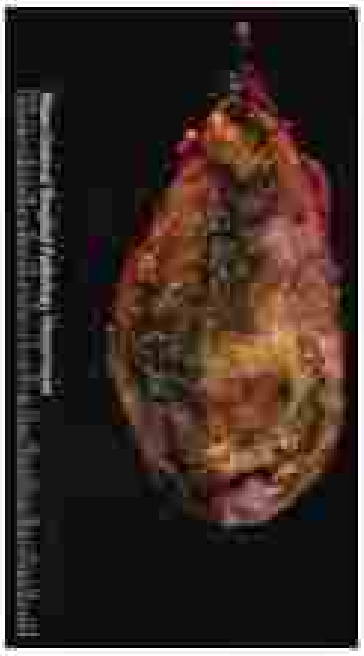

FIG. 2 Incidentally discovered gallbladder cancer. (Courtesy Hatice Gulec, MD, PhD.)

Nonincidentally Discovered Gallbladder Mass

Patients discovered to have imaging suspicious for gallbladder malignancy should be referred to a hepatobiliary center. Before cholecystectomy, patients should undergo appropriate staging including serum tumor markers, cross-sectional imaging including evaluation of the chest for distant disease. Patients with locally advanced disease should be strongly considered for an approach involving neoadjuvant therapy followed by, if appropriate, staging laparoscopy prior to radical resection.

RADICAL RESECTION

The appropriate oncologic operation for a gallbladder adenocarcinoma involves portal lymphadenectomy and partial hepatectomy yielding a microscopically negative (R0) resection margin. Bile duct resection may be performed to achieve negative margins if necessary. There are various facets to this operation which are discussed in detail below and highlighted in Box 1.

Diagnostic Laparoscopy

Currently, the American Hepato-Pancreato-Biliary Association consensus statement recommends the use of staging laparoscopy prior to laparotomy for all patients with suspected gallbladder cancer based on cross-sectional imaging, as well as those with a confirmed diagnosis of gallbladder cancer after a previous operation. Laparoscopy affords the ability to evaluate for distant disease in this aggressive malignancy. Contrary to these recommendations, surgeons often forego redo laparoscopy after a recent cholecystectomy unless the peritoneal cavity was not inspected thoroughly during the index procedure.

Portal Lymphadenectomy

Portal lymphadenectomy is mandatory for a comprehensive staging of gallbladder adenocarcinoma. At a minimum, six portal lymph nodes should be harvested, as survival of patients with node-negative disease is inferior to those who have less than six nodes harvested as compared to those that have six or more harvested, thus indicating that suboptimal lymphadenectomy misses occult nodal metastases.

BOX 1 Important Considerations for the Oncologic Resection of Gallbladder Cancer

- Diagnostic laparoscopy to evaluate for distant disease
- Extended cholecystectomy en bloc resection of gallbladder with hepatic resection of segments IVB/V with frozen section analysis of the hepatic parenchymal margin and cystic duct margin
- Portal lymphadenectomy with harvesting of at least six lymph nodes
- Bile duct excision and reconstruction in the setting of a microscopically positive cystic duct margin

Portal lymphadenectomy should include cystic, pericholedochal, hepatoduodenal, retroportal, posterior pancreaticoduodenal, common hepatic, and right sided celiac nodes. Aortocaval nodes should be considered as distant disease.

Hepatic Resection

Historically, a formal segment IVB/V anatomic liver resection was performed for gallbladder cancer. This has fallen out of favor because this operation has been associated with an increase in perioperative morbidity in comparison to a nonanatomic partial hepatectomy to achieve a negative margin surrounding the gallbladder bed (extended cholecystectomy). Numerous series have demonstrated no oncologic compromise in nonanatomic versus anatomic resection. Therefore, extended cholecystectomy should be performed for any malignancy invading the muscular layer of the gallbladder (T1b).

The operation generally begins with an intraoperative ultrasound evaluation of the liver to exclude distant hepatic metastases and to evaluate the cancer. Ultrasound helps guide the resection by identifying important vascular structures, including the middle hepatic vein and its branches that generally intersect the transection plane. Surgical dissection begins with the porta hepatis and identification of the cystic duct and artery. A formal portal lymphadenectomy is then performed followed by a 2 cm wedge resection of the gallbladder fossa. The thickness of the liver resection should be tailored to the extent of invasion seen by imaging. Frozen section analysis should be performed to maximize the chance of an R0 resection.

Bile Duct Resection

The cystic duct margin should be sent for frozen section analysis early in the operation. Bile duct resection may be necessary when the cystic duct margin is positive. Involvement of the hepatic or common bile duct portends a poor survival with a high rate of nodal metastases; therefore, bile duct excision with reconstruction should be reserved only for carefully selected patients with a microscopically positive margin. Patients who present with gross direct extension into the bile duct identified preoperatively should be treated with neoadjuvant chemotherapy to further test the biology of the tumor. Empiric bile duct resection outside of this setting should not be performed as it has been associated with an increase in perioperative morbidity without an increase in survival. In addition, it does not provide superior portal lymphadenectomy for staging.

Bile duct resection is performed after mobilization of the duodenum followed by transection of the bile duct at the level of the pancreas after confirming margins. Additional hepatic resection or pancreatic resection to obtain a negative margin should not be performed because these do not provide benefit given the increased morbidity of such procedures. Completion of the portal lymphadenectomy is then followed by Roux-en-Y hepaticojejunostomy for reconstruction.

Open Versus Laparoscopic

The safety of the laparoscopic approach has been demonstrated in a retrospective series. However, to date, there have been no randomized studies that have identified the laparoscopic approach to gallbladder cancer as noninferior to an open approach from an oncologic standpoint. Regardless of the approach, the correct oncologic operation needs to be performed with a margin negative hepatic resection and adequate portal lymphadenectomy.

Resection of Previous Port Sites

The practice of resecting previously used laparoscopic cholecystectomy port sites to reduce the chances of recurrence has not been validated and is of historical interest. This practice has been shown to provide no survival benefit, while also increasing the rates of postoperative incisional hernia.

ADJUVANT TREATMENT

Scarce high-quality data currently exist for the optimal systemic strategy in the adjuvant setting for gallbladder adenocarcinoma. Although adjuvant chemotherapy and chemoradiation have been associated with an increase in survival, these modalities seem to be most beneficial to patients with nodal metastases.

Systemic treatment of gallbladder adenocarcinoma is oftentimes guided by the investigation of treatment regimens used in metastatic biliary tract tumors. Two landmark randomized controlled trials evaluating patients with advanced biliary cancers have demonstrated that the combination of gemcitabine and cisplatin is superior to gemcitabine alone in terms of survival. A subgroup analysis has shown the benefit of this regimen in patients with gallbladder adenocarcinoma. Other commonly used regimens include fluorouracil based chemotherapy with the addition of oxaliplatin.

There is currently no level one evidence to support the use of adjuvant chemotherapy over surgery alone or any standard adjuvant regimen over another. An analysis of the National Cancer Database demonstrated a more than 50% increase in survival in favor of adjuvant chemotherapy over surgery alone in patients with T1 to T3 gallbladder adenocarcinomas. However, this population of patients is likely highly selected for in this large retrospective analysis. The landmark BILCAP phase III trial evaluated the benefit of capecitabine in the adjuvant setting over observation after an operation in all biliary tract cancers. Unfortunately, less than 8% of patients included in this trial had a diagnosis of gallbladder adenocarcinoma. The results of this trial suggest a modest improvement in disease free survival rate with the addition of chemotherapy. The complete results of this trial have not yet been published. We await the results of a subset analysis of gallbladder adenocarcinomas, which may shed light as to the true benefit of adjuvant chemotherapy in this rare disease. Likewise, there are no strong data regarding the use of radiation therapy. Ongoing and future clinical trials enrolling patients with gallbladder cancers along with other biliary malignancies will help to guide the care of such patients.

Current guidelines are based on retrospective data as well as expert opinion. The National Comprehensive Cancer Network guidelines state that adjuvant therapy with chemotherapy or chemoradiotherapy should be considered for patients, in particular those with residual disease after resection and as well as patients with nodal metastases.

In patients with locally advanced, potentially resectable tumors, neoadjuvant chemotherapy and chemoradiation should be strongly considered. This strategy provides the opportunity to allow for evaluating response to therapy with the hopes of avoiding a potentially futile operation. If jaundice or biliary obstruction is present, patients should undergo biliary decompression with stenting. Neoadjuvant regimens are similar to those described in the adjuvant setting. If there is a response to therapy, careful selection of patients is required to identify those that are likely to benefit from radical resection which carries a nontrivial rate of perioperative morbidity and mortality.

SUMMARY

Gallbladder cancer is an aggressive malignancy, most often discovered incidentally. The management of incidentally identified gallbladder cancer during elective cholecystectomy should mandate closure followed by appropriate staging before definitive resection. The minimally acceptable of a comprehensive oncologic operation for gallbladder adenocarcinoma include a margin negative resection and portal lymphadenectomy of six or more nodes. Adjuvant therapy should be guided by margin status and involvement of nodes on final pathology. Patients found to have locally advanced disease on presentation should be considered for neoadjuvant chemotherapy with or without chemoradiation. Clinical trials are desperately needed to identify effective systemic strategies for patients with gallbladder adenocarcinoma.

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Management of Gallstone Ileus

Nicholas J. Zyromski, MD

Gallstone ileus is a misnomer; this condition is not a physiologic ileus at all, but a mechanical obstruction of the intestinal lumen (most commonly the small bowel) by a large gallstone that has passed through a cholecystoenteric fistula. Cholecystoenteric fistulae may occur from the gallbladder to the adjacent luminal viscera: duodenum (most common), stomach, or colon. Gallstone obstruction of the stomach at the pylorus is known as Bouveret's syndrome. Cholecystocolic fistula is less common. Colonic obstruction in this situation typically occurs at the sigmoid colon. Most common is cholecystoduodenal fistula, with a large (usually >2 cm) gallstone passing through the small bowel and becoming lodged in the terminal ileum. Cholecystoenteric fistula is felt to be caused by a combination of pressure necrosis and inflammation with chronic longstanding gallstone disease. Up to 25% of patients who develop gallstone ileus will harbor multiple stones in the alimentary tract; therefore, a close inspection of the entire intestine is important at the time of operation.

EPIDEMIOLOGY

Until the year 2000, only about 1000 cases of gallstone ileus had been reported in the medical literature. Over the past few years, however, the incidence of gallstone ileus has been shown to be greater than previously thought. Several recent large population-based series have found that gallstone ileus accounts for approximately 0.1% of all small bowel obstructions. The disease usually affects women (70%) and those in the seventh or eighth decade of life.

Clinical Presentation and Diagnosis

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MANAGEMENT

Operation is required for nearly all patients with gallstone ileus, as spontaneous passage of these large stones is rare once the patient has become symptomatic. It is crucial to optimize the patient physiologically as much as possible in this emergent situation, with the understanding that the majority of gallstone ileus patients are elderly and commonly have numerous medical comorbidities. A nasogastric tube should be placed to decompress the small bowel. Vigorous intravenous fluid resuscitation is necessary to replete electrolytes and ensure hydration. Cardiopulmonary optimization should be undertaken to the best of the clinician's ability, without delaying operation.

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Management of Gallstone Ileus

Nicholas J. Zyromski, MD

Gallstone ileus is a misnomer; this condition is not a physiologic ileus at all, but a mechanical obstruction of the intestinal lumen (most commonly the small bowel) by a large gallstone that has passed through a cholecystoenteric fistula. Cholecystoenteric fistulae may occur from the gallbladder to the adjacent luminal viscera: duodenum (most common), stomach, or colon. Gallstone obstruction of the stomach at the pylorus is known as Bouveret's syndrome. Cholecystocolic fistula is less common. Colonic obstruction in this situation typically occurs at the sigmoid colon. Most common is cholecystoduodenal fistula, with a large (usually >2 cm) gallstone passing through the small bowel and becoming lodged in the terminal ileum. Cholecystoenteric fistula is felt to be caused by a combination of pressure necrosis and inflammation with chronic longstanding gallstone disease. Up to 25% of patients who develop gallstone ileus will harbor multiple stones in the alimentary tract; therefore, a close inspection of the entire intestine is important at the time of operation.

EPIDEMIOLOGY

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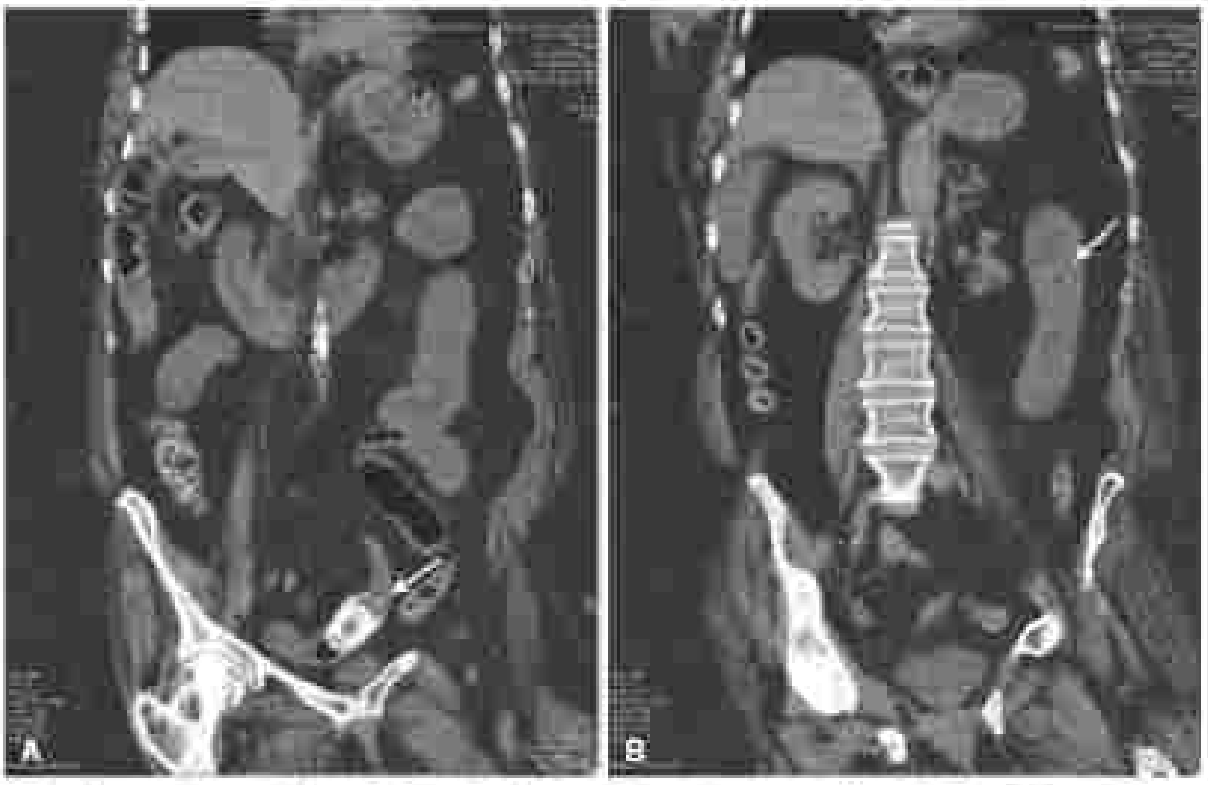

FIG. 1 (A) Coronal computed tomography image of gallstone ileus demonstrating obstructing stone (arrow) in terminal ileum. (B) Second gallstone (arrow) in the upstream small bowel of the same patient.

evacuating the gallstone (enterolithotomy) or to deal with the right upper quadrant biliary pathology at the same operation (i.e., by closing the biliary fistula and performing cholecystectomy). Historically, substantial perioperative mortality has been associated with addressing the biliary pathology. These findings have led to the current general practice of managing the small bowel obstruction during the primary operation and addressing biliary pathology selectively.

When making this clinical decision, the surgeon must consider several factors. First and foremost is the patient's acute and chronic physiologic state. Again, elderly patients with medical comorbidities and acute small bowel obstruction are often best managed with staged operative procedures. A second significant consideration is surgeon experience. The cholecystoduodenal fistula is often associated with a substantial right upper quadrant inflammatory response. Experienced operating on complex hepatobiliary pathology is ideal when addressing the pathology of cholecystoduodenal fistula.

The question of whether to intervene on the biliary pathology at all is reasonable; however, a significant number of patients will have recurrent biliary symptoms if the problem is not addressed. Multi-institutional single-institution series, which can provide longitudinal follow-up, have documented nearly 30% recurrent biliary symptoms such as right upper quadrant pain, cholecystitis, and/or choledocholithiasis when the cholecystoduodenal fistula is left in situ.

Technical operative considerations include the ability to address gallstone ileus laparoscopically. Current nationwide sample registry data show that approximately 10% of gallstone ileus patients were approached initially laparoscopically; however, 30% of these patients underwent conversion to open operation. Should laparoscopy be considered, the surgeon should take into account the presence of dilated small bowel loops. Open access to the abdominal cavity by Hasson approach may be most prudent. The laparoscopic ports should be positioned to address the entirety of the small bowel, as a careful search for additional intraluminal stones competes as important part of the operation.

The small bowel should be evaluated along its length. At the stone and point of obstruction is identified, enterotomy is created upstream from the stone, typically in a longitudinal orientation to the bowel. The stone is then gently evacuated (Fig. 2), and the enterotomy is closed transversely to prevent luminal narrowing. Intraoperative ultrasound is quite useful to identify additional stones in the bowel, gallbladder, or biliary tree. Such findings may influence the surgeon's decision to address biliary pathology at the index operation. A large series of gallstone ileus patients was recently reported in the *Annals of Surgery*. These authors studied the National Inpatient Sample, identifying 3268 patients over the 6 year period between 2004 and 2009. An interesting finding from this study was that patients requiring small bowel resection (presumably for ischemic bowel) had poorer outcomes in terms of mortality and length of stay relative to those who did not require bowel resection.

OUTCOMES

Two contemporary series of registry data have expanded our understanding of gallstone ileus. This condition was once thought to be relatively rare; however, the National Inpatient Sample study identified 3268 gallstone ileus patients, which accounts for approximately 0.1% of all patients admitted to the hospital with mechanical small bowel obstruction during this time period. In this series, overall hospital mortality was substantial at 6.7%. Mortality was significantly higher in patients who underwent cholecystectomy and closure of the biliary fistula compared to those who simply had small bowel obstruction addressed by cholecystolithotomy. Overall, 77% of the 3268 patients had small bowel obstruction palliatively treated and the remaining 23% had biliary fistula closed and cholecystectomy at the same operation. An interesting finding was the substantial incidence of postoperative renal insufficiency, or approximately 30% in the entire group of patients. The latter finding highlights the need for preoperative resuscitation and close attention to perioperative fluid management.

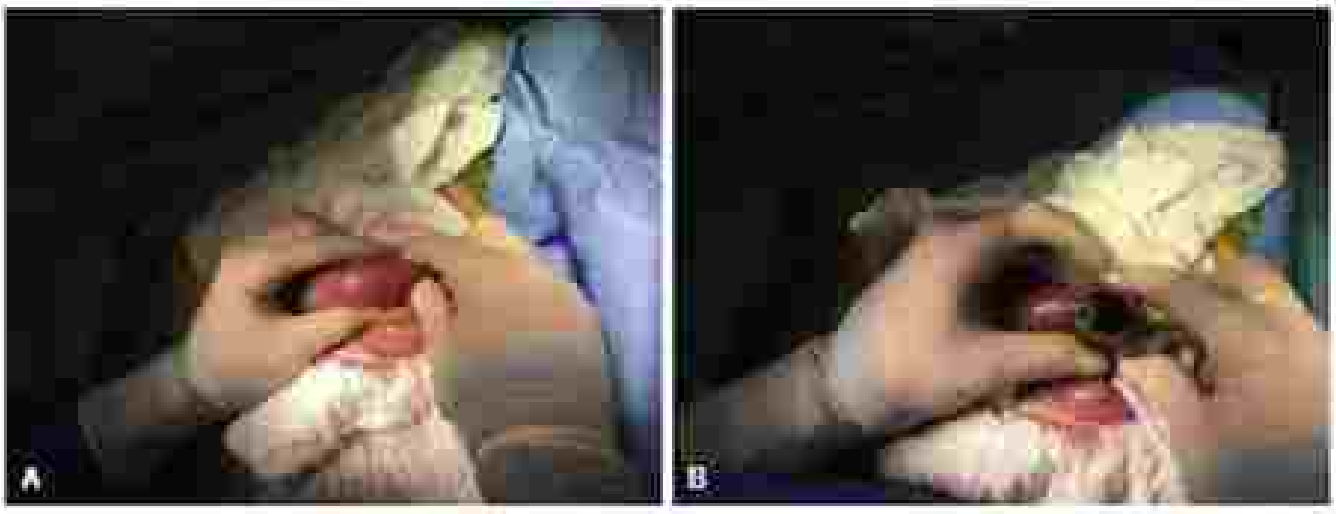

FIG. 2 Intraoperative view of distal ileum.

A second smaller series was reported from National Surgical Quality Improvement Project data collected between 2005 and 2010. These authors identified 127 patients with gallstone ileus. The overall mortality in this series was also fairly high at 5.5%. In this group of 127 patients, 11% had biliary pathology addressed at the same operation as bowel obstruction. Although the operative mortality was higher in this group (7.1% vs. 5.3%) this difference did not reach statistical significance, possibly because of smaller sample size. Patients who underwent cholecystectomy did have a significantly longer length of stay relative to those who simply had the small bowel obstruction pathology addressed.

SUMMARY

Gallstone ileus is a mechanical obstructive problem related to the underlying pathology of biliary enteric fistula. Gallstone ileus commonly affects elderly patients, with a female predominance of 70%. Surgical intervention is indicated to address the small bowel obstruction. At the time of operation careful search for additional enteric stones should be undertaken as these stones are present up to 25% of patients. The surgeon must consider carefully feasibility of same operation intervention to repair biliary pathology. It is safe to defer biliary operation to a later date with a second staged operation. When this strategy of two stage operation is selected, surgeon should consider and counsel their patient regarding the substantial incidence of recurrent biliary symptoms.

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TRANSHEPATIC INTERVENTIONS FOR OBSTRUCTIVE JAUNDICE

John Filton, MD, and Clifford R. Weiss, MD

The patient with obstructive jaundice should be managed with a multidisciplinary team approach. This may involve the combined expertise of multiple healthcare providers and specialties, including primary care physicians, gastroenterologists, surgeons, and interventional radiologists. Percutaneous transhepatic techniques used in the treatment of obstructive jaundice, secondary to both benign and malignant etiologies (Box 1), is the focus of this chapter.

The interventional radiologist uses advanced diagnostic imaging techniques, providing percutaneous image-guided access into the bile ducts and offering multimodal therapies. Since the introduction of percutaneous transhepatic dilation in 1978, percutaneous techniques have become alternatives to surgical and endoscopic treatments. Long-term data on percutaneous treatments are limited, but studies have reported 5-year success rates between 50% and 70%. Imaging modalities include fluoroscopy and ultrasound guidance, and also, less commonly, computed tomography (CT), endobiliary cholangioscopy, and magnetic resonance (MR) imaging (Figs. 1–3). Such therapies may include percutaneous management of benign biliary strictures, biliary ductal injuries and leaks, biliary decompression of cholangitis, biliary duct biopsy, stone removal (using fluoroscopy or cholangioscopy), palliation of malignant biliary obstruction with endoprosthesis, and occasional endobiliary therapies, such as radiation, photodynamic therapy, and drug infusion. Therapy may also include the use of physiologic parameters, such as a biliary manometric perfusion test, to help decide when a biliary drainage catheter may be removed. A dialog among gastrointestinal endoscopists, interventional radiologists, internal medicine specialists, oncologists, primary care physicians, nurses, and other team members is required to manage such patients effectively.

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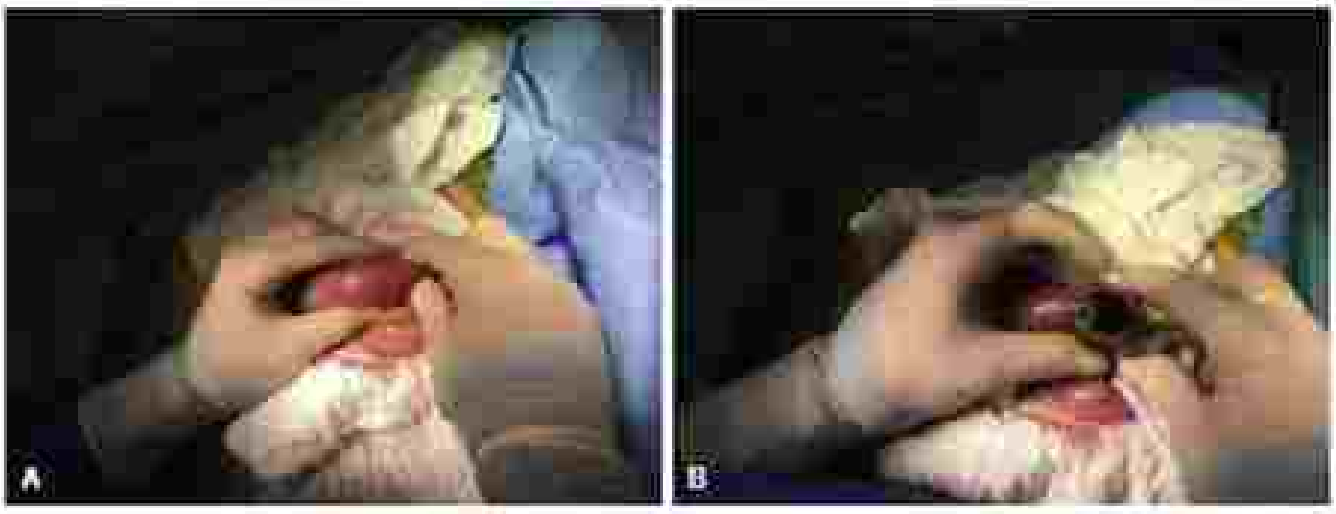
Biliary anatomy in the patient with obstructive jaundice is usually defined using noninvasive imaging techniques. Many centers use cross-sectional imaging techniques, and many have multidetector CT



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BOX 1: Etiology of Obstructive Jaundice

Benign

- Choledocholithiasis
- Papillary stenosis
- Choledochal cystic disease
- Postsurgical stricture
- Mirizzi syndrome
- Pancreatic pseudocyst
- Sclerosing cholangitis
- Parasitic disease

Malignant

- Pancreatic adenocarcinoma
- Cholangiocarcinoma
- Gallbladder carcinoma
- Ampullary/periampullary carcinoma
- Periampullary periportal lymphoma
- Metastatic disease
- Neuroendocrine tumors

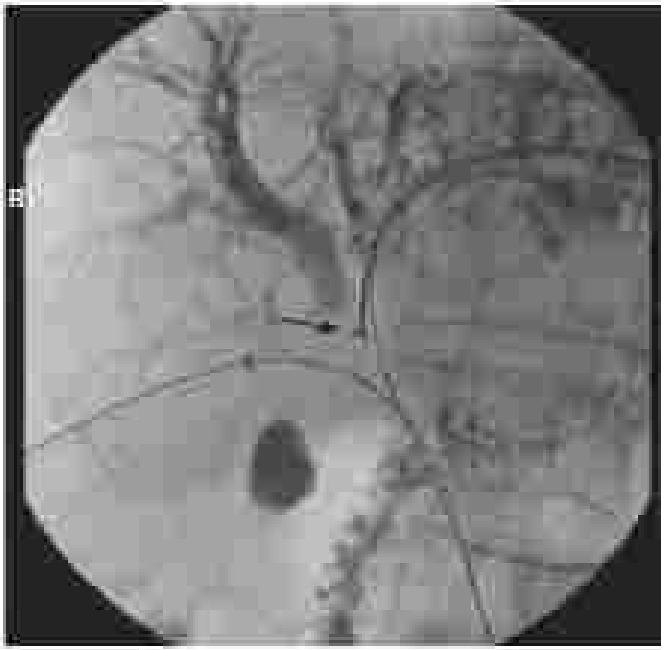

FIG. 1 Digital spot fluoroscopic image in the left anterior oblique projection showing "standard" biopsy gating being performed for a bile duct lesion using a left-sided access. This patient presented with signs and symptoms of obstructive jaundice. Note the lack of contrast in the common bile duct.

scanners that allow for rapid patient evaluation and reformatting of images in multiple anatomic projections. Ultrasound (US) is an inexpensive and generally available imaging modality that provides confirmation of dilated intrahepatic and extrahepatic ducts. It is operator dependent, but, in skilled hands, it provides important information about the possible etiology. For example, it is useful in confirming the presence or absence of dilated biliary ducts and detecting stone disease (choledocholithiasis, cholelithiasis, etc.). It is also advantageous in children because it does not use ionizing radiation. It may also be used at bedside in the critically ill patient to drain the gallbladder (percutaneous cholecystostomy).

When using US to evaluate the liver, the addition of color flow Doppler easily differentiates vascular tubular structures (dilated biliary ducts) from vessels (hepatic artery, hepatic vein, portal vein). Intrahepatic anatomy may not be adequately visualized in patients with extensive bowel gas (ileus or bowel obstruction), or it may not be technically feasible because of a limited "sonic window" for imaging, such as in a patient with multiple drains, wound dressings that cannot be removed, open abdominal incisions with a silo barrier, and so on.

As mentioned earlier, thin-section helical CT images, especially those obtained with newer multidetector scanners, allow rapid evaluation of abdominal anatomy. Studies are reproducible, and axial images may be reformatted to provide anatomic detail of the liver, the biliary anatomy, and other adjacent organs, such as the pancreas and duodenum. CT is more expensive than US, does use ionizing radiation, and generally requires the administration of oral and intravenous contrast; however, initial images without contrast may be useful in detecting bile duct stones. Because of the greater sensitivity of CT to density differences, poorly calcified or noncalcified stones or plaque illness may be readily detected on CT. On the downside, CT is not portable, thus, ill patients must be transported to and from the scanner.

Magnetic resonance imaging is useful in this context, especially given the ability to reformat axial images and produce an MR cholangiogram. The technique requires a significant amount of time, but when performed well it can result in a detailed representation of bile duct anatomy. In some centers, magnetic resonance cholangiopancreatography has replaced routine endoscopic retrograde cholangiopancreatography (ERCP) for defining bile duct anatomy. Because it uses no ionizing radiation, MR is helpful in children; however, in such instances, sedation or anesthesia support may be required to complete the MR examination.

ENDOSCOPIC AND PERCUTANEOUS EVALUATION

After clinical evaluation, laboratory blood work, and cross-sectional imaging, the patient must be evaluated endoscopically. ERCP is often the first invasive procedure performed in patients who require biliary surgery and/or intervention. An ERCP is especially useful in patients with coagulopathies, marked ascites, or in whom intrahepatic lesions, such as multiple hepatic cysts, preclude a safe transhepatic approach. The limitations of ERCP in patients with obstructive jaundice include the inability to cannulate the biliary system because of surgically altered anatomy (biliary enteric anastomosis) and technical limitations to the treatment of intrahepatic or hilar lesions from an endoscopic retrograde approach.

For the patient to be considered an operative candidate for biliary reconstruction, such as with choledochoduodenostomy, precise anatomic definition of the intrahepatic and extrahepatic bile ducts is essential to planning the surgical reconstruction. When ERCP is unable to completely opacify the biliary system, percutaneous transhepatic cholangiography (PTC) is the preferred procedure. PTC accurately depicts the intrahepatic biliary tree, lesion length, and lesion number, and it defines whether the biliary disease involves the bifurcation. Should a bifurcation lesion be found, bilateral (right and left) PTC and biliary drainage procedures may be performed. At our institution, the placement of one or more transhepatic biliary drainage catheters facilitates biliary reconstruction, assisting us in creating one or more biliary enteric anastomoses.

In a clinical situation in which the intrahepatic biliary system has been injured, such as with inadvertent complete clipping of the common hepatic or common bile duct, PTC alone may not fully define the distal intrahepatic bile duct anatomy. ERCP may be required to define distal anatomy up to the clip, and PTC and external percutaneous biliary drainage (PBD) may be used to define anatomy superior to the clipped duct. In this context, precise anatomic detail is demonstrated for eventual biliary reconstructive surgery. At times, combined ERCP and percutaneous transhepatic procedures are required to bridge and reconstruct biliary disruptions (endoscopic procedure) when access points are insufficient to clearly define the entire biliary tree.

PTC is the first step to PBD. The only absolute contraindication to PTC/PBD, performed as a means of access into the biliary system

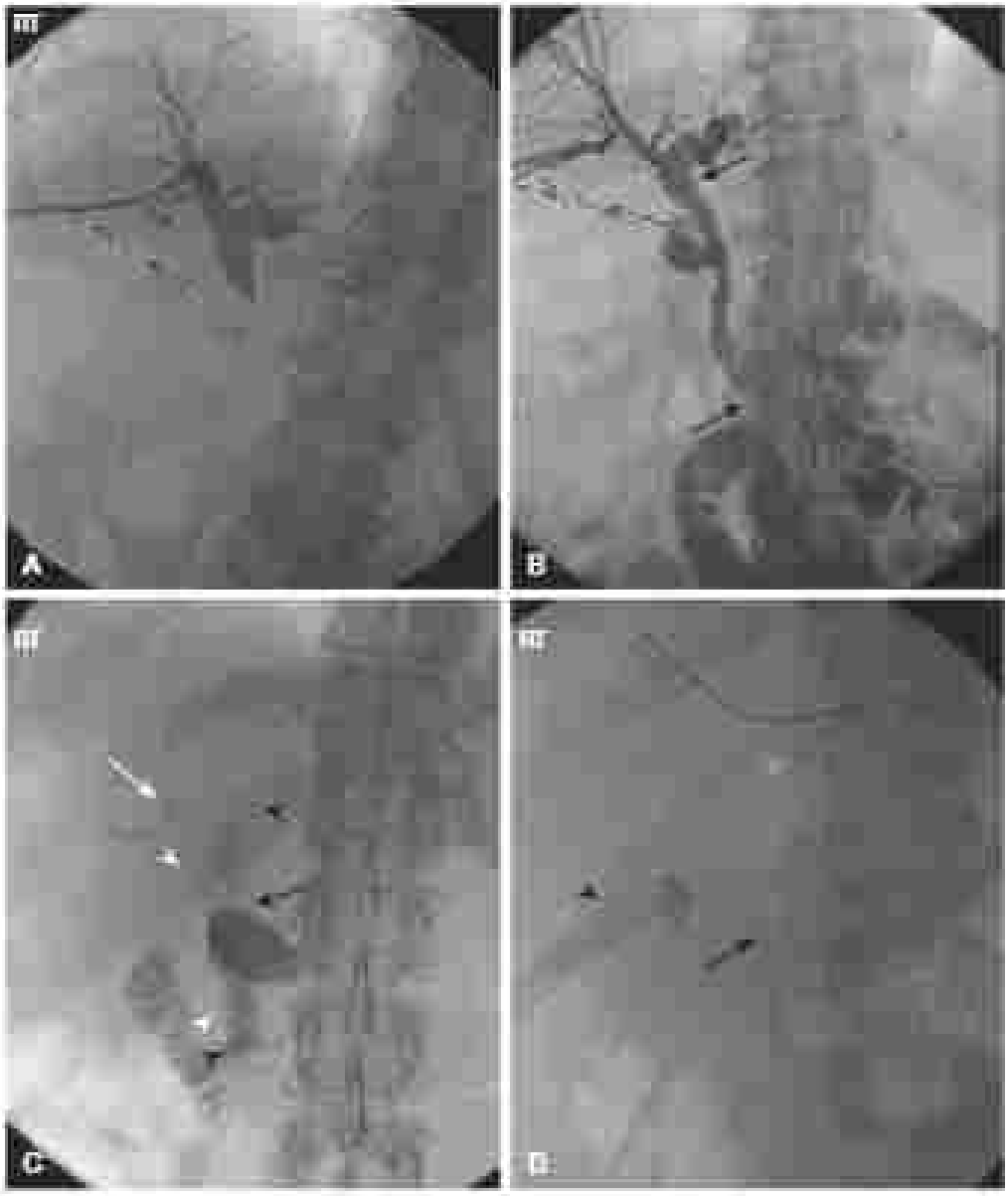

FIG. 2. (A) Digital spot fluoroscopic image of the right upper quadrant in the right anterior oblique projection showing abrupt cutoff of contrast in the common hepatic duct. There is no opacification of the duodenum. Note the contrast injection via a pre-existing right-sided external biliary drainage. (B) Digital spot fluoroscopic image of the right upper quadrant in the same patient. Cholangiogram performed after placement of an expanded polytetrafluoroethylene (ePTFE) endoprosthesis (Viabil; W.L. Gore) shows rapid flow of contrast through the endoprosthesis into the duodenum (arrows mark the ostium of the endoprosthesis because the pancreatic head mass was unresectable, so ePTFE endoprosthesis was placed). (C) Another patient with cholangiocarcinoma who underwent bilateral ePTFE endoprosthesis placement. Note the metallic stent "distractor" (black arrow) and radiopaque rings indicating the edges of the ePTFE covering (underneath). Also seen are associated metallic side adjuncts to the radiopaque rings (white arrow) and anchoring. (D) Another patient with a pancreatic head mass who underwent stented hepatic jejunostomy for common bile duct obstruction. Note the three overlapping 6-cm metal stents (arrows) outlining the common bile duct. Also seen is a jejunostomy tube (arrowhead).

for the treatment of patients with obstructive jaundice, is a significant coagulopathy that cannot be corrected. PBD should also be avoided in patients with diffuse polycystic liver disease or in patients with hepatic cysts due to parasitic infestation (e.g., Echinococcus). Occasionally, cross-sectional imaging and PBD under CT or US imaging guidance may be useful to determine an appropriate, safe window for access into the biliary system in those patients with multiple hepatic lesions.

Ideally, the patient with obstructive jaundice who is undergoing PBD/PBD should not have a coagulopathy. At our institution, PBD is generally not performed if the platelet count is below 50,000 or if the international normalized ratio is greater than 1.2. If the platelet count or international normalized ratio parameters are significantly altered, blood products—such as platelets, fresh frozen plasma, and vitamin K—may be administered to the patient for the biliary drainage procedure.

The presence of active jaundice challenges the percutaneous transhepatic drainage. Should biliary drainage be required in a patient with active, PBD with stent placement is the preferred means of drainage (i.e., internal drainage). The patient with significant ascites who requires a percutaneous transhepatic drainage catheter will often be plagued with leakage of ascitic fluid around the tube, which makes

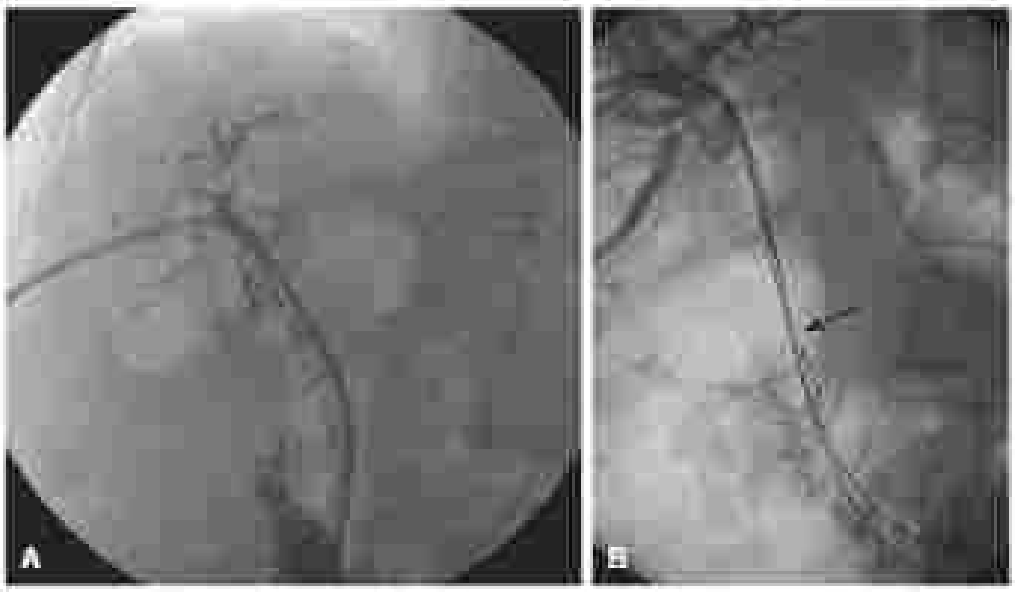

FIG. 7 (A) Digital spot fluoroscopic image of an adult patient who presented with obstructive jaundice, percutaneous transhepatic cholangiography demonstrated biliary findings included numerous intrahepatic filling defects in both intrahepatic and extrahepatic bile ducts. (B) Endoscopic brush biopsy (arrow) performed to confirm the diagnosis through a preexisting right-sided access. Pathologic analysis of the specimen later confirmed this to be a metastatic colon adenocarcinoma.

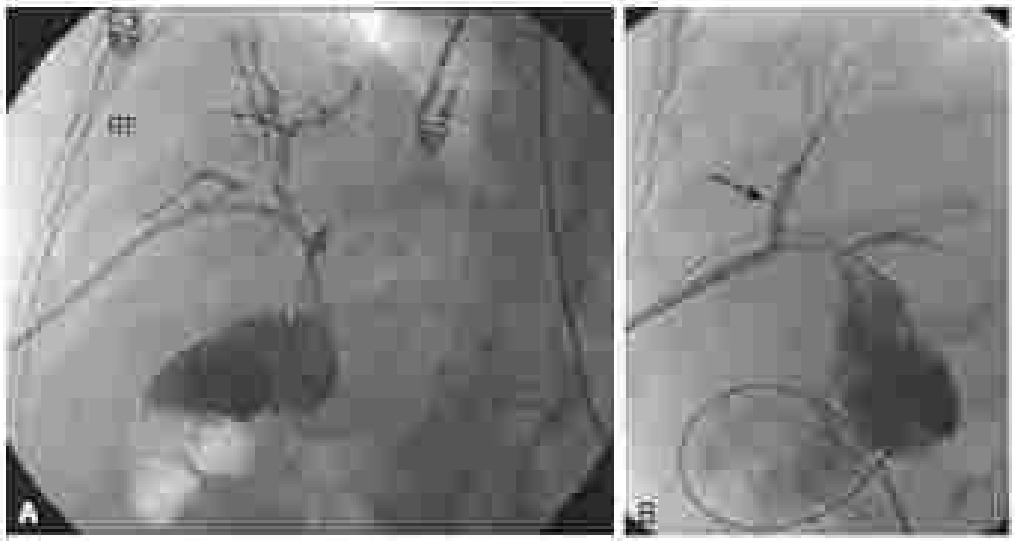

FIG. 8 (A) Digital spot fluoroscopic image of the right upper quadrant in the right anterior oblique projection showing multiple intrahepatic biliary tortuosity in an adult patient who had undergone previous choledocholithotomy. This patient has primary sclerosing cholangitis. (B) Digital spot fluoroscopic image of the right upper quadrant in a right anterior oblique projection in the same patient. Patient underwent balloon cholangioplasty (arrow) for treatment of intrahepatic biliary strictures. RAO, right anterior oblique.

dressings, causes skin irritation and inflammation, and theoretically places the patient at risk of bile leakage into the peritoneum (bile peritonitis). Technically, the presence of ascites can also make percutaneous biliary drain placement difficult. Because the liver floats in fluid, it is easily moved during needle placement. This can make it difficult to accurately access the liver capsule with the needle.

PTC/PBD TECHNIQUE SUMMARY

The technique of PTC/PBD is well described and outlined in the following section; it is a minimally invasive procedure. Intravenous antibiotics are started immediately on admission if a patient has clinical signs and symptoms of biliary sepsis or cholangitis. In patients who are not septic, intravenous antibiotics are administered on the day of the procedure and are generally continued for 24 hours afterward. As mentioned, the complete blood count, coagulation studies, and liver function tests are obtained as part of our routine preprocedure laboratory analysis.

After counseling as to the risks of the procedure, informed consent is obtained. The patient is placed in the supine position, intravenous sedation and analgesia are administered under an institutional conscious sedation protocol, and physiologic monitoring of blood pressure, pulse, and oxygen saturation is recorded frequently. In patients with hypotension and biliary sepsis, the help of an anesthesiologist can be invaluable because he or she can secure the airway and actively manage blood pressure and pain control, allowing a safe, reliable procedure. Although most interventional radiologists prefer initial biliary access from the left subcostal approach, in our institution, a right mid-axillary approach is generally used.

The first step is to anesthetize the skin and subcutaneous tissues inferior to the level of the cutaneous angle and above the level of the colon hepatic flexure. A thin needle (22G Chiba, Cook, Inc.) is advanced under fluoroscopic guidance, entering at the mid-axillary line parallel to the tabletop. The needle is directed medially and superiorly. After removing the stylet, the hub of the needle is connected through tubing to a syringe containing diluted contrast (1:1 dilution of saline to contrast). As the needle is withdrawn, contrast is injected slowly under fluoroscopic guidance. If the tip of the needle is in a bile duct, contrast is seen to flow away from it. On opacification of the biliary anatomy, multiple images are obtained to accurately define anatomy.

Should PBD be considered, and if a peripheral duct has not been entered or the point of duct entry is unfavorable for the advancement of a guidewire, a second thin needle (we use a 21-gauge fascar needle)

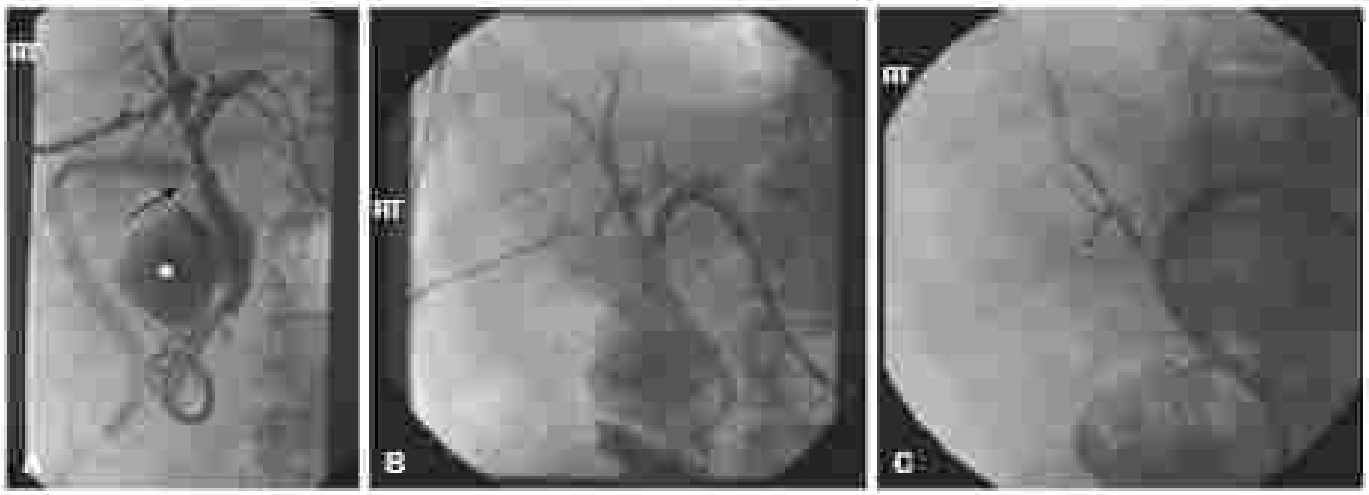

FIG. 8 (A) Digital spot fluoroscopic image of the right upper quadrant in a patient who had undergone cholecystectomy. A postoperative cystic duct stump leak (arrow) was managed by bilateral percutaneous transhepatic internal/external drainage catheter placement to divert bile. The internal/external biliary drainage catheters were left in place for 4 weeks. Note contrast within the duodenal bulb (arrow). (B) Digital spot fluoroscopic image of the right upper quadrant in the right anterior oblique projection in the same patient as that was performed by keeping the catheter distal side proximal to the confluence of the right and left main ducts allowing for internal drainage without the assistance of drainage catheters across the site of postoperative bile leak. (C) Digital spot fluoroscopic image of the right upper quadrant in the left anterior oblique projection showing adequate flow of contrast into the right main duct and common bile duct from a left-sided injection. External biliary drainage catheters were removed after two weeks. The patient remained asymptomatic at the 6-month follow-up.

may be used to select a more peripheral right duct. Having placed the needle in a more peripheral location, a coaxial system that consists of a small caliber, platinum tipped, steerable guidewire and a dilator/allowing cannula is advanced and used to secure biliary access. Using this system, the initial small-caliber guidewire is exchanged for a larger, stiffer guidewire, and a biliary drainage catheter may then be advanced to achieve drainage across a specific bile duct lesion.

In those patients with a high-grade biliary stricture at the bifurcation that isolates the right and the left ductal systems, a left PTC/PBD may be required. Anatomic depiction of the left biliary system requires access from a subxiphoid approach. As part of planning the left PTC/PBD approach, it is important that cross-sectional imaging studies be reviewed to determine whether major organs, such as the transverse colon, are interposed between the subxiphoid skin entry site and the left lobe of the liver. Imaging should also be reviewed to determine whether the left lobe is atrophic due to chronic left-sided biliary obstruction. If the left lobe is atrophic and requires drainage, an approach that is more medial than the standard left-sided subxiphoid percutaneous approach may be required.

When percutaneous transhepatic access to the patient with obstructive jaundice has been achieved, biliary catheter maintenance is required. Initially, the catheter is placed to external (bag) drainage. This is especially true for the patient with septic shock/ill from infected bile.

If the patient is critically ill and hemodynamically unstable, placement of an external drainage catheter alone will achieve biliary decompression (placement of a simple, locking perforated drainage catheter as an external drain). Once hemodynamically stable, the patient may return for a conversion either to an external/internal biliary drainage catheter (biliary stent) or an internal drainage catheter made of plastic or metal (internal biliary stent, or biliary endoprosthesis). The latter is generally reserved for patients with surgically unresectable disease and a limited life expectancy who are receiving palliative care. Specifics on the use of endoprostheses are covered later in this chapter.

Transhepatic internal/external biliary drainage catheter placement in the patient with obstructive jaundice requires crossing the obstructing lesion(s). The ultimate goal is to eventually reestablish the biliary enteric circulation. If left to external drainage alone—that is, given the inability to advance the multiple side hole drainage catheter into the small bowel—the loss of bile may result in significant morbidity to the patient, including dehydration and electrolyte disturbances. In such patients, replacement with intravenous electrolyte-rich fluid (e.g., lactated Ringer's solution) is recommended, or oral ingestion of an electrolyte-rich sports drink if the patient is able to tolerate oral fluids.

Biliary drainage catheters are generally flushed once or twice a day, especially in patients with viscous or infected bile. The patient and healthcare providers must be instructed as to the technique. In the patient with an external/internal biliary drainage catheter, the importance of flushing into the lobe, forward flushing, taking care not to aspirate fluid back into the syringe, must be emphasized. Forceful aspiration with a syringe may rapidly bring bacteria from the gastrointestinal tract into the biliary system (i.e., under pressure), and sepsis may result.

If left in place on a chronic basis, external/internal biliary drainage catheters require a periodic exchange. Generally, catheters are exchanged over a guidewire on an outpatient basis approximately every 2 to 3 months. For this procedure, the patient receives a single dose of intravenous antibiotics before the cholangiogram and biliary catheter exchange. If conscious sedation is required, the patient returns from the interventional suite to the recovery room (usually for 1 hour). During this time, the newly exchanged biliary drainage catheter is connected to an external drainage bag. If the patient is afebrile, he or she is discharged home with instructions to "cap" the biliary tube after 24 hours (i.e., the bag is removed). Should the patient become febrile after a tube exchange, a decision is made as to the subsequent course of therapy. The patient may be observed and later discharged on oral antibiotics with the biliary catheter left to external drainage until the patient is afebrile. The patient is told to return if symptoms worsen. Should an outpatient become septic, the patient should be admitted to the hospital and continue intravenous antibiotics with the biliary drainage catheter left to external (bag) drainage. The clinical presentation of sepsis is fortunately infrequent after routine outpatient catheter exchanges.

Internal Drainage (Biliary Endoprostheses)

The patient who has undergone transhepatic biliary drainage for obstructive jaundice resulting from surgically unresectable malignant disease may receive a palliative biliary endoprosthesis (internal

biliary stent). If the patient is clinically stable at the time of initial biliary drainage, the biliary endoprosthesis may be placed in a single step. This allows rapid treatment and reduces costs, compared with placement of an external/internal drainage with later conversion to a completely internalized catheter system (i.e., a multistage procedure).

The endoprosthesis used is either polymer (plastic) or metallic (bare metal stent mesh or a covered stent). The plastic endoprosthesis are larger in caliber and require transhepatic tract dilation to 10 or 12 Fr. This can cause considerable pain to the patient, and there is a theoretical risk of increased bleeding. Although inexpensive compared to metallic endoprostheses, there are few manufacturers of plastic endoprosthesis for transhepatic deployment. The majority of plastic endoprostheses are placed endoscopically.

In contrast, metallic endoprostheses are smaller in caliber at deployment, but have significantly larger luminal diameters. For example, self-expanding bare metal stents used as biliary endoprostheses may be deployed through a 6 or 7Fr sheath system and expand to 1 cm in diameter. These types of stents provide longer patency times and greater cost effectiveness compared to plastic stents; thus, for palliation, a patient could undergo PTC/PBD followed by placement of a metallic endoprosthesis in a single step.

For malignant biliary obstruction, placement of flare self-expanding bare metal stents should be considered because the location of the stent can be a significant predictor of pancreatitis. To reduce the chances of pancreatitis, the literature suggests supraampullary rather than transampullary placement.

After endoprosthesis placement, the patient's transhepatic access may be removed if there is no significant bleeding. Should bleeding occur, such as with a friable tumor, a temporary external drainage catheter should be initiated for the patient's transhepatic access tract. This maintains access in the event that the endoprosthesis becomes acutely occluded with thrombus. Once thrombus has cleared, generally in 1 to 2 days, the catheter may be removed after a final cholangiogram confirms patency of the metallic endoprosthesis.

PBD followed by metallic biliary stent placement is extremely important in managing hilar biliary obstruction, but deciding whether to decompress the obstructed ducts to one or both hepatic lobes still must be considered. Very few data on unilobar versus bilobar drainage exist in the literature; however, one study showed no difference in survival or stent patency between the two procedures.

Biliary endoprostheses used for palliation are considered permanent implants with patency periods generally limited to 6 to 12 months; thus, they are used in patients with limited life expectancy. Patients should be warned of this and told that should the endoprosthesis occlude, repeat endoscopic or transhepatic access may be required to relieve the obstruction.

Covered biliary endoprostheses have been developed that have improved the long-term patency for palliation of malignant biliary obstruction. Percutaneous transhepatic placement of expanded polytetrafluoroethylene (ePTFE)-covered stent grafts has been approved (Viabil biliary endoprosthesis; W.L. Gore). These stent grafts have been modified to include perforations or fenestrations in the ePTFE covering to avoid occlusion of biliary branches that may otherwise be obstructed by a continuous covering. Such stent grafts also have anchor barbs that prevent migration.

A recent meta-analysis has shown that covered, self-expandable biliary endoprostheses have a longer patency compared to uncovered, self-expandable stents (mean, 61 days). Greater long-term patency of stent grafts provides an additional therapeutic option to enhance the quality of life in patients with unresectable malignant biliary disease. Although covered and uncovered biliary endoprostheses show similar rates of stent dysfunction, the mechanisms of stent dysfunction differ. Covered stent dysfunction usually involves tumor overgrowth around the stent edges, sludge formation, or stent migration. Uncovered stent dysfunction is more commonly the result of tumor ingrowth through the interstices of the stent. Available data show no statistically significant increase in episodes of cholecystitis or pancreatitis with covered biliary endoprostheses.

The relationship between stent occlusion and stent coating material remains undetermined. When plastic stents are used, however, stent diameter relates to stent patency such that 10Fr stents show longer stent patency duration compared to 8Fr stents; a smaller diameter predisposes to occlusion by biliary sludge.

Patients with benign disease and covered stent grafts, regardless of material used (e.g., ePTFE), may be considered for endoscopic removal. This is not the preferred treatment for benign disease, but it may be used as an alternative to patients who could otherwise not undergo biliary reconstructive surgery or percutaneous transhepatic catheters. One study suggests a protocol of staged uprating of internal/external biliary catheters, balloon dilation (8 mm), and prolonged stent treatment at maximum catheter size (10Fr) for benign biliary strictures. Results from this study showed stricture patency probabilities of 84%, 78%, and 74% at 1, 2, and 5 years, respectively.

COMPLICATIONS OF PTC/PBD

The technical success rates of PTC/PBD are high, and major complication rates are generally low (3%–8%). Some reported major complications include hemobilia or hemorrhage, sepsis, biloma, peritonitis, pancreatitis, pleural effusions, and, rarely, death. Another complication is cholangitis, which is found in up to 20% of patients. Fortunately, these episodes of cholangitis are usually brief and not associated with hypotension.

Hemobilia/Hemorrhage

Hemobilia occurs when blood enters the bile duct during catheter exchange. This complication has been reported in 2% to 8% of patients who undergo PTC/PBD. It is usually a result of injury to one of the major vessels, either a hepatic artery or vein or portal vein. These patients generally are seen with bleeding from the biliary drainage catheter and right upper quadrant pain. The patient may also present with melena or hematochezia.

Hemobilia can occur from either the venous or arterial system. If it occurs from the hepatic or portal vein, it is generally nonpulsatile and dark in color; this is generally managed either by repositioning or upsizing the biliary drainage catheter.

If the bleeding occurs from injury of an arterial branch, emergency consult should be obtained for hepatic arteriography. The bleeding is generally bright red and pulsatile and may be due to a hepatic artery–bile duct fistula or a pseudoaneurysm of the hepatic artery with communication to the biliary system. The treatment requires transcatheter arterial embolization, generally with embolic coils. The injured vessel is occluded by advancing a catheter distal to the injury site and coiling across the site. After hepatic artery branch embolization, the transhepatic access need not be abandoned.

Sepsis

If the patient develops a fever, rigor, and hypotension, sepsis should be suspected. Sepsis can arise even with prophylactic antibiotic treatment, and it can be treated with intravenous antibiotics, expansion of intravascular volume, and pressor support. Identification of the causative agent by bacterial culture is imperative to tailor antibiotic use.

Pericatheter Leakage

Transhepatic access may result in leakage of bile around the catheter. This is often due to occlusion of the catheter lumen, and the problem may be addressed by catheter exchange. Occasionally, ascites may also leak around the catheter and may resemble bile leakage. The optimal way to drain the biliary system of a patient with ascites may be with an internal stent (endoprosthesis). If an endoprosthesis is not possible, the catheter may be upsized in an attempt to temporarily tamponade the site, allowing time for tract maturation. A purse-string suture on the skin placed around the catheter may also be used to reduce leakage of ascitic fluid.

BILIARY CATHETER REMOVAL

In addition to the routine biliary exchange every 8 to 12 weeks, the decision about when to remove the biliary drainage catheter in a patient who has undergone treatment for benign biliary strictures is based on clinical and laboratory parameters and on biliary flow dynamics. As mentioned, the duration of stenting is controversial. Most interventionalists will leave a stent in place for at least 3 months before determining whether it can be removed. In our institution, we often have biliary stents in place for 6 to 12 months. Before removing a biliary drain, an over the wire cholangiogram is performed by pulling the biliary drainage catheter back over a guidewire. If the site of the stented stricture looks patent based on an injection of contrast through the tube, the decision may be made to initiate a clinical trial. For this, a shortened biliary drainage catheter is reintroduced over the guidewire, but the tip is placed above the biliary stricture. This functions to maintain percutaneous access and to allow bile to flow across the newly dilated, previously stented stricture. The tube is capped for 1 to 2 weeks, and any signs or symptoms of cholangitis, right upper quadrant pain, fever, jaundice, or leakage around the biliary drainage catheter indicates a probable failure of the trial. Because percutaneous access has been maintained, the stricture can be easily redilated and restented; alternatively the patient may require surgery.

If the patient remains asymptomatic during the clinical trial and there is documented evidence of flow across the stricture on follow-up cholangiography, a biliary manometric perfusion test may be performed. Dilute, iodinated contrast is infused in a stepwise manner via the shortened PBD. Biliary pressure less than 20 cm of H_2O are considered normal. In patients with an asymptomatic clinical trial and normal pressures during the biliary manometric perfusion test, the positive predictive value for biliary duct patency at 1 year approaches 90%. Patients are followed carefully, with follow up liver function tests obtained at periodic intervals after tube removal.

To the medical literature, published data for the results of percutaneous dilation and stenting indicate long term patency of 53% to 76% with follow up periods of 5 and 3 years, respectively. However, most of the data are retrospective in nature. Long term patency rates for surgical repair of similar lesions are 89% at 72 months of follow up. Initial reports of percutaneous balloon dilation showed significant complications that included hemobilia, mainly resulting from clot, angle or transhepatic access. More recently, cutting balloon dilation has been shown to be safe for the treatment of biliary enteric anastomotic strictures that are resistant to conventional balloon techniques.

In patients with malignant biliary obstruction, the biliary drainage catheter may be removed after placement of an internal stent (endoprosthesis), either plastic or metallic. Patients with advancing cholangitis require a combined approached that may involve ipsilateral resection of the dominant stricture, PTC followed by drainage, and balloon dilation of intrahepatic strictures until periodic biliary catheter exchanges. A recent study has shown that percutaneous transhepatic biliary drainage and subsequent metallic stent placement are viable, palliative treatment options in patients with metastatic gastric cancer; subsets of patients with differentiated histology of primary gastric cancer and serum bilirubin levels greater than 7 mg/dl, after biliary drainage, may benefit from the combination therapy of metallic stent placement and chemotherapy.

OTHER INTERVENTIONS

Cholangioscopy

As previously mentioned, the use of cholangioscopy is not as common in biliary interventions, but it is becoming increasingly used in the assessment and treatment of biliary disease. Cholangioscopy was first described in the 1970s but is rarely used because of the high costs. Now, with recent developments, it is starting to become feasible. There are two types of cholangioscopy currently: indirect and direct. Indirect cholangioscopy uses a catheter with an optical probe inside that is inserted within the accessory port of a duodenoscope.

FIG. 8 Cholangioscope. (A) The most generation of mother-therapeutic cholangioscope (CHF-CB30 LA, Boston Scientific) has an outer diameter of 8.9 mm and a working length of 45 cm (5 type) or 70 cm (type shown). This endoscope provides 120-degree angulation in the up or down direction, and a depth of view ranging between 2.5 and 50 mm. (B) Two access ports on the cholangioscope feed into a single channel. One irrigation system is attached to the anterior port (single arrow), while the posterior port (paired arrow) is used for passage of wires and instruments.

Direct cholangioscopy is most often used and uses a very thin upper endoscope percutaneously and transhepatically positioned within the biliary system. The diagnostic uses of percutaneous transhepatic cholangioscopy (PTCS) include visualization of indeterminant biliary structure, verification of bile duct stone clearance, and for staging cholangiocarcinoma. For simple diagnostic PTCS, we allow the tract to mature for 2 weeks after placement of an 8 to 10Fr biliary drain. Cholangioscopy (Fig. 8) is then performed with either a 10Fr access sheath or a bare tract technique without a sheath. This method works for diagnostic visual inspection with or without the use of 3Fr disposable biopsy forceps.

Studies have shown cholangioscopy to have a higher sensitivity and positive/negative predictive value than ERCP. PTCS has been considered a safe procedure, with low incidences of complications (in less than 8% of patients). The most common complication reported was cholangitis (14% of cases in one study), with an overall complication rate of 7.5% (in an international multicenter study). PTCS has also been shown to be effective in providing guidance for numerous tasks that involve occluded metal stents.

Cholangioscopy can be used to treat obstructive stones in the biliary system as well (Fig. 7). Stones small enough to pass through the access sheath can be removed with a retrieval basket. Retrieval baskets consist of wires fused at both ends and are available in a variety of sizes and shapes. We prefer to use the 4.0Fr 90 cm Segura Hemisphere stone retrieval basket (Illusion Scientific), which has a rounded tip to minimize trauma to the biliary tree. To engage the stone for removal or mechanical pulverization, the basket needs to be positioned slightly beyond the target stone. A magnified view of the stone through the endoscope may suggest that it is too large for basket removal when in reality it can fit through the access sheath.

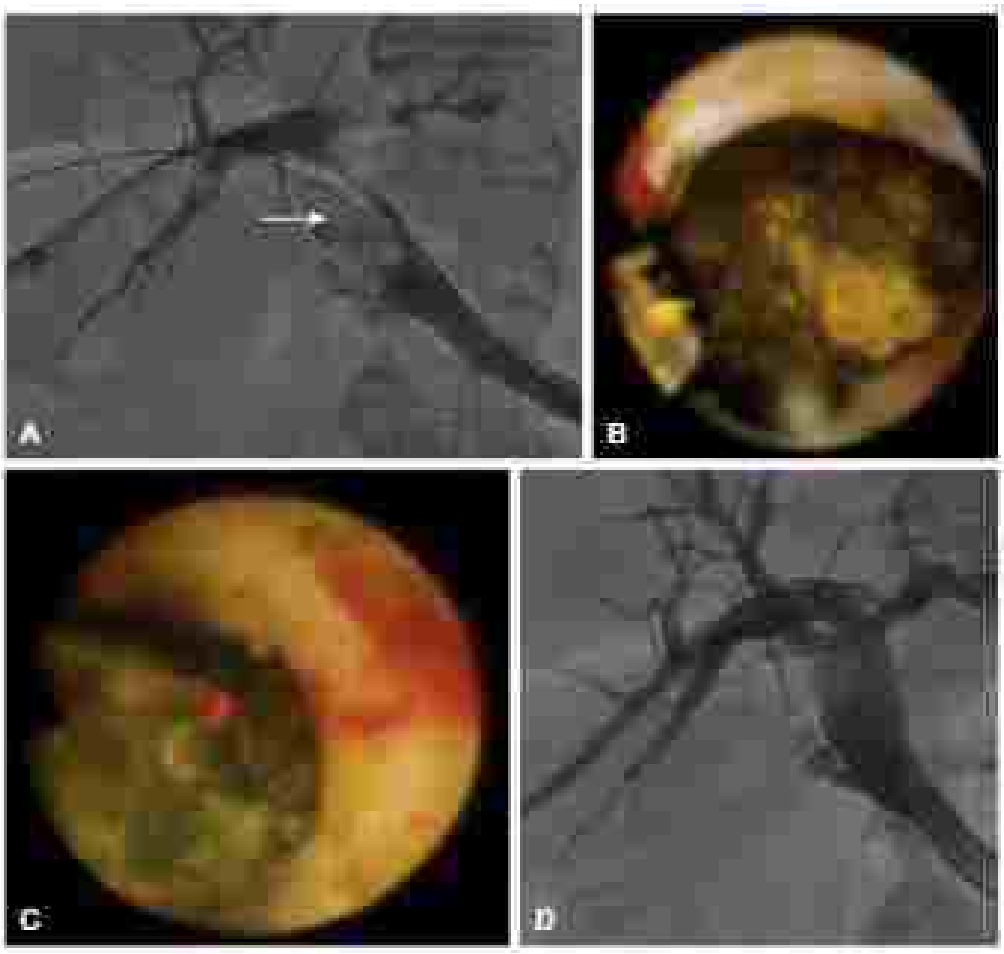

FIG. 7 Laser lithotripsy. (A) Diagnostic cholangiogram demonstrates a large filling defect (arrow) near the hepatic hilum. (B) A large stone is visualized on cholangioscopy, partially covered with yellow mucus. (C) The laser fiber is positioned just proximal to the stone, which allows the laser light to reflect off the stone surface. Laser lithotripsy is performed with care to avoid extraneous firing. Stone fragments are either removed with a basket or flushed down the biliary tract to allow passage through the ampulla. (D) Postprocedure cholangiogram demonstrates complete removal of the large stone with restoration of bile flow.

fluoroscopy with this technique allows the operator to become more adept at accurately judging the size of the stone.

Open-ended graspers, such as alligator forceps, may be used when limited space precludes appropriate positioning and expansion of a retrieval basket. Graspers are usually situated just proximal to the stone and the prongs are closed around the stone for gentle retraction through the access sheath. Graspers, however, provide poor gripping force and there is a risk of dropping the stone before removal through the sheath, which may result in multiplied calculi. The prongs of the grasper are generally hooked at the ends to capture the stone, which increases the risk of damage to the bile duct walls. Graspers should be reserved for small stones or stone fragments. At our institution, we use this instrument only rarely because of its technical limitations.

Lithotripsy is used to fragment stones that are too large to fit into a basket or pass through the access sheath, which is often the case in patients with chronic biliary obstruction. This has been traditionally accomplished with mechanical lithotripsy; however, biliary calculi may resist mechanical fragmentation resulting from stone composition (e.g., bilirubin stones), or anatomical location (e.g., high within the hepatic parenchyma). Electrohydraulic and laser technologies have been used successfully for lithotripsy. Although less expensive than laser, electrohydraulic lithotripsy has a higher risk of duct damage because of poor targeting. In addition, its 10-F probe is usually too large to pass through the working channel of a smaller endoscope. Laser lithotripsy offers several advantages, including greater precision in targeting stones and much smaller caliber probes, and is our technique of choice. The two main categories of lasers used for lithotripsy are flashlamp-pumped, pulsed dye lasers (e.g., coumarin dye and rhodamine 6G dye) and pulsed solid-state lasers (e.g., holmium: YAG and q-switched neodymium: YAG). We use a 20-W holmium: YAG laser (VersaPulse PowerSuite 20W, Boston Scientific) with a starting pulse energy of 0.8 J per pulse and a pulse frequency of 10 Hz for a power between 8 and 10 W, never for more than 5 seconds per pulse. The laser is delivered through a flexible fiber that is available in various sizes, including 200 and 365 μm. The most commonly used fiber is of 365 μm in size, which requires a working channel of 2.2 F or greater. The depth of penetration from the holmium: YAG laser is less than 0.5 mm. In contrast to neodymium: YAG lasers, the holmium laser does not cause forward scatter.

PTCS-guided removal of biliary stones is highly successful, with complete stone removal from the bile ducts occurring in 80% to 100% of cases. The number of stones, stone location, and presence of biliary strictures may have a significant effect on procedural success. Complete clearance of intrahepatic stones tends to be more challenging than clearance of extrahepatic stones, but technical success rates of more than 90% for treating hepatolithiasis have been reported in the literature. Recurrence is reported in up to one third of patients with intrahepatic stones, most commonly when intrahepatic strictures are also present. Complex cases of choledocholithiasis with multiple stones often require more than one session for complete clearance.

Irreversible Electroporation

Irreversible electroporation (IRE) is a nonthermal ablation technique that induces cell death via pulsed direct current. Thermal ablation techniques have increased the 5-year survival rate of hepatocellular carcinoma from under 1% to 33% to 54%, however, most patients are considered ineligible for these procedures because there are tumors in close proximity to the main biliary tracts. IRE induces cell death via formation of nanopores in the cellular membrane, while leaving the extracellular matrix intact so bile ducts can retain function. One study has shown IRE to be effective in treating centrally located liver tumors adjacent to bile ducts, but more studies need to be done to assess safety.

Intraductal Radiofrequency Ablation

Intraductal radiofrequency (RF) ablation has been used to treat malignant tumors that involve the bile duct using endoscopy. More recently, there have been a few studies that have investigated this type of ablation being used with PTC. One study showed that PTC and intraductal RF ablation, followed by biliary stent placement, was safe and effective in the short term. At 6 months postoperation, two of 11 patients in an experimental group (PTC/RF) developed recurrent jaundice and received repeat procedures. In the same study, recurrent jaundice was observed at three months in the control group (without RF ablation).

SUMMARY

Transhepatic access for obstructive jaundice provides several therapeutic options for patients with both benign and malignant obstructions. A range of therapeutic options is available, including emergent drainage, endohepatobiliary biopsy, biliary stricture dilation, long-term stenting, and endoprosthesis for palliation (Figure 1.5). In addition, direct visualization using endoscopic techniques (cholangioscopy) may assist in the treatment of retained intrahepatic stones and may allow a significant reduction in radiation exposure for the patient, the interventional radiologist, and the personnel in the room.

Improvements in the percutaneous transhepatic cholangiography techniques, biliary drainage, and adjunctive biliary interventions provide the interventionalist with ready access to the biliary system to assist in the multidisciplinary management of patients with complex biliary disease. The team approach is warranted because such patients often require management by surgeons, interventional radiologists, gastroenterologists, and primary care physicians.

The minimally invasive treatment of patients using transhepatic interventions for obstructive jaundice continues to expand. It is hoped that this information will assist readers in understanding some of the options available to such patients.

Suggested Readings

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Obstructive Jaundice: Endoscopic Therapy

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Obstructive jaundice is a manifestation of cholestasis, which in turn is an impairment in the bile flow out of the parts hepatic through the biliary ducts and into the duodenum. Symptoms may include fatigue, pruritus, and pale-colored or acholic stools. Abdominal pain may or may not be present, depending on the underlying cause. Cholestasis can be intra or extrahepatic and there are multiple causes. The main causes of extrahepatic cholestasis are summarized in Table 1. Overall, common bile duct stones are the most common cause of obstructive jaundice.

Cholestasis is identified through abnormal findings on biochemical tests of the liver, such as elevated alkaline phosphatase (AP), 5′-nucleotidase, γ-glutamyl transferase levels, and variable levels of bilirubin and prothrombin time. However, elevated AP levels are not completely specific for cholestasis and do not help in identifying the underlying cause. In general, values of AP greater than three times the upper limit is suggestive of extrahepatic biliary obstruction. Different imaging techniques can be performed to identify the cause of obstructive jaundice with variable sensitivities and specificities, such as transabdominal ultrasound, cross-sectional imaging (magnetic resonance cholangiopancreatography [MRCP] or computed tomography), and endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP), both of which can be diagnostic and therapeutic, the latter mainly therapeutic.

This chapter focuses on the different endoscopic techniques available for the treatment of obstructive jaundice. Overall, endoscopic techniques for the management of obstructive jaundice are ERCP guided approaches and EUS guided biliary drainage (EUS-BD).

ERCP

ERCP is one of the most technically demanding and high-risk procedures in gastroenterology, requiring significant training and experience to maximize success and minimize poor outcomes. Currently, ERCP is predominantly a therapeutic procedure. ERCP is effective in the nonsurgical management of a variety of pancreaticobiliary disorders, most commonly removal of bile duct stones and relief of malignant obstructive jaundice. Selective cannulation of one or both ducts can usually be accomplished in more than 90% of the cases. At least 100 procedures are required for a trainee to acquire a level of competence in diagnostic and therapeutic ERCP, defined by deep cannulation of the bile duct in 70% to 80% of cases. ERCP can be accurate in establishing the location, character, and length of strictures in the bile and/or pancreatic ducts, as well as accomplishing drainage in the same session. Failure to drain an obstructed bile duct when performing an ERCP carries a high risk of infection even with the use of antibiotics.

During ERCP, a specialized side-viewing endoscope, called a duodenoscope, is advanced to the descending duodenum to identify the major papilla. Then, dedicated instruments are passed into the bile and pancreatic ducts. The ducts are opacified by injection of an iodine contrast medium permitting their radiologic visualization and therefore allowing for a variety of therapeutic interventions.

The main indications of an ERCP are mentioned in Box 1.

Preprocedure coagulation studies are not routinely indicated but should be considered in selected patients, such as those with a history of coagulopathy or prolonged cholestasis. Endoscopists should consider correction of coagulopathy if sphincterotomy is anticipated, but specific international normalized ratio thresholds for this intervention have not been established. Antibiotic prophylaxis is indicated in the setting of suspected biliary obstruction with incomplete drainage (including primary sclerosing cholangitis [PSC]), postanastomotic bile biliary strictures, or ductal leaks.

The American Society for Gastrointestinal Endoscopy (ASGE) recommends preprocedure testing in the following settings.

- Pregnancy testing for women of childbearing potential who provide an uncertain pregnancy history or who have a history suggestive of a current pregnancy.
- Coagulation studies for patients with active bleeding, known or suspected bleeding disorder (including history of abnormal

Intraductal Radiofrequency Ablation

Intraductal radiofrequency (RF) ablation has been used to treat malignant tumors that involve the bile duct using endoscopy. More recently, there have been a few studies that have investigated this type of ablation being used with PTC. One study showed that PTC and intraductal RF ablation, followed by biliary stent placement, was safe and effective in the short term. At 6 months postoperation, two of 11 patients in an experimental group (PTC/RF) developed recurrent jaundice and received repeat procedures. In the same study, recurrent jaundice was observed at three months in the control group (without RF ablation).

SUMMARY

Transhepatic access for obstructive jaundice provides several therapeutic options for patients with both benign and malignant obstructions. A range of therapeutic options is available, including emergent drainage, endohepatoscopy, biliary stricture dilation, long-term stenting, and endoprosthesis for palliation (Figs. 1–5). In addition, direct visualization using endoscopic techniques (cholangioscopy) may assist in the treatment of retained intrahepatic stones and may allow a significant reduction in radiation exposure for the patient, the interventional radiologist, and the personnel in the room.

Improvements in the percutaneous transhepatic cholangiography techniques, biliary drainage, and adjunctive biliary interventions provide the interventionalist with ready access to the biliary system to assist in the multidisciplinary management of patients with complex biliary disease. The team approach is warranted because such patients often require management by surgeons, interventional radiologists, gastroenterologists, and primary care physicians.

The nonsurgical treatment of patients using transhepatic interventions for obstructive jaundice continues to expand. It is hoped that this information will assist readers in understanding some of the options available to such patients.

Suggested Readings

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Casey RM, Brown KT. Percutaneous transhepatic biliary drainage. Tech Vasc Interv Radiol. 2008;11(1):14–20.

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Saad WE, Wallace MJ, Wojak JC, Kundu S, Cardella JF. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. J Vasc Interv Radiol. 2010;21(6):784–795.

Shah SR, Mallipeddi M, Cotsarelis C. Therapeutic biliary endoscopy. Endoscopy. 2005;37(11):1145–53.

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TABLE 1 Causes of Extrahepatic Cholestasis

Mechanism	Cause
Intraluminal or intramural	Cholangiocarcinoma Choledocholithiasis Primary/secondary sclerosing cholangitis Benign biliary stricture Choledochal cyst Parasites Hemobilia
Obliteration of the bile ducts	Biliary atresia Caroli's disease
Extraluminal or intramural	Pancreatic head mass Gallbladder carcinoma Pseudotumoral chronic pancreatitis
Obstruction at the ampulla of Vater	Duodenal diverticulum Ampullary mass Ampullary stenosis

bleeding), an increased risk of bleeding resulting from medications use (ongoing anticoagulation, prolonged antibiotic use), prolonged biliary obstruction, malnutrition, or other conditions associated with acquired coagulopathies.

- Chest radiograph for patients with new respiratory symptoms or decompensated heart failure.
- Hemoglobin/hematocrit for patients with preexisting significant anemia or active bleeding, or in case of high risk of significant blood loss during the procedure.
- Blood typing for patients with active bleeding or anemia who may likely need a blood transfusion.
- Serum chemistry testing for patients with significant endocrine, renal, or hepatic dysfunction when medications are to be used that may further impair function.

Equipment

A side viewing duodenoscope allows a better view of the major duodenal papilla, making cannulation easier. In patients with altered anatomy, such as Billroth II gastrectomy, Whipple or Roux-en-Y reconstruction, a forward viewing endoscope, such as a pediatric colonoscope or a single or double balloon enteroscope with a cap, is a reasonable alternative in these circumstances, where afferent loop intubation would be easier. Papillary cannulation would be more challenging given the absence of the elevator, only available in the duodenoscope. Different accessories such as sphincterotomes, guidewires, balloon or catheter dilators, extraction balloons, baskets, and stents (plastic vs. metallic) are part of the ERCP armamentarium necessary to treat obstructive jaundice, depending on the cause.

Choledocholithiasis

The most common cause of biliary obstruction is choledocholithiasis. Gallstone disease affects more than 20 million American adults. A subset of these patients will also have choledocholithiasis, including 5% to 10% of those undergoing laparoscopic cholecystectomy for symptomatic cholelithiasis, and 10% to 33% of patients with acute biliary pancreatitis.

ASGE published a risk stratification scoring system where a score is assigned to patients with suspected choledocholithiasis, taking into account patient age, liver function tests, and abdominal ultrasound findings (Table 2). Moreover, based on this proposed scoring system, the same group suggested a management algorithm (Fig. 1).

The sensitivity and specificity of ERCP for detecting common bile duct stones is greater than 90%, although small stones can be missed.

BOX 1 Indications of ERCP

Indications for ERCP

- Jaundice thought to be the result of biliary obstruction
- Clinical and biochemical or imaging data suggestive of pancreatic or biliary tract disease
- Signs or symptoms suggesting pancreatic malignancy when direct imaging results are equivocal or normal
- Pancreatitis of unknown etiology
- Preoperative evaluation of chronic pancreatitis or pancreatic pseudocyst
- Sphincter of Oddi manometry (surgical biliary sphincteroplasty without sphincter of Oddi manometry is not recommended in patients with suspected type III sphincter of Oddi dysfunction)
- Endoscopic sphincterotomy
- Choledocholithiasis
- Papillary stenosis or sphincter of Oddi dysfunction causing disability
- Facilitate biliary stent placement or balloon dilation of biliary structures
- Sump syndrome
- Choledochocele involving the major papilla
- Ampullary carcinoma in poor surgical candidates
- Access to pancreatic duct
- Stent placement across benign or malignant strictures, fistulae, postoperative bile leak, or large common bile duct stones
- Balloon dilation of ductal strictures
- Nasobiliary drain placement
- Pseudocyst drainage in appropriate cases
- Tissue sampling from pancreatic or bile ducts
- Ampullectomy of adenomatous neoplasms of the major papilla
- Therapy of disorders of the biliary and pancreatic ducts
- Facilitation of cholangioscopy and/or pancreatoscopy

ERCP Not Indicated

- Evaluation of abdominal pain of obscure origin in the absence of objective findings that suggest biliary or pancreatic disease. Magnetic resonance cholangiopancreatography and endoscopic ultrasound are safe diagnostic procedures that can obviate the need for ERCP.
- Evaluation of suspected gallbladder disease without evidence of bile duct disease
- As further evaluation of proven pancreatic malignancy unless management will be altered

ERCP, endoscopic retrograde cholangiopancreatography.

Careful injection of contrast and early fluoroscopy may help detect stones and avoid overfilling of the ducts or proximal advancement of stones into the intrahepatic ducts.

ERCP with biliary decompression is the procedure of choice for the treatment of acute cholangitis. The role and timing of ERCP in acute gallstone pancreatitis remains controversial. A systematic review comprising 448 patients concluded that in patients with acute gallstone pancreatitis, there is no evidence that early routine ERCP significantly affects mortality and local or systemic complications of pancreatitis, regardless of predicted severity. Nevertheless, results favored early ERCP in patients with acute biliary pancreatitis and cholangitis.

Endoscopic sphincterotomy and stone extraction are successful in more than 90% of cases, being the treatment of bile duct stone clearance. Stone removal is usually accomplished with extraction balloon catheters or wire baskets. In case of difficult bile duct stones (>1.5 cm), impacted, difficult cannulation, altered anatomy), sphincterotomy and endoscopic papillary large balloon dilation can result in high success rates of complete clearance. When this combined approach is used, a large endoscopic sphincterotomy is not required. Patients with

TABLE 2. ASGE Proposed Strategy to Assign Risk of Choledocholithiasis in Patients With Symptomatic Cholelithiasis Based on Clinical Predictors

Clinical Predictors of Choledocholithiasis
Very strong
CBD stone on transabdominal US
Clinical ascending cholangitis
Bilirubin >4 mg/dL
Strong
Dilated CBD on US (>6 mm with gallbladder in situ)
Bilirubin level 1.8–4 mg/dL
Moderate
Abnormal liver biochemical test other than bilirubin
Age older than 55 years
Dilated CBD on US/cross-sectional imaging

Likelihood of Choledocholithiasis Based On Clinical Predictors	Probability
Presence of any very strong predictor	High (>50%)
Presence of both strong predictors	High (>50%)
No predictors present	Low (< 10%)
All other patients	Intermediate (10%–50%)

ASGE, American Society for Gastrointestinal Endoscopy; CBD, common bile duct; US, ultrasound.

prior biliary sphincterotomy do not need extension of the sphincterotomy before endoscopic papillary large balloon dilation. The diameter of the dilating balloon ranges from 12 to 20 mm (about 3–5.5 cm esophageal, pyloric, or colonic dilating balloons), and is chosen based on the diameter of the stone or stones and the maximal diameter of the bile duct. There are other techniques that can be used for stone extraction of difficult bile duct stones such as mechanical lithotripsy using a basket and the digital single operator cholangioscopy system with electrohydraulic lithotripsy or laser lithotripsy, the latter with more than 90% rate of stone clearance with low rate of adverse events. If stone removal is unsuccessful, biliary decompression should be accomplished by placement of a biliary stent or nasobiliary drain.

Endoscopic sphincterotomy and stone extraction without subsequent cholecystectomy may be appropriate in some patients with comorbidities and high surgical risk. Nevertheless, biliary symptoms recur twice as commonly in patients whose gallbladder remains in situ with a 5-year risk of significant biliary adverse events leading to cholecystectomy as high as 15%.

Benign Biliary Strictures

ERCP is indicated in the evaluation and treatment of benign biliary strictures, congenital bile duct abnormalities, and postoperative adverse events such as anastomotic strictures and biliary leaks. Biopsies and brushings can help define the etiology of benign biliary strictures and diagnostic yield may increase with cholangioscopy directed biopsies.

Biliary injury is rarely recognized during surgery; symptoms appear most often in the early postoperative course or months or years after surgery. Benign biliary strictures may be dilated with bidirectional balloons (maximum biliary dilator diameter 10 mm) or graduated catheters passed over a guidewire. Benign biliary strictures amenable to endoscopic dilation include those secondary to chronic pancreatitis, dominant strictures in PSC, postoperative

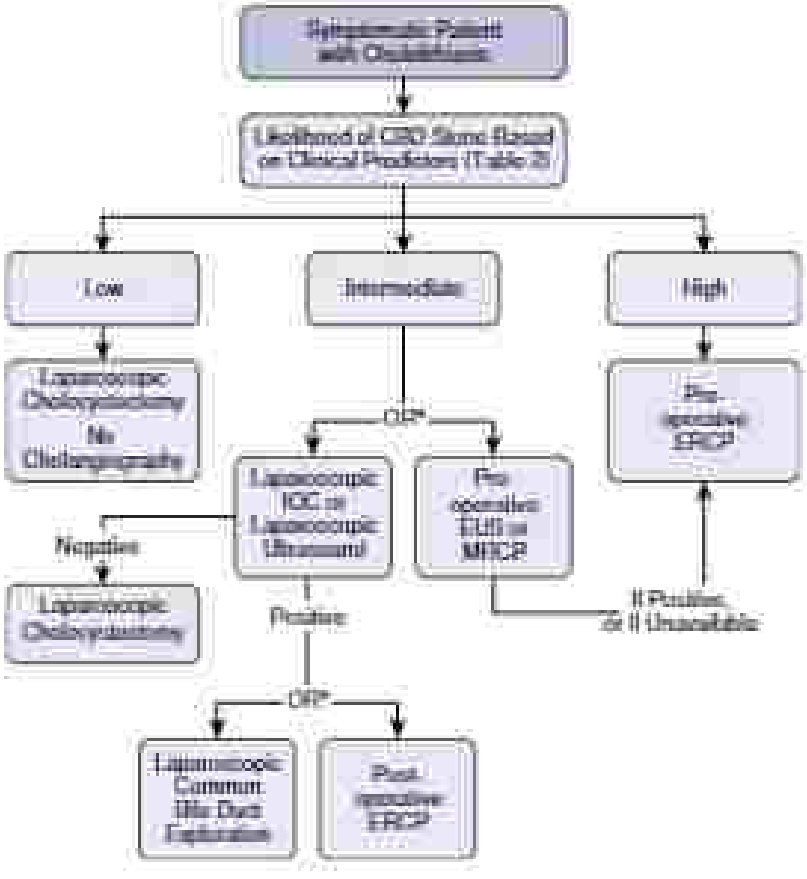

FIG. 1 American Society for Gastrointestinal Endoscopy suggested management algorithm for patients with symptomatic cholelithiasis based on the risk of probability for choledocholithiasis. *Depending on costs and local expertise. (Modified from Tse F, Barkun JS, Barkun AN. Risk stratification of patients with suspected choledocholithiasis undergoing laparoscopic cholecystectomy. Can J Gastroenterol. [year]; [volume]:[issue]:[pages].)

TABLE 3 Bismuth Classification for Benign Biliary Strictures

Type	Criteria
I	Low common hepatic duct stricture with a length of common hepatic duct stump greater than 2 cm
II	Proximal common hepatic duct stricture with a common hepatic duct stump less than 2 cm
III	Hilar stricture, no residual common hepatic duct, but the hepatic ductal confluence is preserved
IV	Hilar stricture with involvement of hepatic ductal confluence and loss of communication between right and left hepatic duct
V	Involvement of an aberrant right sectorial duct alone or with concomitant stricture of the common hepatic duct

strictures, and strictures caused by stone disease. Single or multiple plastic stents may be used to maintain patency after initial dilation. Serial endoscopic dilation and maximal caliber stent placement can be used to achieve prolonged ductal patency in most benign postoperative strictures. Despite high success rates, this approach is technically demanding and requires an average of five ERCPs. Fully covered self-expandable metal stents (cSEMS) are an alternative approach to benign biliary strictures. The cSEMS expand to lumen sizes larger than those of plastic stents, without the risk of tissue ingrowth and embedding such as in uncovered and partially covered metal stents, allowing an indwell time up to 12 months if necessary, and without compromising the ease of removal.

Chronic pancreatitis accounts for 10% of all common bile duct strictures. Treatment is indicated for patients with jaundice and/or cholangitis, those with significant biliary dilation (12 mm), pruritus, and/or strictures, and with abnormal liver function tests (ALP >3 times the normal value for 6 months or longer). In patients with bile duct strictures resulting from chronic pancreatitis the use of multiple plastic stents over a long period (24 months) compared with a single stent increases the chance of long-term overall success of 61.2% with a high risk of relapses (17%).

In patients with PSC, ERCP is no longer indicated for diagnosis in a routine basis. An MRCP is a noninvasive imaging test with comparable diagnostic accuracy to ERCP in the diagnosis of dominant strictures. A dominant stricture is defined as a lumen diameter of 1.5 mm or less in the common bile duct and 1 mm or less in the common hepatic duct and it is seen in 47% to 50% of patients with PSC. In case of unclear results of an MRCP or clinical deterioration of a patient with prior diagnosis of PSC (worsening cholestasis, pruritus, or cholangitis), ERCP can aid in the diagnosis of a dominant stricture. Benign strictures in PSC patients respond well to endoscopic therapy with balloon dilation with or without stent placement. Limited data suggest that balloon dilation is often sufficient and that the use of stents may be associated with an increased risk of adverse events and cholangitis.

Postsurgical strictures occur after orthotopic liver transplantation and laparoscopic cholecystectomy in 3% to 13% and 0.2% to 0.7%, respectively. Also, strictures at bile enteric anastomosis are seen more often every day in clinical practice. Strictures recognized early in the postoperative/operative period are often associated with a bile leak caused by direct trauma, whereas delayed presentation is commonly associated with ischemic injury and resultant fibrosis. A commonly used classification for postoperative strictures is the Bismuth classification, based on location of the stricture within the bile tree (Table 3). Clinical presentation (elevation of liver function tests, pain, jaundice) depends on the degree of bile duct obstruction. Endoscopic treatment usually involves serial placement of multiple large bore plastic stents over a 1-year period, with exchange every 3 to 4 months. Balloon dilation of anastomotic biliary strictures within the first 4 weeks of surgery carries an increased risk of anastomotic dehiscence and thus a less aggressive approach is suggested in this setting. Success rates for this approach range from 74% to 90%, with recurrence rates as high as 30% within 2 years of stent removal. Distal postoperative biliary strictures (Bismuth I and II) are associated with better success rates compared to proximal hilar strictures (Bismuth III). A 2008 randomized control trial comparing plastic stents versus cSEMS in benign biliary strictures concluded that patients with benign biliary strictures and a bile duct diameter 6 mm or more in whom the cSEMS would not overlap the cystic duct, cSEMS should be considered an appropriate option. The main potential benefit of cSEMS in the management of refractory benign biliary strictures is their large caliber and longer duration of patency allowing them to be left in place longer, resulting in fewer procedures for serial dilations and placement of multiple plastic stents.

Malignant Biliary Strictures

The most widely recognized cause of malignant distal biliary obstruction is pancreatic head cancer. Other causes of malignant obstructive jaundice are cholangiocarcinomas (CCA), gallbladder cancer, and metastatic tumors compressing the biliary system. ERCP is the most accepted and widely used method for biliary decompression in these scenarios. In those patients with unresectable malignant biliary obstruction, effective biliary decompression improves symptoms and enables patients to undergo palliative therapies. On the other hand, in those patients who are surgical candidates, routine preoperative biliary intervention may worsen outcomes. In a randomized control trial comparing preoperative biliary drainage using plastic stents versus early surgery without drainage in resectable pancreatic cancer showed that endoscopic preoperative biliary drainage with placement of a plastic stent did not have a beneficial effect on the surgical outcome. In a recent published meta-analysis including 33 studies showed that the available evidence argues against preoperative biliary drainage in patient with resectable pancreatic head adenocarcinoma. With the advent of neoadjuvant chemotherapy used to downstage potentially unresectable tumors in the hope of improving the outcome, preoperative biliary drainage is clinically relevant. Preoperative biliary drainage during the period of neoadjuvant treatment might be best achieved with metal stents, which have a higher patency rate than plastic stents.

In patients with unresectable pancreatic head adenocarcinoma and obstructive jaundice, ERCP with SEMS are superior to plastic stents in the palliative setting. A recent meta-analysis of 19 studies involving 1985 patients, cSEMS were associated with significantly lower occlusion rates, less therapeutic failure (7% vs 15%), less need for reintervention and lower rates of cholangitis (8% vs 21%) than plastic stents. In distal malignant biliary obstruction, there is the option of cSEMS vs uncovered SEMS, each of which have its advantages and disadvantages. A meta-analysis involving eight studies concluded that the group of patients with cSEMS had lower incidence of adverse events, with no significant difference in dysfunctions, however, cSEMS tends to be better, with no difference in stent patency, patient survival, and complications.

Malignant hilar strictures are categorized according to the Bismuth-Corlette classification (Table 4). At the time of presentation, only a minority (<50%) of patients with hilar CCA are candidates for resection or transplantation. The goal of palliative stenting of hilar CCA is drainage of adequate liver volume (50% or more), irrespective of unilateral, bilateral, or multisegmental stenting. Endoscopic stenting in hilar obstructions can be done with plastic or metal stents. Plastic stents are less expensive with easier insertion, removal, and exchange. Nevertheless, they have limited stent patency. On the other hand, metal stents have prolonged stent patency, do not occlude side branches, and have easier passage across biliary strictures because

TABLE 4 Bismuth-Corlette Classification for Malignant Hilar Tumors

Type	Anatomic Location
I	Common hepatic duct distal to the hepatic confluence
II	Involves the biliary confluence
IIIa	Biliary confluence + right hepatic duct
IIIb	Biliary confluence + left hepatic duct
IV	Extends to the bifurcation of the left and right hepatic ducts or multifocal

of relatively smaller delivery sphincterotomes. However, greater cost and difficulty to removal once blocked are the limitations. In those patients with predicted survival greater than 3 months, uncovered cSEMS are superior to plastic stents for palliation with respect to outcome and cost effectiveness. Adequate biliary drainage can be achieved with unilateral, bilateral side by side, or bilateral stent to stent approaches, with evidence currently lacking as to which of these approaches is optimal. The Asian Pacific consensus supports that patients with low grade hilar obstruction (Bismuth I and II), endoscopic stenting is considered a less invasive approach with acceptable outcome. In contrast, patients with advanced hilar obstruction (Bismuth III and IV), endoscopic stenting had a lower success rate of cholestasis palliation and a higher rate of post ERCP cholangitis, making percutaneous stenting a better approach for these patients. In patients with potentially resectable hilar CCA, the Asia Pacific consensus recommendations are to not perform routine preoperative biliary drainage. Nevertheless, in case of hepatectomy or hepatic vein embolization some experts prefer to achieve drainage via percutaneous approach.

ERCP Adverse Events

Post ERCP pancreatitis (PEP) is the most common serious adverse event attributed to the procedure. An elevation in the serum amylase or lipase concentration is common after ERCP, occurring in up to 75% of patients, by comparison, acute clinical pancreatitis (defined as a clinical syndrome of abdominal pain and elevated amylase or lipase more than 3 times the upper value requiring hospitalization) is much less common. The reported rate of PEP varies widely from 1% to 40%, with an average rate of 5% to 7%. In a systematic review of 108 randomized controlled trials, including 15,296 patients undergoing both diagnostic and therapeutic ERCP, the overall rate of PEP was 9.7%, with a mortality rate of 0.7% in the control group (placebo or no pancreatic duct stent arm). Most episodes of PEP are mild and require only a short hospital stay for bowel rest and intravenous hydration. Patients who develop severe pancreatitis may require prolonged hospitalization in the intensive care unit with total parenteral nutrition. The management of patients with PEP is the same as for patients with pancreatitis from other causes. The endoscopist must perform a meticulous technique, and patients deemed to be at high risk for PEP should receive aggressive intravenous hydration using lactated Ringer's solution, rectal indomethacin, and pancreatic stenting.

Bleeding is a serious adverse event after ERCP and is most commonly the result of endoscopic biliary and/or pancreatic sphincterotomy. The rate of postsphincterotomy bleeding after ERCP is estimated to be 0.3% to 2%. Initial management of postsphincterotomy bleeding includes adequate fluid resuscitation, reversal of coagulopathy, and blood transfusion as needed. Endoscopic therapy includes diluted epinephrine injection at the sphincterotomy site (0.5–1 mL), thermal therapy such as multipolar electrocautery or argon plasma coagulation, clipping at the sphincterotomy site, which might be challenging using the duodenoscope; balloon tamponade mostly during intraprocedural bleeding, and cSEMS, which have shown excellent results in multiple series. A recently US Food and Drug Administration approved inert powder developed for endoscopic hemostasis (Hemospray; Cook Medical) has a potential role in postsphincterotomy active bleeding. It is a noncontact, nonthermal, atraumatic technique that will induce hemostasis when in contact with an active bleeding site, the powder absorbs water and adheres to the bleeding site forming a mechanical barrier. It could act as a primary hemostatic or as a bridge to a more definitive hemostatic technique during intraprocedural bleeding. There are no data to support its use in a nonactive bleeding site. Angiographic embolization or surgery is reserved for bleeding unresponsive to endoscopic therapy.

Cholangitis is the most common infectious adverse event associated with ERCP, occurring in 0.5% to 3% of cases. The risk of cholangitis is highest in patients with incomplete biliary drainage (hilar CCA and PSC) and a history of liver transplantation, therefore, periprocedural antibiotics and meticulous biliary drainage techniques are essential in these patients. Other potential infectious events include cholecystitis, duodenoscope related transmission of infections, and infective endocarditis.

Perforations associated with ERCP are rare and can occur in 0.08% to 0.6% of patients. Perforations can occur with the endoscope, after a sphincterotomy, and transmural secondary to the passage of guidewires or stents. ASGE guidelines state that in case of suspected periampullary or instrument related perforations from ERCP without evidence of peritonitis or systemic inflammatory response syndrome, these can be managed nonoperatively.

EUS-BD

In cases where bile duct access cannot be obtained as a result of failed ERCP cannulation, altered anatomy, ampullary distortion or diverticulum, gastric outlet obstruction, or in situ duodenal stents, EUS-BD is increasingly being used as an alternative to interventional radiology or surgery.

EUS-BD is performed by using one of three basic approaches that include the rendezvous (RV) technique, transluminal (TL) stenting, or EUS-guided antegrade transpapillary (or transduodenal) biliary stent placement.

Any of the three approaches is performed using a linear therapeutic endoscopic ultrasound, and in case of the RV approach a combination of a linear echoendoscope and a standard duodenoscope is used. Other instruments needed are a 19-gauge fine needle aspiration needle, a 0.025-inch guidewire (most frequently used), and plastic or metal stents.

The echoendoscope is positioned within the gastric fundus or duodenal bulb to access the intrahepatic and extrahepatic bile duct, respectively. A 19 gauge fine needle aspiration needle is used to puncture the bile duct, and then access is confirmed with EUS or with contrast injection and fluoroscopic confirmation. The 0.025-inch guidewire is advanced into the bile duct and under fluoroscopy is advanced transpapillary into the duodenum (in the RV technique) or proximally into the intrahepatic ducts (TL technique). In the RV approach, once the guidewire is properly placed, the echoendoscope is removed, and a standard duodenoscope is inserted to retrieve the guidewire by using a biopsy forceps or snare, thereby allowing standard ERCP and stent placement (over the wire technique). In the TL approach, once the guidewire is properly placed, the puncture site is dilated using a catheter or biliary balloon dilator creating a fistula. The two common TL approaches are a choledochoduodenostomy or hepaticogastrostomy. The initial puncture in the choledochoduodenostomy technique is done in the duodenum and in the hepaticogastrostomy from the gastric cardia or gastric body into the dilated intrahepatic ducts, liver segment 2 or 3. In both approaches, cSEMS are favored over plastic stents to decrease the risk of bile leak.

In the antegrade stenting technique, the initial steps are the same as in the other techniques. Then, the intrahepatic stent placement is performed by advancing the stent through the echoendoscope over

the guidewire to traverse the stricture and does the papilla (transpapillary) or anastomosis (transanastomotic).

It is important to obtain informed consent from all patients for possible EUS-BD at the time of ERCP, in particular those at high risk of failed biliary cannulation (surgical altered anatomy, previous failed ERCP, periampullary cancer with duodenal invasion on imaging, duodenal tumor covering the ampulla). The consent requires a thorough discussion regarding the potential indications, benefits, and risks after possible failed cannulation and available alternatives such as repeated ERCP versus percutaneous or surgical drainage.

Data mostly from small retrospective series suggest that EUS-BD can be performed with high therapeutic success (87%) but is associated with a 10% to 20% risk of adverse events, most of which are mild to moderate in nature. Many endoscopists favor the RV technique because it avoids the creation of a permanent bilioenteric fistula and luminal tract dilation, which may result in bleeding, pneumoperitoneum, or pneumomediastinum. Data published to date are from tertiary high volume centers. These procedures should be done by experienced endoscopists in both ERCP and EUS and carried out at institutions with backup surgery and radiology to manage failed interventions or adverse events.

Data directly comparing EUS-BD with PTBD are limited, leaving uncertainty about how best to manage patients after failed ERCP. Some studies have reported similar efficacy in both approaches, but EUS-BD may offer more safety at a significantly lower cost with fewer interventions. A potential advantage of EUS-BD is the ability to access various sites of the biliary system, allowing drainage even in the setting of duodenal obstruction or duodenal bypass surgeries. In addition, EUS-BD may also be performed in patients with ascites and liver metastasis, scenarios in which percutaneous approaches may be difficult. Indications and methods for EUS-BD are yet to be standardized, moreover, the approach should be individualized for each patient based on the endoscopist's expertise and the patient's anatomy.

Suggested Readings

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MANAGEMENT OF ACUTE NECROTIZING PANCREATITIS

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DIAGNOSIS AND EVALUATION

PRESURGICAL TREATMENT

Resuscitation

The resuscitation strategy should be tailored to the severity of the disease. In moderately severe and severe pancreatitis, a significant amount of intravenous fluid resuscitation is typically required because most patients with pancreatitis present with intravascular hypovolemia from poor oral intake, vomiting, and third-space sequestration. Prospective studies have demonstrated that ... around Ringer's solution is the preferred fluid of choice over other crystalloid solutions such as normal saline for resuscitation. In general, goal-directed intravenous fluid resuscitation at 5 to 10 mL/kg per hour should be used initially. Under-resuscitation results in worse overall outcomes, more end-organ damage such as acute kidney injury and may result in more pancreatic necrosis because of hypoperfusion. On the other hand, over-resuscitation can lead to acute lung injury and abdominal compartment syndrome. Striking the right balance between over- and under-resuscitation is difficult. Current guidelines call for ongoing fluid resuscitation to be guided by frequent reassessment of fluid responsiveness using urine output, blood pressure and hematocrit levels, or dynamic variables such as pulse pressure and stroke volume variation. When a patient is deemed euvolemic but is persistently hypotensive, vasopressor support should be used, with norepinephrine as the first line agent. Ultimately, the way we conceptualize this is that there are responders and nonresponders to initial fluid resuscitation. ...responders can benefit greatly from rapid, aggressive intravenous fluid administration in accordance with the guidelines presented. ...caution in patients who remain in persistent

organ failure with SIRS, tachycardia, hypotension, and renal failure, additional fluid resuscitation beyond the initial effort will not reverse this underlying process, but may accrue severe complications such as abdominal compartment syndrome from visceral edema and ascites. In patients with persistent hypotension and organ failure in spite of early aggressive fluid resuscitation, we ask, "What will the tenth liter of fluid accomplish that the first nine did not." Usually, nothing beneficial. Although this tipping point from helpful resuscitation to harmful over resuscitation is difficult to identify clinically, it does exist, and avoiding harmful excessive crystalloid administration is as important as providing adequate early crystalloid resuscitation.

TABLE 1 Etiology and Diagnosis of Acute Pancreatitis

Etiology	Diagnostic Options
Gallstone	Ultrasound, MRI
Alcohol	History taking, serum alcohol levels
Hypertriglyceridemia	Serial serum triglyceride levels
Hypercalcemia	Serum PTH
Idiopathic*	Postpancreatitis imaging to assess for mass lesion
Neoplasm	Postpancreatitis imaging to assess for mass lesion
Iatrogenic (ERCP)	Recent history

ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; PTH, parathyroid hormone.

TABLE 2 Contemporary Severity Assessment of Acute Pancreatitis

Mild	Moderately Severe	Severe
Complete absence of systemic inflammatory response syndrome *and* No local pancreatic complications such as necrosis *and* No end organ failure	Local pancreatic complications such as necrosis and acute fluid collections *or* Transient organ failure (resolution within 48 hr)	Persistent organ failure (>48 hr)

Nutrition

Historically, patients with pancreatitis were kept without food or water for prolonged periods on the premise of decreasing stimulation of pancreatic secretion and release of digestive enzymes. Recent evidence has demonstrated that this practice is not beneficial. In patients with mild pancreatitis, oral feeding of a low fat solid diet should be initiated as soon as abdominal pain and inflammatory markers start improving. Feeding as tolerated has been shown to accelerate recovery and to shorten hospital stay. In patients with more severe pancreatitis who are unable to tolerate oral intake, enteral nutrition should be provided within 2 to 3 days of presentation, preferably through nasogastric or nasojejunal tube feedings with an aspiration precaution protocol in place. Enteral feeding has been shown to preserve the gastrointestinal mucosal barrier, which in turn may reduce bacterial translocation and infection of damaged tissues. It is preferred over total parenteral nutrition, which is associated with higher incidences of organ failure, infectious complications, and mortality. Parenteral nutrition should be reserved for patients not meeting nutritional goals via an enteral route after 5 to 7 days. Fig. 1 details our approach to nutritional support in patients with acute pancreatitis.

Infection and the Role of Antibiotics

Prophylactic antibiotics are not indicated in patients with no signs of infection. Historically, prophylactic antibiotics were given on the premise of preventing the progression of sterile pancreatic and peripancreatic necrosis to infected necrosis. However, studies have shown that prophylactic antibiotics confer no benefits, predispose to multidrug resistant and fungal infections, and should not be administered unless there is clear evidence of infection (cholangitis, bacteremia, proven infected pancreatic necrosis). However, it may be difficult to be sure if infection is present because patients with acute pancreatitis often manifest signs and symptoms of SIRS such as fever, tachycardia, and leukocytosis, all of which can mimic infection. When infection is suspected, CT imaging is indicated. Infected necrosis can be diagnosed by imaging demonstrating gas within the areas of pancreatic necrosis. Although this finding is highly specific, it is not sensitive. Until recently, percutaneous sampling by needle aspiration of the necrotic collection for culture was routinely advocated to assess

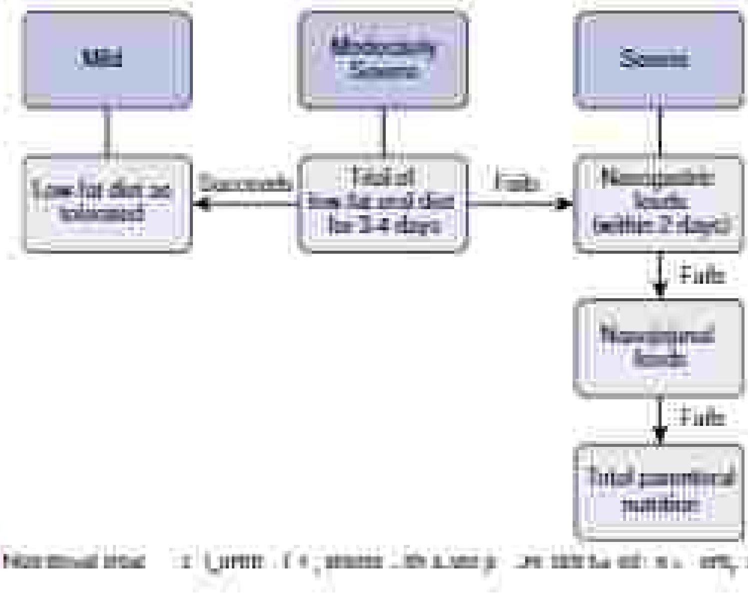

FIG. 1 Nutritional [illegible]

for infected necrosis when there was clinical suspicion for infection but no definitive evidence on imaging. However, it has a relatively high false-negative rate of approximately 20% and should be used selectively. It should be performed if there is no clear cut evidence of infection (i.e., gas bubbles on CT) and prolonged surveillance, and a positive aspirate culture will prompt initiation of antibiotics. If the patient has ongoing inflammatory signs and a negative needle aspiration will not change the treatment plan, a decision to treat empirically based on the clinical diagnosis is justified. Patients with necrosis and "persistent unwellness" (failure to thrive) over a period of weeks often harbor occult infection. Our studies have shown that 46% of these patients have infected necrosis when cultures are obtained, many times after negative needle aspirates.

If infection is suspected or confirmed, antimicrobial therapy should be initiated. The majority of infections are caused by enteric organisms. Empiric antibiotic treatment should consist of a regimen with an appropriate spectrum of antimicrobial activity and known to penetrate pancreatic necrosis such as a carbapenem or gram-negative agent (quinolone or third- or fourth-generation cephalosporin) plus metronidazole. If drainage or debridement is performed, a sample should be taken for culture to guide treatment. If patients are started on antibiotics for infected necrosis in the absence of microbiologic data and continue to clinically deteriorate, the regimen should be empirically broadened to include gram positive, fungal, and multidrug-resistant organisms in addition to performing other maneuvers to achieve source control (e.g., drainage, debridement) and considering extrapancreatic sources of the clinical deterioration.

KEY COMPLICATIONS

Choledocholithiasis and Cholangitis

In patients presenting with pancreatitis caused by gallstones, routine ERCP should not be performed. The majority of tiny stones will pass into the duodenum spontaneously. However, retained stones or cholangitis may occur in parallel with the ongoing pancreatitis. In cases of suspected persistent choledocholithiasis without any concern for cholangitis, a period of watchful waiting of 72 to 48 hours with serial liver function tests and clinical monitoring is reasonable as spontaneous passage of gallstones is common and results in resolution of the obstruction without the need for intervention. These patients should be managed like any other patients with possible choledocholithiasis, which is discussed elsewhere in this text. In cases of suspected cholangitis, blood cultures should be drawn, followed by the initiation of broad spectrum antibiotics and urgent ERCP to relieve the biliary obstruction.

Abdominal Compartment Syndrome

Abdominal compartment syndrome occurs when organ dysfunction, most prominently oliguric acute kidney injury and respiratory failure with high peak inspiratory pressures, is caused by intraabdominal hypertension. Although intraabdominal hypertension is defined as intraabdominal pressure exceeding 12 mm Hg, abdominal compartment syndrome rarely occurs with intraabdominal pressures less than 20 mm Hg. The intraabdominal pressure is measured by instilling a small volume of fluid into the bladder via a urinary catheter and transducing the catheter. Three main factors can contribute to the development of abdominal compartment syndrome in acute pancreatitis: (1) visceral edema from large volume crystalloid resuscitation, (2) ascites similarly related to fluid resuscitation and occasionally to portal venous thrombosis, and (3) space occupying retroperitoneal and peripancreatic necrosis and fluid collections. This complication typically occurs early in the course of illness when the inflammatory response is at its height amid active fluid resuscitation. Initial treatment is the cessation of unnecessary volume infusion, volume removal if possible via diuresis, administration of ultrafiltration, interventions to decrease hollow viscus volume (nasogastric decompression, rectal drainage, prokinetics), and sedation and neuromuscular blockade to increase abdominal wall compliance. In patients with a significant volume of ascites, percutaneous drainage can sometimes result in a dramatic decrease in intraabdominal pressure and should be attempted before decompressive laparotomy is considered. When all other strategies fail, decompressive laparotomy is the definitive treatment for abdominal compartment syndrome. It is critical to note that debridement of pancreatic necrosis should not be performed at the time of abdominal decompression as very early debridement increases mortality. There are a variety of techniques for managing the open abdomen. We prefer to use a vacuum assisted abdominal closure, with closure beginning 24 to 48 hours after the initial decompression and proceeding in a staged fashion every 24 to 48 hours thereafter if primary closure is not possible.

Pseudoaneurysm

Pseudoaneurysms occur when enzyme rich pancreatic fluid autodigests and weakens the walls of pancreatic and visceral arteries, leading to wall defects. The most commonly involved arteries are the splenic, branches of the gastroduodenal arcade, and the hepatic artery (Fig. 2A). These pseudoaneurysms are life threatening because of their potential for major hemorrhage. Pseudoaneurysms are typically asymptomatic until they bleed, and are often incidentally identified during CT or magnetic resonance imaging in the course of serial evaluations. We recommend aggressive angioembolization of virtually all pseudoaneurysms found in pancreatic fields because there is no reliable means of clinical monitoring and the consequences of hemorrhage are potentially grave. When pseudoaneurysms do rupture, they may present initially with a small volume "sentinel" bleed that, if recognized, can provide a window for intervention before massive hemorrhage ensues. In patients with external drainage catheters, any bleeding from the drain must be taken seriously and considered a possible pseudoaneurysm until proven otherwise. Similarly, pseudoaneurysm should be in the differential diagnosis when upper gastrointestinal bleeding occurs in a patient with transgastric stents or a gastric anastomosis to the necrotic cavity (discussed later). In stable patients, CT angiography (CTA) can effectively assess for pseudoaneurysm, provide a picture of any surrounding local complications (such as necrosis or pseudocyst), and provide a road map for angioembolization. In hemodynamically unstable patients with clinical suspicion for a bleeding pseudoaneurysm, there may not be time for CTA; immediate angiography may be required. Surgical control of a bleeding pseudoaneurysm within a bed of pancreatic necrosis is extremely challenging, and operative intervention should be reserved for patients with severe hemodynamic instability when angiography is not immediately available or when angiographic interventions have failed.

Pseudocyst

Acute pancreatic and peripancreatic collections are common local complications of acute pancreatitis. These collections usually do not require intervention, with a minority of them progressing to walled off necrosis or pseudocyst when they are not evacuated. Pseudocysts are organized collections of pancreatic fluid that have a connection to the pancreatic duct system, and persist more than 4 weeks after the index pancreatitis episode. Most pancreatic pseudocysts resolve spontaneously or remain asymptomatic, without intervention. In symptomatic cases, symptoms typically develop as a result of pressure symptoms on adjacent structures (usually stomach or duodenum), resulting in pain or early satiety. Less commonly, infection, rupture, or hemorrhage, may occur (Fig. 2B). In symptomatic patients, standard management consists of internal drainage into the gastrointestinal tract. This is most commonly performed endoscopically. Surgical drainage, which may have a higher rate of resolving the pseudocyst in a single procedure, should be considered when patients have failed endoscopic drainage, when there is a disconnected pancreatic duct (by gaining internal drainage or resection), for larger pseudocysts in dependent locations (i.e.,

parasitic pattern), or when other intraabdominal procedures are indicated (i.e., laparoscopic cystogastrostomy at the time of laparoscopic cholecystectomy to prevent recurrent biliary pancreatitis). For patients with hemorrhage into the pseudocyst, a CTA should be performed to determine the appropriate next steps. Bleeding may be from a single adjacent visceral artery branch or from a small unnamed vessel in the pseudocyst wall. If CTA demonstrates a significant arterial bleed, the bleeding should be treated akin to a pseudoaneurysm and managed as detailed in the previous section. If CTA demonstrates no clear evidence of an arterial bleed, the bleed seen on initial imaging is likely a sidewall bleed within the pseudocyst, and the pseudocyst can be managed without directly addressing the culprit vessel. Be cognizant of the fact that cystic neoplasms can also manifest as pseudocyst, especially in cases in which a prior history of pancreatitis is unclear.

Portal System Thrombosis

Portal system thrombosis is often asymptomatic and is typically found incidentally on imaging (Fig. 2.3). Long-term sequelae are the result of chronic portal hypertension, the most obvious of which is the formation of varices although these are rarely complicated by bleeding. Complete superior mesenteric or portal vein thrombosis can occasionally have more dramatic presentation however, including massive ascites, propagation into the mesenteric venous tributaries with bowel infarction, and encephalopathy. Good evidence for the management of portal system thrombosis in pancreatitis is lacking. We typically anticoagulate with intravenous unfractionated heparin or subcutaneous low molecular weight heparin, with a bridge to oral anticoagulation for 3 to 6 months when no further invasive procedures planned. Anticoagulation seems to be effective, with partial recanalization of the portal venous system occurring in ~3% to ~8% of patients, and complete recanalization in 34% to 87%. If recanalization occurs, it typically happens within the first 6 months, and anticoagulation beyond that point is unlikely to be effective. In case of acute symptomatic thrombosis, endovascular thrombectomy or thrombolysis can be considered, and in the very rare case with associated bowel infarction requiring laparotomy, surgical thrombectomy is an option.

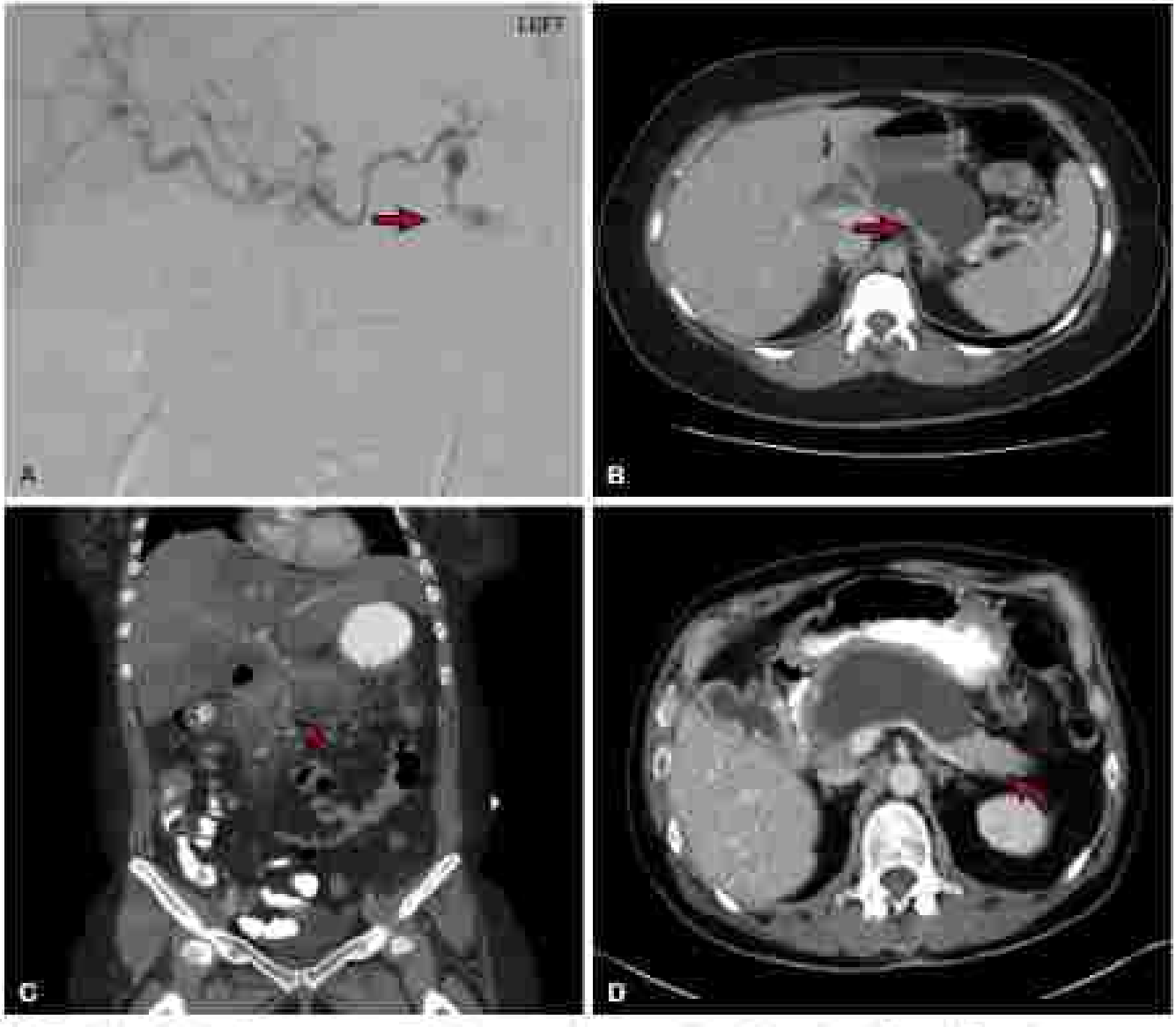

FIG. 2 Potential complications of acute pancreatitis. (A) Splenic artery pseudoaneurysm with a tiny hemorrhage [red arrow] into the stomach pseudocyst [green arrow] posterior to the stomach [red arrowhead]. (B) Superior mesenteric vein thrombosis [red arrow]. (C) "Disconnected duct syndrome." An out of the notation a "tube" segment of pancreatic tissue disconnected from the tail with a cyst at the end of a pancreatic ductal

Disconnected Duct Syndrome

The disconnected duct syndrome refers to complete necrosis of a central portion of the pancreas with associated disruption of the main pancreatic duct such that a viable tail segment is "disconnected" from any drainage pathway to the ampulla of Vater (Fig. 27). After resolution of the necrosis, this can present a number of problems including external pancreatic fistula if external drainage is in place, recurrent pseudocyst, or chronic recurrent pain resulting from obstructive pancreatitis because the disconnected segment produces exocrine secretions that have nowhere to go. If a disconnected duct is identified early in the course of pancreatitis, then the management strategy for the necrosis should incorporate some form of internal drainage (see the sections on endoscopic and surgical transgastric necrosectomy and dual modality therapy later in this chapter) to avoid prolonged external drainage. If endoscopic therapy is chosen, then soft plastic transgastric stents should be left in place indefinitely. In case of recurrent obstructive pancreatitis in the disconnected tail, endoscopic pancreatic duct stenting may be able to reestablish drainage to the ampulla. Surgical options include minimal drainage, usually into a Roux limb of jejunum, or resection of the disconnected distal segment. Distal pancreatectomy has a slightly higher rate of successful symptomatic management (90% vs 80% in one recent series) but at the cost of more intraoperative blood loss, worse long-term endocrine function, and usually splenectomy. One of the most important aspects of this syndrome is to recognize it. In our experience, many patients referred with this problem have been told "this is life after a bad episode of acute pancreatitis," sometimes for years, when in fact therapeutic options may be available.

INTERVENTIONAL MANAGEMENT

The primary indication for operative intervention in necrotizing pancreatitis is known or suspected infected pancreatic necrosis. Patients with sterile necrosis with gastric outlet or intestinal obstruction or persistent failure to thrive beyond 8 weeks may also benefit from necrosectomy and, as mentioned previously, a significant minority of them may also have occult infection. When intervention is required, it should ideally be delayed for a minimum of 4 weeks whenever possible to allow for encapsulation and demarcation of the necrosis. This waiting period applies to all of the techniques described later. The strategy for intervention for infected necrosis typically involves a step-up approach. Patients undergo percutaneous or endoscopic drainage of the infected cavity as the first intervention, with necrosectomy reserved for those who fail to improve after the initial drainage. The step-up approach is associated with less major morbidity and in some studies lower mortality rates compared with primary open necrosectomy. In 30% to 40% of cases, percutaneous or endoscopic drainage alone may obviate the need for necrosectomy. The question of when to step up should be tailored to the individual patient depending on the extent and location of the necrosis and clinical progress after initial drainage, but there are no hard criteria established for when to step up. It is worth emphasizing that the majority of patients with infected necrosis require some form of necrosectomy, not just drainage and antibiotic treatment alone. Because the step-up approach has been popularized and the number of facilities capable of percutaneous and endoscopic intervention has proliferated, it has been our impression that the misconception that drainage suffices for the management of infected necrosis has grown in parallel. This frequently results in cases in which an appropriate initial intervention (such as percutaneous drainage) is undertaken, but patients are inappropriately allowed to languish because of a failure to recognize the need to step up and debride. A complete strategic plan should be established before the initial intervention because the route and method of percutaneous drainage may dictate or limit subsequent options. Fig. 1 depicts our algorithm for selecting the optimal method of intervention. Table 3 depicts their relative strengths and weaknesses.

Video-Assisted Retroperitoneal Debridement

Video-assisted retroperitoneal debridement (VARD) is the technique most closely associated with minimally invasive necrosectomy because it was used almost exclusively in the landmark 2010 study

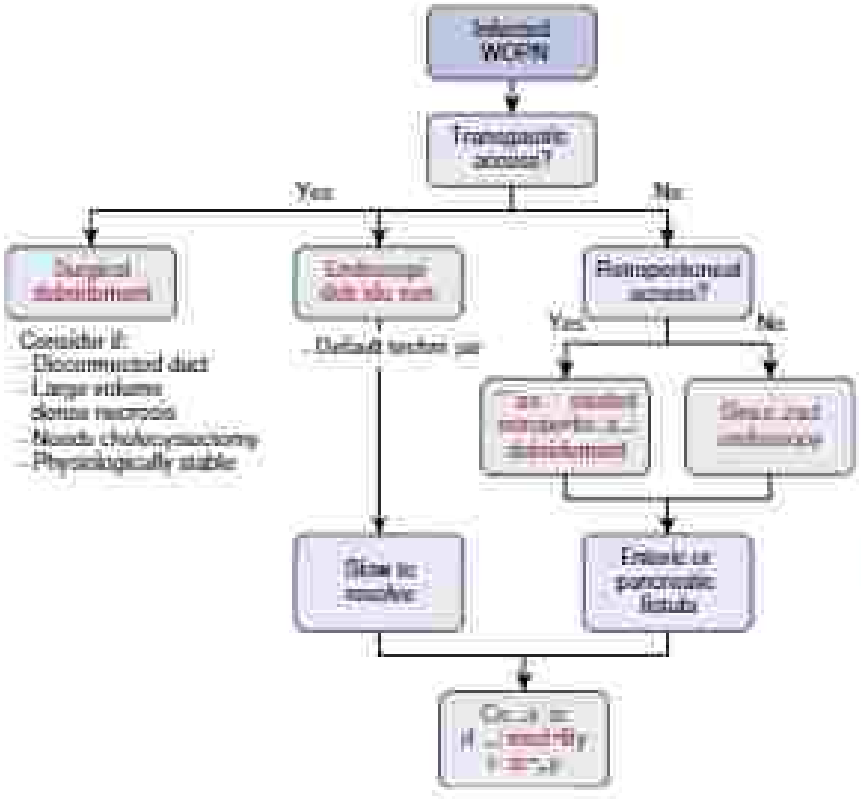

FIG. Decision algorithm for selecting the optimal interventional approach in patients with infected walled-off pancreatic necrosis. Surgical debridement refers to transgastric debridement, which can be performed open or laparoscopically. Dual modality therapy refers to a combination of endoscopic transgastric drainage and a single necrosectomy via video-assisted retroperitoneal debridement or direct endoscopy. WOPN, walled-off pancreatic necrosis.

TABLE 3 Advantages and Disadvantages of Different Approaches to Necrosectomy

	Open Transperitoneal Necrosectomy	Transgastric Necrosectomy	Video-Assisted Retroperitoneal Debridement	Sinus Tract Endoscopic Debridement
Advantages	Flexibility to access	Lacks external drainage system Endoscopic approach has decreased morbidity when compared to open necrosectomy Surgical approach allows rapid debridement and simultaneous cholecystectomy	Does not require a transgastric window Decreased morbidity compared with open transperitoneal necrosectomy Uses equipment familiar to surgeons	Flexibility to access (transperitoneal, retroperitoneal, intramural) Decreased wound morbidity compared with open necrosectomy or video-assisted retroperitoneal debridement
Disadvantages	High rates of morbidity and mortality	Requires a clear anatomic window with posterior stomach Endoscopic approach usually requires multiple reintervention	Increased wound complications compared with sinus tract endoscopic debridement Requires a retroperitoneal drainage route Pancreatic fistula	Requires familiarization with equipment (right nephroscope, intraoperative fluoroscopy) Often requires multiple interventions Pancreatic fistula

that established the step-up approach as the usual standard of care. VARD relies on a retroperitoneal drain placement as the initial intervention. This is most commonly placed via the left flank in the window between the left kidney and descending colon. If drainage alone does not resolve the infected necrosis, the drain is used as a guide for the VARD procedure. Thus, careful attention to the exact route of placement is critical and should be discussed in detail with the radiologist performing the drainage procedure.

When the decision is made to proceed with VARD, the patient is placed in a partial lateral decubitus position at a 30- to 45-degree angle, with the percutaneous drain propped into the field. A 4- to 5-cm lateral flank incision is made over the drain, and electrocautery is used for the dissection along the tract through the retroperitoneum into the necrotic cavity. It is critical for the surgeon to have diligently studied the preoperative CT scan to understand the relationship of the surrounding structures (colon, kidney, splenic vessels) to the course of the drain tract to avoid injury to them (Fig. 4). Retractors and a laparoscope are used to provide visualization. On entering the cavity, suction and irrigation are used to clear liquid debris. If the cavity is superficial enough, ring forceps can be used to excavate the necrotic material. For deeper cavities, longer right retractors are used to create a working space, and laparoscopic graspers can be used for debridement. Once debridement has been completed, drains are placed. We typically bring the drain(s) out through a separate stab incision(s) and close the initial wound in multiple layers to reduce the risk of leakage through the wound. A video of the procedure can be found at https://youtu.be/9SrPSAuwOA4.

VARD uses equipment familiar to surgeons, such as a laparoscope for visualization, as well as ring or laparoscopic forceps for debridement. Similar to open necrosectomy, VARD allows rapid and large-volume debridement of necrosis, and complete debridement is usually achievable in a single procedure. VARD has a number of limitations, however. First, there is a relatively high rate of external pancreatic fistula. Second, wound complications, although generally minor, are fairly common. Finally, it requires a retroperitoneal window that is wide and safe enough for a cadaver along the drain tract into the cavity.

Sinus Tract Endoscopic Debridement

Sinus tract endoscopic debridement (STD) is another step-up option when percutaneous drainage fails to resolve pancreatic necrosis. STD is relatively free of anatomic requirements because any necrotic collection that can be accessed percutaneously can be accessed by STD. Thus, STD is an especially good option when the optimal drainage routes into the necrosis are transperitoneal, intercostal, or through very small windows between vital structures. As with VARD, planning for STD should begin at the time of percutaneous drainage in collaboration with interventional radiology. The path of the percutaneous drain should be chosen in a manner that allows access to the entire necrotic cavity, typically by entering at one end. Positioning of the patient on the table can be supine or in partial decubitus position based on the location of the drain. The drain is cut at the skin level, and propped and draped into the surgical field (Fig. 5).

Under fluoroscopic guidance, a guidewire is threaded through the percutaneous drain into the necrotic cavity, and the drain removed over the wire. A nephrostomy balloon dilator catheter is then introduced over the wire until the tip of the balloon is within the cavity, and the balloon inflated with contrast to a pressure of 10 psi. The balloon is kept inflated for 1 minute to allow for tract dilation. Subsequently, a 30Fr working sheath is inserted over the balloon dilator catheter, and a rigid nephroscope then inserted with continuous irrigation of the cavity to facilitate visualization. A grasper is then introduced through the nephroscope and debridement performed in a systematic manner to develop a working space within the cavity. The goal is to debride until a healthy circumference of granulation tissue is identified. However, it is unnecessary and dangerous to debride necrotic tissue that is tightly adherent to the walls of the cavity because of the risk of bleeding. During sinus tract endoscopy, even minor bleeding can be problematic because it impairs visualization in the relatively small working space, especially when swirling to the irrigant. In this circumstance, the bleeding areas can be managed by packing the cavity with a half inch gauze packing strip through the sheath for a few minutes. This is often enough to allow the procedure to proceed. Advancing the sheath past the point of bleeding to "plug" and tamponade the bleeding tissue can also be effective and allow debridement to continue at a different point in the cavity. An alternative is to stop the continuous irrigation and continue the debridement in a dry fashion, so that the blood can pool on the floor of the cavity (instead of swirling in the irrigant (pictured in the video)). If complete debridement cannot be achieved at the time of the first STD, it is always safer to irrigate the cavity and return in 2 to 3 days to repeat the debridement, at which time the necrosis is typically much less adherent. Once the debridement procedure is completed, a new drainage catheter is placed over the wire before it being removed. If a repeat procedure is planned, a separate 7Fr catheter is placed adjacent to the drainage catheter to allow for continuous irrigation, which loosens tightly adherent necrotic tissue within the cavity. The drain is

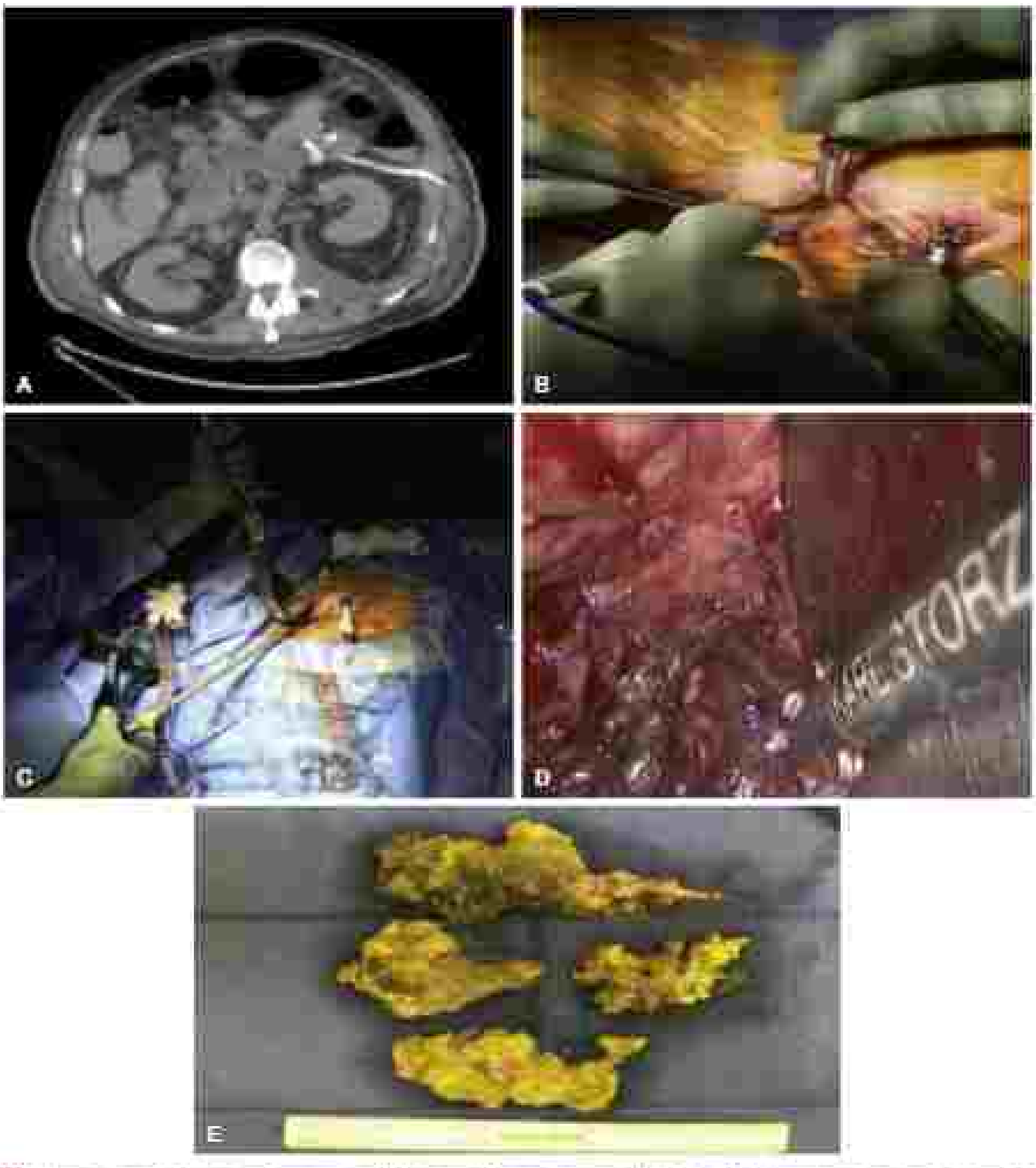

FIG. 4 Operative steps for video-assisted retroperitoneal debridement of pancreatic necrosis. (A) Axial view of the percutaneous catheter that is used as a guide as the dissection is carried out into the retroperitoneum. (B) The cut down on the percutaneous drain tract out through the bowel with electrocautery. (C) Retractors and a laparoscope are inserted through the incision into the necrotic cavity. (D) A laparoscope is used for better cavity visualization and laparoscopic graspers are used to manually debride and remove necrotic material. (E) Necrotic specimen at the end of the procedure.

FIG. 1. Operative steps for step-up minimally invasive debridement of pancreatic necrosis. (A) An Amplatz wire is inserted through the cut end of the drain into the necrotic cavity. (B) A 30Fr nephrostomy balloon dilator catheter is inserted over the wire until the tip of the balloon is within the cavity of the necrotic tissue. (C) A balloon dilator is inflated with contrast for dilation of the tract. (D) A 33Fr working sheath is inserted over the balloon into the cavity. (E) A right nephroscope is advanced into the cavity through the sheath and a grasper is passed through the nephroscope for debridement of the necrotic cavity.

then according to the skin, concluding the procedure. A full video of the procedure can be found at https://youtu.be/ed5S3-1 [1].

Aside from versatility in allowing access to almost any intra-abdominal collection, the other main advantage of STE is that wound complications are uncommon because the drain entry site is the only incision. However, STE requires familiarization with equipment not frequently used by surgeons, such as fluoroscopically guided dilators and the rigid nephroscope, and the relatively small graspers mean multiple procedures are usually required for full debridement of larger necrotic collections.

Endoscopic Transluminal Necrosectomy

Endoscopic transluminal necrosectomy is typically performed through the gastric wall but can also be done through the duodenal wall. Endoscopic transgastric necrosectomy is our preferred approach for the majority of cases where there is a clear transgastric window into the necrotic cavity, and where the burden of pancreatic necrosis is in continuity with the posterior stomach. A lumen-apposing metal stent can be placed to facilitate transluminal drainage after the initial debridement and to simplify reintervention. The primary benefits of this approach are the resultant low rate of new onset organ failure, minimal pain, and absence of an external drain, thus obviating any pancreatic fistula. The primary drawbacks are that it can only be applied to necrotic collections that are accessible through the gastrointestinal tract, and that it usually requires multiple re-interventions. Outcomes of these interventions in the Pancreatitis, Endoscopic Transgastric Versus Primary Necrosectomy in Patients With Infected Necrosis trial1 and occasionally requires other modalities to complete debridement (20% in the same trial).

Surgical Transgastric Necrosectomy

Operative transgastric necrosectomy can be performed in an open or laparoscopic fashion. It accrues the main benefit of endoscopic transgastric necrosectomy—namely the lack of external drains or pancreatic fistula—but typically does not require multiple procedures as surgical instrumentation generally allows for a more complete debridement at the initial operation. Additionally, it allows for a simultaneous cholecystectomy to be performed when required to reduce the risk of recurrence in patients with gallstone pancreatitis. By combining transgastric debridement with what essentially is a cystgastrostomy, it also allows for more durable control of high-grade pancreatic fistulas such as that with a disconnected distal remnant. As with the endoscopic approach, surgical transgastric necrosectomy should be reserved for patients whose main necrotic burden lies in the lower sac posterior to the stomach.

Dual-Modality Drainage

Dual-modality drainage consists of combining endoscopic transgastric drainage with percutaneous drainage. In the initial description, this was performed as drainage alone without necrosectomy by either approach. The result was a low mortality and low rate of external fistula but a long duration of external drainage. Combining this approach with either transgastric or minimally invasive surgical necrosectomy may reduce the overall duration of drainage. We use this combined approach in two scenarios. (1) When planned transgastric endoscopic necrosectomy reveals a large volume of dense necrosis which will require multiple endoscopic necrosectomies, but which could be efficiently and effectively managed with the larger instrumentation available surgically. (2) When a large volume of necrosis tracks away from the stomach inferiorly through the retroperitoneum or down the retrocolic gutters, which can be most efficiently addressed via a surgical retroperitoneal approach, but we wish to incorporate internal drainage to minimize the duration of external drainage and the risk of prolonged pancreatic fistula. Incorporation of internal drainage minimizes the duration of external drainage and the risk of prolonged pancreatic fistula. Essentially, dual-modality drainage accrues the main benefit of endoscopic drainage (the low rate of external fistula formation and the main benefits of surgical necrosectomy), larger instrumentation that allows more rapid debridement and the ability to access portions of the necrosis that are difficult to reach endoscopically.

Transperitoneal Necrosectomy

Although the benefits of minimally invasive approaches to necrosectomy have been largely adopted by centers managing patients with necrotizing pancreatitis, it is important to remember that open operative debridement still represents a useful tool in appropriately selected patients. Most trials supporting the use of the step up approach only enrolled patients with necrosis anatomically amenable to these interventions, and also report an unusually high mortality rate with patients undergoing open debridement (~40%), which limits the generalizability of the results to the operative group. In these studies, surgical necrosectomy was not used as part of a step up approach (there was no preoperative drainage), but using it only if percutaneous drainage failed would likely improve outcomes. A contemporary series from our institution analyzing 48 patients who underwent open necrosectomy demonstrated an in-hospital mortality rate of 8.8% despite severe disease by prognostic indices on admission. This suggests that, in part owing to advances in critical care and better understanding in the timing and indications for operative intervention, surgical transperitoneal necrosectomy remains a useful tool, especially if the expertise and resources for minimally invasive necrosectomy are not available. We still occasionally use it for patients with widespread necrosis that is not completely accessible endoscopically and percutaneously. Because the necrosis in this scenario is typically multifocal and/or encysted between vital structures, it is typically difficult to access laparoscopically, and so most of our surgical necrosectomies are done open.

RECURRENCE PREVENTION

The recurrence prevention strategy for pancreatitis is dependent on its etiology. Almost one half of all cases of acute pancreatitis are caused by gallstones, with the true prevalence likely even higher because some pancreatitis with undefined etiology may be due to unrecognized biliary sludge or microlithiasis. The risk of recurrent biliary complications from gallstones after an episode of biliary pancreatitis nears 35%; the most effective mitigation strategy is cholecystectomy, which reduces recurrence rates to 0% to 5%. In mild biliary pancreatitis, same admission cholecystectomy is the standard of care. In cases in which there are peripancreatic fluid collections, current guidelines recommend waiting until peripancreatic collections resolve, or ≥4 weeks from the onset of pancreatitis to allow the collections to organize. Cholecystectomy can generally be performed safely at the time of laparoscopic or open necrosectomy unless the biliary tree is obscured by the inflammatory mass. When using a minimally invasive step up approach to necrosis, we typically wait until the necrosis is fully treated to perform cholecystectomy; however, this delay may expose the patient to the risk of further biliary tract complications. If necessary, choledocholithiasis or cholangitis can be treated endoscopically, and acute cholecystitis can be treated with endoscopic or percutaneous decompression as a bridge to eventual cholecystectomy. In patients who are poor surgical candidates, an endoscopic sphincterotomy may be adequate prophylaxis as it reduces biliary complication rates significantly. An unknown proportion of apparently idiopathic pancreatitis cases may be caused by undetected gallstones or biliary microlithiasis. One randomized trial demonstrated a reduced incidence of recurrent pancreatitis after cholecystectomy in patients who had been evaluated for typical causes of pancreatitis, did not have an etiology identified, and were randomized to cholecystectomy or watchful waiting. The odds ratio for recurrence was 5 in the nonoperative group compared with the cholecystectomy group, and the number needed to treat was 5 to prevent an episode of recurrent pancreatitis. In patients who initially present with idiopathic pancreatitis, the decision to perform a cholecystectomy should be individualized. We currently offer cholecystectomy to idiopathic pancreatitis patients who are good surgical candidates and avoid it in poor surgical candidates when we believe the risks outweigh the potential benefits.

For patients presenting with alcoholic pancreatitis, the root cause needs to be addressed: alcohol dependence. Alcoholic acute pancreatitis is usually a result of 5 to 10 years of overconsumption of alcohol and it rarely lives an isolated binge. As such, it is prudent for surgeons to recognize that it may be beyond their means to successfully achieve behavioral change to a deep-seated habit cultivated over years. Randomized controlled trials have shown that behavioral interventions that include counseling and longitudinal assistance for associated psychosocial issues significantly decrease alcohol consumption and dependency scores. Such patients should be enrolled in institutional programs that provide the necessary support to minimize the risk of future recurrences.

Hypertriglyceridemia can typically be successfully managed with diet modification and fibrate therapy. As noted in the section on etiology, hyperparathyroidism is the most common cause of hypercalcemia-induced pancreatitis and is most commonly treated with parathyroidectomy. Finally, surgeons should be wary of the possibility of a pancreatic neoplasm as a possible etiology, especially in elderly patients or patients with "idiopathic" pancreatitis. Early stage pancreatic adenocarcinoma or ampullary neoplasms can obstruct the pancreatic duct and cause pancreatitis. Detecting them in follow up imaging may provide an opportunity to intervene and treat at an early stage.

SUMMARY

Acute pancreatitis is a common but potentially life-threatening disease. Imaging is not always necessary to establish a diagnosis and is more helpful in delineating the demarcation of necrosis from healthy tissue later in the disease process. Patients should be expeditiously fluid resuscitated early in the course of disease while remaining conscious of the potential complications of over resuscitation. Institution of an oral diet early in the course of mild pancreatitis and enteral tube feeding in severe disease form the foundation of nutritional support; parenteral nutrition being reserved for patients who cannot tolerate enteral feeding. Antibiotics should not be administered prophylactically in the absence of clinical suspicion or evidence for infection. Infected necrosis is the primary indication for nonclinical intervention in acute pancreatitis. Infection is usually diagnosed by a combination of radiographic and clinical factors. Intervention, when indicated, should be initiated with a step-up approach; decisions about the best modality and route for intervention should optimally be made by a multidisciplinary group of surgeons, interventional radiologists experienced with percutaneous drainage, and interventional endoscopists capable of endoscopic transluminal intervention. A variety of techniques are now available for interventional management of necrotizing pancreatitis and its sequelae with the different strengths and weaknesses of the alternatives as described previously. An individualized approach based on patient anatomy, physiology, and preference should be used to choose the best technique in each case to obtain optimal results.

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GALLSTONE PANCREATITIS

John C. Alverdy, MD, FACS, Richard A. Jacobson, MD, and Fenna van den Esker, MD

Acute pancreatitis (AP) remains a leading cause of emergency department visits, hospital admissions, and healthcare costs worldwide. In the United States, the incidence has risen concordantly with an aging population and the increased prevalence of obesity. AP resulting from gallstones is the most common etiology in the developed world, followed by alcohol ingestion, although locoregional rates vary based on population characteristics.

In patients with mild disease, cholecystectomy should be performed during the same admission to prevent complications of recurrent disease. Twenty percent of all patients admitted with a diagnosis of AP develop severe disease for which minimally invasive therapy and interventional procedures other than cholecystectomy may be appropriate. In this latter population, the surgical community has been slow to fully adopt more minimally invasive techniques that are associated with lower morbidity and improved survival.

EPIDEMIOLOGY

AP accounts for more than 300,000 emergency department visits and contributes to roughly 3400 deaths per year in the United States. More than US$2.5 billion are spent annually on the treatment of AP and its complications. Gallstone pancreatitis (GSP) is the most common etiology, accounting for up to 60% of all cases, followed by alcoholic AP. Risk factors for GSP are patient related, stone related, or anatomic. Factors such as age, female gender, gallstones smaller than 5 mm, biliary sludge, 20 or more gallstones, and a large cystic duct diameter have been demonstrated to influence the incidence, course, and outcome of the disease.

PATHOPHYSIOLOGY

The molecular pathophysiology of GSP is defined by inappropriate and excessive activation of intrapancreatic processes that lead to autodigestion of the pancreatic tissue. The subsequent inflammatory response results in local and systemic complications of AP as outlined in the following section. Anatomically, it is recognized that obstructive biliary events incite this cascade of pancreatic inflammation and autodigestion; however, the full process is incompletely understood. Three leading theories include: (1) obstruction of the sphincter of Oddi leading to back pressure and stasis in the pancreatic duct; (2) bile reflux into the pancreatic duct; and (3) duodenal contents refluxing into the pancreatic duct. Irrespective of these mechanical events, the burst of protease activation that follows is what damages the pancreatic acini, which in some cases leads to ductal disruption, local inflammation, secondary infection, and all subsequent complications.

Infection of a peripancreatic fluid collection or necrotic pancreatic parenchyma is the leading cause of morbidity and mortality in AP. Importantly, these are not primary necrotizing infections that destroy pancreatic tissue, but rather secondary infections by translocated bacteria presumed to originate from the gastrointestinal tract. The morbidity and mortality associated with infected pancreatic necrosis has resulted in several attempts to prevent the translocation of intestinal bacteria with prophylactic intravenous antibiotics, selective digestive decontamination with oral antibiotics, or probiotic regimens. The timing, dose, route, and utility of such antibiotic-altering regimens remains controversial in GSP.

CLINICAL PRESENTATION

Patients presenting with AP appear constitutionally similar to those in septic shock. They often appear unwell and complain of acute onset, constant visceral type pain in the epigastrium, usually

SUMMARY

Acute pancreatitis is a common but potentially life-threatening disease. Imaging is not always necessary to establish a diagnosis and is more helpful in delineating the demarcation of necrosis from healthy tissue later in the disease process. Patients should be expeditiously fluid resuscitated early in the course of disease while remaining conscious of the potential complications of over resuscitation. Institution of an oral diet early in the course of mild pancreatitis and enteral tube feeding in severe disease form the foundation of nutritional support; parenteral nutrition being reserved for patients who cannot tolerate enteral feeding. Antibiotics should not be administered prophylactically in the absence of clinical suspicion or evidence for infection. Infected necrosis is the primary indication for mechanical intervention in acute pancreatitis. Infection is usually diagnosed by a combination of radiographic and clinical factors. Intervention, when indicated, should be initiated with a step-up approach; decisions about the best route and route for intervention should optimally be made by a multidisciplinary group of surgeons, interventional radiologists experienced with percutaneous drainage, and interventional endoscopists capable of endoscopic transluminal intervention. A variety of techniques are now available for interventional management of necrotizing pancreatitis and its sequelae with the different strengths and weaknesses of the alternatives as described previously. An individualized approach based on patient anatomy, physiology, and preference should be used to choose the best technique in each case to obtain optimal results.

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GALLSTONE PANCREATITIS

John C. Alverdy, MD, FACS, Richard A. Jacobson, MD, and Fons van der Berg, MD

Acute pancreatitis (AP) remains a leading cause of emergency department visits, hospital admissions, and healthcare costs worldwide. In the United States, the incidence has risen concordantly with an aging population and the increased prevalence of obesity. AP resulting from gallstones is the most common etiology in the developed world, followed by alcohol ingestion, although locoregional rates vary based on population characteristics.

In patients with mild disease, cholecystectomy should be performed during the same admission to prevent complications of recurrent disease. Twenty percent of all patients admitted with a diagnosis of AP develop severe disease for which intensive care therapy and interventional procedures other than cholecystectomy may be appropriate. In this latter population, the surgical community has been slow to fully adopt more minimally invasive techniques that are associated with lower morbidity and improved survival.

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The molecular pathophysiology of GSP is defined by inappropriate and excessive activation of intrapancreatic processes that lead to autodigestion of the pancreatic tissue. The subsequent inflammatory response results in local and systemic complications of AP as outlined in the following section. Anatomically, it is recognized that obstructive biliary events incite this cascade of pancreatic inflammation and autodigestion; however, the full process is incompletely understood. Three leading theories include: (1) obstruction of the sphincter of Oddi leading to back pressure and stasis in the pancreatic duct; (2) bile reflux into the pancreatic duct; and (3) duodenal contents refluxing into the pancreatic duct. Irrespective of these mechanical events, the burst of protease activation that follows is what damages the pancreatic acini, which in some cases leads to ductal disruption, local inflammation, secondary infection, and all subsequent complications.

Infection of a peripancreatic fluid collection or necrotic pancreatic parenchyma is the leading cause of morbidity and mortality in AP. Importantly, these are not primary necrotizing infections that destroy pancreatic tissue, but rather secondary infections by translocated bacteria presumed to originate from the gastrointestinal tract. The morbidity and mortality associated with infected pancreatic necrosis has resulted in several attempts to prevent the translocation of intestinal bacteria with prophylactic intravenous antibiotics, selective digestive decontamination with oral antibiotics, or probiotic regimens. The timing, dose, route, and utility of microbiome-altering regimens remain controversial in GSP.

CLINICAL PRESENTATION

Patients presenting with AP appear constitutionally similar to those in septic shock. They often appear unwell and complain of acute onset, constant visceral type pain in the epigastrium, usually

radiating to the back. Associated symptoms include nausea and vomiting. The pain is exacerbated by oral intake and may be relieved when the patient leans forward. Other diagnoses to be considered are acute cholecystitis, choledocholithiasis, and peptic ulcer disease.

On examination, patients can present with tachycardia driven, in part, by the pain associated with AP in mild cases or by severe hypovolemia in more moderate to severe cases. Low grade fevers are common and not necessarily indicative of an acute infectious process. Abdominal tenderness can be a prominent finding on physical examination. The presence of bruising in the flank areas, umbilicus, or inguinal regions indicates hemorrhagic pancreatitis that has resulted in dissection of blood along the retroperitoneal planes. The presence of fever, jaundice, or scleral icterus may indicate obstructive choledocholithiasis or cholangitis.

DIAGNOSIS

The diagnosis of GSP is generally made in the emergency setting and is based on clinical, radiographic, and biochemical factors. Blood chemistries suggestive of AP in the setting of gallstones documented by ultrasound usually confirm the diagnosis. The pancreatic enzymes amylase and lipase are usually elevated in patients with AP. Sensitivity and specificity of these assays depends on the specific enzyme measured and the threshold used to define a positive test. Amylase is considered nonspecific, whereas lipase is considered specific for AP, but neither delineates GSP from other etiologies. Most centers use a threshold of positivity defined as three to four times the normal value; however, the duration of symptoms should be considered when interpreting levels of these enzymes. Other circulating factors such as C-reactive protein and interleukin-6 have been validated as useful markers of the severity of AP, but they do not discriminate AP from other inflammatory or infectious processes. Elevated alanine aminotransferase or lymphocyte/neutrophil ratio may distinguish GSP from other etiologies of AP; however, this distinction is generally based on the absence of a history of alcohol abuse and evidence of obstructing biliary stones or sludge on imaging. Other markers of the acute phase response induced by AP such as interleukin-8 have been validated to rise in the setting of AP but are uncommonly used in clinical practice.

Ultrasound is the initial imaging test of choice as it is a noninvasive and highly sensitive test to detect the presence of gallstones. Because patients with GSP may present with a significant ileus, the sensitivity of ultrasound may be decreased by overshadowing of bowel gas. A limitation of ultrasound in this setting, however, is that it cannot assess the severity of pancreatic inflammation and therefore contrast-enhanced computed tomography (CT) is the test of choice to determine the extent of the AP. Ideally, a pancreas protocol CT with arterial and portal phases is most useful to delineate the degree of inflammation and disruption of the pancreatic parenchyma and main duct. Most authors recommend a CT scan at least 72 hours after the onset of symptoms because radiographic signs of local complications may not be evident before this and therefore are not actionable. On CT, peripancreatic edema (in the anterior pararenal space, transverse mesocolon, or small bowel mesentery), fat stranding, or nonenhancement of the pancreatic parenchyma (indicating necrosis) are indicative of AP.

Severity

The severity of GSP is a function of the degree of acute cholecystitis and the degree of pancreatic necrosis and inflammation that is present. Most often, the gallbladder is not inflamed because the disease is more of a consequence of the migration of gallstones into the common bile duct than acute gallbladder inflammation. However, it is important to recognize the severity of both as an important aspect of the treatment strategy. Stratification by severity is of prognostic value and predicts which patients will require intensive care and invasive drainage procedures. The severity of systemic inflammation generally dictates the need for intensive care monitoring and can usually be assessed on admission. Although most patients present with mild or moderate disease, up to 20% of patients can present with severe AP as defined by the 2012 revision of the Atlanta criteria (Table 1). This revision classifies organ dysfunction as transient (<48 hours) or persistent. When organ failure develops, the systems most commonly affected are the respiratory, renal, and cardiovascular systems (to this order). Dysfunction is defined by the Marshall criteria (Table 2).

TABLE 1 Severity of AP According to 2012 Revision of the Atlanta Criteria

Severity	Characteristics
Mild	No organ failure No local or systemic complications
Moderately severe	Transient organ failure (<48 hours) Local or systemic complications without persistent organ failure
Severe	Persistent organ failure

TABLE 2 Organ Failure as Defined by the Marshall Criteria

Organ system	Criteria for failure
Pulmonary	PaO_2/FiO_2 ratio ≤300
Renal	Serum creatinine >1.9 (if normal at baseline)
Cardiovascular	SBP <90 mm Hg, not responsive to fluids

From Marshall JC. A scoring system for multiple organ failure (or dysfunction). *Arch Surg*. 1995;130:871–872.
SBP, systolic blood pressure.

As many as 20% of patients with severe AP (SAP) will progress to develop necrotizing disease of the pancreas or peripancreatic tissues. Up to 70% of these patients can develop infected necrosis, which will significantly complicate their course and worsen their prognosis. This so-called rule of 20s (20% of all AP is severe, 20% of SAP is necrotizing, 20% of necrotizing disease develops infection) is a useful clinical pearl.

MANAGEMENT: INITIAL TREATMENT

Patients diagnosed with GSP are admitted to the hospital and, if determined to have severe disease, will require monitoring in an intensive care unit. Aggressive fluid resuscitation, preferably with lactated Ringer's solution, remains the cornerstone of initial management and is recommended for all patients. Pain should be managed adequately with standard-of-care protocols. Patients presenting with mild AP should resume oral intake as early as is feasible once the pain is resolving. Initiation of enteral feeding, be it with oral intake or nasoenteric feeding of a chemically defined diet, has been shown to have an adverse effect on the natural history of pancreatitis even when the feeding is jejunally tolerated, at which point it can be discontinued. The Pancreatitis, Very Early Compared with Selective, Delayed Start of Enteral Feeding trial compared very early with on-demand enteral feeding in patients with predicted severe pancreatitis and found no difference in infectious complications or death. Tube feeding, either nasogastric or nasojejunal, should be reserved for patients that do not respond to a trial of oral nutritional intake.

An absolute indication for an emergency endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) is acute cholangitis. Evidence indicates that mild GSP does not warrant ERCP. The risks of the procedure itself coupled with the likelihood of spontaneous passage of gallstones and/or sludge diminishes enthusiasm for an aggressive approach using ERCP in GSP. Whether ERCP with ES should be applied in cases of severe

GSP remains controversial and will require further research before it is recommended.

SYSTEMIC COMPLICATIONS OF GSP

In severe GSP, persistent multiple organ failure is a dreaded complication that warrants admission to an intensive care unit and treatment by both critical care specialists and pancreatic surgeons. Persistent organ failure in the first 2 weeks of admission is a function of a dysregulated systematic inflammatory response, an altered microbiome, and thus immune dysregulation. Late onset sepsis associated with highly resistant and virulent pathogens generally occurs after 2 weeks when necrotizing organ dysfunction mandates dialysis, ventilator support, vasopressors, total parenteral nutrition, and multiple antibiotics. The initial hyperinflammatory response can develop into an immunosuppressive state, allowing highly resistant healthcare associated pathogens opportunity to cause life threatening infected pancreatic necrosis, pneumonia, urinary tract infections, catheter-associated bloodstream infections, and spontaneous bacteremias. Continuous vigilance is imperative for these infections and application of multiple infection control measures such as daily chlorhexidine baths, oral hygiene, and enteral nutrition are useful.

Necrotizing Gallstone Pancreatitis

Patients who develop necrotizing GSP should be managed in specialty centers where an experienced interdisciplinary team of surgeons, gastroenterologists, and interventional radiologists are available. Secondary bacterial infections that invade the necrotic pancreas can arise from multiple sources and can lead to infected pancreatic necrosis (IPN), a dreaded and often fatal complication with mortality rates as high as 30% and reaching nearly 100% when endoscopic, radiologic, or surgical services are not immediately available. The diagnosis of IPN is made by the presence of gas in the peripancreatic collections seen on CT scan, ultrasound, or endoscopic ultrasound with or without fine needle aspiration confirming the presence of bacteria. Clinical suspicion of IPN is based on new onset of organ failure after 2 weeks of hospital admission combined with fever and rising inflammatory markers in the absence of other infectious foci. Confirmed infection by fine needle aspiration is not mandatory for treatment but is useful to guide antibiotic treatment. ...ost antibiotic treatment targets presumptive organisms because cultures often do not represent all pathogens present in a given sample. It is preferable to use antibiotics with a known penetration profile into the pancreatic parenchyma and necrotic pancreatic collections.

Because the gallbladder per se is noninflamed in most cases of GSP, treatment strategies are largely similar to those of nonbiliary AP. The past several decades of experience have taught surgeons that the longer surgery can be safely delayed, the more favorable the outcome. Aggressive, early surgical intervention for SAP is no longer recommended because of the attendant high mortality rates associated with this approach. The step-up approach (first described in the Pancreatitis, Necrosectomy versus Step-up Approach [PANTER] trial in 2010) is recommended and follows international guidelines that have become the standard of care. Briefly, management of IPN consists of percutaneous catheter drainage, followed by video assisted retroperitoneal debridement (VARD) and failing that, necrosectomy. The PANTER trial showed that the step-up approach significantly decreased mortality and major complications, including new onset multiple organ failure, perforation of a visceral organ, bleeding, and/or the development of an enterocutaneous fistula. Aggregate complications were decreased from 69% for open necrosectomy to 40% for patients in the step-up group. A management algorithm based on step-up therapy is illustrated in Fig. 1. The more recent Transluminal Endoscopic Step-up Approach Versus Minimally Invasive Surgical Step-up Approach in Patients With Infected Pancreatic Necrosis superiority trial compared an endoscopic with a surgical step-up approach, with the former consisting of endoscopic ultrasound guided transluminal drainage followed by endoscopic necrosectomy. There was no difference in mortality and major complications; however, the endoscopic step-up was associated with a reduced incidence of pancreatic fistulas and a reduction in length of hospital stay. Centers with immediate access to interventional endoscopists experienced in this procedure are encouraged to use this approach. The optimal timing of intervention is still unclear; the ongoing Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis trial is comparing early with postponed drainage until the infected collections are completely walled off, which is the current standard of care.

The first step in surgical step-up management is CT guided percutaneous catheter drainage, preferably through the left retroperitoneum to later facilitate thorascopic access for the VARD procedure, if indicated. Furthermore, because the catheter remains in the retroperitoneal space, it avoids contamination of the abdominal cavity. If sepsis persists and drainage is deemed to be inadequate, drains should be upsized to the largest size available. Repeat imaging and the clinical course should dictate whether further drainage is indicated. In this circumstance, a VARD procedure can be performed to facilitate more complete source control. A 5 cm incision is made to the left flank at the drain site and the retroperitoneal space is accessed for debridement of necrotic tissue under direct vision. Laparoscopic instruments are introduced in the cavity for debridement, irrigation, and suction. The catheter drain is removed, replaced by two surgical drains, and lavaged as needed. This hybrid minimal invasive procedure reduced major complications and mortality to 35% and 13%, respectively, compared with 54% to 95% and 11% to 39% in open necrosectomy.

Although open and retroperitoneal laparoscopic necrosectomy were once considered standard of care, today these approaches have become outdated in favor of VARD. However, if indicated during an intraabdominal emergency, an open or an intraabdominal laparoscopic approach can be used. Several endoscopic techniques have been described, and the major interventions for IPN are increasing in popularity owing to their minimally invasive nature. The first step is the endoscopic ultrasound guided placement of transgastric or transduodenal stents to provide temporary decompression and drainage. If further intervention is needed, the stents can be used as guides to facilitate endoscopic necrosectomy. Recent innovations in stents, such as the lumen-apposing metal stent, make it possible to safely drain collections even when the distance between the gastric or duodenal wall and necrotic collection exceeds 1 cm. The established tract can be used for endoscopic debridement of the necrotic cavity.

Prophylactic Interventions for Infectious Complications

The mechanism by which pancreatic collections and parenchymal necrosis become infected remains speculative, but it is hypothesized to occur from intestinally derived bacterial and fungal pathogens. Clinically, bacteremia does not occur in most cases and therefore the route by which pathogens travel from the gut to the necrosis remains unknown. The "Trojan horse" hypothesis suggests that pathogens enter neutrophils or macrophages, which then silently home to pancreatic tissues. These conditions of the pancreas with pancreatitis or necrosis are receptive to these bacteria carrying immune cells, which can lodge and release their infectious payload into pancreatic tissue, causing infection. Such processes may explain why many patients develop infected necrosis late after the acute inflammatory process has abated and when blood cultures are negative. Further work will be needed to establish causality of such a mechanism. The gut is considered the origin of pathogens that cause IPN. However, attempts to preemptively eliminate potentially translocating pathogens have been tested with controversial results. In general, neither selective digestive decontamination nor aggressive intravenous antibiotics are recommended to achieve this because of the inability to completely delineate the gut and for fear of emergence of antibiotic resistance. Thus, the role of prophylactic

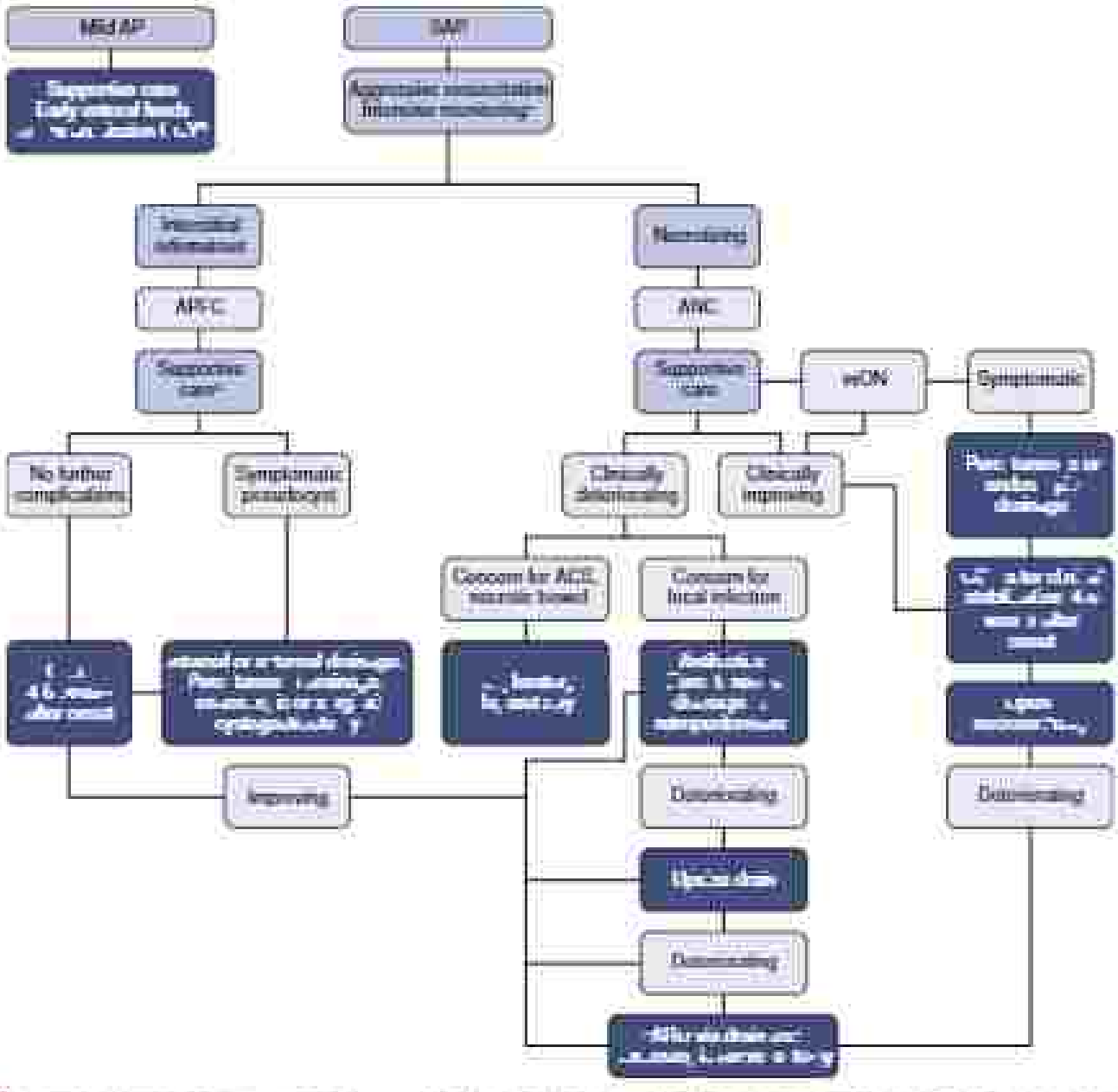

FIG. [illegible]

antibiotics in SAP or GSP in the absence of cholangitis remains debated. Once infected SAP is confirmed or suspected, antibiotics are indicated.

Probiotics have been tested in severe AP as a strategy to contain potential pathogens that drive systemic inflammation, translocate, and cause IPN. The use of probiotics has been shown to have a beneficial effect on the outcome of pancreatitis in animal models and small human studies. However, a randomized controlled trial designed to evaluate the efficacy of Prophylactic Probiotics in Patients With Predicted Severe Acute Pancreatitis demonstrated an increase in mortality in the treatment group presumed to be due to bowel ischemia. Prophylactic treatment with probiotics is therefore contraindicated in the treatment of pancreatitis. Possible explanations for these paradoxical results may involve the choice of bacteria in the probiotic mixture, the route of administration (oral feeding) or an inappropriate metabolic microenvironment. Fecal microbiota transplantation is an emerging research field and could potentially be applied to prevent infections in SAP.

FOLLOW-UP

Among the most contentious aspects of the treatment of GSP beyond halting the progression of the pancreatitis is the timing of the cholecystectomy. If the presentation of GSP is mild and the

TABLE 3 Current Trials

Population	Intervention	Outcomes	Country
Mild AP	Rectal indomethacin	Systemic inflammatory markers, organ failure, disease progression	UK
Mild AP	Cholecystectomy within 72 hours of onset	Hospital stay, perioperative complications	Chile
All AP	Contrast-enhanced CT with additional image processing	Microvascular permeability markers as predictors of severe disease	France
SAP	Early percutaneous drainage of sterile acute peripancreatic collections	Mortality, secondary infection, hemorrhage, fistula formation	China
SAP	Goal-directed fluid resuscitation based on PiCCO parameters	Organ failure, change in APACHE II score, ICU days	Germany
SAP	Fecal microbiota transplant via nasojejunal route	Mortality, infectious complications, inflammatory markers	China (3 separate trials)
SAP	Oral ketorolac	Inflammatory markers, organ failure, local complications	Iran
AP with SIRS	Experimental compound CM-8620	Drug safety, radiographic disease severity	USA
Necrotizing AP	Pancreatic duct stenting 1–2 weeks after the onset of symptoms	Incidence of walled-off necrosis, rates of intervention, procedural complications	USA
Necrotizing AP	Early drainage of necrotic collections before walling off	Mortality, major complications, length of stay	The Netherlands
Predicted SAP without cholangitis	Early ERCP	Mortality, major complications, length of stay	The Netherlands
Idiopathic pancreatitis	Diagnostic endoscopic ultrasound	Incidence of previously undetected gallstone disease	The Netherlands

AP, acute pancreatitis; APACHE, Acute Physiology, Age, Chronic Health Evaluation; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; PiCCO, pulse contour cardiac output; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome.

pancreatitis resolves over a few days, cholecystectomy with intraoperative cholangiogram is recommended. If choledocholithiasis is found during cholecystectomy, postoperative ERCP with ES is a safe and effective treatment. Although intraoperative common bile duct exploration, lithotripsy, and stone removal are possible, in most institutions, postoperative ERCP is performed. In many cases of moderate to severe pancreatitis, cholecystectomy is deferred. Imaging with magnetic resonance cholangiopancreatography as an outpatient to rule out the need for ERCP once the pancreatitis and its sequelae have resolved can be useful. If the pancreatitis has been severe, however, cholecystectomy too soon after the acute episode is risky and complicated because of ongoing inflammation and scarring. Clinical judgment as to the timing of the cholecystectomy must be judiciously applied. Given the clear advantages of laparoscopic cholecystectomy over open cholecystectomy, the risk of an open procedure if surgery is planned too soon following recovery should be noted.

The Pancreatitis of Biliary Origin, Optimal Timing of Cholecystectomy trial compared same admission versus interval cholecystectomy (after 25–30 days) in mild AP and showed a significant reduction in recurrence in favor of same admission cholecystectomy. For reasons mentioned previously, it is advisable to postpone cholecystectomy in cases of necrotizing pancreatitis until the time at which all collections are either successfully drained or sufficiently walled off and the patient is fully stable and eating. In cases in which gallstones are suspected but not observed, performing an ERCP or magnetic resonance cholangiopancreatography as a method to identify microlithiasis and/or biliary sludge may be useful. If positive, cholecystectomy should be performed to prevent recurrence. Patients with recurrent idiopathic pancreatitis should be referred for genetic counseling and evaluation for autoimmune pancreatitis. Finally, pancreatic insufficiency of either endocrine or exocrine function can occur after a bout of GSP. Timely recognition and treatment of these complications are needed to prevent complications from diabetes and malnutrition in those patients that develop chronic disease.

CURRENT TRIALS

At least 32 trials are actively enrolling patients in interventional or prognostic studies of GSP (Table 3).

SUGGESTED READINGS

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Pancreas Divisum and Other Variants of Dominant Dorsal Duct Anatomy

David L. Adams, MD, and Gregory A. Coté, MD, MS

There struggles are used in the surgical management of biliary and pancreatic disorders of the pancreas: improve drainage, resect damaged tissue, or combine the first two with a simultaneous resection and drainage procedure. These principles apply to the management of recurrent acute pancreatitis and chronic pancreatitis associated with dominant dorsal duct anatomy, which is more commonly called pancreas divisum. The prudent surgeon always remembers that pancreas divisum is as common as left handedness: 10% of the population has pancreas divisum. The anatomic variant known as pancreas divisum develops in the boxy 6 week old embryo (Fig. 1). Migration, rotation, and vascularization are happening everywhere in the 6- to 8-week embryonic foregut. During this developmental period, the dorsal and ventral pancreatic buds fuse and realign their ductal systems. In the usual fusion of the ductal system, the ventral duct or duct of Wirsung becomes the main pancreatic duct (Fig. 2A–B). The dorsal duct, the duct of Santorini, is the minor duct (Fig. 2A). When dorsal and ventral ductal fusion is incomplete, the duct of Santorini drains the majority of the pancreas through an orifice that is notably smaller than the orifice of a normal sphincter of Oddi (Fig. 2C–D). The duct of Santorini may have a narrow filamentous pathway to the duct of Wirsung or may drain a portion of the head independently (Fig. 2E). Hence the concept was promulgated in the 1970s that in pancreas divisum there is an anatomic impediment to the normal drainage of pancreatic exocrine secretions, which results in an obstructive pancreatopathy.

In pancreas divisum, which is the main pancreatic duct? Avoiding the descriptor "main" prevents confusion in discussion of pancreas divisum. When divisum anatomy is present, the dorsal duct, formerly known as the duct of Santorini, is called the "*[illegible]* duct". The terms *complete* (fusion) and *incomplete* (fusion) have been used to describe variants of pancreatic ductal anatomy associated with dominant dorsal duct anatomy. Complete divisum typically denotes a dominant dorsal duct with no vestigial communication to the ventral system (duct of Wirsung). Incomplete divisum denotes a dominant dorsal duct with a residual, albeit minuscule, communication between the dorsal duct and the ventral duct. Variations of the dominant dorsal duct are many and infrequent enough that radiologic and endoscopic delineation may be confusing. The classic radiographic image has the dominant pancreatic duct crossing the terminal bile duct and entering the descending duodenum (Fig. 3). Usually a small ductal system drains the ventral head of the pancreas and enters the duodenum through the major papilla with the terminal bile duct. Be aware of the entity called *[illegible] pancreatitis*, which is associated with chronic pancreatitis and malignancy. Either process may result in total occlusion of the ventral duct, causing the duct of Santorini to assume responsibility for pancreatic exocrine outflow via the minor papilla. Whenever there is a question of acquired pancreas divisum (also called *pseudodivisum*) without a demonstrated mass on magnetic resonance imaging (MRI) or computed tomographic scan (CT scan), endoscopic ultrasound (EUS) scan should be undertaken to rule out malignancy.

In the nineteenth century, ductal surgeons were commonly valvulotomists. In the twentieth century, physiology was of increasing importance to the innovative surgeon. The twenty first century has seen the addition of molecular biology to the management of surgical disorders. The history of the understanding and treatment of pancreas divisum has followed a similar pathway. In the past, pancreas divisum was labeled a congenital anomaly that could cause obstructive pain and pancreatitis. With the development of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in the 1970s, idiopathic recurrent pancreatitis was attributed to pancreas divisum, and became a target for surgical management with dorsal sphincterotomy and minor duct sphincteroplasty. As therapeutic endoscopy developed, endoscopic minor duct sphincterotomy or papillotomy supplanted the open surgical approach. Although sphincteroplasty was successful in the majority of patients in early studies, long term failures became evident, improving patient selection based on physiologic and anatomic parameters with measurement of pancreatic ductal response and exocrine output to hormonal stimulation of the exocrine pancreas was used. However, early optimism of improving patient selection via physiologic assessment did not meaningfully improve long term outcomes.

Chronic pancreatitis and acute recurrent pancreatitis are disorders that lack strong evidence on which surgical practice can be based. Many other similar "gray zone" disorders are multifactorial in origin. Scurvy is a disease with a single and simple cause that can be cured with vitamin C. If chronic pancreatitis were like scurvy and had a single cause, it would be easily curable. Chronic pancreatitis has many known risk factors, many of which are overlapping, such as alcohol and smoking. Anatomic, environmental, and genetic factors are likely to interact with the divisum phenotype in causing or contributing to pancreatitis. Pancreas divisum is clearly associated with a higher prevalence of genetic mutations that predispose to pancreatitis; this has led to the current concept that pancreas divisum is not a cause of pancreatitis by itself but acts as a partner with genetic mutations. In patients with idiopathic pancreatitis, pancreas divisum is not an independent risk factor when compared with controls without pancreas divisum. However, pancreas divisum frequency is higher in patients with genetic mutations and pancreatitis, especially those with CFTR mutations or polymorphisms, suggesting a cumulative effect of these two disorders. SPINK1 and PRSS1 functional genetic anomalies are also associated with pancreas divisum and in the recurrent and chronic pancreatitis.

DIAGNOSIS

The clinical presentation of pancreatitis associated with dominant dorsal duct anatomy has two phenotypes: acute recurrent pancreatitis and chronic pancreatitis. Current concepts suggest that the former leads to the latter. Rarely does chronic pancreatitis associated with pancreas divisum result in severe fibrosing pancreatitis associated with biliary, duodenal, or sphincter vessels obstruction. Pain intractable to medical management is the main reason patients with pancreas divisum seek the help of surgeons and gastroenterologists. Patients with acute pancreatitis associated with pancreas divisum present in the same manner as patients with other etiologies for pancreatitis. Pain that triggers nausea and vomiting is the predominant symptom. The pain is notable for its intensity, character, and location. Patients localize the pain to the epigastrium with radiation into the retroscapular region. Pain is commonly characterized by the sensation of someone twisting a knife in the upper abdomen. The pain is often rated as 11 on a scale of 1 to 10. Serum lipase is elevated, as may be the leukocyte count and other inflammatory serologic markers. When the acute illness is severe, pancreatic and peripancreatic inflammatory changes will be seen on CT scan and MRI studies. If pancreatic necrosis develops in the presence of pancreas divisum, other pancreatitis risk factors should be considered. It is uncommon for acute pancreatitis associated with pancreas divisum to lead to pancreatic and peripancreatic necrosis. The usual course is that of a self limited illness that resolves with expectant, nonoperative

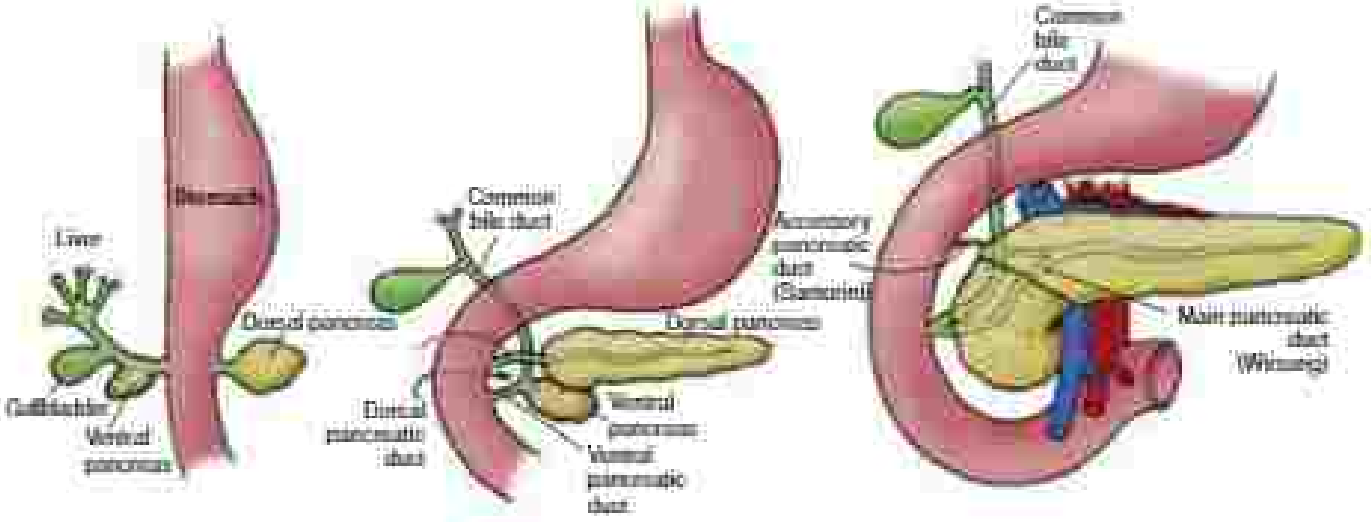

FIG. 1 Embryologic development of the pancreas.

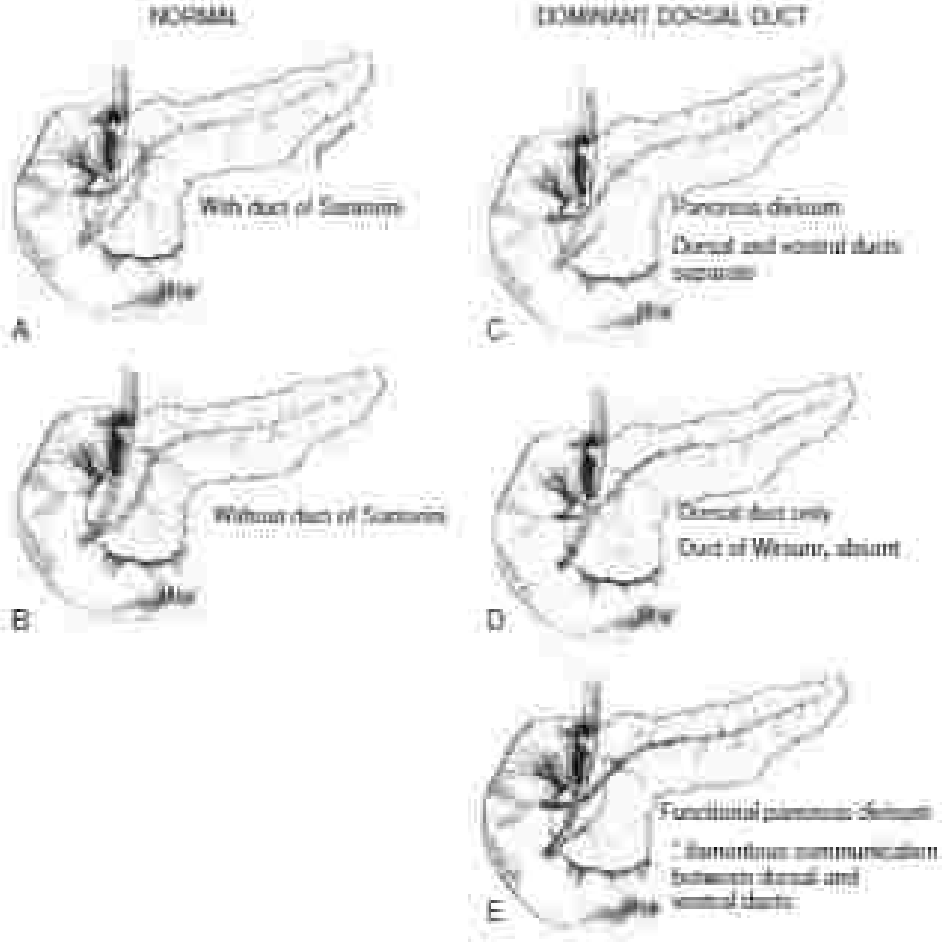

FIG. 2 Most common pancreatic ductal anatomy (A, B) and pancreas divisum and its variants (C–E).

management and hospitalization of less than 1 week. With resolution of the acute illness, patients return to normal function and activities and pancreas morphology presumably returns to normal. If recurrent bouts of acute pancreatitis continue, changes of chronic pancreatitis may become evident on cross-sectional imaging.

A hopeful hypothesis recommends that endoscopic minor duct sphincterotomy be undertaken before the development of chronic inflammatory and fibrotic changes. The goals of endoscopic therapy are to (1) eliminate future episodes of acute pancreatitis, (2) reduce the frequency or severity of recurrent bouts of acute pancreatitis, and (3) prevent the development of overt chronic pancreatitis and its complications, primarily the development of peripancreatic neural inflammatory pathways that lead to centralization of pain. It is generally assumed that if acute pancreatitis bouts can be eliminated, the third objective would follow suit. However, the chief indication for surgical therapy of pancreas divisum is pain; endocrine and exocrine insufficiency is rare, as are biliary, duodenal, and splanchnic venous occlusion.

The more difficult patient is one who has had one bout of acute pancreatitis or no documented evidence of pancreatitis but who has pancreas divisum and chronic pain that is characteristic of pancreatitis. Work patient quality of life is diminished by frequent emergency department visits, work absences, and loss of social contacts, evaluation with MRI and EUS is indicated. If objective evidence of obstructive chronic pancreatitis is noted, then endoscopic or surgical intervention may be indicated. However, the difficulty in waiting for chronic morphologic changes to develop is that once chronic fibrosis has developed in the head of the pancreas, endoscopic and surgical minor duct sphincterotomy have a limited success rate. Division of the sparse smooth muscle fibers of the minor sphincter is unlikely to affect the hardened fibrosis of the surrounding pancreatic parenchyma. The prudent surgeon remembers that when you cut scar tissue, you get more scar tissue. When you operate for pain, you get pain. The splanchnic neural architecture is vast and lacks specificity. Biliary, gastric, esophageal, and intestinal disorders all may appear similar to pain and nausea associated with chronic pancreatitis. Therefore, surgeons and gastroenterologists who undertake the care of patients with chronic pancreatitis and pancreas divisum engage in changing what is possible and offer the hope of helping a patient whose quality of life is diminished by unpredictable hospital visits and isolation from work and family. This care requires the collaboration of pancreatic surgeons, endoscopic specialists in pancreatic disease, behavioral psychologists, and pain management specialists. In general, endoscopic therapy for pancreas divisum is typically recommended for pancreatic type pain in association with obstructive morphology (e.g., a main pancreatic duct stone or stricture) or documented recurrent acute pancreatitis without another clear and reversible cause. Minor sphincterotomy for abdominal pain alone is unproven and a slippery slope; once the orifice is compromised, there is always the possibility of orifice restenosis and bona fide duct obstruction. For patients with idiopathic acute recurrent pancreatitis and pancreas divisum, the impact of minor endoscopic sphincterotomy is currently being investigated in a sham-controlled, multicenter randomized trial (NCT00699946).

FIG. 3 Pancreas divisum magnetic resonance cholangiopancreatography with the dorsal duct (*arrowhead labeled with downward arrow*) crossing the common bile duct, which joins with the ventral duct remnant (*Wirsung labeled with upward arrow*). Dorsal and ventral ducts terminate respectively as major and minor papilla.

ENDOSCOPIC TREATMENT

Identifying the Minor Papilla and Positioning the Endoscope

Although the pathogenicity of pancreas divisum remains controversial, the endoscopic approach to minor papillotomy is more elegant. The first technical challenge in therapy is successfully identifying the minor papilla. Duodenoscopes are designed for optimal orientation at the level of the major papilla, so positioning the endoscope for minor papilla cannulation usually requires a "scout long" position. This is illustrated in Fig. 4, in which the scope is resting along the greater curvature of the stomach. This position is less stable than

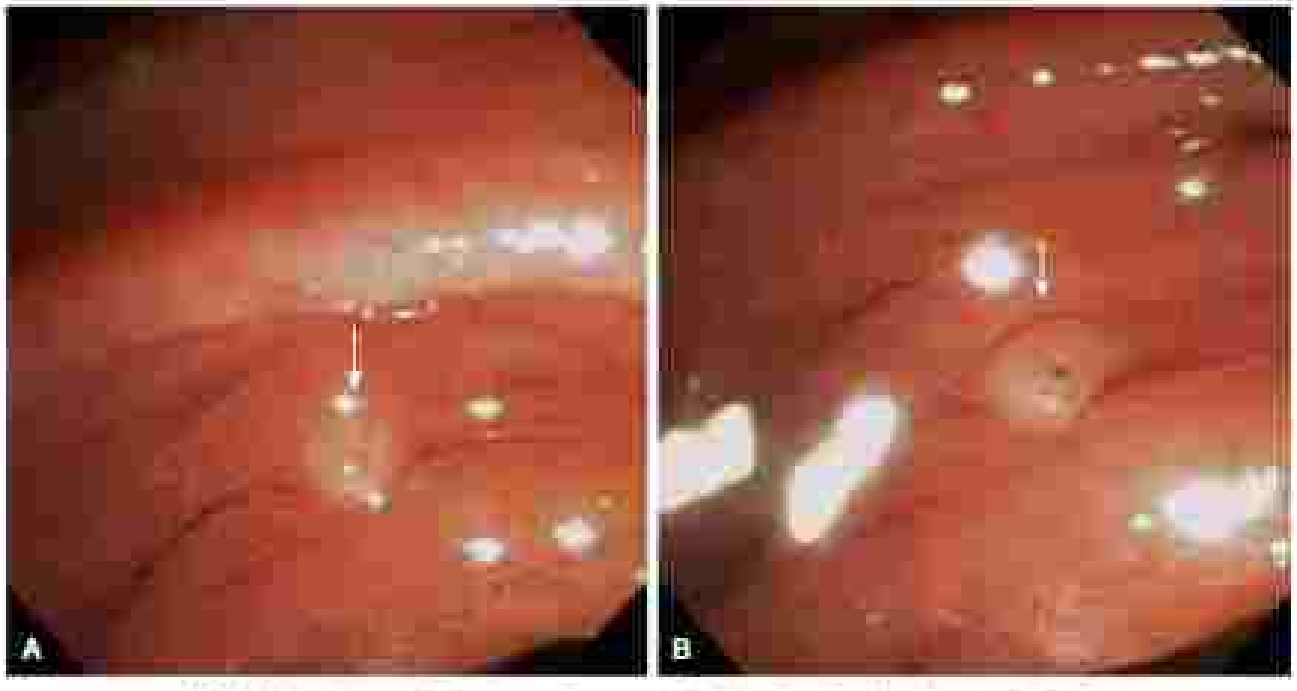

FIG. 4 Endoscopic image of the minor papilla (*arrow*) with a "closed" orifice (A) and an "open" orifice (B).

the traditional "short" position of the duodenoscope used for the majority of major papilla cases. Nevertheless, the semi-long position typically orients the minor papilla directly in front of the working channel; the minor papilla is usually located 2 to 3 cm superior to the major papilla, along the medial wall but slightly lateral to the major papilla. In some cases, the minor papilla may be located underneath an overlying duodenal fold that requires retraction with a catheter or other device before cannulation ensues. Because this procedure requires a long scope position that is uncomfortable for patients who are prone on a fluoroscopy table, it is almost universally performed with anesthesia-administered sedation with or without endotracheal intubation.

Occasionally, the minor papilla is patulous and the actual orifice unidentifiable even after minutes of careful endoscopic observation. Blindly probing with catheters and guidewires rapidly may cause periampullary edema and transform a straightforward procedure into a complicated one. Probing often leads to false tracks adjacent to the true lumen, rarely causing perforation but often making cannulation impossible. Therefore, if a minor papillary orifice is unidentifiable, the minor papilla can be sprayed with a dilute dye such as methylene blue or India ink. After this maneuver, pancreatic juice outflow should lead to clearing of the dye at the minor orifice (Fig. 5). Alternatively, or in conjunction with this approach, secretin may be administered (0.2 μg/kg) intravenously over 1 minute to stimulate pancreatic juice flow. This often unveils the minor papillary orifice within minutes of administration and continued careful endoscopic observation.

An absolute last resort involves the use of a needle-tipped catheter that is gently pressed into the minor papilla, followed by light injection of radio contrast dye to delineate the configuration of the Santorini duct. If the needle is inserted into the submucosal layer of the minor papilla or duodenum, such an injection may result in a submucosal blush and obliterate the papillary anatomy for a short period, often making minor papillary cannulation impossible during that procedure.

Cannulation

Once the minor papillary orifice is clearly delineated, most endoscopists prefer to gain access using a tapered cannula or sphincterotome (5Fr or 6Fr tip) with a hydrophilic, straight guidewire. Most experts prefer a smaller caliber (0.018", 0.025", or 0.035" inch) guidewire because the orifice is considerably smaller than the major papilla. The leading 3 to 4 mm of guidewire protruding from the catheter tip is used to grip the minor orifice; at this point, the endoscopist or assistant may probe gently with the guidewire under fluoroscopic guidance; if the guidewire advances with minimal resistance, then 2 to 3 cm of guidewire may be advanced into the duct before contrast injection. Guidewires should not be advanced deeply in the body or tail of the pancreas without antecedent injection of a small amount of contrast to delineate the course of the duct and avoid side branch puncture. Alternatively, the cannula or sphincterotome may be inserted gently over the minor orifice first, followed by probing with the guidewire. This is suboptimal in many cases because the orifice is usually less than 1 mm (3Fr) and the smallest cannulating devices are 3Fr at the tip.

Once the guidewire is clearly seated in the main pancreatic duct, it should be advanced carefully along the main duct to the distal body or pancreatic tail. This provides adequate rail support over which the cannula or sphincterotome can be advanced deeply into the duct for further opacification and positioning for sphincterotomy.

FIG. 5. Endoscopic image of minor papilloscopy "in progress," which also shows the major papilla downstream for reference (arrow).

Minor Endoscopic Sphincterotomy

There are two approaches to minor endoscopic sphincterotomy, each of which has advantages and disadvantages. There are no data to support one approach over the other. The first approach is a pull-type minor sphincterotomy that mimics the standard technique for biliary and pancreatic sphincterotomy at the major papilla. With a sphincterotome, the device is bowed within the minor orifice, and electrocautery is applied to cut the superior aspect of the "smile." This word is in quotations because many minor papillae have no or minuscule mouth muscle, losing the characterization as a "sphincter muscle" very much in doubt. Electrocautery is typically a blend of (thermally) mixed cut and coagulation currents, to minimize char while permitting an adequate incision to enlarge the orifice. Some experts advocate using a pure cut current for minor sphincterotomy, to minimize the risk of orifice ruin/stenosis; this comes with a slightly higher risk of bleeding and has not been shown to affect long-term outcomes. The advantage of the pull-type technique is that it is most likely to minimize the risk of an incomplete incision; however, if an excessive amount of cut wire is left inside the pancreatic duct during the sphincterotomy, this is likely to induce post-ERCP pancreatitis and delayed high-grade strictures at the orifice.

An alternative and widely accepted approach is to perform a needle-knife sphincterotomy over a pancreatic stent. In this case, a small caliber (3Fr to 5Fr) pancreatic stent is deployed over the guidewire. With a needle-knife sphincterotome, the minor sphincterotomy is performed by cutting in the superior aspect of the stent until the stent is exposed within the duct itself. This technique is believed to have a lower risk of post-sphincterotomy perforation but may be associated with a higher rate of incompletely dividing the minor orifice. In cases of failed minor cannulation, a precut or fistulotomy (without the guidance of a pancreatic stent) needle-knife sphincterotomy may be attempted to expose the minor orifice for deeper access. Given the higher rates of post-ERCP pancreatitis and uncommon technical benefits, this maneuver should be used very sparingly. Unlike the biliary sphincter complex, the duct of Santorini rarely has a long intraductal segment to guide the depth and orientation of the incision.

Pancreatitis Prevention

For the past two decades, the mainstay for preventing post-ERCP pancreatitis has been the use of small caliber pancreatic stents (3Fr to 5Fr). These have been shown to reduce the risk of post-ERCP pancreatitis in multiple randomized clinical trials, presumably by reducing intraductal pressure in the critical hours or days after ERCP and its associated papillary trauma. The efficacy of prophylactic stents after minor papilla endotherapy mirrors that for patients with standard pancreatic duct anatomy. Importantly, patients with pancreas

diseases who undergo ERCP solely for major papilla therapy have a lower baseline risk of post-ERCP pancreatitis, since minor papilla cannulation is attempted, however, the risk approaches that of the highest risk populations. Therefore, most experts are uncomfortable performing an endoscopic minor sphincterotomy without placement of a small caliber pancreatic duct stent immediately before or after the incision. The stents pass out of the minor orifice spontaneously in more than 90% of cases, the minority require a second endoscopy to pull the stent if it is retained after 10 to 14 days on a follow-up radiograph.

Postprocedure, rectal indomethacin (100 mg) is the first widely accepted pharmacologic intervention to minimize the risk of post-ERCP pancreatitis. The medication is administered anytime immediately before, during, or at the completion of the ERCP, and presumably reduces the risk of post-ERCP pancreatitis by interrupting the earliest inflammatory cascades triggered by papillary trauma and intraductal hypertension. Its efficacy as a first-line preventive modality—without pancreatic stents—remains unproven for patients with pancreas divisum undergoing minor endoscopic sphincterotomy. However, the medication is inexpensive and low risk, so has become widely popular as an adjunct for high-risk patients.

Postprocedure Management

The majority of patients undergoing ERCP may be discharged within 2 hours after the procedure. Preprocedure and early postprocedure pain or nausea are important predictors of unplanned admission after ERCP. Intravenous fluids, preferably Lactated Ringer's solution, should be administered during ERCP and in the recovery room in case pancreatitis ensues. If there are no symptoms concerning for post-ERCP pancreatitis and the procedure was otherwise uneventful, patients may be discharged home after a short period of observation.

Approximately 10% to 15% of patients will require overnight observation after ERCP; admission rates after endoscopic minor sphincterotomy are unknown but the post-ERCP pancreatitis rate is also 10% to 15%. The majority of these patients will improve within 72 hours of the procedure, but a small minority (1% to 2% of all patients with post-ERCP pancreatitis) may develop severe acute pancreatitis and local complications such as pseudocysts or necrosis. The potential for post-ERCP pancreatitis—mild or severe—must be considered when weighing the risks and benefits of endoscopic therapy.

SURGICAL TREATMENT

Minor Duct Sphincteroplasty

Operative sphincteroplasty of the sphincter of Oddi was the main stay of therapy before the development of endoscopic sphincterotomy. It is hard to imagine how an operative sphincteroplasty can be better than an endoscopic sphincterotomy, given the sparseness of smooth muscle fibers that surround the pancreatic duct as it courses into the duodenum. Occasional patients with bypassed foregut anatomy may elect open surgical sphincteroplasty and forgo a retrograde endoscopic approach or a hybrid laparoscopic and endoscopic prograde approach. Surgical outcomes with open sphincteroplasty are best when endoscopic sphincterotomy has not been done before. The first cut is the best one. It is tempting to undertake open sphincteroplasty in patients with altered foregut anatomy, such as patients with gastric bypass. These patients may be well served by a hybrid procedure with concomitant laparoscopic gastrostomy of the bypassed stomach and endoscopic prograde sphincterotomy. A gastrostomy tube is left in place to secure access for removal of the anastomotic stent later. Patients who have previously undergone successful endoscopic sphincterotomy with recurrent illness may be candidates for operative sphincteroplasty. The concept is that open minor duct sphincteroplasty with loop magnification and fine absorbable suturing of the duct will have better outcomes than endoscopic sphincterotomy. The difficulty in undertaking this course of action is that patients with chronic illness of the head of the pancreas do poorly with sphincteroplasty, and preoperative identification of pancreatic fibrosis is imperfect.

Technique

The most recent ERCP and magnetic resonance cholangiopancreatography are displayed on the operating theater monitors closest to the surgeon, who has on a headlamp and magnifying loupe. The abdomen is entered through an upper midline incision. The falciform ligament is divided when it limits placement of a wound protector or retraction of the liver. A self-retaining retractor is placed to retract the abdominal wall to divide the lateral duodenal attachments and the ligamentous attachments of the transverse colon to the duodenal pancreatic union. After the wide kocherization of the duodenum and mobilization of the hepatic flexure of the colon inferiorly and laterally, the duodenum is mobilized medially to the midline. Exposure is maintained with the self-retaining retractor placed around the wound circumference, retracting liver, stomach, and transverse colon out of sight. A laparotomy pad is placed behind the duodenum to elevate it toward the midline. A longitudinal duodenotomy is made in the descending duodenum, angled slightly from medial to lateral as the electrocautery knife goes from proximal to distal duodenum. Intraluminal exposure is maintained by grasping the medial and superior duodenal wall with a Babcock clamp or with stay sutures of 3-0 silk. The major papilla is identified with palpation and visualization of bile expressed with manual compression of the gallbladder and common bile duct. Centimeters proximal to the major papilla, the minor papilla can be palpated on the medial wall of the duodenum. Care is taken not to distort duodenal mucosa by direct suction and grasping with forceps, as minor mucosal trauma can obscure visualization of the minor papilla. The minor papilla is palpated and cannulated with a biliary duct probe (Fig. 4). When the papilla cannot be found, secretin stimulation can be used, but this increases the risk of postoperative pancreatitis, particularly if operative drainage has limited success. Sphincterotomy is accomplished by dividing the sphincter muscle with needle knife low-energy cautery over the lateral duct probe. Care is taken to cut only mid muscle fibers. When yellow pancreatic tissue is encountered, the sphincterotomy is complete.

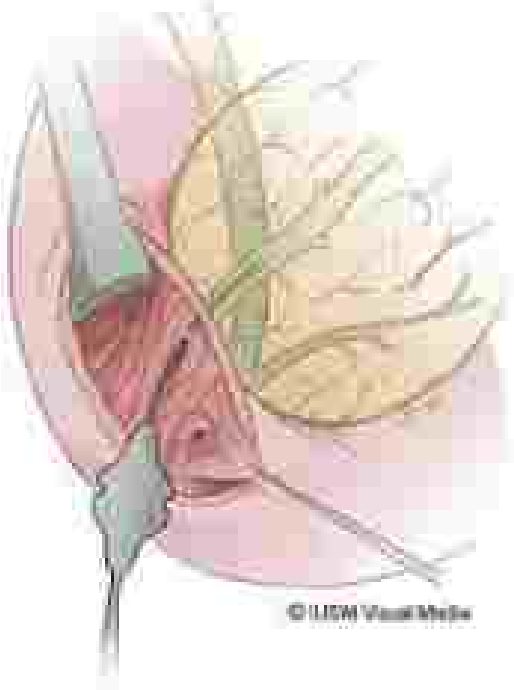

FIG. 4 Through a longitudinal duodenotomy, the minor papilla is identified and cannulated with a biliary duct probe.

Two or three interrupted sutures of 5-0 monofilament absorbable suture are placed to reapproximate duodenal and ductal mucosa (Fig. 7). Minor duct sphincteroplasty is distinctly different from that of a biliary sphincteroplasty in which the common bile duct lies parallel and juxtaposed to the duodenum, which allows for a lengthy sphincterotomy. The minor duct enters the duodenum at right angles from the pancreas. There is not a lot of room to cut this sphincter. A 3Fr or 5Fr double pigtail stent is placed across the anastomosis. It is removed endoscopically a week later. The duodenotomy is closed with a running suture of 3-0 absorbable monofilament suture, reinforced as needed with interrupted sutures of 3-0 silk. The fascia is reapproximated with interrupted non absorbable sutures. The skin is closed with a 4-0 running subcuticular suture. Closed suction drainage of the retroduodenal space is not used routinely. Because stenosis of the major papilla is associated with pancreas divisum, some would advocate performing biliary sphincteroplasty and pancreatic ductal sphincteroplasty whenever minor duct sphincteroplasty is undertaken. This indication is exceptional but not irrational.

Postoperative Management

Patients are managed on a fast track much as one would manage a patient after an open cholecystectomy. Nasogastric and urinary bladder intubation are avoided. Diet is advanced early as tolerated. Complications particular to this operation are pancreatitis and duodenotomy dehiscence (Table 1). Postoperative pancreatitis is uncommon and presents in typical fashion with pain, tachycardia, and serum lipase and leukocyte elevation. Duodenal dehiscence presents in a subtle fashion, similar to a duodenal stump leak after Billroth II gastrectomy. Vague upper abdominal pain and nausea precede by days the appearance of systemic toxicity with fever, tachycardia, tachypnea, and leukocytosis. Alert vigilance for this complication is needed because it is uncommon, subtle in presentation, and devastating if unrecognized early.

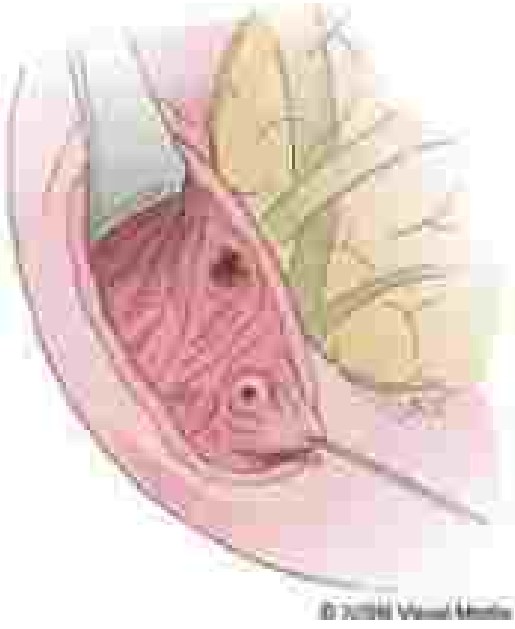

FIG. 7 After division of the muscular fibers of the sphincter of Helm with needle-knife electrocautery, the termination of the dorsal pancreatic duct is anastomosed to the duodenal mucosa with interrupted sutures.

Lateral Pancreaticojejunostomy

Dominant ductal dilation is an indication for lateral pancreaticojejunostomy (LPJ) in chronic pancreatitis associated with pancreas divisum. Outcomes after LPJ are similar to those reported with chronic pancreatitis not associated with pancreas divisum. In particular, the patient with the borderline dilated pancreatic duct not greater than 7 mm in diameter may benefit from LPJ when diffuse fibrosis of the pancreas is present with a fibrotic encapsulation of the pancreas. LPJ has the theoretic advantage of relieving the pancreas from its so-called pancreatic compartment syndrome. Part of the discussion of LPJ in the management of chronic pancreatitis of all causes is that of LPJ fails and the patient progresses to consideration of total pancreatectomy with islet autotransplantation (TPIAT), islet yields are diminished in patients who have had LPJ, related to either the underlying disease state or technical challenges presented by islet isolation in patients who have a longitudinal disruption of the pancreatic duct. The technique of LPJ in pancreas divisum does not differ from that discussed elsewhere in this book. Because the pancreas dissection is extended medially adjacent to the duodenum, the gastroduodenal artery should be ligated before its division.

Whipple Procedure

Pancreaticoduodenectomy may be indicated in patients with pancreas divisum who have failed minor duct sphincteroplasty when changes of chronic pancreatitis develop in the head of the pancreas. The operative technique is not different from that described elsewhere in this book. When a resection of the head is indicated in pancreas divisum, the dorsal neck of the pancreas is usually left with a modified pancreatic duct, not at risk for anastomotic leak. Therefore internal and external anastomotic stenting and postoperative octreotide infusion may diminish the risk of postoperative pancreatic fistulas. If head resection in pancreas divisum fails and patients become candidates for TPIAT, islet yields may be unacceptable. Islet volume is greater in the tail and body than in the head of the pancreas, and islet loss is limited in a head resection for pancreas divisum. When autoimmune obstruction occurs after a Whipple procedure, acinar cells atrophy before destruction of the islets. The resultant islet-rich, acinar poor atrophied pancreas may be favorable isolation for islet autotransplantation. The issue of whether patients with pancreas divisum with chronic pancreatitis should undergo a speculative Whipple procedure or a TPIAT is unanswered.

Hybrid Procedures

Variations of the Whipple procedure and the Puestow procedure have been used in chronic pancreatitis associated with pancreas divisum in a fashion similar to their use in chronic pancreatitis not associated

TABLE 1 Surgical Outcome After Minor Duct Sphincteroplasty in Patients With Pancreas Divisum

Study	N	Morbidity	Mortality	Good Response	Mean Follow-up (mo)
[illegible] et al. (1998)	88	NR	0	71%	53
Bradley (1994)	31	NR	0	58%	40
Madura (1993)	8	25%	0	63%	NR
Morgan et al. (2008)*	1.	10%	0	54%	63

*R, not reported.

with pancreas divisum. Although typically the Roger and Frey procedures are selected for patients with an inflammatory mass in the head of the pancreas, they have been used in pancreas divisum not associated with enlargement of the head of the pancreas. The Frey procedure was developed because of the ascribed failure of the LPT to drain the head and uncinate process of the pancreas. In pancreas divisum, the head should be drained efficiently with a longitudinal duct-to-stomach. The use of multiple resection and drainage techniques is an indication of the difficulty in patient selection and management of chronic pancreatitis associated with pancreas divisum.

Total Pancreatectomy With Islet Autotransplantation

TPIAT is indicated in patients with chronic pancreatitis with intractable pain who have failed medical, endoscopic, and surgical management. Pancreas divisum is a risk factor for chronic pancreatitis in about 10% of the cohort in the reports of TPIAT in the management of chronic pancreatitis. Typical patients with pancreas divisum who are selected for TPIAT have undergone endoscopic sphincterotomy, operative sphincteroplasty, and pancreatic head resection to succumb over many years. The unanswered question is whether TPIAT should be undertaken sooner rather than later if endoscopic treatments fails. That discussion is beyond the scope of this chapter.

CONCLUSIONS

Given the paucity of comparative effectiveness studies evaluating the impact of endoscopic or surgical minor papilloplasty on unobstructive recurrent acute and chronic pancreatitis, the management of pancreas divisum is primarily based on experience. Although the divisum anatomic variant is common, its association with chronic pancreatitis is by no means a *sine qua non*. When pancreas divisum is associated with intractable pain associated with chronic pancreatitis or with recurrent pancreatitis, the approach should mimic that for patients with standard duct anatomy: (1) alcohol and tobacco cessation is necessary; (2) a trial of pancreatic enzyme replacement therapy may be considered, especially if exocrine pancreatic insufficiency is documented; and (3) genetic mutations and polymorphisms should be investigated, knowing that the odds identifying high risk mutations are higher in the setting of divisum. A management strategy based on a regional experience extending with the surgical management of pancreas divisum is suggested in Table 2. The pathway outlined in Table 2 differs from much of the experience in the current literature and underscores the influence of regional population differences and their attendant practices. As the pathogenesis of pancreatitis is better understood, treatment strategies will become less intuitive and experience based and more effective.

To seek and to find evidence on which to base the management of pancreas divisum is to repeat Samuel Johnson's experience described in the preface to his 1755 *A Dictionary of the English Language*, saying: "I saw that one inquiry only gave occasion to another, that book referred to book, that to search was not always to find, and to find was not always to be informed, and that this is pursue perfection, was, like the first inhabitants of Arcadia, to chase the sun, which, when they had reached the hill where he seemed to rest, was still beheld at the same distance from them."

TABLE 2 Management Strategies for Pancreas Divisum in the Setting of Chronic Pancreatitis Intractable to Medical Management or with Recurrent Acute Pancreatitis

Condition	Strategy
Nonfunctional, dilated duct >5 mm	Lateral pancreaticojejunostomy
Familial	Total pancreatectomy with islet autotransplantation
Nondilated duct with recurrent acute pancreatitis	Endoscopic minor papillotomy
Nondilated duct endotherapy failure	Operative sphincteroplasty
Nondilated duct endotherapy failure with moderate to severe chronic pancreatitis in the head	Pancreaticoduodenectomy
Operative sphincteroplasty failure	Pancreaticoduodenectomy
Pancreaticoduodenectomy failure	Total pancreatectomy with islet autotransplantation

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MANAGEMENT OF PANCREATIC NECROSIS

David B. Adams, MD, and William P. Lancaster, MD

Consider the pancreas. It sits quietly in the retroperitoneum, excellently churning out proteins to regulate endocrine and exocrine homeostasis. However, when acutely inflamed with activation of pancreatic enzymes in the retroperitoneum, a localized process, pancreatic and fat necrosis may be accompanied by a cytokine-mediated inflammatory response that causes widespread injury to lungs, kidneys, heart, brain, and liver. Fortunately, acute pancreatitis is usually a self-limited disease that responds to supportive care with complete resolution of symptoms and without long-term sequelae. Approximately 20% of patients with acute pancreatitis will develop a more severe form of disease with transient or persistent organ failure and abdominal complications. The most severe complication of severe acute pancreatitis is glandular and retroperitoneal tissue destruction resulting in pancreatic and peripancreatic necrosis. Approximately 5% to 10% of patients with severe acute pancreatitis will develop pancreatic necrosis, and 30% of patients with pancreatic necrosis will develop infected pancreatic necrosis. Conventional wisdom once dictated that infected pancreatic necrosis was an absolute indication for operation. Considering that the attendant mortality of laparotomy in the early course of pancreatic necrosis approaches 100%, this approach has largely been abandoned in favor of thoughtful multidisciplinary management involving surgeons, gastroenterologists, interventional radiologists, and intensivists. Current concepts support the view that operating on patients earlier than 4 weeks after the onset of severe necrotizing pancreatitis is associated with poor outcomes, which can be ameliorated by delaying surgery until after 4 weeks into the disease course. The exceptions to this guideline require a positive answer to this question: What is an operation going to do to improve the patient's physiology and diminish, rather than increase, cytokine release? Operative intervention should be planned in a sequential delayed fashion as much as possible in a stepwise approach from least invasive to more invasive. When this sequence is followed, morbidity and mortality can be minimized.

CLINICAL COURSE

There is a bimodal distribution of mortality in severe acute pancreatitis marked by an early phase (<14 days) and a late phase (>4 weeks). Mortality in the early phase of illness is due to severe systemic inflammatory response syndrome (SIRS) and multisystem organ failure, and mortality in the late phase is most commonly due to infectious complications. The inflammatory insult of pancreatic necrosis leads to organ dysfunction in the first 2 weeks of illness. Patients will often have pulmonary insufficiency requiring mechanical ventilation, acute renal failure, and hemodynamic instability. Aggressive supportive therapies are the mainstay of treatment during the early phase of illness. Usually within 2 weeks, the capillary endothelial leak resolves and the patient stabilizes. During this time frame, the surgeon must be vigilant for the development of complications.

Diagnosis

The 2012 revised Atlanta classification provides expert consensus definition of the severity of acute pancreatitis distinguishing between three forms of disease based on the degree of associated organ failure and the presence of local complications (Table 1). The classification system further defines local complications according to imaging findings and timing relative to the onset of symptoms. Patients with moderately severe or severe acute pancreatitis, by definition, have some degree of associated organ dysfunction, and the surgeon should be suspicious of local complications in patients with persistent or worsening SIRS, fever, worsening abdominal pain, or ileus/paralytic ileus. Contrast-enhanced computed tomography is the imaging study of choice to diagnose local complications of severe acute pancreatitis and can demonstrate the presence of acute peripancreatic fluid collections and necrosis.

Antibiotic Therapy and Nutritional Support

Numerous studies have investigated the role of prophylactic antibiotics in the treatment of severe acute pancreatitis given the high mortality associated with infectious complications. Prophylactic antibiotics are not recommended and may be associated with increased mortality and mortality secondary to the selection of resistant organisms. Antibiotics should be used when infection is highly suspected or when definitive culture data are available from retroperitoneal fluid. Clinical findings that are highly suggestive of infection include worsening physiologic status, increasing leukocytosis, and persistent fever. Radiographic findings that support the presence of infected peripancreatic fluid include air within the retroperitoneum on cross-sectional imaging.

Nutritional support is paramount to severe acute pancreatitis because the metabolic demands are enormous secondary to severe systemic inflammation. Historically, total parenteral nutrition (TPN) was thought to be superior to fight of the abdominal distention and adynamic ileus that is often present in severe acute pancreatitis. It was also believed that parenteral nutrition would minimize pancreatic stimulation and thereby avoid worsening of the disease. Several studies have shown that enteral nutrition is superior to parenteral nutrition. The benefits of enteral feeding are numerous and include maintaining gut mucosal integrity, improved immune function, and decreased cost. Clinical trials comparing enteral and parenteral nutrition have shown enteral nutrition is associated with decreased severity of illness, decreased need for surgical intervention, and decreased length of hospital stay. Feeding can be initiated via nasojejunal tube either into the stomach or distal to the pylorus. Although further study is needed, we feel that postpyloric feeding is the safest approach given the associated gastric and intestinal dysfunction that is frequently present in acute pancreatitis. However, if gastric feeding is tolerated, there is not good evidence not to do so. Similarly, if patients can eat, let them eat. In the rare case that the patient is intolerant of enteral feeding, TPN should be initiated.

Fluid Therapy: Too Much or Too Little?

Aggressive intravenous fluid resuscitation has historically been the mainstay in the management of severe necrotizing pancreatitis. However, as the early complication of renal injury owing to hypovolemia was supplanted by fluid overload and pulmonary failure, fluid management became problematic and how best to prevent organ failure and reduce mortality involved controversies related to rate and type of fluid infusion. Most agree that rapid fluid infusion in the first 12 hours of treatment is indicated, recognizing pulmonary complications if more than 4 L of fluid is given in the first 24 hours. There is an experimental rationale to suggest that lactated Ringer's solution is better than normal saline solution in terms of precipitating an SIRS response. There is little evidence to suggest that fluid resuscitation has a role in altering the rate-limiting step in necrotizing pancreatitis that is the SIRS response. Aggressive resuscitation strategies may protect some organs at the cost of pulmonary failure and abdominal compartment syndrome. Recent consensus guidelines recommended that fluid volume for replacement should be between 2500 and 3000 mL during the first 24 hours, with infusion rates guided

TABLE 1 2012 Revised Atlanta Classification of Acute Pancreatitis

Severity	Definition
Acute pancreatitis	Acute inflammation of the pancreas
Mild acute pancreatitis	Minimal organ dysfunction and disease that responds to fluid administration
Severe acute pancreatitis	One of the following: • Local complications (pancreatic necrosis, pancreatic pseudocyst, pancreatic abscess) • Organ failure • ≥3 Ranson criteria • ≥8 APACHE II points
LOCAL COMPLICATIONS	
Acute fluid collections	Fluid collections in or near the pancreas, occurring early in the clinical course, lacking a well-defined wall
Pancreatic necrosis	Nonviable pancreatic tissue diagnosed by intravenous contrast enhanced computed tomography scan
Acute pseudocyst	Fluid collection containing pancreatic secretions (high amylase level) and a well-defined wall
Pancreatic abscess	Collection of pus, usually near the pancreas, with little or no associated pancreatic necrosis

APACHE II, Acute Physiology and Chronic Health Evaluation II.

by heart rate, mean arterial pressure, urinary output, hematocrit, and thermodilution measured intrathoracic stroke volume.

Local Complications—Bleeding and Fistulas

The inflammatory environment in pancreatic necrosis is driven by leakage of pancreatic enzymes into the retroperitoneum. The enzymes digest surrounding tissues that can include blood vessels and viscera. Arterial bleeding can occur from any visceral artery but is most often from the splenic artery and gastroduodenal artery. The presentation is often heralded by gastrointestinal bleeding or an unexpected decrease in hematocrit. A high index of suspicion must be obtained to ensure timely diagnosis. Diagnosis is made with computed tomography angiography and is manifest radiographically as a pseudoaneurysm (Fig. 1). Treatment is by conventional angiography with either coil embolization or stenting. Attempts at surgical control of bleeding should be reserved for the direst cases as mortality is much lower with angiography. It is not beyond the scope of practice to utilize damage control principles in the operative management of arterial bleeding with the application of abdominal packs and subsequent source control with interventional radiology techniques. Venous bleeding is usually a self-limited process and is treated nonoperatively. In a bleeding patient without evidence of arterial bleeding, correcting coagulopathy and decreasing splanchnic blood flow with an octreotide infusion is usually sufficient.

Enteric fistulae develop as a result of pancreatic enzymes either destroying the blood supply to a segment of bowel causing ischemia or by direct luminal erosion. They occur more commonly postoperatively after debridement but can also occur preoperatively. The most common organs affected are the duodenum and colon. With adequate drainage and nutritional support, approximately 75% will heal without surgical intervention.

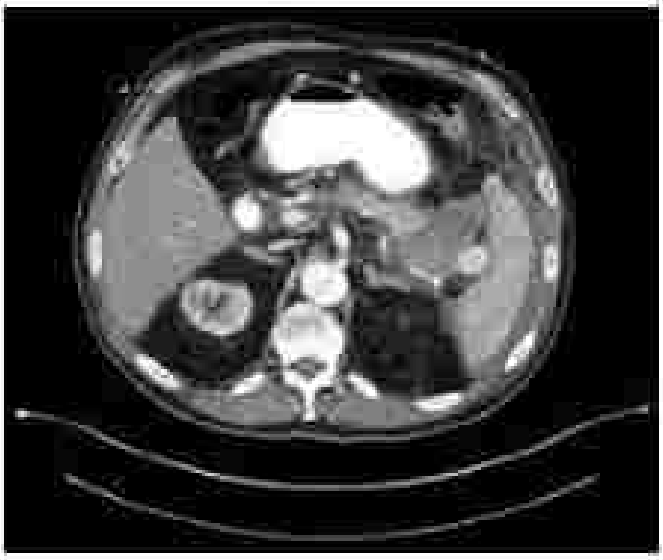

FIG. 1 Computed tomographic image showing arterial pseudoaneurysm at the splenic hilum.

Indications and Timing of Debridement

Indications for surgery in pancreatic necrosis include infected necrosis, failure to thrive, and persistent symptoms. In the early phase of illness, surgery should be deferred because of prohibitive perioperative mortality. An additional inflammatory insult to a maximally physiologically stressed patient is the principal reason for high mortality with operative intervention in the early phase. An exception is in abdominal compartment syndrome. In patients with the constellation of findings consistent with abdominal compartment syndrome and concurrent physiologic decline, a laparotomy should be performed. Importantly, pancreatic debridement should not be pursued at the time of laparotomy.

In general, debridement should be pursued only after 4 weeks from the initial onset of symptoms. This allows for systemic inflammation to subside and organ compromise to resolve. Percutaneous drains should be liberally used in patients who develop suspected or confirmed infected necrosis during the first 4 weeks of illness (Fig. 2). The drains serve as a temporizing measure that allow for drainage of infected material and bridge the patient to a time most suitable for definitive debridement. In many cases, percutaneous drainage alone is definitive treatment, especially in cases without a significant solid component within the fluid collection. Percutaneous drains can also be used as part of a "step-up" approach to video-assisted retroperitoneal debridement (VARD).

Percutaneous Drains and Video-Assisted Retroperitoneal Debridement

Percutaneous drains are a useful temporizing measure to treat infectious complications in the early phase of illness. Drains are effective at draining retroperitoneal fluid and pus but are less effective at draining solid debris. In patients with a significant degree of solid necrosis burden, more definitive debridement can be achieved by VARD, termed a step-up approach. This technique utilizes well-placed percutaneous drains as a pathway to the retroperitoneum and the necrotic cavity. An incision is made over the drain and the drain tract is followed into the necrotic cavity. The tract is enlarged and a laparoscope is inserted for direct intracavitary visualization. The necrosis is debrided bluntly with laparoscopic instruments. The advantages of VARD are adequate mechanical debridement through a limited approach, minimizing morbidity. This approach also allows for the placement of large bore drains with lavage capability.

Endoscopic Treatment

Endoscopic techniques offer a minimally invasive approach to pancreatic debridement. The technique is based on the principal of endoscopic cystgastrostomy to allow drainage of peripancreatic fluid and debris into the stomach. Plastic or metal stents are available to maintain patency of the cystgastrostomy. The necrosis cavity can be directly visualized and mechanically debrided with endoscopic instruments. Contained retroperitoneal collections with a relatively low degree of solid necrosis are suitable for endoscopic management. The disadvantage of this technique is that it is labor intensive, often requiring multiple procedures to achieve adequate debridement.

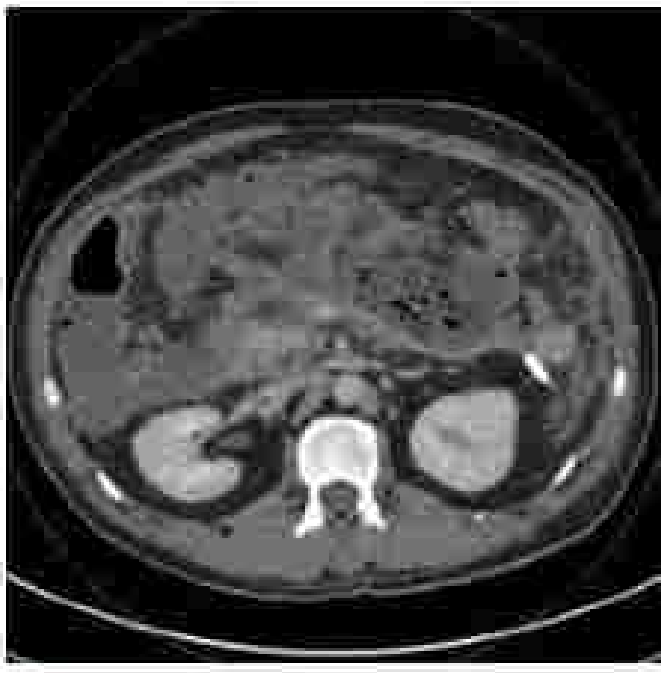

FIG. 2 Computed tomographic image showing percutaneous drain entering the left flank into a retroperitoneal collection.

Principles of Operative Management

The goals of operative management are to reduce septic mortality, decrease septic complications, and minimize the inflammatory insult to the patient. Open debridement via laparotomy is the gold standard, but a number of less invasive techniques can also be used based on the pattern of disease. Fig. 3 outlines a general decision pathway for patients with pancreatic necrosis. The decision as to which approach to utilize depends largely on the distribution of necrosis.

Operative Management—Open and Laparoscopic Transgastric Debridement

Similar to cystgastrostomy, transgastric debridement establishes a communication between the lumen of the stomach and the necrosis cavity. This approach is best when applied for collections that are contained within the retroperitoneal space and to the left of the mesenteric vessels (Fig. 4). There is limited access to the mesenteric root, pancreatic head, and paracolic spaces. The anterior stomach is opened in a longitudinal fashion and the impression of the necrotic cavity is identified. Intraoperative ultrasound can also be used to guide placement of the posterior gastrotomy. The posterior wall of the stomach is incised and the necrosis cavity is entered. All fluid and necrotic debris are removed. A nasogastric tube can be placed within the cavity for lavage and suction. The posterior stomach is sutured to the wall of the necrosis cavity with running absorbable suture for hemostasis. The anterior gastrotomy is closed in a transverse fashion. In many cases, laparoscopic techniques can be used.

Operative Management—Open Debridement

Outcomes for open debridement remain the measure by which less invasive therapies for pancreatic necrosis are measured. Although step-up strategies are usually equal in historical outcomes, open debridement is the definitive treatment when less invasive techniques fail. In the past, management of pancreatic necrosis involved a bilateral subcostal incision, retroperitoneal and pancreatic debridement, wide drainage, cholecystectomy, gastrostomy, and feeding jejunostomy. Following a few basic principles, we now advocate entering the abdomen through a midline laparotomy. The necrosis cavity is accessed through the lesser sac, either through the gastrocolic omentum or through an incision at the base of the transverse mesocolon, usually to

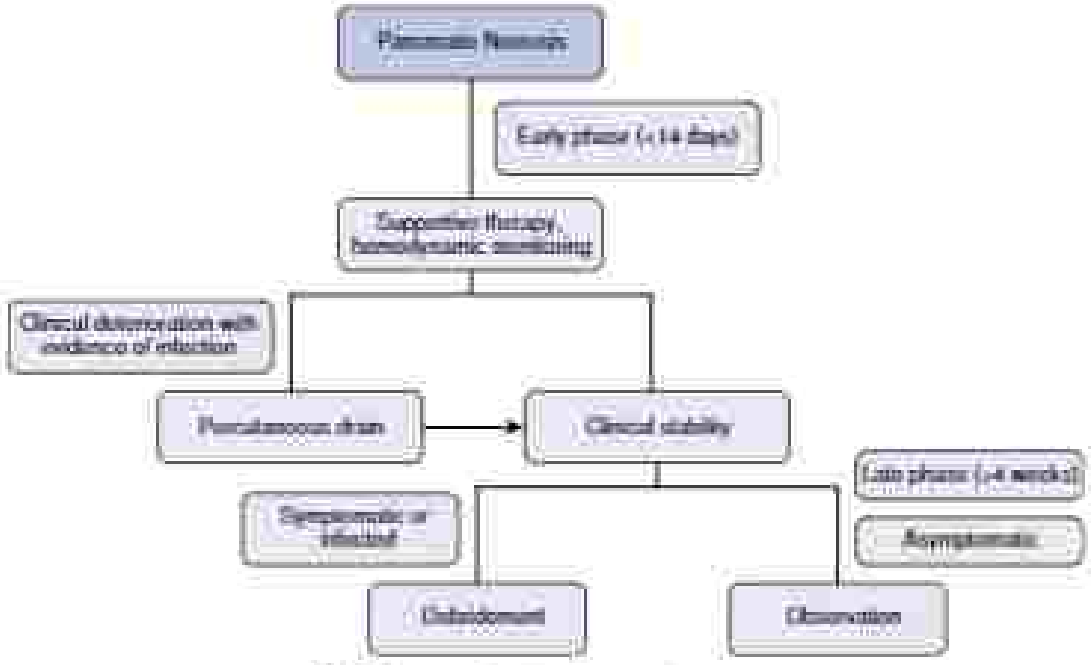

FIG. 3 Treatment algorithm for pancreatic necrosis.

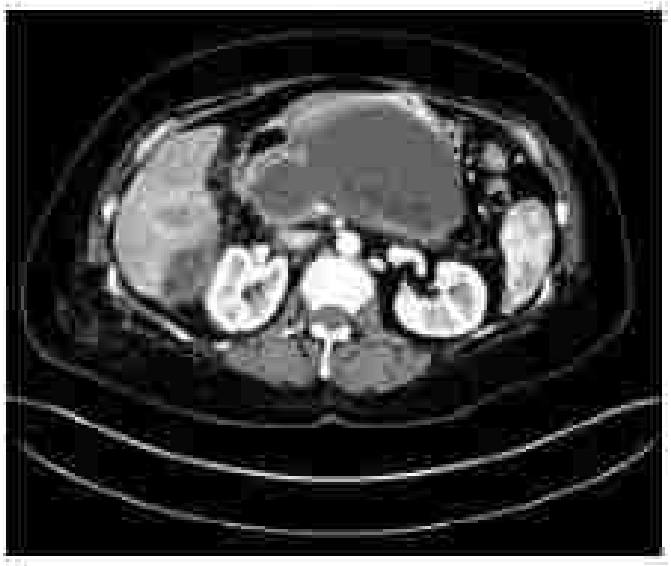

FIG. 4 Computed tomographic image showing a contained heterogeneous necrotic collection.

the left of the middle colic vessels. Necrotic debris is removed bluntly and the cavity irrigated. Ringed forceps and high pressure irrigation help get the job done. Care must be taken to avoid injury to the mesenteric and splenic vessels, as life threatening and difficult to control bleeding can occur. Open debridement is useful in cases in which necrosis extends from the retroperitoneum posterior and tracks bilaterally into the root of the mesentery and the paracolic spaces (Fig. 5).

■ CONCLUSIONS

Pancreatic necrosis remains a surgical disease that requires all the skills that a general surgeon can muster; knowledge of the evidence-based surgical literature, operative experience with the pancreas, empathy with patients who are walking a tight rope between life and death, and surgical intuition that may be the only thing that tells one when to operate, and when to wait. Advances in critical care and thoughtful reassessment of traditional operative strategies and utilization of minimally invasive approaches have decreased the morbidity of pancreatic necrosis, and when carefully applied can diminish mortality. Pancreatic necrosis is a formidable foe, but when confronted head on with perseverance and attention to detail, the result is a patient who returns to a high quality of life at home and at work.

Suggested Readings

Bakker OJ, van Santvoort HC, van Brunschot S, et al; Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;308(22):2355–2363.

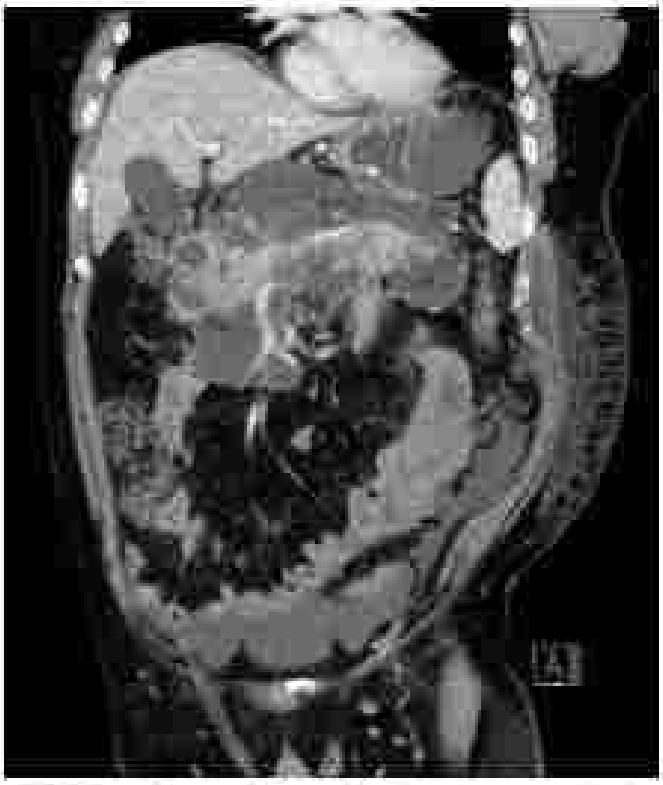

FIG. 5 Computed tomographic image showing extensive retroperitoneal necrosis with extension into the mesenteric root.

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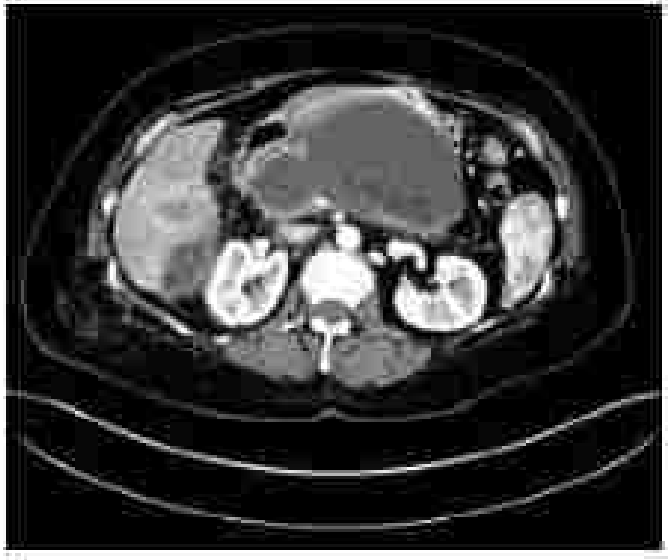
Management of Pancreatic Pseudocyst

Matthew J. Martin, MD, FACS, FASMBS, and Carlos V.R. Brown, MD

Acute pancreatitis is an extremely common disease process and represents the most common gastroenterologic diagnosis requiring hospital admission in the United States. Although most cases are still limited and resolve without complications, there is a well defined subset of patients that will develop local complications including necrosis, infection, or persistent peripancreatic fluid collections that prompt a surgical consultation or referral. Thus, the managing surgeon must have a thorough knowledge and understanding of the disease process and specific complicating factors, and a well developed algorithm to select from the myriad of currently available diagnostic and interventional options. This is particularly important when dealing with pancreatic pseudocysts (PS) because of the history of highly variable and confusing terminology, definitions, and classification systems for pancreatitis and peripancreatic fluid collections that have been used in the literature and that continue to be used in



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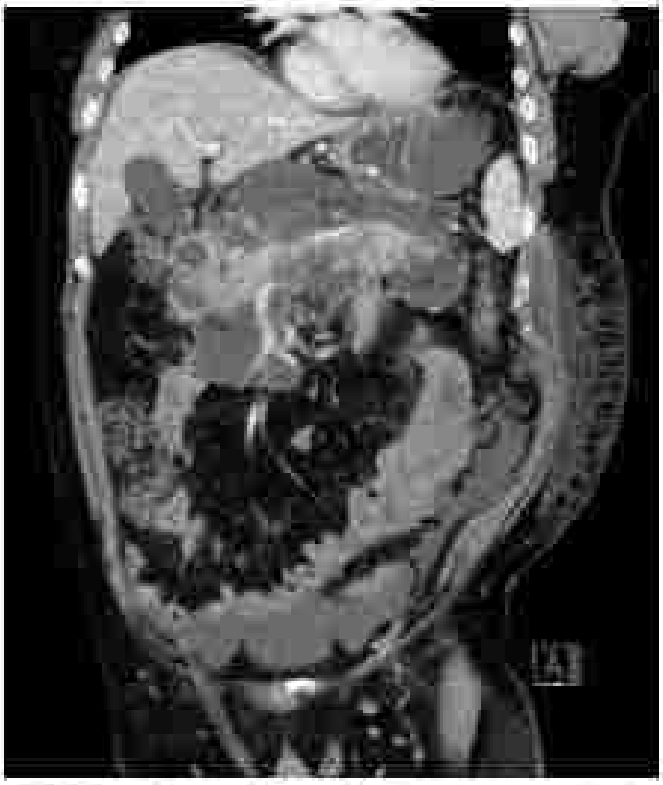

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clinical practice. This chapter will present a practical, straightforward, and evidence-based approach to the patient with suspected or proven pancreatic pseudocyst.

TERMINOLOGY AND CLASSIFICATION

Arguably the most important foundation for approaching the evaluation and management of a potential PS is the use of accurate and clinically relevant definitions and terminology. We have found that the term *pseudocyst*, has been poorly defined in prior published literature, has been applied to a wide variety of pathologies that are not true pancreatic pseudocysts, and continues to be used by radiologists and other specialties as a catch all term for any well-formed peripancreatic fluid collection. Thus, the first step in the evaluation process should be an accurate determination of whether the pathology truly meets the current diagnostic criteria for a PS or for another entity. This is important not only for nomenclature purposes, but also because the evaluation and management algorithm will often be markedly different. Fortunately, the medical and surgical community has increasingly adopted the more uniform definitions and criteria outlined in the 2012 revised Atlanta classification system for acute pancreatitis. This has ensured vague and confusing terminology such as *pancreatic phlegmon* and *acute pseudocyst* and replaced them with more exact and clinically relevant categorizations.

As outlined in Fig. 1, the revised Atlanta classification divides acute pancreatitis into necrotizing or interstitial edematous (no necrosis present) variants. It then classifies any associated peripancreatic fluid collections based on the time interval from the onset of pancreatitis and using 4 weeks as the cutoff between an early versus "mature" fluid collection. PS is diagnosed as a persistent mature fluid collection (>4 weeks) in association with interstitial edematous pancreatitis (IEP). Before the 4 week time point, the fluid collection is described as an *acute peripancreatic fluid collection*. Most important, the term *pseudocyst* is no longer used in the presence of necrotizing pancreatitis (NP), in favor of the alternative diagnoses of acute necrotic collection at less than 4 weeks or walled off necrosis (WON) after 4 weeks. Thus, a PS is most specifically defined as a mature and sterile simple cystic fluid collection in association with edematous acute pancreatitis. In rare cases in which the PS becomes infected, it may be most accurately described as a pancreatic abscess or infected PS. Although PS is most commonly described and reported as a consequence of acute pancreatitis, it may also be seen in association with chronic pancreatitis (CP) or following pancreatic trauma.

Although the revised Atlanta classification is based on the best available current evidence and uses a clearly defined temporal dividing line at 4 weeks, it is important to realize that this cutoff is largely based on averaged observational data and limited animal models. This should not be strictly interpreted as meaning that a well-formed PS capsule cannot form earlier than 4 weeks, or that all acute peripancreatic fluid collections will have matured to a true PS at the 4 week time point. For any individual patient, this timeline may be markedly different, and in modern practice the most useful modality to make this determination will be the appearance of the fluid collection and the PS capsule on computed tomography (CT) and/or magnetic resonance imaging (MRI) studies. Arguably the most important aspect of maintaining this 4 week cutoff in the definition is to minimize attempts at early unnecessary and often nontherapeutic interventions for peri-pancreatic fluid collections in both IEP and NP.

EPIDEMIOLOGY

Although the reported incidence of PS following acute pancreatitis is 5%, the true incidence and natural history of PS are unknown because many resolve spontaneously and without symptoms. PS has become increasingly recognized and characterized from the more liberal use of CT and/or MRI in the evaluation of acute pancreatitis and postpancreatitis complications. Arguably the most important epidemiologic aspect of PS that must be appreciated is the fact that most peripancreatic fluid collections in association with IEP will be asymptomatic or minimally symptomatic, and 75% to 90% will resolve spontaneously and not require any invasive interventions or surgery. This is in contrast to fluid collections associated with NP, and particularly with infected NP, where the majority will require some type of interventional procedure or surgery. Overall, approximately 5% to 15% of patients with IEP will develop one or more local complications, including PS, and the risk for these complications will generally correlate with the severity of the index episode of pancreatitis. Although less common overall, PS may also be seen in association with CP in up to 40% of cases, and without an identified antecedent episode of acute pancreatitis. The exact underlying etiology and risk factors for PS in the setting of CP remain unclear.

Another potential but much less common cause of PS is pancreatic trauma, which may be secondary to either blunt or penetrating injuries with some element of injury to the pancreatic ductal system (grade 3 or higher injury). These typically present in a delayed fashion, and often in cases where the presence of the pancreatic injury was not visualized on the initial CT scan. The PS is usually identified on a repeat imaging study performed because either symptoms of abdominal pain, fulminant early satiety, or elevated serum amylase/lipase levels. Although any associated traumatic injuries and pathology must also be taken into account, the management of a posttraumatic PS will largely mirror that of the usual pancreatitis-associated PS.

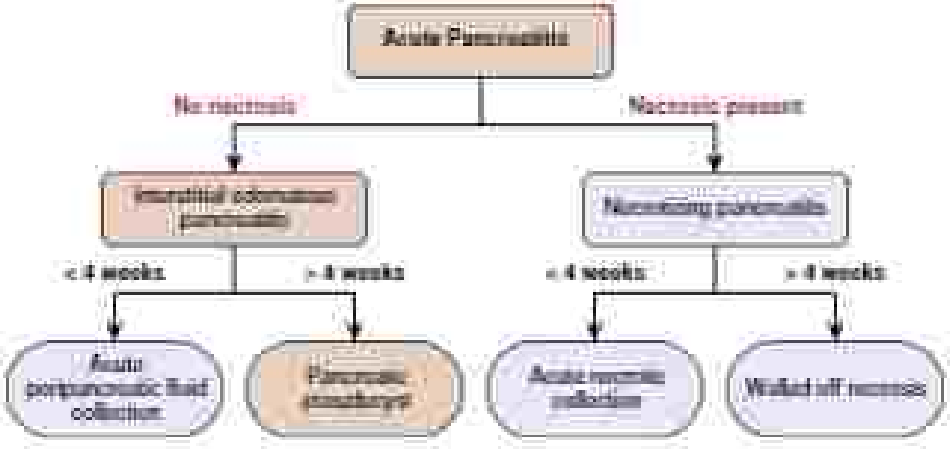

FIG. 1 2012 modified Atlanta classification for acute pancreatitis and associated fluid collections. Pink-shaded boxes indicate the pathway to diagnosis of a pseudocyst.

PATHOPHYSIOLOGY

Pancreatic pseudocyst is a well-formed fluid-filled cystic mass that typically abuts the pancreas, although it less commonly can be partially or wholly intrapancreatic. The primary etiology of the cyst is disruption of the main pancreatic duct or associated ductal branches, with consequent leakage of pancreatic ductal fluid and parenchymal secretions. Therefore, the cyst is typically filled with bicarbonate-rich and high amylase content fluid with inactivated pancreatic enzymes. Although there is certainly a moderate amount of microscopic debris and inflammatory exudates within the typical PS, there should be little to no macroscopic debris or solid component present. The fluid typically collects in the lesser sac and, over time, develops a well-formed capsule that can be distinguished from a true cyst by the lack of an endothelial lining. Interestingly, the incidence of PS is higher with alcoholic pancreatitis versus gallstone related and other causes. Whether this is due to a true pathophysiologic difference between these types of pancreatitis or to confounding factors including higher severity and recurrence rates with alcohol-induced pancreatitis is unknown.

Unlike necrotizing pancreatitis and WON where the risk of infection is extremely high (30%–70%), infection of a PS is rare. In most cases where infection does occur, it is secondary to percutaneous/endoscopic instrumentation of the PS or adjacent pancreas, or in the presence of associated pancreatic necrosis that was initially not recognized or that represents progression of disease from IEP to NEC. Unlike a noninfected PS, infected pseudocysts are rarely asymptomatic and will typically manifest local signs of inflammation, a relatively rapid increase in the size of the PS, and systemic signs of sepsis if not promptly addressed.

Finally, there are relatively rare scenarios where PS may be seen in association with necrotizing pancreatitis, and it is important to be able to clearly differentiate this from walled-off necrosis. This usually happens as a delayed complication following the necrosis of a segment of pancreas or following endoscopic/surgical debridement of a segment of the pancreatic body or tail, and with a persistent pancreatic ductal leak leading to PS formation. In these cases, the diagnosis of PS is made based on the absence of any solid or necrotic components of the fluid collection and is purely related to the ductal leak and not active pancreatic necrosis. Among the most challenging of these cases is the patient with a "disconnected duct" syndrome, caused by necrosis of the mid-body segment of the pancreas resulting in an essentially free-floating distal pancreatic body/tail segment and open ductal system that is no longer in continuity.

INITIAL PRESENTATION AND EVALUATION

Clinical Evaluation

As described in the preceding sections, the underlying etiology and presenting symptoms or complaints of patients with PS are highly variable. There are essentially no symptoms or examination findings that are specific to PS, and the majority of patients will have either minimal or no symptoms. If symptoms are present, they most commonly will feature vague upper abdominal and/or back pain, abdominal fullness or bloating, early satiety, or pain shortly after meals, or less commonly symptoms of gastric outlet obstruction. More acute presentations featuring concerning abdominal exam findings and abnormal hemodynamics are uncommon, and usually only seen in cases of infection of the PS (pancreatic abscess) or in PS-related hemorrhage. In many cases in current practice, the diagnosis of a peripancreatic fluid collection is made based on either screening or surveillance radiographic imaging studies. There are often alone as part of the workup for an identified episode of severe acute pancreatitis or for persistent symptomatology concerning for a possible PS or other local complication associated with acute or CP, or pancreatic trauma. Elevated serum amylase levels are seen in approximately 50% of patients with PS and are often mistakenly attributed to "recurrent pancreatitis" or to failure of resolution of the index episode.

Similar to the physical examination, there are no patient history questions that are high yield or specific for the diagnosis of PS. However, the history can be critical in identifying the likely etiology and in narrowing down the differential of a pancreatic/peripancreatic cystic mass identified on imaging. These questions should focus on the timing of any current or prior episodes of pancreatitis or acute abdominal pain episodes, symptomatology consistent for CP, any prior major abdominal trauma, and then common etiologic factors for pancreatitis including alcohol use, biliary disease, and medications. Patients with a possible PS who have no history of acute/CP episodes or symptoms (or trauma) should prompt consideration of an alternative diagnosis of cystic neoplasm of the pancreas. However, up to 15% of those with PS have no clearly identified antecedent pancreatitis episode or trauma, and a significant percent of pancreatic cystic neoplasms may initially present as an episode of acute pancreatitis. The correct diagnosis can usually be made using a combination of patient history and findings on imaging studies (as outlined in the following section), and less commonly may require percutaneous or endoscopic evaluation with fluid sampling and/or biopsy. Signs and symptoms of pancreatic insufficiency should also be elicited, as this may significantly impact surgical management decisions involving pancreatic resection.

Diagnostic Imaging for PS

Abdominal radiologic imaging with CT and/or MRI has become the standard for evaluating the patient with a known or suspected PS, and for surveilling patients to determine resolution versus persistence of the PS (Fig. 2). In addition to providing critical information about the size, location, and characteristics of the PS, these studies allow for evaluation of the local anatomy to guide any planned intervention, help to differentiate PS from other cystic neoplasms, and can identify any major associated pancreatic abnormalities that may drastically alter the treatment plan. In particular, CT scan is highly accurate for identifying pancreatic necrosis and for differentiating a true PS from necrotizing pancreatitis with walled-off necrosis. CT scan is also the modality of choice for surveillance of an identified early peripancreatic fluid collection to evaluate for resolution versus progression to a PPC, or to assess resolution versus progression to a known PS. It is particularly important for the surgeon to integrate the patient history and carefully review the CT scan characteristics to differentiating true PS from WON or other diagnoses as we continue to see the term pseudocyst erroneously applied as a catch all diagnosis in radiologic reports. Although transabdominal ultrasonography has little role in the initial diagnostic imaging for PS, it can be useful for characterization and serial surveillance imaging in patients with a known PS and to avoid the need for multiple repeat CT or MRI scans.

The role of MRI with cholangiopancreatography (MRCP) as an alternative or complementary study has also increased over time because of the improved ability to evaluate details of the pancreas and biliopancreatic ductal system compared with CT. This can provide critical information that will significantly alter the management, including signs of CP with ductal strictures and dilation, ductal communication with the PS, pancreatic atrophy or calcification, disconnected duct anatomy, and signs suggestive of cystic neoplasm or malignancy rather than PS. In the past, many surgeons advocated for routine endoscopic retrograde cholangiopancreatography (ERCP) in these patients to assess the ductal anatomy and to demonstrate any patient communication between the main pancreatic duct and the PS cavity. We have found that the detail and reliability of MRCP evaluation of the ductal system has supplanted the need for routine ERCP, and that an MRCP will often be requested by most pancreatologists before proceeding to ERCP. In cases in which MRCP is not available or indeterminate, or has identified a ductal abnormality requiring further delineation or intervention, the patient should usually proceed to ERCP for definitive delineation of pancreatic ductal anatomy and any communication with the PS. In addition to being diagnostic, ERCP can provide adjunctive or even definite

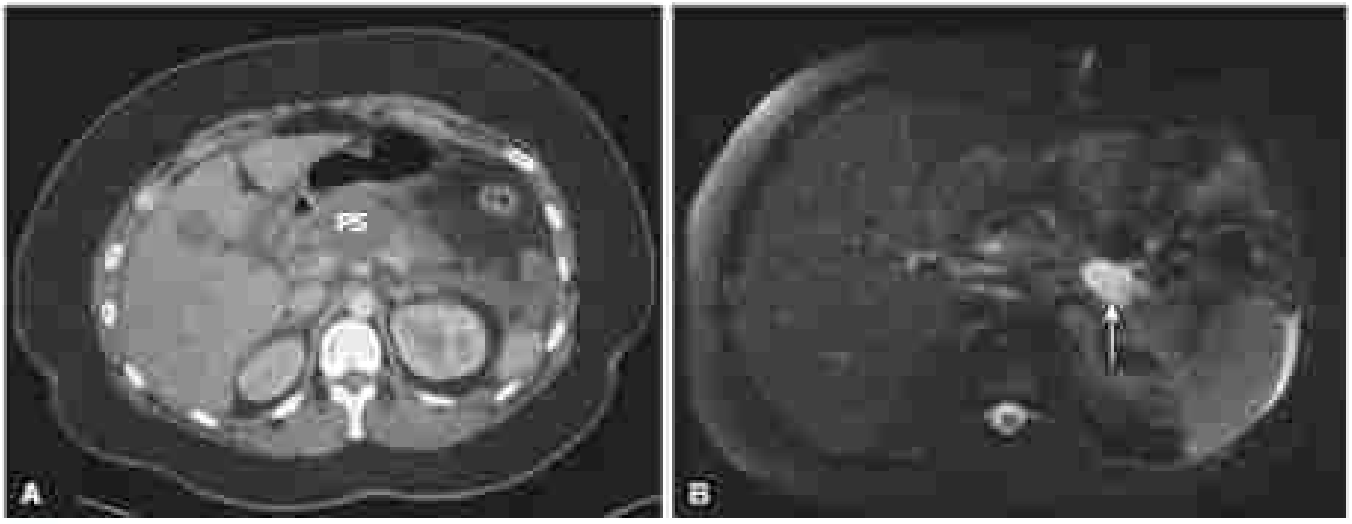

FIG. 2 (A) Computed tomography scan demonstrates a small pseudocyst in relation to the mid-body of the pancreas. (B) Magnetic resonance imaging with T2-weighted imaging shows round and homogeneously enhancing lesion (arrow) in the distal pancreatic body consistent with a pseudocyst. PS, pseudocyst.

TABLE 1 Comparison of Characteristics of PS, WON, and Cystic Neoplasms of the Pancreas

	PS	WON	Cystic Neoplasm
History	Acute HP episode or trauma	Acute NP episode	No prior pancreatitis or acute mild episode
Timing	>4 weeks from HP event	>4 weeks from NP event	Mature cyst present at initial imaging
Symptoms	Minimal to asymptomatic	Systemically ill/sepsis	Minimal to asymptomatic
CT appearance	Round/oval, well formed wall, no debris/septations	Irregular, thick wall, debris, loculations, associated pancreatic necrosis	Irregular, multiple septations, dilated main pancreatic duct, duct wall nodules (IPMN)
Pancreas involvement	Extrapancreatic	Extrapancreatic	Intrapancreatic
Usual location	Body and tail	Body and tail	Pancreatic head (IPMN), body/tail (MC and IC)
Cyst wall	Thick, no epithelialization	Very thick, no epithelialization	Epithelialized cyst wall
Cyst fluid	High amylase, low CEA, no mucin, no epithelial cells	High amylase, low CEA, no mucin, no epithelial cells	Low amylase, high CEA, mucin (IPMN or MC), epithelial cells
Malignant potential	No	No	Yes, highest for IPMN

CEA, carcinoembryonic antigen; HP, interstitial edematous pancreatitis; IPMN, intraductal papillary mucinous neoplasm; MC, mucinous cystic neoplasm; NP, necrotizing pancreatitis; PS, pseudocyst; SC, serous cystic neoplasm; WON, walled-off necrosis.

therapy via balloon dilation of ductal strictures, stenting across pancreatic ductal defects, or providing internal drainage of the PS by transpapillary stent placement. Endoscopic ultrasound (EUS), either alone or in conjunction with ERCP, is an increasingly used modality that can provide additional detailed pancreatic and ductal anatomy information and ultrasound-guided cyst fluid sampling or tissue biopsy. This is most commonly indicated when there is concern that the PS may in fact be a pancreatic cystic neoplasm, and in particular with concern for a possible intraductal papillary mucinous neoplasm (IPMN). In this setting, EUS has a reported sensitivity of up to 90% and specificity approaching 100% and can also reliably distinguish benign from malignant lesions. Findings consistent with an IPMN or other cystic neoplasm on ERCP or EUS include mucin extruding from the ampulla, hypervisible nodules in the duct wall, cyst septations, cyst fluid with mucin or elevated CEA, and epithelial cells on cytology or needle biopsy.

Differential Diagnosis

As should be obvious from the preceding material, one of the most critical components to assessing these lesions and determining the optimal management strategy is to narrow down the differential diagnosis to the correct conclusion. Of utmost importance is not taking a radiologic report stating "pancreatic pseudocyst" at face value and assuming that is the correct diagnosis. Fortunately, the differential is usually limited to only several likely possibilities, and these can readily be discerned by careful review of the history, imaging findings, and select use of additional diagnostic modalities such as ERCP or EUS. The potential diagnoses in these cases usually consists of PS versus walled-off necrosis or a cystic neoplasm of the pancreas, and Table 1 lists some of the key factors and diagnostic criteria that can be helpful in making the correct diagnosis. However, it must be emphasized that very few of these criteria are absolute, and individual factors should not be considered in isolation but rather in relation to one another to

correct diagnosis. One example of this is the common pitfall that a cystic mass in a patient with a current or recent history of acute pancreatitis is likely to be a PS, but epidemiologic studies have demonstrated that 20% to 30% of cystic neoplasms may initially present as an episode of acute pancreatitis. However, unlike PS, which takes weeks to mature, cystic neoplasms are fully formed with a mature cyst wall on the initial imaging studies done at the time of admission or within the first several days. This should prompt additional diagnostic evaluation to evaluate for an IPMN or other cystic neoplasm, and to ensure that a malignant or premalignant lesion is not written off as a PS. Fig. 3 shows side by side examples of characteristic cross-sectional imaging appearance and features of PS versus WON versus a cystic neoplasm (IPMN).

Ductal Evaluation

A key component of the assessment and deciding on the optimal management strategy for PS is an understanding of the interplay between the pancreatic ductal anatomy or associated anomalies and the likely response of the PS to specific interventions. In discussing this in teaching conferences, a standard assertion is that after a PS is identified on cross-sectional imaging an ERCP should be performed to determine "if it communicates with the pancreatic duct" (Fig. 4). However, actual practice is not that straightforward, and has also evolved significantly as noninvasive imaging of the ductal anatomy has improved dramatically. By definition, if the lesion is a true PS, then it either has a communication with the pancreatic ductal system, or it had one that has subsequently sealed. In addition to the issue of an active communication with the duct, other ductal abnormalities associated with pancreatitis that can be seen with PS are critical to delineate. These include the disconnected duct syndrome described previously, ductal stricture with obstruction, and irregular dilation or the string of beads ductal appearance consistent with CP. A useful system for categorizing the duct anatomy and anomalies associated with a PS has been described by Nealon and colleagues (Fig. 5). This ductal characterization is not only important for planning, but is also has major implications to selecting the appropriate intervention and in the risk of failure or complications following intervention. The ductal anatomy can besides be categorized as type I to type IV, and then within each type can be subcategorized (using "a" or "b") by whether a demonstrable connection with the PS is present or absent.

MANAGEMENT AND INTERVENTIONS

Arguably, the most important distinction in selecting the optimal management strategy and intervention for PS is the presence or absence of associated symptomatology. We generally concur with the recommendations from the 2013 evidence-based guideline on acute pancreatitis by the American College of Gastroenterology, stating: "Asymptomatic pseudocysts and pancreatic and/or extrapancreatic necrosis do not warrant intervention regardless of size, location, and/or extension (moderate recommendation, high quality of evidence)." However, there are exceptions to this rule such as the stability rule on a cystic neoplasm, rapidly enlarging PS, and patients in high-risk occupations or locations where immediate medical attention will not be readily available. In addition to the lower likelihood of spontaneous resolution, the risk of subsequent complications such as rupture or infection are higher in larger lesions (>10 cm) and therefore the decision for intervention versus observation should be individualized to each patient. The oft-quoted "rule of nines" that intervention is indicated for PS larger than 6 cm and persisting longer than 6 weeks should largely be abandoned in favor of a more individualized and nuanced approach as outlined here.

For symptomatic PS or those associated with pancreatic or pancreatic ductal pathology that requires intervention, there are now a wide variety of options that range from minimally invasive endoscopic or percutaneous interventions to major open surgery. Key factors in selecting the optimal intervention include not only

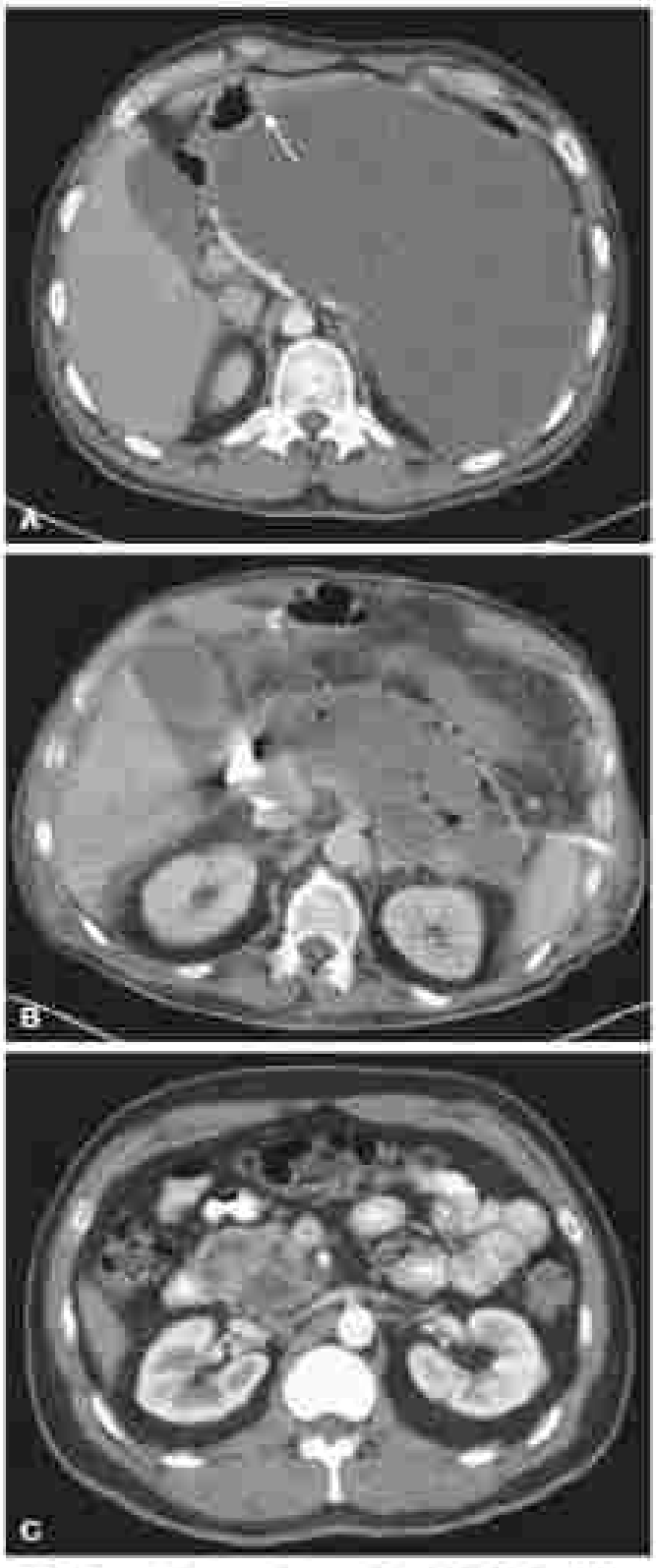

FIG. 3 Characteristic computed tomographic imaging findings for (A) large cystic mass displaying stomach (arrow) with mixed, regular shape and solid components consistent with pseudocyst, (B) irregular cystic fluid collection with debris and air consistent with walled-off necrosis (C) irregular septated cystic mass in head of pancreas consistent with a cystic neoplasm.

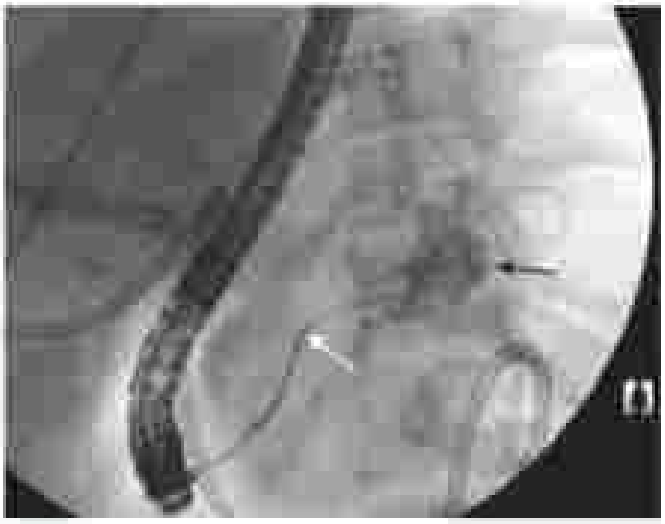

FIG. 4 Endoscopic retrograde cholangiopancreatography in a patient with a pseudocyst demonstrates normal main pancreatic duct (white arrow) with distal communication into pseudocyst cavity (black arrow).

the individual procedure's efficacy and complication profile, but also the likelihood of recurrence or need for multiple interventions. In addition, many of these options, particularly some of the advanced endoscopic interventions, are technically difficult and require a significant level of advanced skills and comfort by the gastroenterologist or surgeon. We have found that in many review papers or chapters about PS, these options are all laid out as if they are all routinely and equally available, whereas in reality they may be limited to select settings (urban, high volume, academic), and either patient transfer or proceeding with an alternative intervention must be decided.

Percutaneous Drainage

Image-guided percutaneous drainage (PD) is among the least invasive of the available options for PS, but it should be used in only very specific scenarios as the primary intervention. Although PD can usually achieve complete cyst drainage/decompression, it is associated with a higher rate of treatment failure and PS recurrence, as well as the complication of a persistent pancreatic fistula if used in the setting of a patent communication between the PS and the pancreatic ductal system. In a large national study of more than 14,000 patients comparing PD with open surgery for PS, PD was independently associated with increased complications, PS recurrence, and mortality. However, this (and most) study suffers from significant selection bias, and it did not have an endoscopic intervention group for comparison. Another concern with performing PD, particularly for minimally symptomatic PS, is bacterial seeding and infection which then requires urgent drainage. Although there is a risk of converting a PS to a pancreatic abscess with any instrumentation or surgical intervention, the risk appears to be higher for percutaneous drainage versus most other endoscopic or surgical drainage procedures.

Percutaneous drainage of the PS also does nothing to address any proximal pancreatic duct pathology if present, and therefore we are concerned using PD as a primary therapeutic option only to the setting of a PS with a normal pancreatic duct and no communication (type Ia). When used in the setting of type II to IV pancreatic ductal anatomy, the reported failure rates of PD are high (50%–90%). However, PD may be indicated even in the setting of known ductal pathology as a temporizing and/or initial diagnostic maneuver. These scenarios would mainly include patients with severe physiologic disturbance or comorbid disease that are prohibitive for other more invasive interventions, or in patients with an acutely infected PS (pancreatic abscess). PD has also been proposed by some experts to help with the

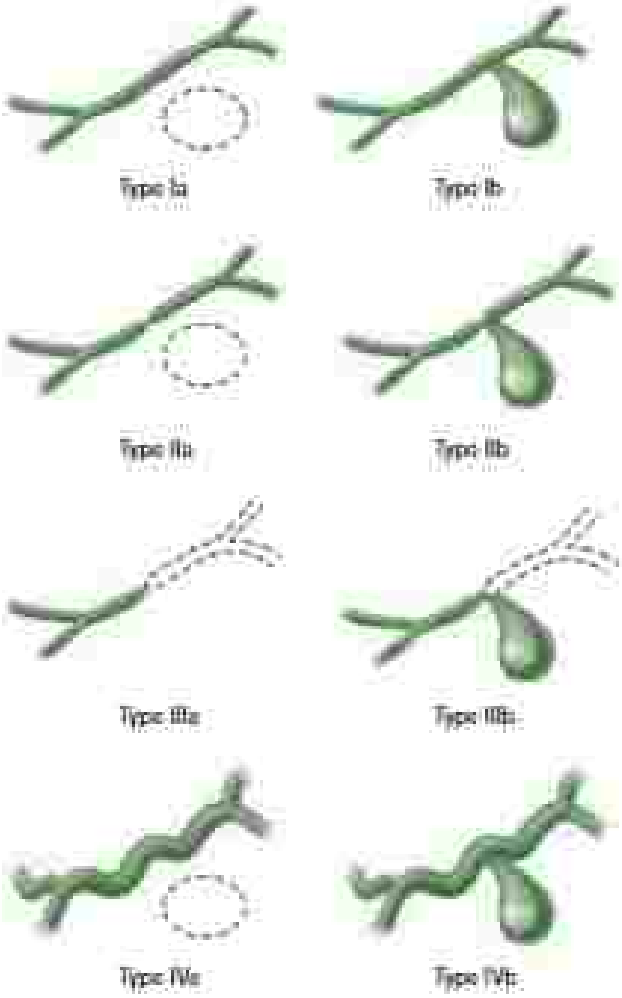

FIG. 5 Classification of associated pancreatic duct anatomy and anomalies: type I, normal ductal; type II, ductal stricture/obstruction; type III, disconnected distal duct; and type IV, irregular main dilation, common with chronic pancreatitis. Subgroups are identified by "a" for no ductal communication with pseudocyst and "b" ductal communication present. (From Adams MA, [illegible])

diagnosis and delineation of the distal pancreatic duct segment when imaging via standard modalities is not possible (i.e., the disconnected duct). In these cases, imaging of the distal pancreatic duct segment can be done with injection of contrast via the percutaneous drain under fluoroscopy, which can aid with characterization of the disconnected ductal segment and planning for the optimal endoscopic or operative intervention.

Endoscopic Interventions

Endoscopic techniques, equipment, and experience with both diagnostic and therapeutic interventions for PS have advanced dramatically over the past decade, and are now arguably the mainstay for management of most uncomplicated PS. In addition to being less invasive than surgical drainage procedures, endoscopic techniques can be used to simultaneously address both drainage of the PS and many of the associated pancreatic ductal lesions or injuries. Endoscopic drainage procedures for PS can be broadly categorized as either internal (via the pancreatic duct) or transmural (via the abutting stomach or

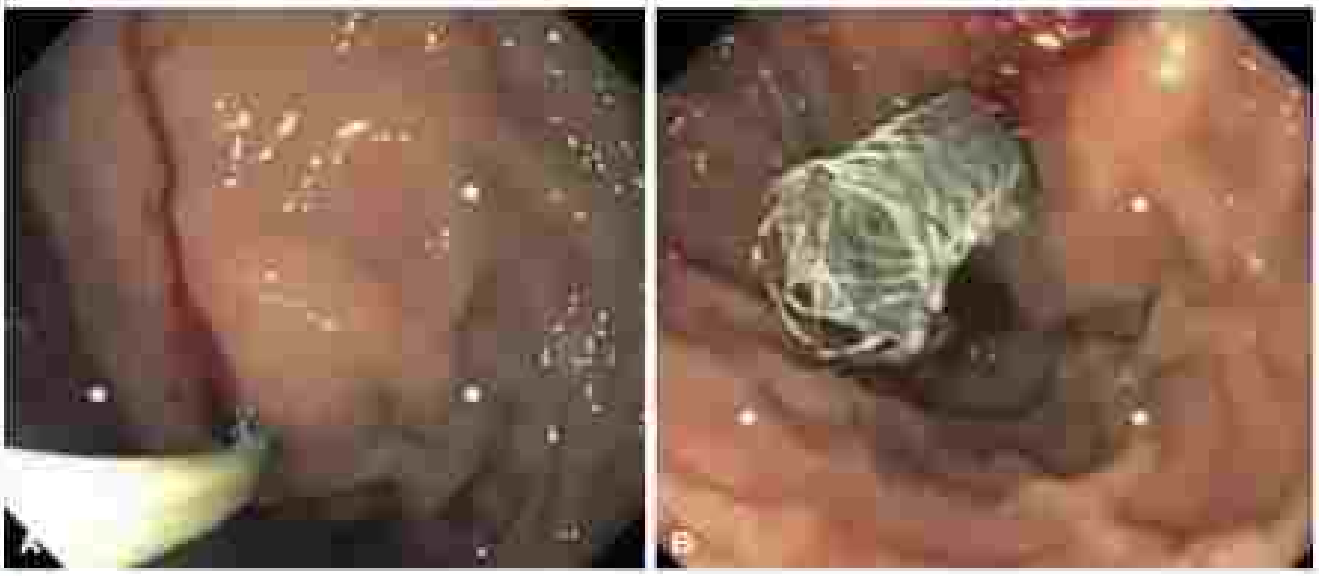

FIG. 8 (A) Endoscopic cystgastrostomy with cystgastric needle aspiration to confirm pseudocyst location, which is usually identified by the bulging of the posterior gastric wall. (B) A covered self-expanding metal stent is deployed to create and maintain the cystgastrostomy tract.

duodenum). In addition, these procedures can either be performed via standard endoscopy or with the addition of EUS guidance. Unlike percutaneous drainage, the presence of a known ductal communication with the PS (Fig. 4) is not a relative contraindication to internal or transmural endoscopic drainage procedures and can often be simultaneously addressed during the endoscopic drainage procedure.

An internal endoscopic PS drainage procedure refers to accessing and transpapillary stenting of the main pancreatic duct to allow internal drainage of the PS fluid back into the duct and duodenum. This obviously is only applicable to PS with a clearly identified and patent communication with the pancreatic ductal system and without proximal obstruction or discontinuity of the duct and is most suitable for the type IIa or IIb duct (Fig. 5). Although this can also be effective for the type IVb duct, there is a higher recurrence rate and likely continued severe symptomatology related to the accompanying CP that should be addressed as outlined below. For the type IIIb duct (disconnected duct), this is usually not a viable alternative because the duct is in discontinuity. There are published descriptions of attempting blind or image-guided stent placement across the defect, or alternatively accessing the distal duct segment through the gastric wall under EUS guidance and placing a transgastric stent. However, these advanced endoscopic procedural skillsets are relatively uncommon and it does not address the long-term problems of the disconnected duct and the isolated distal pancreatic segment.

Endoscopic transmural drainage procedures have become increasingly common, and in many centers have largely replaced surgical drainage for uncomplicated PS or in patients who have prohibitive risk factors for surgical intervention. These are done by creating a wide communication between the PS and the lumen of either the stomach (most common) or duodenum (less common). This is typically done in sequence by: (1) endoscopic inspection of the gastric lumen to identify the site of "bulging" of the posterior wall due to extrinsic compression from the PS, (2) needle aspiration to confirm the location (Fig. 6A), (3) creation of a small gastrotomy into the PS via needle knife, (4) balloon dilation of the tract, and (5) placement of either multiple small double pigtail stents or a single larger self-expanding covered metal stent (Fig. 6B). Tissue from the cyst wall should be collected for pathologic evaluation to definitively rule out a cystic neoplasm or malignancy. In select cases of larger PS or with significant debris present, a nasocystic drain may be left behind for continued cavity irrigation and drainage. Prior or simultaneous ERCP is performed if there is a patent ductal communication or a proximal pancreatic duct stricture requiring transpapillary stenting or other endoscopic intervention to optimize internal drainage and prevent PS recurrence. These stents or pigtail catheters should be left in place for at least 4 weeks because recurrence has been found to be significantly higher with stent/drain removal before 4 weeks. Repeat imaging should be performed to document successful drainage and resolution of the PS prior to stent or drain removal (Fig. 7). A small randomized trial and multiple non-randomized series have demonstrated improved outcomes with endoscopic versus surgical PS drainage, although the incidence of requiring additional interventions is higher. In addition, these studies used open surgery as the comparison group, and it is unclear if different results will be seen with the increased utilization of minimally invasive surgical approaches to PS.

EUS is an important adjunct to these procedures as it can help exactly localize the PS and guide the drainage procedure, assess for complete evacuation and collapse of the PS, and assess for any additional anatomic abnormalities or signs of an alternative diagnosis. There have now been two randomized trials demonstrating the superiority of EUS-guided versus standard endoscopic PS drainage, and we recommend maximal use of this adjunct if available. This is particularly critical if endoscopic cyst-duodenostomy is being performed because there will often not be a visible bulge to locate the optimal puncture site and EUS can readily identify critical structures including the pancreatic duct and common bile duct to avoid iatrogenic injury.

It is important to both the safety and success of endoscopic transmural drainage procedures that enough time has lapsed to allow the PS to mature and have a well-formed capsule that is adherent to the stomach or duodenum. In addition to simply estimating the time interval, it is critical to review the preoperative cross-sectional imaging for signs of an adequately thick and well-formed PS wall, and to assess the location and anatomic relationship of the PS to the adjacent stomach or duodenum. A PS that is not directly adjacent to and abutting the gastric or duodenal wall is generally not a candidate for safe transmural drainage and usually will require a surgical drainage procedure. Optimal endoscopic candidates should also have a PS wall thickness of between 3 and 10 mm, with a common recommendation for surgical drainage in PS with wall thickness greater than 10 mm.

Surgical PS Drainage Procedures

With the marked improvements in endoscopic equipment, techniques, and experience over the past several decades, the need for operative

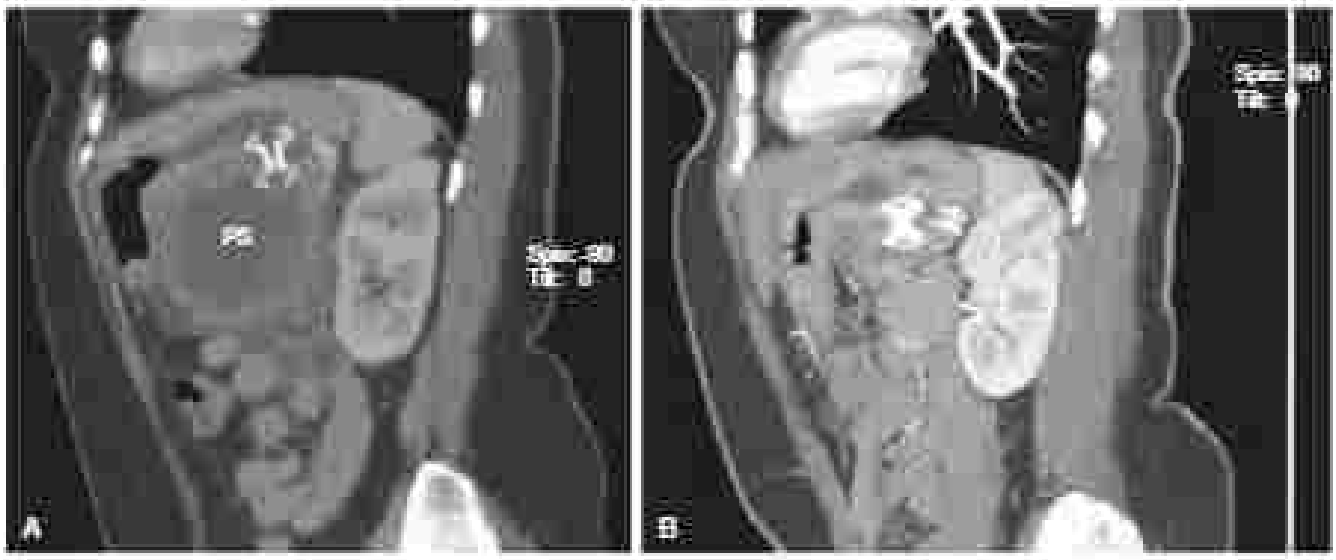

FIG. 7 (A) Computed tomography (CT) scan after endoscopic cystogastrostomy shows stent in good position between the stomach and pseudocyst. (B) CT scan 4 weeks later shows successful cystic drainage with collapse of pseudocyst (PS).

intervention for PS has decreased significantly. However, surgical interventions remain a key and important aspect of PS management and are still frequently required in cases of PS with complex associated ductal or pancreatic pathology. In addition, operative drainage or resectional procedures are still required in cases of failure of percutaneous or endoscopic treatments and may also be used more frequently in settings where there is low access to advanced therapeutic endoscopists. It is not uncommon to see patients who have undergone multiple percutaneous and/or endoscopic attempts at drainage and associated complications prior to any surgical referral. In cases where there has been clear failure or recurrence after an adequate endoscopic drainage procedure, we encourage an initial consultation with an experienced surgeon for input on the pros and cons of additional endoscopic or percutaneous attempts versus prompt surgical intervention.

Surgical treatment for PS typically involves creation of an anastomosis between the cyst wall and the gastrointestinal tract to facilitate drainage and decompression of the fluid, any debris, and obliteration of the cavity. The two most common procedures for accomplishing this are cystogastrostomy and cystojejunostomy, and less commonly cystoduodenostomy, which is typically reserved for smaller PS in the head of the pancreas. Although these operations have traditionally been performed as an open procedure, they can now be readily accomplished using minimally invasive techniques such as laparoscopy and more recently robotic assisted surgery. Although this discussion is often presented as either endoscopic or surgical therapy, the optimal results are obtained with a combined multimodality approach (if needed) to address both the PS and the underlying etiology, particularly for PS with an identified ductal communication. Most commonly this means confirming surgical drainage with endoscopic interventions such as ERCP and pancreatic duct stenting and/or stricture dilation to optimize transpapillary drainage. In highly select cases of large PS that are very well encapsulated and not adherent to surrounding structures, the cyst can be excised en bloc with concomitant ligation or obliteration of any patent fistula with the pancreatic duct.

Selection of the optimal drainage procedure should be based on careful review of the anatomic relationships identified on preoperative cross-sectional imaging, and with consideration of any factors, such as gastric varices or prior gastrointestinal surgery, that would dictate a different surgical plan. Because the majority of PS is limited to the lesser sac and directly abuts the posterior wall of the stomach, cystogastrostomy is the simplest and most commonly performed transmural drainage procedure. Advantages of this approach include minimal manipulation of the gastrointestinal tract, the avoidance of any direct dissection into the lesser sac and pancreas, and shorter operative times. Disadvantages include the usual need for an anterior gastrotomy to access the site and a possibly increased risk of infectious and bleeding complications versus cystojejunostomy, although this continues to be debated in the literature. We have found surgical cystogastrostomy to be a safe and effective intervention, and with a complication profile similar to cystojejunostomy.

Cystogastrostomy is most commonly performed using a transgastric approach through the anterior gastric wall (Fig. 8). For open cystogastrostomy, a longitudinal gastrotomy is made in the anterior wall of the mid stomach and centered as much as possible over the PS. This incision will be more forgiving if extensions proximally and/or distally is needed and can be easily closed in longitudinal or transverse fashion to avoid narrowing the gastric lumen. Stay sutures on each edge of the gastrotomy are helpful to retract the edges and widely expose the posterior wall of the stomach. Inspection typically reveals an obvious bulge at the location of the PS, but if unclear then needle aspiration or intraoperative ultrasound can be performed to confirm the location. Entry into the PS through the posterior stomach wall is then made and the cyst fluid and any debris are suctioned. An adequate anastomosis is then created between the PS wall and the posterior stomach which can either be handsewn or stapled. We prefer a stapled anastomosis for both speed and simplicity. A fragment of the cyst wall should be excised for pathologic analysis, and any remaining fluid or debris is evacuated through the wide anastomosis. The anterior gastrotomy can then be closed with either a running suture or stapled. Less commonly, cystogastrostomy can be performed via an exogastric approach by direct exposure of the PS in the lesser sac and then direct creation of the anastomosis to the posterior wall of the stomach. This is typically reserved for smaller pseudocysts that make transgastric localization more difficult, and that can be readily exposed without risk of cyst rupture or damage to the stomach or pancreas.

Minimally invasive cystogastrostomy typically uses the same basic sequence to approach the pseudocyst and create the anastomosis (Fig. 9A). Although either a handsewn or stapled anastomosis (Fig. 9B) can be performed laparoscopically, the stapled approach is much simpler versus laparoscopic intracorporeal suturing for both the anastomosis and the anterior gastrotomy closure. An alternative technique uses a transgastric laparoscopic approach in which the trocars are inserted into the gastric lumen, which is then insufflated to allow a working space to perform the cystogastrostomy. Either balloon tipped trocars

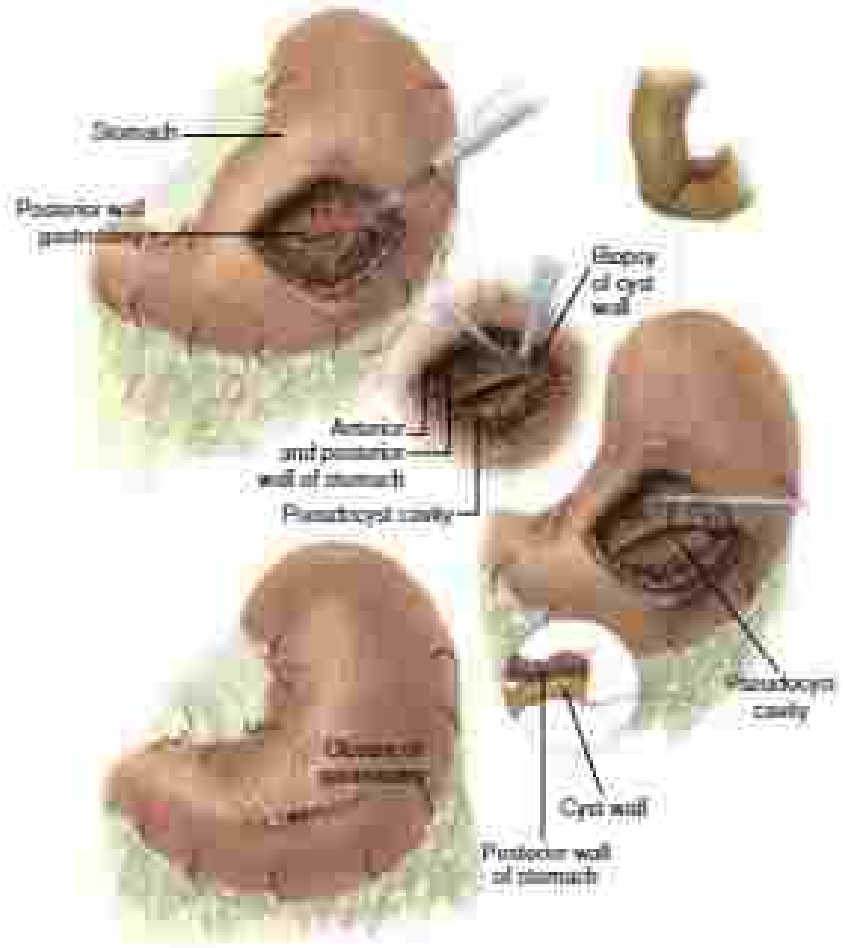

FIG. 8 Surgical cystogastrostomy procedure showing anterior and posterior gastrostomies to expose and then enter the pseudocyst (upper left and inset), creation of full-thickness cystogastrostomy anastomosis (middle), and closure of anterior gastrostomy (bottom).

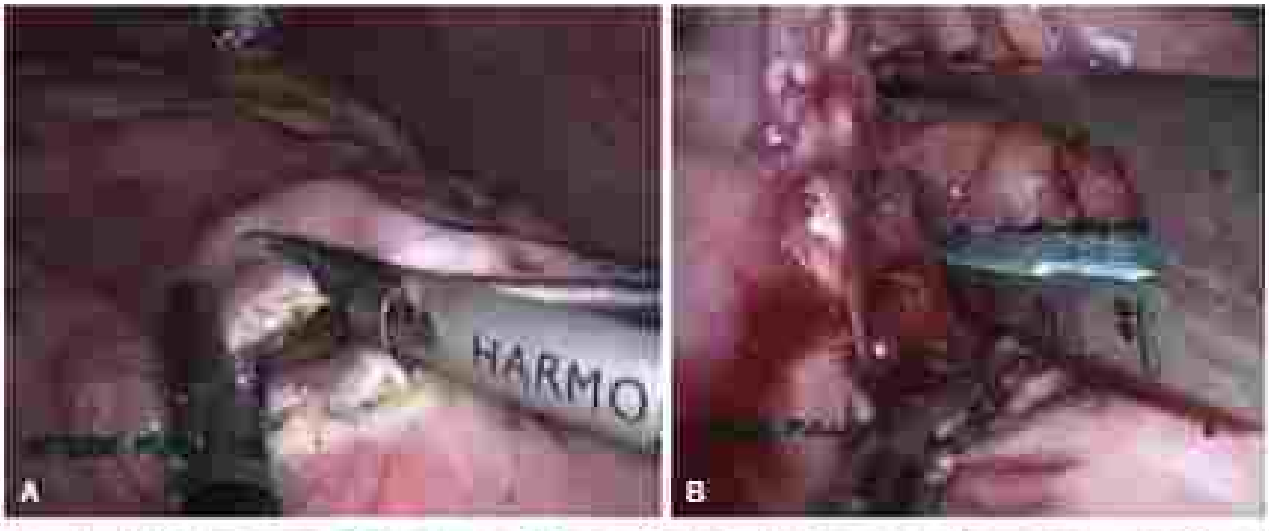

FIG. 9 Laparoscopic or robotic-assisted surgical cystogastrostomy is performed by (A) making an anterior enteral gastrostomy to expose the posterior gastric wall and (B) insertion of linear stapler with one end into pseudocyst cavity and the other end in the stomach to create the cystogastrostomy anastomosis.

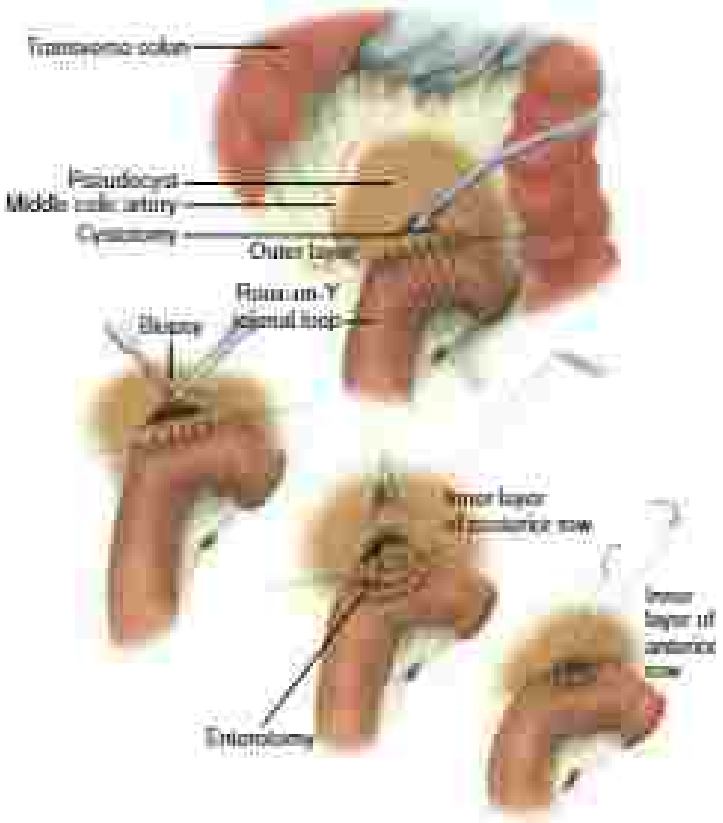

FIG. 18 Surgical cystojejunostomy between a jejunal Roux limb and a large pseudocyst bulging into the transverse colon mesentery (top) with completion of full-thickness posterior layer (middle two panels) and then completion of anterior layer (bottom). (From Isaac SM, Ho Q, Bailey J, Kothari SN, Kothari AN. Surgery of the Abdomen, 3e, 3 Volume Set. Elsevier; 2019.)

or anterior gastric stay sutures at each trocar site are used to prevent the trocars from dislodging and to maintain gastric insufflation. More recently, these procedures have been described using a robotic surgery platform, which are nearly identical to the laparoscopic approach but with much better camera optics and visualization, and with greater ease of intracorporeal robotic assisted suturing.

Cystojejunostomy is the second most commonly performed drainage procedure for PS and offers similar efficacy and success rates as cystogastrostomy. This is typically performed using a proximal segment of jejunum that reaches easily to the area of the PS, and then constructed as a Roux-en- with the cystojejunostomy to the Roux limb and then a jejunojejunostomy to restore continuity (Fig. 18). Cystojejunostomy is clearly indicated for pseudocysts that are not abutting the stomach or duodenum or are located outside of the lesser sac, but can be used for transmural drainage of almost any PS. Advantages over cystogastrostomy include the ability to drain PS in almost any abdominal location and the ability to drain multiple PS, whereas disadvantages include the need for two anastomoses and the more technically demanding nature of the anastomosis. Unlike the cystogastrostomy, it does usually require exposure and visualization of the PS wall for at least enough length to create an anastomosis. Technically, the anastomosis is similar to the cystogastrostomy, and can be stapled (circular or linear) or handsewn. There are some data suggesting that a stapled cystojejunostomy is associated with increased complications (bleeding and infection) compared with a handsewn method, although the series are relatively small and underpowered. The most important factor for technical success with cystojejunostomy is waiting until a thick and well formed wall is present that can readily hold sutures and support an anastomosis. If a linear stapled anastomosis is performed, then particular attention should be paid to closure of the common enterotomy to avoid narrowing of the intestinal lumen which can lead to failure to resolve the PS or to an anastomotic leak.

Surgery for PS With Major Pancreatic or Ductal Pathology

A distinction of successful management and long-term resolution for PS is that the evaluation and management strategy must also focus on identifying critical, related pancreatic or ductal disease that requires concomitant intervention. Several series have shown that failure and recurrence rates are high when a drainage procedure alone is performed in patients with major ductal strictures or obstruction, and that continued symptoms are the rule in patients with PS associated with CP. In these cases, we recommend approaching these scenarios with the mindset that the pancreatic/ductal pathology is the primary issue that requires intervention, and the PS is a secondary effect or manifestation that can only be resolved by treating the underlying cause.

For patients with disconnected duct syndrome (type III in Fig. 5) associated with mild body necrosis and loss of the central segment of the main pancreatic duct, surgical intervention should focus on either resecting drainage to the distal disconnected pancreatic segment or performing operative resection of that segment. Characterization of the distal pancreatic duct is important for preoperative planning, and often, an MRCP can be adequate. If not, then percutaneous drainage of the PS can be performed as an initial measure to decompress the PS and then to perform a fistulogram via injection of contrast through the drain. Surgical options then would include a PS drainage procedure alone (cystogastrostomy or cyst jejunostomy), restoration of pancreatic duct drainage via a pancreaticojejunostomy to the distal segment, or resection via distal pancreatectomy/splenectomy. Intraoperative decompression or excision of the PS is performed, but no formal PS drainage procedure needs to be performed. Deciding among these options is a complex and highly individualized process, and referral or consultation with an experienced pancreatic surgeon is strongly recommended. In addition to the anatomic considerations, a key consideration in the likelihood of postoperative pancreatic insufficiency or

diabetes with resection of the disconnected segment versus preservation and drainage. It is also important to clearly distinguish this patient population from the less common cohort who has a disconnected duct and distal segment resulting from a traumatic injury to the pancreas. These patients usually have an otherwise normal pancreas outside of the zone of injury, may have multiple associated injuries that impact the treatment plan, and will have a different risk/benefit ratio for operative drainage versus resection of the distal pancreatic segment.

These operations can be particularly difficult because the frequent presence of significant scarring, inflammation, and distorted anatomy, and may require opening the PS cavity to access the distal pancreatic segment. If drainage via pancreaticojejunostomy is selected, this should be done with a Roux-en-Y reconstruction and passage of the roux limb through a window in the transverse mesocolon. The type of anastomosis (duct to mucosa, intraluminal, lateral) will be based on the size of the duct, the presence of any strictures, the character of the pancreatic parenchyma (hard vs soft) and individual surgeon preference and experience. An alternative option that has been described is drainage into the stomach via a pancreaticogastrostomy. This option has the advantage of obviating the need for any small bowel manipulation and requires only one anastomosis instead of two. However, many surgeons have less familiarity with this type of anastomosis, and the inflammation of the posterior gastric wall from the pancreatitis and the PS often makes this option less feasible.

Resection of the disconnected pancreatic segment via distal pancreatectomy is the other viable option. Although at first glance this would seem to be the simpler and superior option versus a complicated drainage procedure and high-risk pancreatic anastomosis, resection may have significant longer-term adverse effects that must be considered. Although distal pancreatectomy is routinely performed for other indications (neoplasm, trauma) without significant concern for a functional impact, this should not be extrapolated to these scenarios. Among patients who have had a significant episode of necrotizing pancreatitis with loss of some or all of the tail pancreas (and likely dysfunction of the remaining pancreas), the impact of removing the disconnected distal pancreatic segment must be carefully considered. This can result in significant and lifelong problems, including pancreatic exocrine insufficiency and a high risk of new-onset diabetes or conversion of any insulin dependent diabetes to permanent insulin dependence. An additional concern with resection is the need for concomitant splenectomy, and the long-term risk of postsplenectomy infectious complications. Although spleen preserving distal pancreatectomy is routinely performed in other patient populations, in these scenarios, it is often not practical or possible because of the dense inflammatory and fibrotic changes that make it difficult and risky to attempt to separate the pancreas from the splenic artery and particularly the splenic vein. We advocate for resection in patients who have preservation of a significant portion of the proximal pancreas and no existing pancreatic exocrine or endocrine deficiencies, and where intraoperative inspection confirms that a safe mobilization and resection can be performed. Although this option is less ideal for most patients with pancreatitis-associated ductal loss, we consider distal pancreatectomy with or without splenectomy to be the better option for most patients with disconnected duct anatomy resulting from trauma.

The final cohort that must be clearly distinguished and approached differently are those with PS and symptomatic CP with associated irregular ductal dilation (type IV in Fig. 5). Longitudinal studies have demonstrated that spontaneous resolution of a PS in this patient population is significantly lower (<10%) than in PS associated with acute pancreatitis and the majority will have a patent communication between the PS and the pancreatic duct (type IVb). In addition to delineating whether a communication between the pancreatic ductal system and the PS is present, it is critical to not automatically attribute all existing abdominal symptomatology to the PS rather than the CP. In most cases in our experience, the common symptoms of abdominal pain, anorexia, nausea, and dietary intolerance are much more likely to be secondary to the CP than the PS. This is supported by published series showing that drainage of the PS alone in this setting has a high failure and recurrence rate, and also fails to relieve the major abdominal symptoms in the majority of patients. Thus, a comprehensive management plan that addresses both the PS and the CP, and that focuses on optimizing pancreatic ductal drainage, should be developed. ERCP with dilation and transpapillary stent placement may be effective for select patients, such as those with a focal proximal pancreatic duct stricture and distal dilation. However, for most patients with CP and more diffuse ductal pathology, endoscopic therapy has a high failure rate and limited durability and was found to be inferior to surgery in two randomized trials. The highest success rates for resolution of the PS and relief of the CP associated symptoms have been reported in association with surgical drainage or combined resectional drainage procedures for the CP. Once effective drainage or resection and drainage for the CP has been performed, the PS will typically resolve spontaneously.

SPECIAL SCENARIOS AND CONSIDERATIONS

Preoperative and Postoperative Concerns

There are a number of uncommon but significant associated problems or complications that may be seen in patients with suspected or proven PS that may be directly related to the PS or may be coexisting but not causally related. Infection of the PS, which is then more accurately characterized as pancreatic abscess, typically occurs after some type of instrumentation of the lesion and should prompt immediate source control via percutaneous or endoscopic drainage. Bleeding from the PS is another complication that can occur spontaneously or following a drainage procedure, and is usually from the splenic, gastroduodenal, or pancreaticoduodenal arteries. Emergent angiography and embolization are the preferred interventions, with overall poor outcomes reported with attempts at surgical hemorrhage control. Splenic vein thrombosis due to either the pancreatitis or the PS can result in gastric varices that may alter any treatment or intervention plan. This has traditionally been a relative contraindication to attempting endoscopic drainage, but safe endoscopic cystogastrostomy can be performed with EUS guidance to avoid any variceal vessels. The presence of gastric varices (on imaging or endoscopy) is also an indication for concurrent splenectomy with any operative procedure for the PS. Obstruction of the gastrointestinal tract (typically gastric or duodenal), bile duct, or pancreatic duct can occur from mechanical compression by the PS and represents an additional indication for intervention. However, this is relatively uncommon and should raise the concerns for an associated malignancy or for a benign intrinsic stricture as the true cause. Additional diagnostic workup (EUS/CT/MRI, MRCP) should be performed to better characterize the PS and ductal system rather than performing an immediate intervention that could compromise future options. Finally, the rupture of a PS may result in a picture of diffuse intraperitoneal free fluid (pancreatic ascites) that may be misinterpreted as evidence of diffuse hemorrhage or of ascites related to carcinosis. CT scan analysis of the fluid can usually distinguish blood from ascites, and the history and rapidity of accumulation of the ascites can usually distinguish pancreatic from hepatic sources. Sampling of the fluid for analysis including an amylase level confirms the diagnosis. Because the fluid contains inactivated pancreatic enzymes, there is usually little to no associated abdominal pain, although subjective fullness, bloating, and discomfort can be seen. Urgent intervention for the ascites is not required, and the treatment plan should focus on management of the PS and pancreatic ductal system as outlined here.

Walled-Off Necrosis

Necrotizing pancreatitis with an associated mature, solid-debris–containing infection consistent with walled-off necrosis (WON) must be clearly distinguished from acute nonnecrotizing pancreatitis with subsequent PS formation (Fig. 3). This critical distinction should be made early in

the diagnostic evaluation and treatment planning phases because it will drive key decisions on the type and timing of interventions that will be markedly different versus those for a PS. The optimal approach for WON has evolved from major open surgical debridement to more minimally invasive options including video assisted retroperitoneal debridement (VARD) and endoscopic drainage with necrosectomy. The widely used step-up approach utilizes sequential escalating interventions starting with percutaneous drainage, drain upsizing, and then a VARD procedure if needed. The surgical step-up approach has been validated in the Pancreatitis, Necrosectomy Versus Step-Up Approach randomized trial to be superior to open necrosectomy, and a more recent randomized study found that endoscopic drainage and necrosectomy is equally effective but with less morbidity. We have not infrequently seen both the diagnostic and interventional approach for PS confused with that of WON, which then results in suboptimal outcomes and unnecessary or futile interventions. Among the key differences in approaches are (1) WON carries a much higher infection risk versus PS, (2) percutaneous drainage is usually the first intervention of choice for WON but not for PS, (3) surgical or endoscopic intervention for WON must include debridement of all necrotic pancreatic and debris whereas PS typically requires no debridement, and (4) a VARD procedure *or* the step-up approach is for WON and should not be used for PS.

CONCLUSIONS AND CRITICAL DECISIONS

The evaluation, diagnosis, and management options for pancreatic PS have evolved significantly over the past decade and can be expected to continue to evolve with improvements in imaging, endoscopic, and surgical techniques and technology. The optimal modern management of the patient with a suspected or proven PS involves a stepwise series of critical decisions as shown in Fig. 11 and starts with using the current terminology and definitions as outlined in the 2012 revised Atlanta classification system for acute pancreatitis. Among the most important of these is accurately diagnosing and characterizing any associated pancreatic ductal pathology which will frequently drive decisions on which intervention has the highest likelihood of success and when combined endoscopic and surgical interventions are indicated. Although the trends in the management approach to PS have moved toward expanded use of observation only, percutaneous, and endoscopic interventions, there remains a defined role and need for surgical interventions to select patients with more complicated PS or after failure of less invasive alternatives. Exciting advances in minimally invasive surgical equipment and techniques, including advanced laparoscopic and robotic surgery platforms, are now being applied to the management of this patient population and can be expected to reduce or eliminate much of the morbidity associated with traditional open PS surgery.

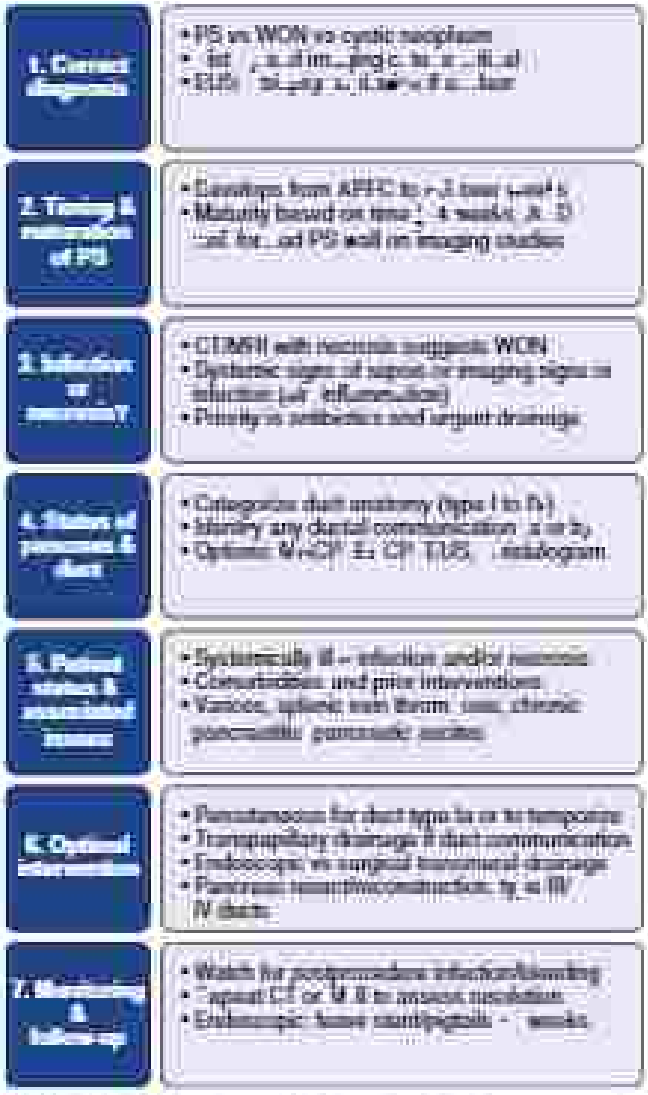

FIG. 11 Critical information and decision points for the management of pancreatic pseudocysts from initial diagnostic workup through postoperative care and follow-up. APFC, Acute peripancreatic fluid collection; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PS, pancreatic pseudocyst; WON, walled-off necrosis.

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Pancreatic Ductal Disruptions Leading to Pancreatic Fistula, Pancreatic Ascites, or Pancreatic Pleural Effusions

Roxanna L. Mansoori, MD, and Z. Jia Hines, MD

DEFINITIONS

Following is a list of terms commonly associated with pancreatic ductal disruption:

- **Acute peripancreatic fluid collection:** A fluid collection near the pancreas that occurs within the first 4 weeks after the onset of pancreatitis. This is to be differentiated from a pseudocyst that occurs later.
- **Pancreatic ductal disruption:** A disruption in the main pancreatic duct resulting in a disturbance of the flow of pancreatic juice from the upstream (body/tail) to the downstream (uncinate) portions of the pancreas. This often occurs as a result of pancreatic necrosis and is commonly found in the watershed neck portion of the pancreas where the splenic and pancreaticoduodenal arcades meet (Fig. 1A). When the ductal disruption is complete and at its most extreme, it will be evident on abdominal imaging, such as a computed tomography (CT) scan.
- **Pancreatic fistula:** A pancreatic fistula that communicates with the peritoneal cavity, usually beginning as a leak into the lesser sac. When a pseudocyst is also present, it is presumed that the leak is from the pseudocyst. This is typically well tolerated unless the pancreatic enzymes are activated, which can happen if the collection is secondarily infected with microorganisms.
- **Pancreatic ductal disruption:** Disturbance in any of the pancreatic ducts along the length of the main pancreatic duct or pancreatic duct branches. Disruptions may be demonstrated by imaging or is assumed to be present in the case of amylase rich fluid sampled from a drain or collection.
- **Pancreatic fistula:** Loss of pancreatic fluid through an area of ductal disruption out of the pancreas. A pancreatic fistula can develop to the intraperitoneal, retroperitoneal, or thoracic cavities and also to other organs or the skin.
- **Pancreatic necrosis:** An area of the pancreas that has lost the blood supply; this is diagnosed by contrast-enhanced CT scan as a lack of enhancement of a portion of the pancreas. When the necrosis is to the tissue outside of the parenchyma, it is termed peripancreatic necrosis. Clinically, the development of necrosis is important because this indicates a more severe condition with both local and systemic complications.
- **Pancreatic pleural effusion:** A leak of pancreatic fluid from a disrupted duct into either one of the pleural spaces. The leak will first communicate with the retroperitoneal cavity and then would connect into the thoracic cavity via the esophageal hiatus or directly through the diaphragm. A ductal leak near the portal vein would likely communicate with the right chest and a leak in the distal duct to the left chest.
- **Pancreatic pseudocyst:** A well-circumscribed intra- or peripancreatic fluid collection that forms from pancreatitis. A fluid collection is characterized as pseudocyst 4 to 6 weeks after an episode of acute pancreatitis.
- **Walled-off pancreatic necrosis:** A parenchymal or peripancreatic collection of fluid and necrotic tissue surrounded by a well-defined inflammatory wall occurring 4 to 8 weeks following pancreatitis.

CLINICAL PRESENTATION AND DIAGNOSIS

When to Suspect Ductal Disruption

Inflammation of the pancreas, whether from pancreatic pathology, pancreatic surgery, or trauma, can lead to a pancreatic ductal disruption. Although a certain amount of hyperamylasemia and/or abdominal pain can be normal and transient with pancreatitis or after surgery, persistent symptoms, or suspicious laboratory results after 1 week are concerning for a ductal leak. Often, the surgeon will be suspicious of this event after reviewing initial imaging. A certain level of ductal disruption can be expected when a patient is noted to have a peripancreatic fluid collection, abscess, pseudocyst, or pancreatic necrosis. After pancreatic trauma, grades III through V can be expected to develop a pancreatic ductal disruption and leak. High suspicion must also be maintained after a major pancreatic surgery and is a main reason for leaving a drain to control the leak.

Diagnosing a Ductal Disruption

Because pancreatic enzymes can be particularly caustic to the retroperitoneum and peritoneal cavity, prompt diagnosis and treatment of a pancreatic duct disruption is critical. The first step for diagnosis is a CT scan with intravenous contrast; this will often show a peripancreatic fluid collection or, in the case of a chronic condition, a pancreatic duct dilation. The location of a fluid collection may help discern the area of duct disruption. For example, ventral leaks often gather in the lesser sac, dorsal tail leaks into the retroperitoneum near the left paracolic space, and dorsal head leaks into the retroperitoneum near the right paracolic space. Given the enclosed space, these fluid collections are unlikely to cause peritonitis and instead often form pseudocysts.

Other initial imaging modalities include endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography. In the perioperative setting, drains are typically left in the vicinity of the surgery and comparing a drain with serum amylase level can aid in diagnosis. If no drain is present, fluid can be drained percutaneously under imaging guidance. When a fistula is present, the drain amylase is often more than or equal to three times the serum amylase.

A disrupted pancreatic duct can also present as a pleural effusion if pancreatic fluid leaks into the thoracic cavity. This can occur in the left chest from a disruption of the pancreatic body or tail and travel through the pleuroperitoneal foramina or hiatus to in the chest. Pancreatic fluid can also enter the right thorax with a disruption in the pancreatic neck or the dorsal pancreatic head and travel behind the hepatoduodenal ligament, also ultimately tracking up through the pleuroperitoneal foramina into the chest. When a leak is near the esophagus, pancreatic fluid can track up into the mediastinum. Studies have shown that patients who undergo early operative intervention tend to have earlier resolution of their pancreaticopleural fistula.

Persistent pancreatic fluid leakage requires drainage. Inadequate drainage can lead to pancreatic pseudocyst formation, erosion into surrounding structures such as blood vessels or organs, pancreatic necrosis, or communication with another body compartment such as the mediastinum, pleural cavity, or abdomen. Patients who are left untreated for prolonged periods may develop further pancreatic damage secondary to surrounding inflammation around the pancreas. This could begin a vicious cycle ultimately leading to sepsis and multisystem organ failure.

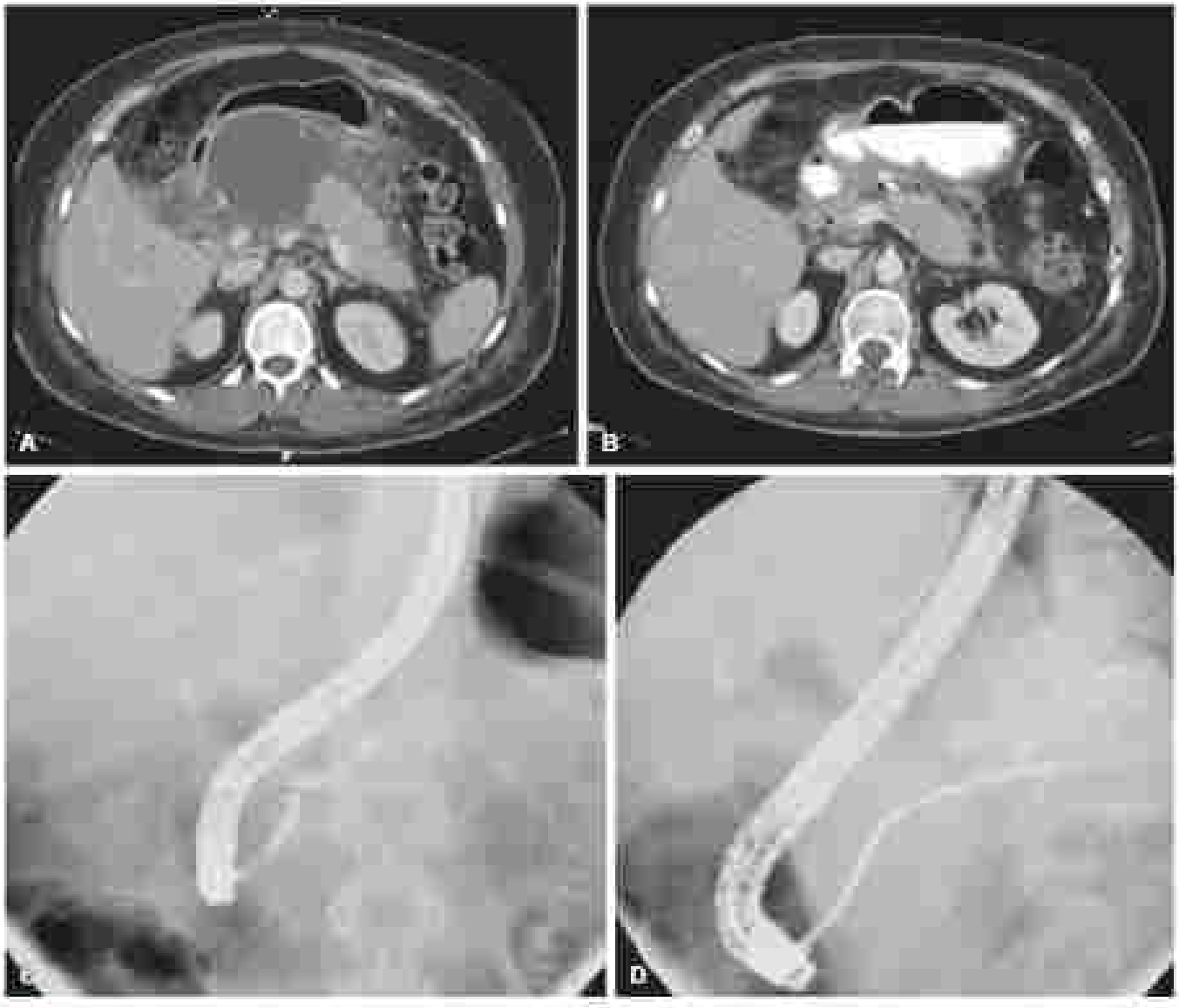

FIG. 1 (A) This patient, with severe acute necrotizing pancreatitis, developed sizeable and an acute peripancreatic fluid collection resulting in a disconnected pancreatic duct (B). Initial management was percutaneous drainage, which resulted in near-complete resolution of the collection but a persistent high-output pancreatic fistula. Endoscopic retrograde cholangiopancreatography revealed a disrupted duct in the neck of the pancreas (C) that was stented, resulting in resolution of the remaining collection and healing of the disruption (D).

TREATMENT

Percutaneous and Transgastric Catheter Drainage: Options

After maintaining a high index of suspicion in at-risk patients and locating a fluid-derived fluid collection on imaging, early drainage is imperative. Because the peripancreatic area is often very inflamed, these patients are a high surgical risk, and treatment should be as minimally invasive as possible to the stable patient. Percutaneous drainage is the gold standard for the treatment of fluid collections from pancreatic ductal disruption.

Percutaneous drainage is typically performed transabdominally via CT guidance through a window clear of major vessels, intestines, or organs. Drains are usually about 12Fr in diameter and can be upsized as needed; sometimes, multiple catheters are required to control the leakage. The drains are attached to a bag with external suction (such as an accordion bag or bulb) and should be flushed with 10 to 20 mL of normal saline multiple times per day to maintain patency. The size of the drained fluid collection will need to at first be frequently monitored to confirm correct placement and functioning. Repeat CT scans are performed on postprocedure days 3 to 5. Once there is confirmation that the drain is functioning appropriately, this interval can be increased to weekly or as needed for an acute change in the patient's clinical status.

The need to upsize the drain if it is not functioning well or add additional drains is common. If possible, drains should be positioned near the site of the ductal disruption and drainage (and not necessarily in the center of the collection) for maximal efficacy. Drain fluid should be sent for amylase level, white blood cell count, bacterial culture, and gram stain. Once the patient is clinically improved, the drainage is minimal, and/or there is confirmation of fluid collection collapse on imaging, the drain can be removed. Once adequate drainage is

achieved, pancreatic necrosis is typically halted. During this process, secondary fluid collections, pancreatic ascites, or pleural effusions may appear. These secondary collections should be drained as well if clinically significant; however, priority should remain adequate drainage at the leak source.

In general, after operating on the pancreas, particularly after a pancreaticoduodenectomy, a drain is left in the operated vicinity in the case of a pancreatic fistula. Recent studies, however, have shown that in patients at a low risk for leak, routine drain placement may be unnecessary. Moreover, most patients who have undergone pancreaticoduodenectomy and develop a pancreatic fistula, can be best managed nonoperatively with percutaneous drainage, as described here.

As mentioned previously, to perform a percutaneous drainage, a clear window for access into the cavity must be available. In some instances, this window is not available and if the collection is in close proximity to the stomach, a transgastric approach is preferred. Further advantages of this approach include an internal system of drainage and avoidance of the formation of future pancreatic cutaneous fistulas.

The drainage process could take between days to months but is preferred to open surgical necrosectomy for most patients. Drainage is minimally invasive and can be completed in the stable patient prophylactically, whereas surgery is typically reserved for patients in which drainage has been inadequate or there is concern for other pathology such as injury or necrosis of other organs. Patients treated with drainage have also shown superior long term outcomes and tend to have lower rates of morbidity and mortality.

Endoscopic Drainage Options

Endoscopically, pancreatic fluid collections can be drained via an ERCP placed stent into the main pancreatic duct (Fig. 1). Placing this stent will allow pancreatic juice to flow down the path of least resistance and through the proper anterograde direction into the intestines, rather than leaking into the retroperitoneum. When distal disruption is mid-main pancreatic duct, the stent can be used to traverse the defect and connect the proximal and distal ends of the ventral duct. One possible drawback to this endoscopic approach is the risk of post ERCP pancreatitis.

In the setting of a pancreatic pseudocyst, endoscopic ultrasound-guided stenting can provide a route for internal drainage when the area of walled off necrosis is adjacent to either the stomach or the duodenum. This can be performed as either a cyst gastrostomy or cyst duodenostomy. Necrosectomies can also be performed endoscopically, rather than surgically.

Although endoscopic drainage has the advantage of avoiding painful external catheters, it is not without its own set of risks. Internal drainage may introduce foreign material into the pancreatic space and transgastric stents can erode into surrounding vessels and organs. There is also the disadvantage of not being able to further characterize the drain fluid by assessing its appearance or sending it for laboratory tests. Procedures combining percutaneous and endoscopic drainage have been described.

Surgical Management

Although the traditional approach to pancreatic necrosis was early surgical necrosectomy, the standard of care is now the minimally invasive step up approach. The step up approach advocates for initial percutaneous drainage, followed by video assisted retroperitoneal dissection, and with the last option being open necrosectomy. When following the step up approach, it was found that approximately 35% of patients were able to avoid open surgery, but mortality was similar between the two treatment methods.

Surgical treatment for a pancreatic leak is dependent on the location of the duct disruption. Distal leaks can be controlled with distal pancreatectomy. Repeated drainage before an attempt at surgery, however, is warranted and the distal pancreas may become atrophic and the leak volume may decrease. Although this may be a long process and involve many drainage procedures, it will spare the patient a surgery and preserve some pancreatic endocrine/exocrine function. Proximal duct leaks refractory to drainage would require operative drainage with a Roux en Y jejunal limb anastomosed to the most proximal aspect of the leak. Often, this involves tracing a drainage catheter, which by definition is in the fistula tract, toward the pancreas. However, failure of both endoscopic and percutaneous drainage in this area is fortunately rare. Retroperitoneal dissection in this setting can be difficult secondary to the dense adhesions in the area and the left sided portal hypertension caused by a thrombosed or scarred splenic vein.

Pancreatic Ascites

Pancreatic ascites occurs when pancreatic fluid drains into the abdominal cavity and traditionally was felt to be a surgical emergency requiring while drainage. This is no longer the case, and it is now largely treated medically with bowel rest, total parenteral nutrition, and anti secretagogues such as octreotide. Other anti secretagogues that been used include atropine, glucagon, acetazolamide, galactose morphate, and aprotinin. The ductal anatomy is interrogated with imaging to identify the duct leak location, and interventions to control this include percutaneous and endoscopic with drainage and ductal stenting. In most cases of acute pancreatitis, pancreatic ascites resolves with these interventions and over time as the pancreatitis resolves. For patients with chronic pancreatitis, this is less likely because of the scarred nature of the duct and ductal stones obstructing pancreatic juice flow, and may require a surgical drainage procedure Roux en Y.

Pancreatic Pleural Effusions

Although pancreatic pleural effusions can result from acute pancreatitis, it is more often a complication of chronic pancreatitis with ductal disruption (Fig. 2). Treatment begins with bowel rest, total parenteral nutrition, repeated thoracentesis, tube thoracostomy, and secretagogues such as octreotide, interventional techniques using ERCP aided stenting or nasopancreatic drainage, or surgery typically consisting of excision of the damaged portion of the pancreatic duct and drainage of fluid collections or remaining pancreatic tissue with a Roux en Y limb of jejunum. Conservative treatment has an historical efficacy of 20% to 60% with a recurrence rate of 15%. Surgical therapy has been typically reserved for patients in whom medical therapy has failed and has a success rate as high as 90%, but with up to 20% rate of recurrence. The operative strategy is highly variable and depends on the ductal anatomy. After reviewing the literature, we found that in patients with complications from pancreatic pleural effusions surgery was successful more often than medical therapy (94% vs 31%).

Multidisciplinary Team Approach

The treatment of pancreatic ductal disruptions can be highly complex and a multidisciplinary team of surgeons, gastroenterologists, interventional radiologists, dietitians, nursing staff, hospitalists, pharmacists, and intensive care staff is critical to the success for the patient. The management is best guided by a weekly conference attended by members of the team where the patient's case is presented, imaging is reviewed, and a plan formulated. Pancreatic ductal disruption is an uncommon and complex condition requiring particular expertise in order to resolve the complications that accompany this diagnosis.

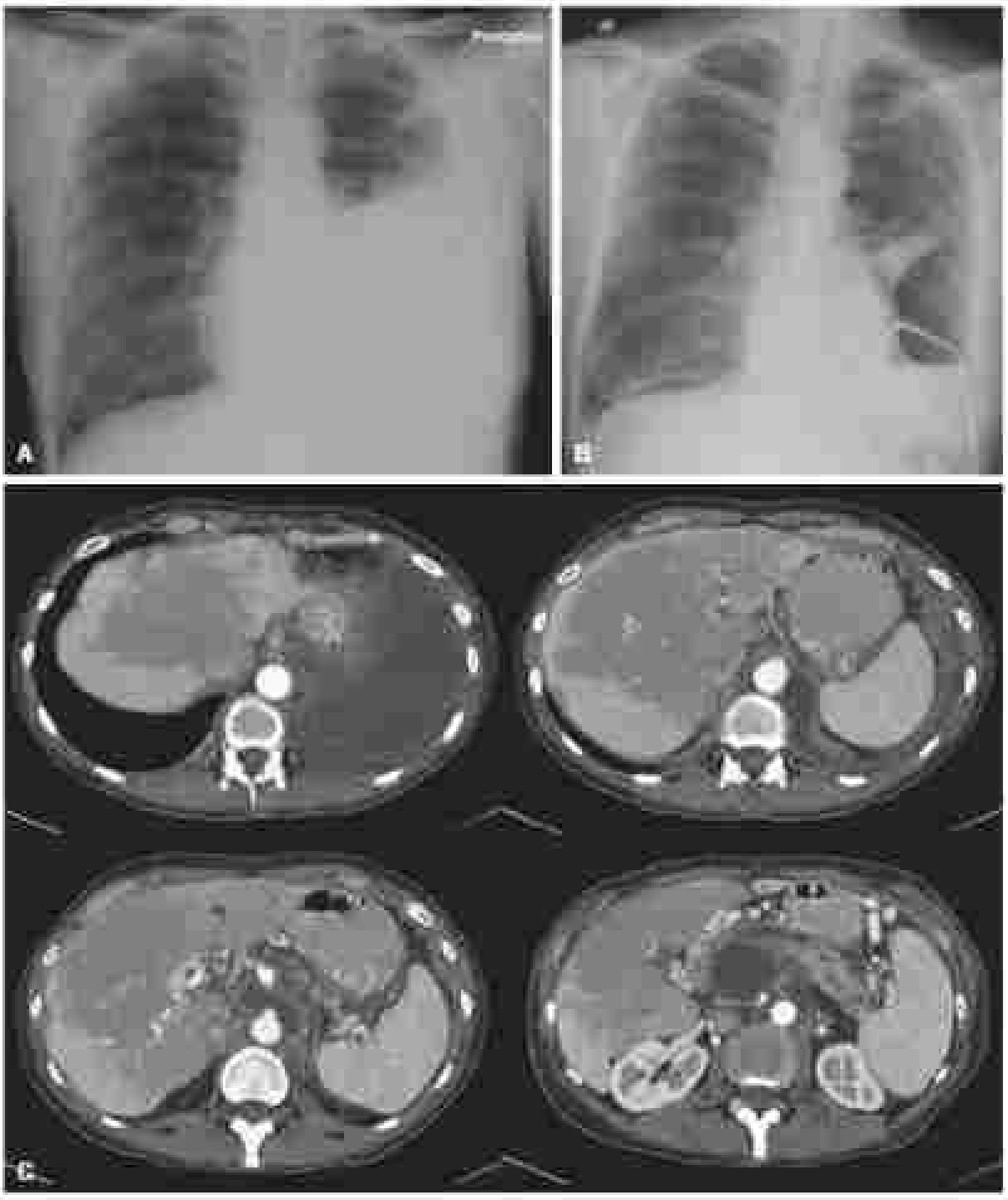

FIGURE 2 Patient with a pancreatic pleural effusion and fistula. (A) Initial chest radiographic demonstrates opacification of the left middle and lower lung zones consistent with moderate sized pleural effusion. (B) After interval drainage of the left pleural effusion, there was a left lower hydropneumothorax with a dense surrounding pleural lining consistent with a trapped left lung. In addition, a curvilinear lucency was seen under the right hemidiaphragm representing intraperitoneal air following a laparotomy to address the fistula. (C) Intravenous contrast tomography scan demonstrates evidence of chronic pancreatitis with parenchymal cystic collections and pseudocysts. One such pseudocyst extends superoposteriorly into the left upper quadrant, where it communicates with the pleural space. A large left pleural effusion is associated with this finding. Other findings include portal vein thrombosis, splenic vein thrombosis, and a 15-mm splenic artery aneurysm.

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Management of Chronic Pancreatitis

William P. Lancaster, MD, and David B. Adams, MD

Chronic pancreatitis (CP) is a chronic, progressive, inflammatory disease of the pancreas that is characterized by irreversible destruction of functional pancreatic parenchyma and subsequent fibrosis. In the United States, the estimated incidence is 14 per 100,000 with annual healthcare costs estimated to be greater than $2 billion.

The predominant clinical feature of CP is abdominal pain, most frequently epigastric, often with radiation to the back. The pancreas is the most highly innervated visceral organ and the pain associated with CP is unmatched by other abdominal viscera. Characteristic of the CP pain syndrome is allodynia, hyperalgesia, and centralization of pain. Other common clinical features include signs related to loss of pancreatic parenchyma. Symptoms of exocrine pancreatic insufficiency include bloating, steatorrhea, weight loss or inability to gain weight. Progressive islet cell loss is manifested clinically as diabetes mellitus (type 3c). The exocrine, endocrine, and neurologic (chronic pain) dysfunction associated with CP do not follow a parallel course and each may progress at a different rate.

CP is a multifactorial disease with a strong genetic predisposition. Several risk factors known to contribute to the development of CP are summarized conveniently by the TIGAR-O classification in Box 2. Alcohol remains the most common risk factor for the development of CP in Western countries. However, the North American Pancreatitis Study group has recently reported that excessive alcohol consumption is responsible for only 44.3% of CP cases, with the remaining cases attributable to other causes. It is likely that alcohol plays a lesser causative role in the development of pancreatitis with the actual mechanism being alcohol as an exacerbating factor of preexisting physiologic or genetic circumstances. Mutations in several genes, including cationic trypsin (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), and cystic fibrosis transmembrane conductance regulator (CFTR) contribute to the development and irreversible progression of CP. Although the genetic underpinnings of CP are continually and currently being elucidated, hereditary pancreatitis is an entity distinct from genetic pancreatitis with a more aggressive natural history. This disease is responsible for 2% to 3% of cases of CP in the United States and is caused by a germline mutation resulting in gain of function of the PRSS1 gene resulting in constitutively active cationic trypsin and subsequent pancreatic autodigestion and inflammation. Patients experience early onset CP developing symptoms in many cases before the age of 20 years.

Autoimmune pancreatitis is a rare cause of CP seen in less than 3% of patients. It is characterized by distinct radiologic and histologic features, most often an inflammatory pancreatic head mass and biopsy showing lymphocytic infiltration without malignant cells. It is treated with corticosteroids with complete resolution in most cases.

Diagnostic Evaluation

The evaluation of patients with suspected CP begins with a careful history and physical examination. The presenting complaint is most often abdominal pain that is often life limiting and without clear etiology. Attention should be paid to the location and character of the pain. Most commonly, patients describe epigastric bursting pain that radiates to the middle of the back. The pain is often constant with few identifiable aggravating or alleviating factors. The patient should be questioned regarding dietary and bowel habits. Especially in the later stages of disease, patients will restrict their diet to carbohydrates alone and consume very little protein and fat because these cause them pain to worsen, and, in many cases, patients are malnourished though they are of normal or even overweight. Greasy, foamy, floating, and frequent stools suggest steatorrhea and associated exocrine pancreas insufficiency.

Imaging studies are helpful in the diagnosis of CP. The most common imaging findings in the setting of CP were described recently in the MAPSS study and include pancreatic duct dilation (68%), atrophy (57%), calcifications (55%), pancreatic duct irregularity (53%), and pancreatic pseudocysts (32%).

Historically, plain abdominal x-ray was the initial imaging study of choice for the diagnosis of CP, with the finding of upper abdominal calcifications considered pathognomonic, but this is only demonstrated in a subset of cases and in the setting of advanced disease. Computed tomography (CT) is now the most common initial imaging study and has a sensitivity of 67% to 80% and specificity of 90%. However, pancreatic calcifications seen on CT must be interpreted with caution as approximately 40% of patients will have other pancreatic pathology. CT is also useful for the identification of the complications associated with CP, such as pancreatic pseudocysts, infection, hemorrhage, pseudoaneurysm formation, pancreatic fistula, and biliary or gastrointestinal obstruction. Magnetic resonance cholangiopancreatography produces detailed images of the hepatobiliary and pancreatic systems in the setting of advanced disease. It has a sensitivity of 75%, but it is of low yield in the early stages of disease, in which the sensitivity is only 25%.

Endoscopic imaging techniques have the highest sensitivity and specificity for the diagnosis of CP. There are criteria for establishing the diagnosis for both endoscopic retrograde cholangiopancreatography (Cambridge classification) and endoscopic ultrasonography (Endoscopic Ultrasound Rosemont criteria). Both diagnostic systems are based on imaging findings that support the diagnosis of CP such as ductal dilation and calcifications. Endoscopic retrograde cholangiopancreatography (ERCP) is arguably the most sensitive and specific test (ranging from 70% to 100%) for the diagnosis of CP. Endoscopic ultrasound can be a valuable aid in the diagnosis of CP in early stage disease before the development of overt anatomic abnormalities. These modalities are of limited utility for the surgeon because surgical intervention is primarily aimed at alleviating the consequences of longstanding disease.

Medical Management

The goals of medical management of CP are to control pain, treat pancreatic exocrine insufficiency, and maintain glucose homeostasis. Alleviation of severe abdominal pain can be treated with nonnarcotic analgesics, although this is often unsuccessful and thus opioids are often required to achieve adequate pain control. Unfortunately, adjuncts to opioid therapy are palpable and gabapentin and frequently can reduce the total dosage of opioids required. In patients with steatorrhea or inability to maintain weight, pancreatic enzyme replacement therapy should be instituted.

Endoscopic Treatment

Endoscopic therapies commonly are used as first line interventions in the setting of obstructive CP. The goal is to relieve pressure in the pancreatic duct and to facilitate drainage of pancreatic secretions into the duodenum. ERCP is the modality of these treatment modalities because it allows dilation of pancreatic duct strictures, division of the sphincter of Oddi, stent placement, and stone removal. ERCP-based therapies are most effective in the setting of main pancreatic duct obstruction caused either by strictures or stones.

Pancreatic duct strictures can be dilated endoscopically and often require stent placement followed by serial stent exchanges usually every 3 months for a period of 2 years. Pancreatic stent removal is associated with a 30% to 40% risk of restenosis. Endoscopic

BOX 1 Indications for Surgery in Chronic Pancreatitis

- Pain
- Relapsing pancreatitis (inflammatory mass in the head, pancreatic ductal stricture)
- Complicated pancreatic pseudocyst
- Biliary obstruction
- Duodenal obstruction
- Bleeding pseudoaneurysm
- Sinistral portal hypertension with recurrent bleeding
- Concern for malignancy

BOX 2 TIGAR-O Classification of Etiology of Chronic Pancreatitis

Toxic-Metabolic

Alcohol
Tobacco
Hypercalcemia
Chronic renal failure
Other toxins

Idiopathic

Early onset
Late onset
Tropical

Genetic

PRSS1 (hereditary pancreatitis)
CFTR
SPINK1
Alpha-1-antitrypsin deficiency

Autoimmune

Recurrent acute pancreatitis

Obstructive

Pancreas divisum
Tumor (intraductal papillary mucinous neoplasm, adenocarcinoma, etc.)

sphincterotomy is performed commonly during ERCP in the setting of CP because it facilitates pancreatic duct decompression, stent placement and stone extraction. Recurrence occurs in 14% of cases after sphincterotomy. Pancreatic duct stones can be removed endoscopically, but stones larger than 7 mm in diameter often require mechanical or extracorporeal shock wave lithotripsy before extraction. Complications associated with ERCP include bleeding, perforation, and post-ERCP pancreatitis.

SURGICAL MANAGEMENT

Surgical management of CP is primarily reserved for patients who have failed medical and endoscopic therapy and/or patients that have developed adjacent organ anatomic complications related to peripancreatic fibrosis such as biliary obstruction, duodenal obstruction, and splenic vein occlusion with gastric variceal hemorrhage. The goals of surgical therapy are palliation of abdominal pain, improvement in quality of life, and relief of secondary complications (Box 1). To that end, the selection of which operation is appropriate for a given patient is based on the pattern of disease evident on cross-sectional imaging. Broadly, the different operations for CP can be categorized as drainage procedures, resection procedures, or combination resection and drainage procedures.

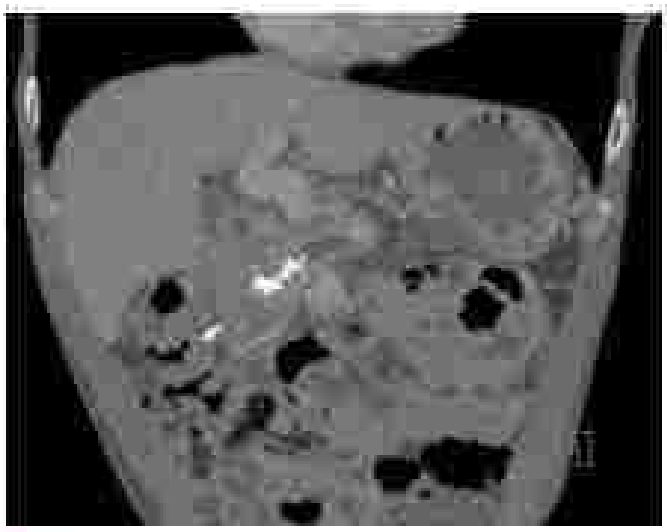

FIG. 1 Computed tomography scan showing calcific proximal pancreatic duct stricture with a dilated distal duct.

Drainage Procedures

Longitudinal Pancreaticojejunostomy

The goal of a drainage procedure is to provide surgical relief of pancreatic ductal obstruction. The mainstay of the management of chronic fibrocalculic pancreatitis is the Puestow procedure, originally described by Puestow and later modified by Partington and Rochelle. The pancreatic duct is opened longitudinally along the anterior aspect of the pancreas and a side-to-side pancreaticojejunostomy is created to Roux-en-Y limb of jejunum. The anastomosis can be created in one layer or two, typically with permanent suture. Lateral pancreaticojejunostomy is reserved for patients with a pancreatic duct size of 6 mm or greater and without significant enlargement of the pancreatic head. It is important to clear the duct of all stones and debris to optimize drainage. Pancreatoscopy and electrohydraulic lithotripsy can be a useful adjunct to this regard (Fig. 1). The calcific pancreas with a dilated duct also lends itself to a laparoscopic approach.

Lateral Pancreaticojejunostomy

Lateral pancreaticojejunostomy results in partial or complete pain relief in up to 90% of patients and is accomplished with acceptable morbidity and mortality. At least 25% of patients will develop transient diabetes during long-term follow-up, and this likely reflects the progressive and irreversible course of the disease. Persistent tobacco smoking and alcohol consumption are significant risk factors for recurrent abdominal pain and surgical failure.

Combined Resection and Drainage Procedures

Frey Procedure

Combined resection and drainage procedures were developed to enhance drainage of the dominant duct in the head of the pancreas and the duct in the uncinate process while preserving pancreatic parenchyma and the duodenum. This operation is best suited for patients with pancreatic duct dilation secondary to obstruction with an enlarged pancreatic head. It combines the lateral pancreaticojejunostomy with local pancreatic head resection. The advantages of the Frey procedure are that it is not necessary to divide the pancreatic neck, which can be particularly treacherous in the setting of severe

chronic inflammation. There are presumed benefits with regard to long term metabolic function with parenchymal and duodenal preservation. The gastroduodenal artery to the right sided boundary of the pancreatic head resection and often must be ligated when encountered. Local pancreatic head resection is limited to the portion of pancreas that is superficial to the intrapancreatic portion of the common bile duct. If the bile duct is entered, it can be effectively drained into the ileum limb. The bile duct edges can be sutured to the surrounding pancreatic head to prevent late stricture. If stricture does occur, a choledochoduodenostomy can be performed. Care must be taken to avoid injuring the underlying portal vein as substantial hemorrhage can occur.

Beger's Procedure

The Beger procedure is an operation that combines pancreatic head resection with drainage of the distal pancreatic duct while preserving the duodenum. Along with the Frey procedure, the Beger procedure is referred to as duodenal preserving pancreatic head resection. It is best applied to circumstances where the pancreatic head is enlarged without significant distal pancreatic duct obstruction. In this operation, the pancreatic neck is divided and a subtotal resection of the pancreatic head is performed. A Roux limb is then used for two pancreatic anastomoses, one in a side to side fashion to the pancreatic head and one in an end to side fashion to the pancreatic body and tail. The Beger operation affords a greater degree of local pancreatic head resection but has the disadvantages of requiring division of the pancreatic neck and the construction of two pancreatic anastomoses. The Berne modification of the Beger procedure preserves pancreatic parenchyma overlying the SMV and portal vein, and, like the Frey procedure, affords a degree of safety when CP presents as a large inflammatory mass in the head of the pancreas. The downside of the Berne, Beger, and Frey procedures is reoperation for biliary stenosis and pancreatic cancer.

Several studies have compared the results of the Frey and Beger operations and the rates of pain relief and endocrine dysfunction are similar. Pain relief can be achieved in up to 94% of patients with either operation and the rate of endocrine dysfunction ranges from 10% to 30%. Rates of exocrine dysfunction are similar. Most of the randomized prospective studies comparing resection and drainage procedures originate from Eastern European experience where genetic and environmental factors appear to be associated with markedly enlarged pancreatic head masses associated with obstructive complications. In the United States, experience with this scenario is less common and the predominant indication for surgery in the United States is pain, less frequently associated with biliary, duodenal, and splenic vein stenosis.

Resection Procedures

Pancreaticoduodenectomy

Pancreaticoduodenectomy (Whipple operation) involves resection of the pancreatic head, duodenum, and distal bile duct. It is most commonly applied to patients with an enlarged pancreatic head but is also useful in cases of head dominant disease with biliary or duodenal obstruction or in situations where malignancy is suspected (Fig. 2). It can be applied for both large and small pancreatic ducts. Classically, the operation involves resection of the duodenum with antrectomy but the pylorus can be preserved in some cases by division of the first portion of the duodenum and creation of a duodenojejunostomy (pylorus preserving pancreaticoduodenectomy). It is our experience that, in cases where it is technically possible, preservation of the pylorus results in a high rate of delayed gastric emptying and intolerance of oral intake and that it is our standard practice to divide the stomach proximal to the pylorus (pylorus sparing pancreaticoduodenectomy). Patients with CP have chronically elevated levels of CCK that leads to impaired gastric emptying, which may be improved with pyloric resection. Opponents of pancreaticoduodenectomy argue that it is an overly aggressive operation performed for benign disease and that efforts should be made to preserve pancreatic parenchyma

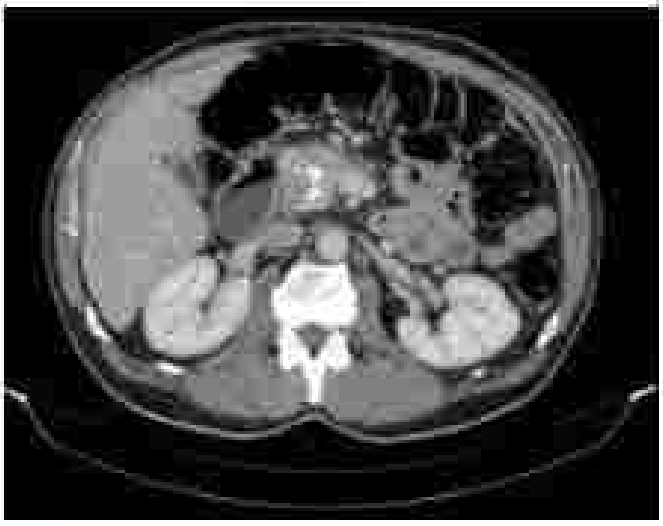

FIG. 2 Computed tomography scan showing an enlarged pancreatic head with calcification.

to allay future risk of endocrine and exocrine dysfunction. In cases where malignancy is suspected or cannot be excluded, pancreaticoduodenectomy should be undertaken.

In appropriately selected patients, pancreaticoduodenectomy provides improvement in abdominal pain and quality of life. It is thus noted that the radical nature of pancreaticoduodenectomy would lead to high rates of endocrine and exocrine dysfunction, with some studies reporting rates of 50%. However, in a recent randomized controlled trial comparing pancreaticoduodenectomy to duodenal preserving pancreatic head resection, rates of endocrine dysfunction were quite low (<5%) for either operation, whereas rates of exocrine dysfunction were also similar (90% for duodenal preserving pancreatic head resection and 89% PD). Importantly, there was no difference in postoperative quality of life.

Distal Pancreatectomy

Distal pancreatectomy usually involves removing some or all of the left side of the gland (i.e., body and tail to the left of the superior mesenteric vein). Indications for distal pancreatectomy include splenic vein thrombosis with minimal (left sided) portal hypertension (Fig. 3), proximal pancreatic duct obstruction that is not amenable to endoscopic management (Fig. 4), disconnected left pancreas, and CP limited to the body or tail of the pancreas. With regard to cases of proximal duct obstruction, the question arises as to remove the obstructed segment of pancreas or to perform internal drainage with Roux-en-Y pancreatojejunostomy. We typically perform distal pancreatectomy unless the duct is 8 mm or greater and there is an appreciable amount of viable parenchyma. When distal pancreatectomy is indicated in CP, the inflammation and fibrosis are advanced to the degree that attempts to save the spleen or to undertake a laparoscopic approach are hazardous and imprudent.

Total Pancreatectomy With Islet Cell Autotransplantation

Total pancreatectomy was viewed historically as a highly morbid and futile operation in the treatment of CP, particularly in alcoholic patients who perished from complications of brittle diabetes. With improvements in islet cell processing and transplantation technique, total pancreatectomy with islet cell autotransplantation (TPIAT) is a safe and useful treatment option in the treatment of CP intractable to medical management. This operation can be applied in patients who have failed other operations and with small duct or so-called minimal change disease. There is increasing evidence that patients with hereditary and genetic pancreatitis can be treated with upfront TPIAT and achieve long term improvements in quality of life.

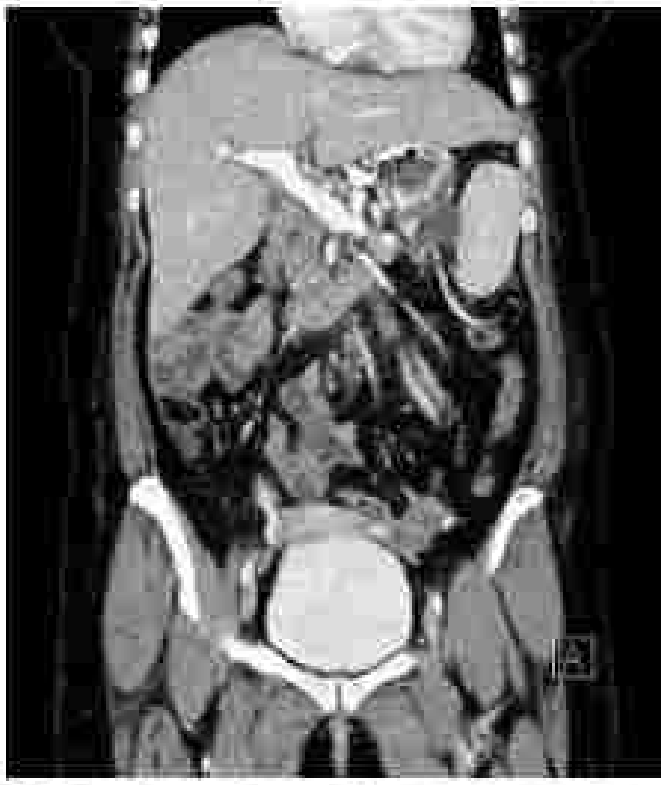

FIG. 3 Computed tomography scan showing splenic vein occlusion with prominent gastric varices. Also seen is a pseudocyst within the splenic hilum.

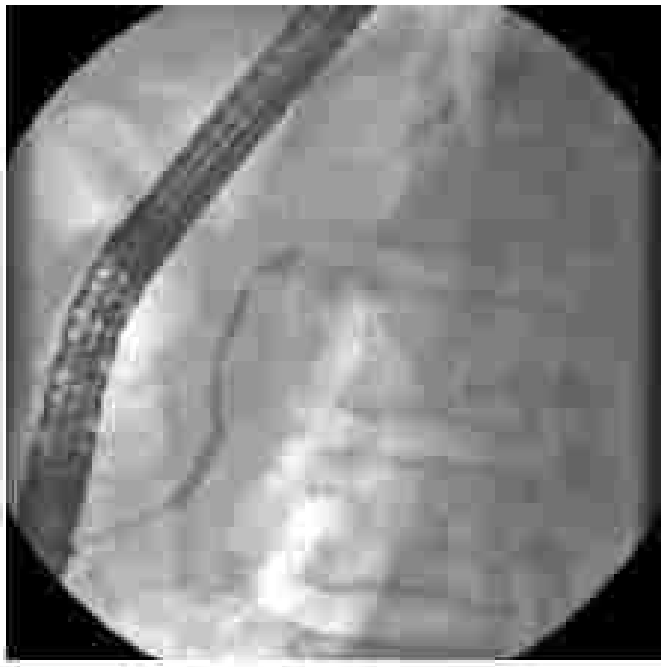

FIG. 4 Pancreatogram demonstrating a severe pancreatic duct stricture in the pancreatic neck.

The principal morbidity of TPIAT is the removal of the gland with complete loss of endocrine and exocrine function. The consequences of endocrine ablation are ameliorated by islet cell autotransplantation with many patients remaining insulin independent or on minimal insulin doses postoperatively. Those patients who require insulin to maintain glucose homeostasis have diabetes that is easier to manage than in patients without islet cell autotransplantation because the counterregulatory islet hormones are also produced by transplanted islets. Quality of life is equivalent in TPIAT patients who are insulin-free and those who are not. Lifelong oral pancreatic enzyme replacement is required and management of pancreatic exocrine insufficiency is frequently more problematic than endocrine insufficiency.

The TPIAT operation involves removal of the entire pancreas, which is then enzymatically digested, and the islets are isolated and infused via the portal vein into the liver. Pancreatectomy can be accomplished en bloc or by pancreaticoduodenectomy and distal pancreatectomy and splenectomy. Reconstruction is with a choledochojejunostomy and downstream antecolic gastrojejunostomy. Islet isolation can be accomplished either in the operating room or in a clean cell facility. Numerous techniques of islet cell autotransplantation have been described. Our practice is to transplant via intraportal injection, either through a catheter placed in the portal vein through a tributary of the middle colic vein or through direct portal venous puncture under radiographic control in the radiology suite. Most centers inject islets directly into the portal vein in the operating room.

Total pancreatectomy with islet cell autotransplantation provides pain relief and improvement in quality of life with acceptable rates of insulin independence (Table 1). Postoperative improvements in quality of life are durable. Remodeling of centrilobular pancreatic pain pathways and resulting patients narcotic free is a long term process that takes months to years with assistance of behavioral medicine pain experts. Patient selection is crucial and patients must undergo thorough preoperative testing and psychological evaluation prior to operation. Patients with genetic pancreatitis, autoimmune, and those who have not had prior pancreatic surgery have the best postoperative outcomes.

TABLE 1 Summary of Outcomes After Total Pancreatectomy With Islet Cell Autotransplantation

Study	No. of Patients	Complete or Partial Pain Relief (%)	Insulin Independence (%)	Mean Follow-up (mo)
Ihnat et al.	22	82	40	19
Gruessner et al.	112	Unreported	30	Unreported
Wilson et al.	132	73	27	60
Morgan et al.	195	82	89	Unreported
Chinnakotla et al.	501	80	12.5	12

Suggested Readings

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Management of Periampullary Cancer

Jonathan G. Shaw, MD, Bradley N. Reames, MD, M , and Jin Ma, MD, PhD, FACS

The term periampullary cancer is broadly used to describe four common malignant neoplasms occurring near the ampulla of Vater. Situated in the second portion of the duodenum, the ampulla of Vater is formed by the junction of the distal common bile duct (CBD) and the main pancreatic duct as it traverses the sphincter of Oddi. As such, neoplastic changes to the epithelium of each of these structures may progress to a primary malignancy. Pancreatic ductal adenocarcinoma (PDAC) accounts for a vast majority of periampullary cancers, followed by distal cholangiocarcinoma, ampullary adenocarcinoma, and duodenal adenocarcinoma. Although not traditionally included in the term periampullary cancer, less common neoplasms occurring near the ampulla of Vater include neuroendocrine tumors, cystic lesions of the pancreas (intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and serous cystadenomas), acinar and squamous cell carcinomas, solid pseudopapillary neoplasms (Hamoudi tumor), gastrointestinal stromal tumors, sarcomas, lymphomas, and metastases (most commonly renal cell carcinoma, melanoma, and lung cancer). Regardless of the tissue of origin, the definitive surgical management for most periampullary malignancies is pancreaticoduodenectomy (PD).

CLINICAL PRESENTATION

Patients with periampullary cancer most commonly present with obstructive jaundice. Additional symptoms may include pruritus, steatorrhea, dark urine, gastrointestinal distress (nausea, vomiting, diarrhea), and pain (abdominal, epigastric, or back). Other symptoms may include weight loss, anorexia, gastrointestinal bleeding, and episodes of cholangitis, which may cause fevers, chills, diaphoresis, and rigors. The presence of ascites or palpable lymph nodes in the periumbilical (Sister Mary Joseph's) or left supraclavicular (Virchow's) regions may indicate advanced disease.

Following a complete history, physical, and regular laboratory testing, tumor markers including carbohydrate antigen 19-9 should be checked. If concern exists for autoimmune cholangitis or pancreatitis, serum IgG4 levels should be measured.

DIAGNOSIS AND STAGING

Dedicated Imaging

High-quality pancreatic protocol computed tomography (CT) is most useful in delineating tumor vessel relationships and determining resectability, identifying aberrant anatomy, and assessing metastatic spread. Recent studies suggest that more than 25% of hepatic metastases may be missed on nonbiphasic abdominal imaging with suboptimal contrast timing.

Esophagogastroduodenoscopy and endoscopic ultrasound (EUS) can be used to assess tumor location and obtain tissue biopsy. EUS with fine-needle aspiration is necessary for guiding systemic therapy (both neoadjuvant and palliative) and may allow for genetic testing to further personalize therapy. If biliary obstruction is present, endoscopic retrograde cholangiopancreatography can be utilized to decompress the biliary tree with endobiliary stenting for patients with severely symptomatic hyperbilirubinemia, cholangitis, and those requiring biliary decompression prior to the administration of neoadjuvant chemotherapy. Other complementary studies may include a pancreatic protocol magnetic resonance imaging scan and a positron emission tomography-CT scan, which may assist the evaluation of extrapancreatic metastases.

Resectability and Staging

As complete surgical resection is the only curative therapy for periampullary cancer, the primary objective of preoperative imaging is to assess resectability. In PDAC, numerous groups have published standardized criteria for the determination of resectability. At diagnosis, patients with PDAC are classified as resectable, borderline resectable, or locally advanced mainly based on imaging characteristics, and subsequent therapies are tailored to this determination. Resectability criteria focus on the degree of tumor involvement with arterial (aorta, celiac, common hepatic, superior mesenteric, splenic, gastroduodenal) and venous (inferior vena cava, portal hepatis, superior mesenteric, splenic) structures. For patients without distant metastases, the type and sequence of therapy will be determined by the resectability classification and the response to therapy. It is important to note, however, that numerous retrospective studies suggest high-quality imaging may not reliably characterize resectability in borderline resectable and locally advanced patients following neoadjuvant therapy, as 50% to 80% of patients without progression may be successfully resected if explored at high-volume centers. In addition, select centers are investigating resection of both solitary and oligometastatic PDAC on study protocol, as long as the patient's disease has demonstrated favorable biology and response to systemic neoadjuvant therapy.

Following resection, periampullary cancers are staged according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system (Table 1).

MULTIDISCIPLINARY MANAGEMENT

All patients with a diagnosis of periampullary cancer should be discussed in a multidisciplinary setting. Although complete surgical resection remains the cornerstone of curative therapy, advancements in chemotherapy, radiotherapy, and targeted systemic agents have resulted in an increasingly multidisciplinary approach to treatment.

Given its aggressive biology and penchant for systemic spread, there is universal agreement that the vast majority of patients with PDAC should receive chemotherapy at some point during their treatment regimen, regardless of TNM stage. Based on recent clinical trials in Europe, gemcitabine and capecitabine (from the JSWOG 4

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Management of Periampullary Cancer

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The term periampullary cancer is broadly used to describe four common malignant neoplasms occurring near the ampulla of Vater. Situated in the second portion of the duodenum, the ampulla of Vater is formed by the junction of the distal common bile duct (CBD) and the main pancreatic duct as it traverses the sphincter of Oddi. As such, neoplastic changes to the epithelium of each of these structures may progress to a primary malignancy. Pancreatic ductal adenocarcinoma (PDAC) accounts for a vast majority of periampullary cancers, followed by distal cholangiocarcinoma, ampullary adenocarcinoma, and duodenal adenocarcinoma. Although not traditionally included in the term periampullary cancer, less common neoplasms occurring near the ampulla of Vater include neuroendocrine tumors, cystic lesions of the pancreas (intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and serous cystadenomas), acinar and squamous cell carcinomas, solid pseudopapillary neoplasms (Hamoudi tumor), gastrointestinal stromal tumors, sarcomas, lymphomas, and metastases (most commonly renal cell carcinoma, melanoma, and lung cancer). Regardless of the tissue of origin, the definitive surgical management for most periampullary malignancies is pancreaticoduodenectomy (PD).

CLINICAL PRESENTATION

Patients with periampullary cancer most commonly present with obstructive jaundice. Additional symptoms may include pruritus, steatorrhea, dark urine, gastrointestinal distress (nausea, vomiting, diarrhea), and pain (abdominal, epigastric, or back). Other symptoms may include weight loss, anorexia, gastrointestinal bleeding, and episodes of cholangitis, which may cause fevers, chills, diaphoresis, and rigors. The presence of ascites or palpable lymph nodes in the periumbilical (Sister Mary Joseph's) or left supraclavicular (Virchow's) regions may indicate advanced disease.

Following a complete history, physical, and regular laboratory testing, tumor markers including carbohydrate antigen 19-9 should be checked. If cancers exist for autoimmune cholangitis or pancreatitis, serum IgG4 levels should be measured.

DIAGNOSIS AND STAGING

Dedicated Imaging

High-quality pancreatic protocol computed tomography (CT) is most useful in delineating tumor vessel relationships and determining resectability, identifying aberrant anatomy, and assessing metastatic spread. Recent studies suggest that more than 25% of hepatic metastases may be missed on nonbiphasic abdominal imaging with suboptimal contrast timing.

Esophagogastroduodenoscopy and endoscopic ultrasound (EUS) can be used to assess tumor location and obtain tissue biopsy. EUS with fine-needle aspiration is necessary for guiding systemic therapy (both neoadjuvant and palliative) and may allow for genetic testing to further personalize therapy. If biliary obstruction is present, endoscopic retrograde cholangiopancreatography can be utilized to decompress the biliary tree with endobiliary stenting for patients with severely symptomatic hyperbilirubinemia, cholangitis, and those requiring biliary decompression prior to the administration of neoadjuvant chemotherapy. Other complementary studies may include a pancreatic protocol magnetic resonance imaging scan and a positron emission tomography-CT scan, which may assist the evaluation of extrapancreatic metastases.

Resectability and Staging

As complete surgical resection is the only curative therapy for periampullary cancer, the primary objective of preoperative imaging is to assess resectability. In PDAC, numerous groups have published standardized criteria for the determination of resectability. At diagnosis, patients with PDAC are classified as resectable, borderline resectable, or locally advanced mainly based on imaging characteristics, and subsequent therapies are tailored to this determination. Resectability criteria focus on the degree of tumor involvement with arterial (aorta, celiac, common hepatic, superior mesenteric, splenic, gastroduodenal) and venous (inferior vena cava, portal hepatis, superior mesenteric, splenic) structures. For patients without distant metastases, the type and sequence of therapy will be determined by the resectability classification and the response to therapy. It is important to note, however, that numerous retrospective studies suggest high-quality imaging may not reliably characterize resectability in borderline resectable and locally advanced patients following neoadjuvant therapy, as 50% to 80% of patients without progression may be successfully resected if explored at high-volume centers. In addition, select centers are investigating resection of both solitary and oligometastatic PDAC on study protocol, as long as the patient's disease has demonstrated favorable biology and response to systemic neoadjuvant therapy.

Following resection, periampullary cancers are staged according to the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system (Table 1).

MULTIDISCIPLINARY MANAGEMENT

All patients with a diagnosis of periampullary cancer should be discussed in a multidisciplinary setting. Although complete surgical resection remains the cornerstone of curative therapy, advancements in chemotherapy, radiotherapy, and targeted systemic agents have resulted in an increasingly multidisciplinary approach to treatment.

Given its aggressive biology and penchant for systemic spread, there is universal agreement that the vast majority of patients with PDAC should receive chemotherapy at some point during their treatment regimen, regardless of TNM stage. Based on recent clinical trials in Europe, gemcitabine and capecitabine (from the JSWOG 4

TABLE 1 American Joint Committee on Cancer Pancreatic Adenocarcinoma Staging

T1	Tumor ≤2 cm T1a: tumor ≤0.5 cm T1b: tumor >0.5 cm and <1 cm T1c: tumor >1 cm but no more than 2 cm		
T2	Tumor >2 cm but no more than 4 cm		
T3	Tumor >4 cm in greatest dimension		
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery		
N1	Metastases to 1 to 3 nodes		
N2	Metastases to 4 or more nodes		
M Category Unchanged			
STAGE			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging Manual. Vol. 8. New York: Springer International; 2017. Courtesy the American College of Surgeons.

trial) or FOLFIRINOX (from the PRODIGE 24 trial) should be considered first line therapy in the adjuvant setting. Recent data from the PRODIGE 13 trial support a total neoadjuvant therapy approach to optimize therapy for true micrometastatic disease, maximize completion of therapy, and test tumor biology. In the metastatic setting, both FOLFIRINOX (from the PRODIGE trial) and gemcitabine with nab-paclitaxel (from the MPACT trial) have been shown to improve survival compared to gemcitabine alone and are considered standard of care.

Unlike PDAC, few trials exist to support the multimodality treatment of distal cholangiocarcinoma. Although retrospective studies of adjuvant radiotherapy are heterogeneous and show mixed results, the regimen of gemcitabine and capecitabine chemotherapy followed by capecitabine chemoradiation has recently gained favor based on phase II data suggesting a median survival of 36 months and 2-year survival of 69% in patients with extrahepatic cholangiocarcinoma and gallbladder carcinoma (from the SWOG S0809 trial). However, current guidelines support observation, gemcitabine- or fluoropyrimidine–based chemotherapy, or fluoropyrimidine chemoradiation may be considered in the adjuvant setting. In patients with advanced (unresectable and metastatic) biliary tract cancer, the largest phase III trial to date (the ABC-02 trial) established gemcitabine and cisplatin combination chemotherapy as the standard of care. Additional chemotherapies considered in this setting include oxaliplatin, capecitabine, and 5-fluorouracil, and radiotherapy (external beam or brachytherapy) may be considered in select cases.

Like distal cholangiocarcinoma, randomized data to support management of ampullary and duodenal adenocarcinoma are sparse, aside from the early trials evaluating mixed periampullary cancers discussed earlier. Currently, patients with ampullary adenocarcinoma are treated in accordance with the ESPAC-4 trial. Although supported by multiple retrospective series, the use of chemoradiation in ampullary adenocarcinoma is controversial, and little data exist to guide the management of advanced disease. Similarly, data evaluating multimodality therapy in duodenal adenocarcinoma are scant. As a result, patients are often treated by extrapolating the literature of colon cancer, as node positive patients and those with advanced disease are offered oxaliplatin and fluoropyrimidine based chemotherapies as first line systemic therapy.

SURGICAL MANAGEMENT

Pancreaticoduodenectomy

PD can be divided broadly into three phases: (1) abdominal exploration to confirm the absence of metastases, (2) resection of the malignancy, and (3) pancreaticobiliary and enteric reconstruction. Multiple variations on the procedure exist including standard PD (which includes en bloc distal gastrectomy) versus pylorus preserving PD (PPPD) (Fig. 1), antecolic versus retrocolic, gastrojejunostomy (GJ), and numerous variants of pancreaticojejunostomy (PJ). However, none of these technical details have been shown to significantly augment perioperative outcomes and largely vary by a surgeon's institution and training history. What follows here is a generalized description based on commonly performed techniques at The Johns Hopkins Hospital.

Abdominal Exploration

The abdomen is explored through either a limited midline laparotomy or via diagnostic staging laparoscopy depending on the surgeon's preference. An initial exploration is emphasized. The peritoneal cavity is closely inspected for evidence of tumor spread, including all visceral and parietal peritoneal surfaces, the omentum, and entire bowel. Intraoperative ultrasound enables better

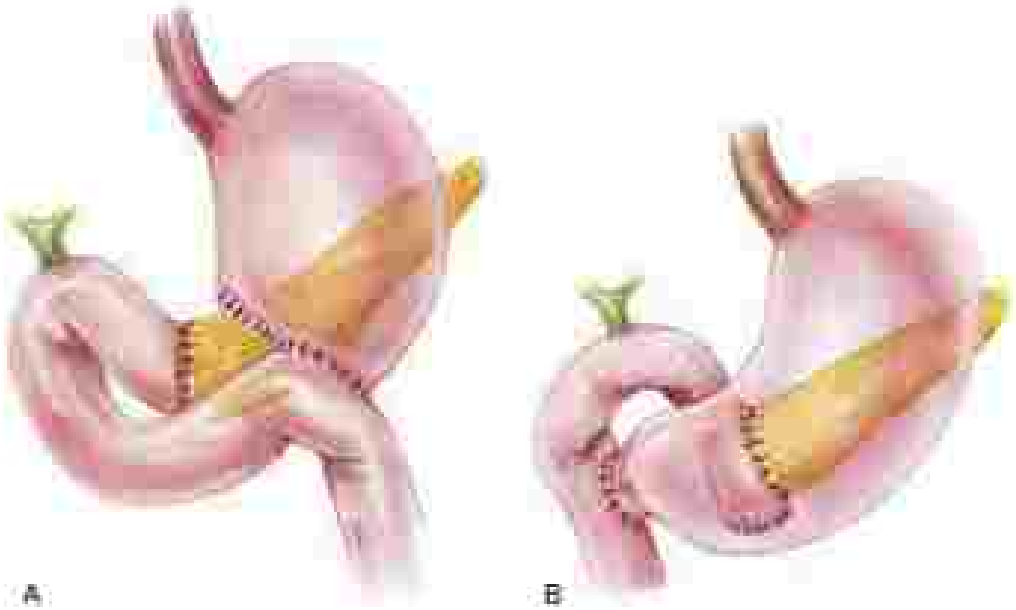

FIG. 1 Standard pancreaticoduodenectomy with hemigastrectomy and gastrojejunostomy (A) versus pylorus-preserving pancreaticoduodenectomy with duodenojejunostomy (B). (From Cameron JL, Sandler C. Atlas of Gastrointestinal Surgery, vol 1. 2nd ed. Shelton CT: People's Medical Publishing House; 2007.)

characterization of indeterminate hepatic lesions found on preoperative imaging, and biopsy with frozen sectioning allows for definitive evaluation of suspicious tissue prior to committing the patient to PD.

Open Resection

After it is deemed appropriate to proceed with PD, the incision may be extended or if a diagnostic staging laparoscopy was utilized, a laparotomy may then be performed. Many surgeons mobilize the hepatic flexure of the colon and the proximal transverse mesocolon with a generous Kocher's maneuver. Extensive Kocher's maneuver to the level of the left renal vein allows better exposure posterior to the portal vein (PV) and superior mesenteric vein (SMV). After removing lymphatic tissue around the left renal vein and retroabdominal aorta (station 16), the root of the superior mesenteric artery (SMA) can be exposed. The lesser sac is entered and the transverse mesocolon is separated from the base area of the duodenum and pancreatic head. The middle colic vein is traced down to its union with the right gastroepiploic vein, which classically forms a common trunk (i.e., gastrocolic trunk or trunk of Henle) draining into the SMV. The gastroepiploic vein is ligated and anterior exposure of the SMV is obtained.

Portal lymphadenectomy is performed after dissecting the gallbladder down from the hepatic cystic plate with the goal to skeletonize the three portal tubular structures. The common hepatic duct (CHD) is divided near the cystic duct junction. The PV is skeletonized and followed down to the pancreatic neck. Care is taken to identify and preserve any variant hepatic arterial anatomy, most commonly a replaced right hepatic artery, which can be found in up to 15% of patients. After identifying the origin of the gastroduodenal artery (GDA) from the common hepatic artery (CHA), the GDA is test clamped to ensure the patient has adequate flow to the proper hepatic artery (PHA). Some patients with celiac stenosis become reliant on retrograde flow from the GDA to supply the liver, therefore ligating the GDA in these patients can be catastrophic. Celiac stenosis identified from preoperative imaging should be addressed prior to proceeding with the PD. After GDA test clamping, the GDA is doubly ligated with silk tie and suture ligated with Prolene and divided. We add a surgical clip to the GDA stump to aid in angiographic identification should a GDA pseudoaneurysm develop postoperatively. In a standard PD, the stomach is divided proximal to the antrum with a GI or linear GIA stapler.

The jejunum is divided with another firing of the stapler 20 cm distal to the ligament of Treitz (Trotz). Dissection of the small bowel mesentery is carried proximally until the Treitz is divided and the distal duodenum and proximal jejunum can be passed underneath the superior mesenteric vessels into the previous plane of dissection on the patient's right side. At this point, a tunnel between the SMV-PV confluence and the pancreatic neck is carefully made from above and below. The pancreatic neck is divided with attention to protect the underlying PV and SMV.

The pancreatic neck and head can now be carefully dissected off of the PV-SMV junction, taking care to identify and control major venous tributaries that include the vein of Belcher (superior pancreaticoduodenal vein) and the first jejunal branch of the SMV. The PV and SMV are retracted to the patient's left to expose the uncinate process and the right side of the SMA. The inferior pancreaticoduodenal artery should be ligated during the separation of uncinate from the SMA. The surgical specimen should now be free and sent to pathology for evaluation. We routinely check intraoperative frozen sections of the pancreatic neck and uncinate margins, and the CBD margin if applicable.

Open Reconstruction

Sequential reconstruction includes PJ, hepaticojejunostomy (HJ), and GJ for standard PD or duodenojejunostomy for PPPD. For construction of a retrocolic PGHJ, the jejunal limb is passed through the transverse mesocolon to the right of the middle colic vessels. The GJ is typically created to an antecolic fashion via a Hofmeister or Reichel-Polya anastomosis.

As various elements of the PD have evolved and improved over the past several decades, the proclivity for the PJ to leak remains the operation's Achilles' heel. A variety of techniques have been developed in an attempt reduce the incidence of PJ leak, some of which have been shown to be superior. These include the broad categories

of anastomotic suture dehiscence. We commonly perform an end-to-side two layer duct-to-mucosa PJ consisting of an interrupted, nonabsorbable outer layer and interrupted absorbable inner layer. We typically use a 3.5 Fr pediatric feeding tube as a stent across the PJ. The JJ is created 5-10 cm distal on the antimesenteric jejunal limb in a position that prevents undue tension or twisting on either anastomosis. This is performed in a single layer interrupted fashion with absorbable suture. Finally, the GJ is created in an antecolic fashion using either a two layer handsewn technique with absorbable suture, or with a stapler near the greater curve of the stomach with the common enterotomy closed with two layers of absorbable suture.

Two soft, closed suction drains are placed anterior and posterior to the JJ and PJ in most cases to monitor for and drain a postoperative pancreatic fistula (POPF). Recent multiinstitutional data suggest that drains can safely be precluded altogether in patients at low risk for POPF as determined by their Fistula Risk Score. If a drain is placed, early removal based on drain amylase levels has been associated with lower clinically significant POPF rates as well as shorter hospital stays.

Major Vascular Resections

Venous Resections

Resection of the portomesenteric confluence is performed when it is not technically feasible to dissect the pancreatic tumor off the underlying veins without leaving gross disease behind or if dissection cannot be performed safely. If venous resection is to be undertaken, vascular control proximal and distal to the PV-SMV confluence must be obtained. The type of venous reconstruction is based on the longitudinal and circumferential degree of vein involvement. When a limited aspect (less than one third circumference) of the vein requires resection, tangential resection with primary closure or patch venoplasty is sufficient. More extensive involvement generally requires segmental resection with either a primary anastomosis or interposition graft repair. Defects of up to 3 cm can be anastomosed primarily with appropriate mobilization (Fig. 2). If the vein ends cannot be reapproximated without undue tension, we prefer using an autologous vein graft (e.g., left renal, saphenous, jugular vein) over synthetic (e.g., polytetrafluoroethylene, Gore-Tex) grafts owing to the potential for infection and reduced long-term patency rates.

Finally, in selected patients with preoperative venous occlusion in whom adequate portomesenteric collateralization has developed, SMV resection without reconstruction can be performed safely. However, this approach should be reserved for high volume centers with experience in this technique.

Arterial Resections

Major arterial resections for PDAC remain controversial. Poor overall survival combined with significant morbidity associated with arterial reconstructions limit the potential benefit of these procedures. Isolated CHA resection can be amenable to primary anastomosis. SMA resection with autologous vein or arterial transposition can be performed in highly selected cases. We do not recommend routine use of SMA resection, as the aggressive biology of PDAC often supersedes the survival benefit of these radical resections.

Minimally Invasive Approaches

PD via minimally invasive surgical (MIS) approaches has gained popularity over the last decade. Included among these are laparoscopic PD, robotic PD (RPD), and combined modalities. Multiple reports have demonstrated oncologic equivalence when comparing MIS and open PD, and associate the MIS approach with decreased pain, shorter length of stay, and fewer wound

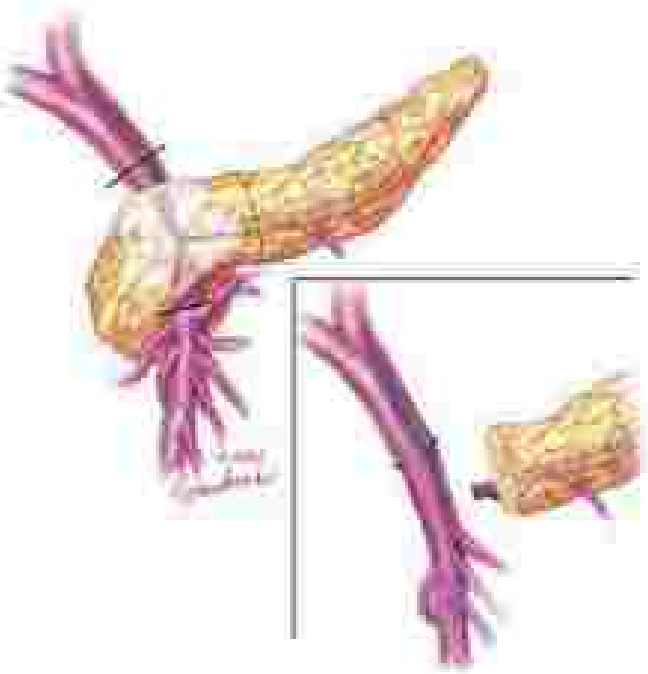

FIG. 2 Resectable tumor involvement at the portal vein–superior mesenteric vein (PV-SMV) confluence. Title is considered resectable because involvement is limited to a single target vessel above and below the accessory region of resection (black line) and does not extend too high on the PV. The vein segment and tissue are resected en bloc, followed by a primary end-to-end reconstruction (vein). Ligation and division of the splenic vein, even absent direct involvement, is often necessary to mobilize the PV and SMV sufficiently for primary anastomosis. (Courtesy Carrie Cunningham, Johns Hopkins Medicine.)

complications. Although no study has clearly demonstrated an oncologic benefit with MIS PD, many proponents believe it has the potential to decrease postoperative complications that may delay or even prevent delivery of adjuvant therapy. A key for successful execution of MIS is careful selection of anatomically and pathologically favorable candidate patients, especially for surgeons new to the approach. Although multiple techniques have been reported, what follows is a description of the approach to RPD at The Johns Hopkins Hospital.

Robotic Pancreaticoduodenectomy Setup and Resection

The supine split leg position is convenient for the bedside assistant. After establishing pneumoperitoneum, we insert a 12-mm trocar in the umbilical position and utilize the robotic camera for a diagnostic staging laparoscopy to evaluate for both metastatic disease and anatomic features (e.g., adhesions) that may prohibit successful RPD. If deemed appropriate to proceed, four robotic trocars (8 mm) are placed transversely across the abdomen at the midpoint of the anterior superior iliac spine and the 12th rib, and the da Vinci Si system (Intuitive) is docked from the patient's left side (Fig. 3).

The ligamentum teres and falciform ligament are divided and secured with an endoloop that is then passed transabdominally to retract the liver anteriorly and cranially. The lesser sac is entered by dividing the gastrocolic ligament and the right gastroepiploic artery is controlled. After controlling the right gastric artery, an Endo GIA stapler is used to divide the stomach approximately 5 cm proximal to the pylorus. The portal triad is skeletonized to expose the CHA, CBD, PHA, and PV. The CBD is transected with scissors and controlled with a clipped vessel loop to limit bile leakage for the remainder of the resection. The PHA is traced proximally to identify the right gastric

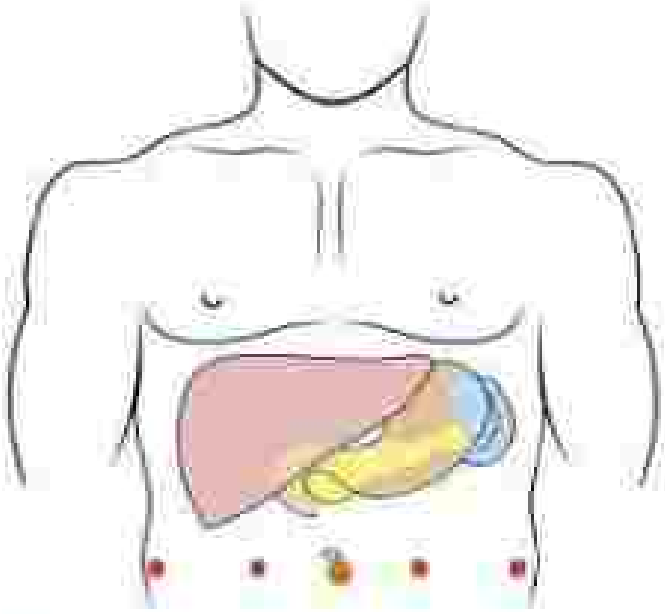

FIG. 3 Trocar placement for robotic pancreaticoduodenectomy. (Modified from Cubertt G, et al. Technical considerations for the fully robotic pancreaticoduodenectomy. JAMA Surg. 2013;148:1.)

FIG. 4 Intraoperative view of the cruse of Henle (arrow). SMV, superior mesenteric vein.

artery, GDA, and CHA. The right gastric artery is controlled with a clip and the GDA is ligated in a similar fashion to the open technique. The GDA is triply ligated with a 2-0 silk tie and clips and divided with the robotic scissors.

The PV is identified at the superior border of the pancreas, taking care not to divide the superior pancreaticoduodenal vein on the lateral side of the PV. The SMV is identified at the inferior border of the pancreas, taking care to identify the gastrocolic trunk of Henle. The trunk of Henle is dissected out sharply and the right gastroepiploic vein is ligated with clips and divided preserving the middle colic vein if technically feasible (Fig. 4). A retropancreatic tunnel on top of the PV is carefully created with blunt dissection. The neck of pancreas is divided with electrocautery or harmonic scalpel.

A Kocher maneuver is performed using a combination of electrocautery and the surgical energy. The inferior vena cava and abdominal aorta are exposed from the patient's right side. However, in contrast to open PD, the fascia can often be divided from the right side of the superior mesenteric vessels and the first portion of the jejunum is pulled through the native duodenal tunnel prior to division with the linear GIA stapler.

Transection of the uncinate along the right side of the SMA is the most challenging aspect of RPD. A vessel sealer can be used to separate the uncinate from the nearby SMA. However, in the setting of tumor abutting SMA, we will often use a combination of hook cautery, harmonic scalpel, and a bipolar Maryland clamp to more finely dissect the tissue off the SMA. Finally, the gallbladder is taken down from the cystic plate. The Whipple specimen and the gallbladder are removed from a Pfannenstiel's incision using a large Endo Catch (Medtronic) bag.

Robotic Pancreaticoduodenectomy Reconstruction

After hemostasis is confirmed, the anastomoses are performed in the same order as open PD: PJ, followed by HJ, and finally the GJ. We favor a retrocolic and to side two layer PJ, with the posterior row comprised of a 3-0 running V Loc suture (Covidien), 5-6 pulse rapid PDS for the inner duct to mucosa layer, and the anterior row comprised of an additional 3-0 running V Loc suture. As in open PD, we typically stent the PJ with a pediatric feeding tube. The HJ is created 5 to 10 cm distal to the PJ using 3-0 PDS suture in an interrupted fashion. The anastomosis typically requires 10–12 interrupted sutures depending on the size of the bile duct. Finally, we create an antecolic side to side isoperistaltic GJ with a blue load Endo GIA stapler, closing the enterotomy with a 3-0 V Loc suture in two layers. We routinely use the existing lateral robotic port sites to place two 19Fr closed suction Blake drains anterior and posterior to the PJ.

POSTOPERATIVE CARE

Over the past decade, enhanced recovery after surgery (ERAS) protocols have introduced evidence based pathways to standardize and improve the postoperative care of patients undergoing PD. Although specific ERAS guidelines vary by institution, the ERAS Society has published PD specific recommendations based on available evidence. These include preoperative smoking cessation, avoidance of hyperglycemia, an attempt at near zero fluid balance, early drain removal, early feeding, and early/scheduled postoperative mobilization (Table 2). ERAS programs have repeatedly demonstrated an ability to decrease the length of hospital stay, however, high quality studies showing their effects on other important endpoints are limited. These serve as general guidelines to help specialize postoperative care systems, and should not take precedence over a clinician's clinical judgment while caring for individual patients.

POSTOPERATIVE COMPLICATIONS

As PD entered the second decade of the twenty first century mortality continues to decrease at high volume centers. However, morbidity associated with the procedure remains high even in experienced hands. The most common postoperative complications are delayed gastric emptying (DGE; 10% to 45%), POPF (7% to 25%), and wound infection (10% to 40%). Postpancreatectomy hemorrhage (PPH) is another important complication that occurs less frequently, however, has potentially devastating and life threatening consequences if not managed appropriately.

Delayed Gastric Emptying:

DGE is a functional postoperative commonly occurring after PD. The International Study Group of Pancreatic Surgery (ISGPS) definition subcategorizes DGE into three classifications based on the severity

TABLE 2 Enhanced Recovery After Surgery Society Guidelines for Perioperative Care for Pancreaticoduodenectomy

Item	Summary and Recommendation	Evidence Level	Recommendation Grade
Preoperative counselling	Patients should receive dedicated preoperative counselling routinely	Low	Strong
Preoperative biliary drainage	Preoperative endoscopic biliary drainage should not be undertaken routinely in patients with a serum bilirubin concentration <250 μmol/L	Moderate	Weak
Preoperative smoking and alcohol cessation	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted.	Alcohol abstention: low Smoking cessation: moderate	Strong
Antithrombotic prophylaxis	Low molecular weight heparin reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk.	High	Strong
Antimicrobial prophylaxis and skin preparation	Antimicrobial prophylaxis prevents surgical site infections and should be used in a single dose manner initiated 30 to 60 minutes before skin incision. Repeated intraoperative doses may be necessary depending on the half life of the drug and duration of procedure.	High	Strong
Nasogastric intubation	Prophylactic use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely	Moderate	Strong
Fluid balance	Near zero fluid balance, avoiding overload of salt and water, results in improved outcomes. Perioperative monitoring of stroke volume with transesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9% saline solution.	Fluid balance: high esophageal Doppler: moderate Balanced crystalloids vs 0.9% saline solution: moderate	Strong
Perianastomotic drain	Early removal of drains after 72 hours may be advisable in patients at low risk (i.e., amylase content in drain <5000 U/L) for developing a pancreatic fistula. There is insufficient evidence to recommend routine use of drains, but their use is based only on low-level evidence.	Early removal: high	Early removal: strong
Somatostatin analogues	Somatostatin and its analogues have no beneficial effects on outcome after pancreatic oduodenectomy. In general, their use is not warranted. Subgroup analyses for variability in the texture and duct size of the pancreas are not available.	Moderate	Strong
Urinary drainage	Transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated.	High	Strong
Delayed gastric emptying	There are no acknowledged strategies to avoid delayed gastric emptying. Artificial nutrition should be considered selectively in patients with delayed gastric emptying of long duration.	Very low	Strong
Stimulation of bowel movement	A multimodal approach with epidural and near zero fluid balance is recommended. Oral laxatives and chewing gum given postoperatively are safe and may accelerate gastrointestinal transit.	Laxatives: very low Chewing gum: low	Weak
Postoperative artificial nutrition	Patients should be allowed a normal diet after surgery without restrictions. They should be continued to begin carefully and to ensure intake according to tolerance over 3 to 4 days. Enteral tube feeding should be given only on specific indications and parenteral nutrition should not be employed routinely.	Early diet as well: moderate	Strong
Early and scheduled mobilization	Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet daily targets for mobilization.	Very low	Strong

Modified from Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2013;37:240–258.

TABLE 3 International Study Group of Pancreatic Surgery Consensus Definition of Delayed Gastric Emptying

Grade	Nasogastric Tube Requirement	Days of Oral Intolerance (POD)	Vomiting and Gastric Distention	Use of Prokinetics
A	6 to 7 days or reinsertion >POD 3	7	+	+
B	8 to 14 days or reinsertion >POD 7	14	+	+
C	>14 days or reinsertion >POD 14	21	+	+

Definition: functional gastropareses after surgery without mechanical obstruction as determined by upper gastrointestinal contrast series or endoscopic evaluation.

Modified from Wente MN, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–768.

POD, postoperative day.

BOX 1 2016 International Study Group of Pancreatic Surgery updated criteria for postoperative pancreatic fistula

Amylase >3 times upper limit institutional normal serum amylase value

↓

Biochemical leak

↓

Persistent drainage >3 weeks*; clinically relevant change in management of postoperative pancreatic fistula, percutaneous or endoscopic drainage*; angiographic procedures for bleeding*; signs of infection without organ failure*

↓

Grade B pancreatic fistula

↓

Reoperation;* organ failure;* death*

↓

Grade C pancreatic fistula

Modified from Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 13 years after. Surgery. 2017;161:584–591.

*Condition exists postoperative pancreatic fistula criteria.

of symptoms and the necessity of required interventions (Table 3). The pathophysiology of DGE is not fully understood but is likely multifactorial and modulated by both technical factors and consequent patient morbidity. The management is primarily supportive and involves ruling out other causes of oral intolerance with diagnostic and cross-sectional imaging. A 2016 Cochrane review found no difference in DGE rates when comparing standard PD versus PPPD and antecolic versus retrocolic GJ. When compared to end-to-side GJ, several studies have demonstrated lower rates of DGE when performing side-to-side GJ; however, both are commonly performed at high volume centers.

Pancreatic Fistula

POPF remains one of the most recalcitrant complications after all types of pancreatic surgery. Its severity can range from an asymptomatic laboratory finding to a life threatening systemic condition (Box 1). Multiple technical adaptations to the PJ have been attempted over the years, including invaginations, duct to mucosa anastomoses, and multiple layer closures, none of which have demonstrated a difference in rates of POPF. Stenting across the PJ has also failed to show any effect on POPF rates in multiple studies, but is still commonly performed. Over time, the most reliable predictors of POPF development have been patient- and procedural-related factors including gland texture, duct diameter, intraoperative blood loss, and underlying pancreatic pathology. These factors comprise a commonly used Fistula Risk Score calculator, which some surgeons use to determine the need for postoperative percutaneous external drainage. Conservative management results in spontaneous fistula closure in up to 90% of cases, usually within 4 weeks. Parenteral nutrition and octreotide analogues may also play a role in reducing fistula output. On rare occasions, patients with severe clinical instability or signs of sepsis and organ dysfunction may require surgical reexploration and repair or revision of the PJ anastomosis.

Postpancreatectomy Hemorrhage

PPH is potentially one of the most lethal complications following PD, particularly if not diagnosed and treated expeditiously (Table 4). Early PPH is most commonly the result of inadequate surgical hemostasis and is best treated with a return trip to the operating room. Late PPH often results from inflammatory process (e.g., intestinal ulceration, POPF) leading to arterial pseudoaneurysm formation, rupture, and hemorrhage. CHA pseudoaneurysm rupture is classically seen 5 or more days postoperatively and can be preceded by a "so called *herald bleed*." Interestingly, the presenting location of the hemorrhage can be either an intraluminal or intraabdominal, often obfuscating the diagnosis. In either case, pseudoaneurysmal bleeding is best treated with endovascular coil embolization or covered stenting, depending on the precise location and anatomy.

TABLE 4 International Study Group of Pancreatic Surgery Consensus Definitions of Postpancreatectomy Hemorrhage

A. DEFINITIONS	
Time of Onset	
Early hemorrhage (< 24 hours after the end of the index operation)	
Late hemorrhage (> 24 hours after the end of the index operation)	
Location	
Intraluminal (anastomotic suture line, cut surface of the pancreas, ulceration, pseudoaneurysm)	
Extraluminal (arterial or venous vessels, diffuse bleeding from resection area, anastomotic suture lines, pseudoaneurysm)	
Severity of Hemorrhage	
Mild	
Decrease in hemoglobin concentration <3 g/dL	
No significant clinical impairment	
Transfusion of no more than 2 to 3 units packed cells within 24 hours of surgery or 1 to 3 units beyond 24 hours	
No requirement for reoperation or interventional angiographic embolization	
Severe	
Decrease in hemoglobin concentration >3 g/dL	
Clinically significant impairment (tachycardia, hypotension, oliguria, hypovolemic shock)	
Transfusion requirement >3 units packed cells	
Need for invasive treatment (interventional angiographic embolization or relaparotomy)	

B. GRADING SCALE		
Grade	**Onset, Severity, and Location**	**Clinical Condition**
A	Early, mild, intraluminal or extraluminal bleeding	Good
B	Early, severe, intraluminal or extraluminal bleeding Late, mild, intraluminal or extraluminal bleeding	Good to moderately impaired
C	Late, severe, intraluminal or extraluminal bleeding	Severely impaired, life-threatening

Modified from Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142:20–25.

SUMMARY

Periampullary cancer is a heterogeneous group of malignancies presenting unique challenges in its diagnosis and management. Modern therapies require a multidisciplinary treatment team and multimodality therapy. PD is the surgical treatment for these cancers and prognosis is overwhelmingly determined by a patient's disease biology. Advances in MIS techniques and new multimodal therapies offer the prospect for improved outcomes to patients with these difficult diseases.

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Vascular Reconstruction During the Whipple Operation

Ammar A. Javed, MD, and Christopher L. Wolfgang, MD, PhD

The development of multidrug regimens such as gemcitabine/nab paclitaxel or the FOLFIRINOX regimen for use in patients undergoing oncologic resection of localized pancreatic cancer (pancreatic ductal adenocarcinoma [PDAC]) has resulted in improved systemic control. Over this same time, improvements in radiation delivery in the form of stereotactic body radiation have improved the ability to achieve an R0 resection in patients with major vessel involvement (stage III). Taken together, the improved systemic control and ability to achieve clear margins had led to more aggressive surgical approaches to PDAC. The cancer specific outcomes with these more complex operations are superior to what was reported historically with less advanced tumors. Moreover, these operations can be performed with low mortality, acceptable morbidity, and a high likelihood of returning to a good quality of life. Resection and reconstruction of the portomesenteric axis with a Whipple operation has become commonplace. The resection and reconstruction of major arteries such as common hepatic artery and superior mesenteric artery (SMA) remains controversial and is performed infrequently currently. The exception to this is the resection of cancers of the body of the pancreas that involve the celiac axis and are resected through a distal pancreatectomy/splenectomy with en bloc resection of the celiac trunk.

This chapter discusses what determines resectability in patients with stage III (major vessel involvement) PDAC of the head of the pancreas, as well as the pertinent surgical anatomy and surgical technique.

PREOPERATIVE EVALUATION AND DETERMINING RESECTABILITY

A high quality pancreas protocol computed tomography (CT) is the single most important test in determining resectability as it is very accurate in assessing the local tumor relationships with the major vessels. A pancreas protocol CT consists of a dual phase CT with arterial and venous phase imaging. Arterial phase images are acquired at 25 to 30 seconds after intravenous (IV) contrast injection, and venous phase images are acquired 60 to 70 seconds postinjection. The contrast is infused through a peripheral IV at 4 to 5 mL/s and water (1000 mL) is used as an oral contrast agent. All images are reviewed in axial, multiplanar (coronal and sagittal planes), and three-dimensional volume rendering and maximum intensity projection. Recent improvement in imaging and the introduction of cinematic rendering (Fig. 1), has significantly improved the ability to appreciate the extent of vascular involvement, and its use is recommended for the evaluation of these patients at all centers where this modality is available. This should not be accomplished by routine exploration of stage III disease. Fig. 1 shows examples of each.

Localized pancreatic cancer that involves the main arteries of the upper abdomen (SMA, common hepatic artery, or celiac trunk) or the portomesenteric axis is classified as stage III. The degree of vascular involvement is determined and can be classified according to the classification system proposed by Ishikawa (Fig. 2). Two joint consensus statements divided stage III pancreatic cancer into either borderline resectable or locally advanced based on the extent of vessel involvement. The details of this staging system are beyond the scope of this chapter; however, controversy exists among high volume surgeons in regard to what defines resectable and on whom should be explored. In general, borderline resectable consists of patients whose have portomesenteric involvement that is technically reconstructible or no more than abutment of a major artery, while locally advanced patients have portomesenteric involvement that cannot be reconstructed or complete encasement of a major artery. Patients with borderline resectable tumors have a high probability of an oncologic resection and should undergo exploration. Certainly a significant percentage of patients classified as locally advanced and "unresectable" can actually undergo an oncologic resection. Determination of which patients in this category should undergo exploration is much more nuanced than borderline resectable and beyond the scope of this chapter.

PDAC is a highly systemic disease marked by early dissemination and most often presenting as metastatic disease. Even in the minority of patients who are diagnosed with localized and potential curable cancers, the predominant pattern of failure following resection is systemic. Thus, to cure localized pancreatic cancer two battles need to be won, a local battle fought with surgical resection and in some cases with the addition of radiation, and a systemic battle fought with chemotherapy and/or biological therapy. All stage III patients should undergo preoperative therapy (neoadjuvant to borderline resectable and induction to locally advanced) before exploration.

SURGICAL ANATOMY OF THE PORTAL VEIN AND SUPERIOR MESENTERIC VEIN

The confluence of the superior mesenteric, splenic, and portal veins is located posterior to the pancreatic neck. The main trunk of the superior mesenteric vein (SMV) is constituted from the jejunal and ileal branches that merge caudal to the pancreas. This main trunk drains the gastrocolic, and middle colic veins. The inferior mesenteric vessel can either drain into the splenic vein before its confluence with the portal vein (PV)/SMV or may directly drain into the SMV (Fig. 3).

The first jejunal branch of the SMV is frequently located posterior to the SMA as it enters the posteromedial ileal branch. This is the junction where these two structures merge to form the main trunk of the SMV. The jejunal branch also receives a branch from the uncinate process as it passes posterior to the SMA.

SURGICAL TECHNIQUE

Tumors of the head of the pancreas are resected through a Whipple operation that removes the distal stomach, the duodenum, and a small portion of the proximal jejunum, the gallbladder, distal bile duct, and the head of the pancreas. The enteric reconstruction consists of three anastomoses: pancreaticojejunostomy (or less commonly pancreaticogastrostomy), hepaticojejunostomy, and a gastrojejunostomy. The details of the standard Whipple operation are described elsewhere in this text. The modifications of the procedure for involvement of the portal vein, splenic vein, and SMV confluence are described within this chapter.

The general principle of approaching tumors of the confluence is to perform the entire dissection leaving the specimen attached only to the PV/SMV and then clamping and resecting the vein to remove the specimen. Specifically, the colon is mobilized off of the head of the pancreas, the duodenum is Kocherized, the common hepatic duct and stomach are divided. The jejunum is divided beyond the ligament of Treitz, the ligament is opened and the third and fourth portions of the duodenum and proximal jejunum are pulled beneath the superior mesenteric vessels into the right upper quadrant. Vascular control is then obtained with vessel loops on the portal vein superiorly and the SMV inferiorly. If the inferior mesenteric vein (IMV) aberrantly enters the SMV and not the splenic vein, a common variant, control of this vessel can also be obtained. In addition,

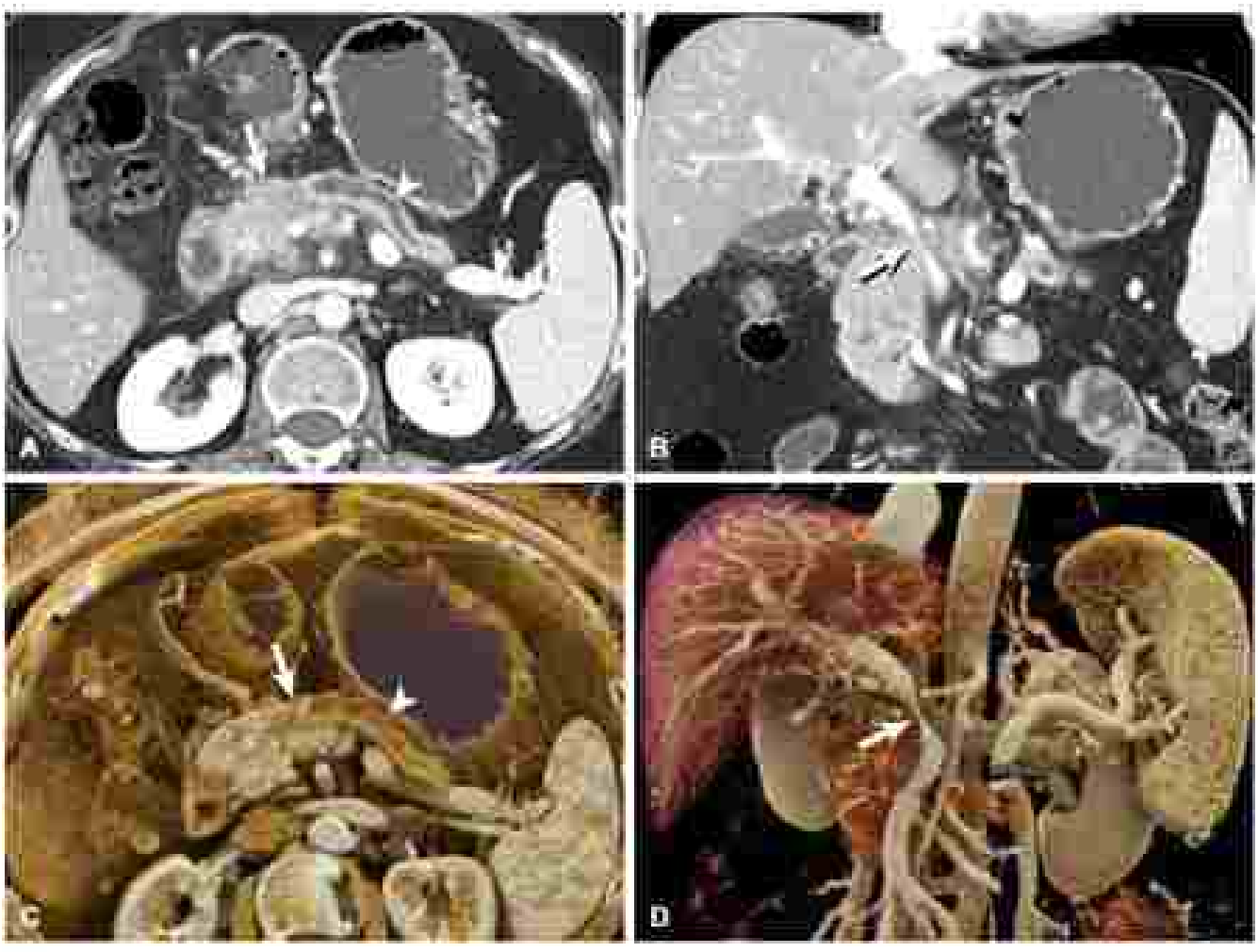

FIG. 1 Pancreatic adenocarcinoma with assessment of the portal vein–superior mesenteric vein confluence. (A) Axial portal venous phase computed tomography image demonstrating an ill-defined hypoenhancing mass in the pancreatic head (arrow) with abrupt caliber change of dilated main pancreatic duct (arrowhead). (B) Coronal portal venous phase computed tomography image shows tumor involvement and severe narrowing of the portal vein–superior mesenteric vein confluence (arrow). (C) Cinematic rendering of the pancreatic head mass (arrow) with dilated main pancreatic duct (arrowhead). (D) Cinematic rendering better illustrates the degree of portal vein–superior mesenteric vein narrowing (arrow) compared with (B) two-dimensional coronal reconstruction. *From Chu LC, Fishman EK. Cinematic rendering of pancreatic neoplasm: preliminary observations and opportunities. Radiol Imaging Cancer. Radiol. 2019;1:e190021.*

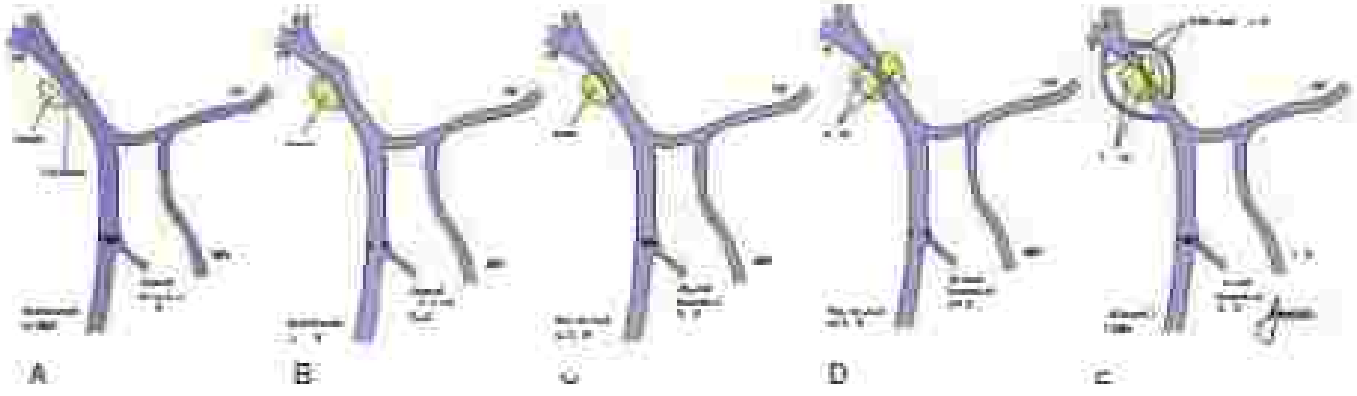

FIG. 2 Vascular classification of portal vein (PV), superior mesenteric vein (SMV) involvement. (A) Lateral venous wall tip plane between tumor and vessel. (B) Smooth shift of vessel with normal caliber. (C) Bilateral narrowing of vessel. (D) Bilateral narrowing of vessel with parietal lesion. (E) Bilateral narrowing of vessel with dilated lumen and formation of collateral veins. IMV, Inferior mesenteric vein; S, splenic vein.

the coronary vein entering the portal vein from the left should be ligated and divided. At this point, the tunnel can be created behind the neck of the pancreas realizing that the only major tributary that is not controlled is the splenic vein. Controlling the splenic vein is difficult prior to the division of the neck. Once the neck is divided, vessel loop control of the splenic vein should be obtained. The final step prior to en bloc resection of the PV/SMV is to divide the uncinate process in a manner that clears the right side of the SMA for 270 degrees in axial plane. The easiest way to accomplish this is to divide the splenic vein thus exposing the anterior wall of the SMA. This will allow retraction of the specimen to the right and the uncinate process can be divided to the left of the vein (Fig. 4). Alternatively, if the tumor involves the SMV only below the insertion of the splenic vein, the splenic vein can be preserved and the uncinate can be divided by retracting the PV/SMV anteriorly. Either way, at this time, the only structure attaching the Whipple specimen to the abdomen in the region of vascular involvement is the PV/SMV. Based on the extent of vascular involvement, appropriate resection and reconstruction is performed as detailed later in this chapter.

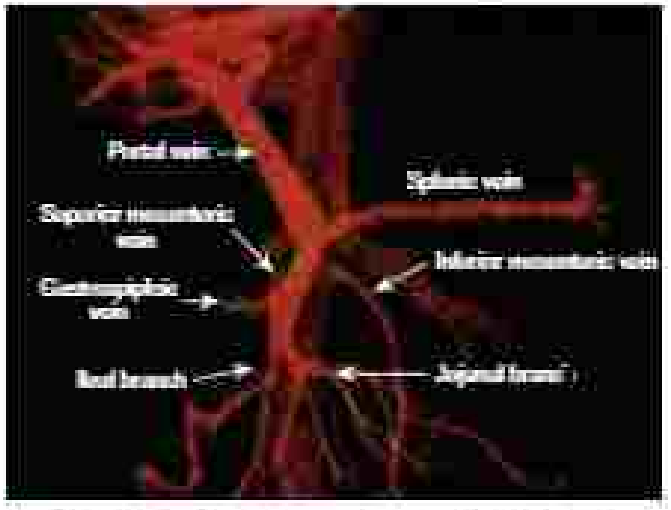

FIG. 3 Peripancreatic vascular anatomic structures. Volume-rendered computed tomography images show normal peripancreatic venous anatomic structures.

■ VENOUS RESECTION AND RECONSTRUCTION

Several techniques have been described to resect and reconstruct venous involvement of the PV/SMV. Four types have been proposed by the IHPBS (Fig. 5). The selection of the appropriate technique depends on the extent of vascular involvement, caliber of the vessel, extent of narrowing of vessel, and the surgeon's preference.

When there is invasion of a small circumference of the vessel, a vascular clamp can be placed to partially occlude the vessel, and a small tangential resection of the involved vessel can be performed (Fig. 6). This can be achieved by longitudinal dissection along the lateral aspect of the clamp. The use of a longitudinal incision is debatable, however, and some surgeons prefer a transverse incision because it minimizes the extent of narrowing of the vessel. Depending the size of the opening in the vessel and its caliber, the resulting defect can be closed primarily using a running 5-0 Prolene suture (lateral venorrhaphy or transverse venorrhaphy) (Fig. 7). If significant narrowing of the vessel is anticipated, the closure can be performed using a venous patch (patch venoplasty), which can be fashioned from the saphenous vein, portosomal patch, or a bovine pericardial patch (Fig. 7).

In the event of a more extensive encasement (circumferential involvement) of the confluence, a segmental resection may be required (Fig. 8). This can be reconstructed using multiple techniques depending on the length of the resected segment as well as the tension on the remaining distal and proximal ends (Fig. 9). For all cases requiring a segmental resection, the inflow and outflow control is established both proximal and distal to the tumor involvement by

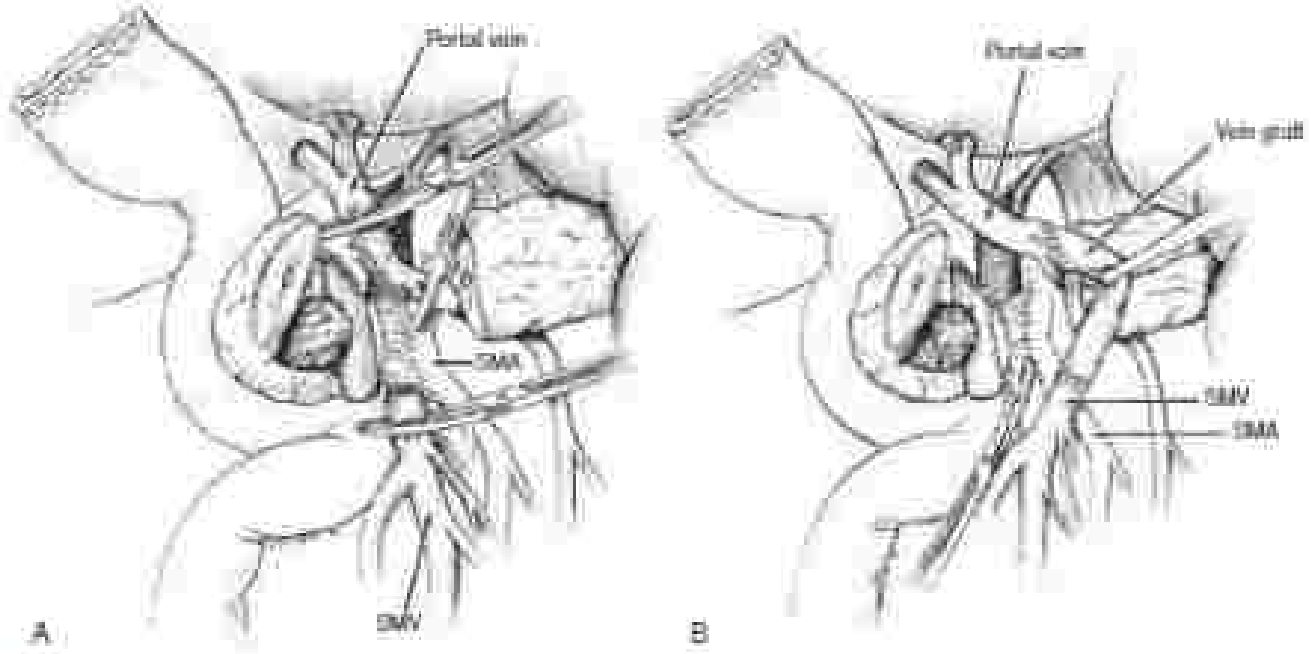

FIG. 4 Technique of venous resection and reconstruction. (A) Segmental resection of the superior mesenteric vein (SMV) is performed while the specimen is still attached to the superior mesenteric artery (SMA) before completion of the retroperitoneal dissection. (B) An internal jugular vein interposition graft enables distal retraction of the reconstructed superior mesenteric-portal vein confluence, allowing access to the retroperitoneum for standard dissection of the tumor from the lateral wall of the SMA. (From Hackert T, Loos M, Chermenegeli C, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. Br J Surg. 97:805[6]:811-817.)

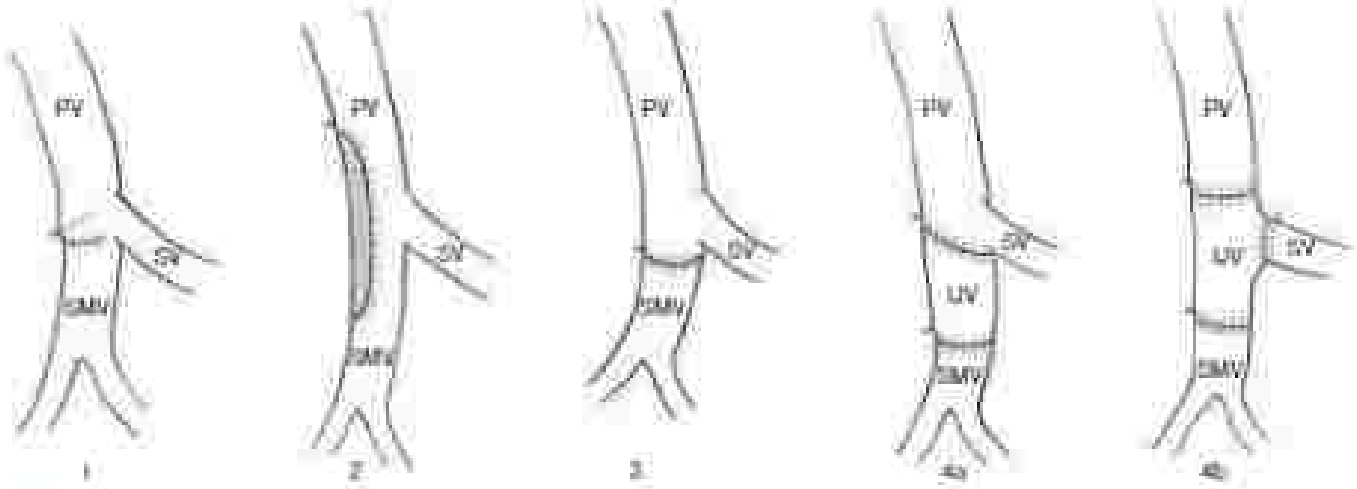

FIG. 3 Techniques of venous reconstruction according to International Study Group of Pancreatic Surgery classification. (1) Transverse venous closure. (2) Venous patch angioplasty. (3) Segmental venous resection and primary anastomosis. (4a) Interposition of the internal jugular vein (IJV) graft. (4b) Interposition of the SV graft with reanastomosis of the splenic vein (SV) to the IJV graft. *PV*, portal vein.

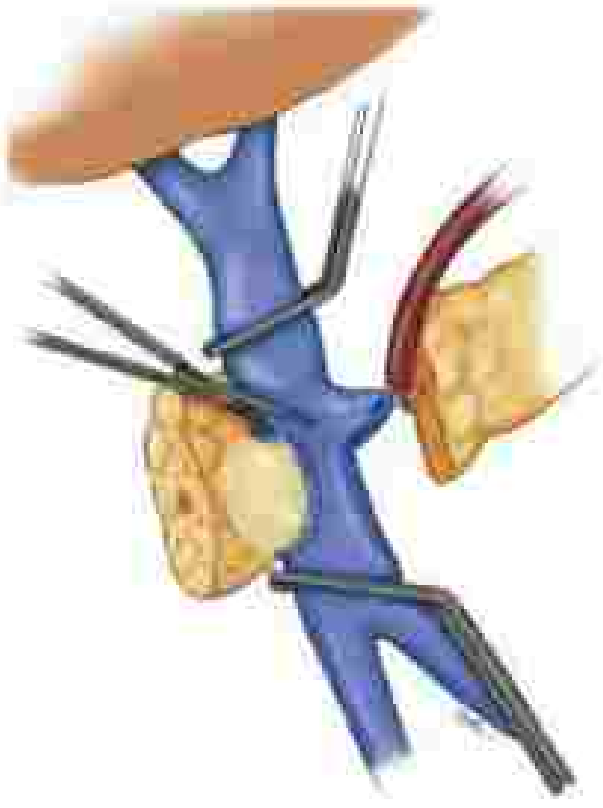

FIG. 4 Pancreatic tumor adherent to a small segment of the portal vein-superior mesenteric vein complex requiring tangential resection. (From Jarufe NP, Bond K, Fagenson A, et al. Pancreatic resections: comparison with venous resection and reconstruction. Current surgical techniques and associated postoperative imaging findings. Abdom Imaging. 2015;40(4):741–754.)

placing vascular clamps. The vessels are then divided both proximal and distal to the location of the tumor. Typically for a resected segment that is 3 to 4 cm in length a primary anastomosis can be performed by approximating the vessels. Once approximated, both ends are sutured together using a 5-0 Prolene suture in usual fashion to perform the anastomosis in a running manner (Fig. 9.4, B).

Rarely, the resected segment of vein is long and a primary anastomosis cannot be performed. In these cases, a venous interposition graft may be needed (Fig. 9.4, C) (3). The most suitable grafts are the internal jugular vein or the left renal vein between the SMV and the gonadal vein as their caliber is similar to that of the portal and superior mesenteric veins. The use of polytetrafluoroethylene as a graft is associated with high incidence of postoperative thrombosis and should not be performed.

It is unclear whether the splenic vein needs to be reimplanted when divided to resect and reconstruct the confluence. The rationale to do so is to avoid left-sided portal hypertension and gastric varices. In our practice, we implant the splenic vein if it receives flow from the IMV. If the IMV enters directly into the SMV, we do not reimplant the vessel.

We do not routinely systemically heparinize to reconstruction of the PV-SMV. However, it is performed by some groups using the intravenous administration of 2500 to 3000 units of heparin 2 to 3 minutes before the occlusion.

Recently, our institution has reported on a few cases of vascular resection without reconstruction in cancers with complete occlusion of the SMV with left-sided collateralization of venous return. In these cases, intraoperatively, the superior mesenteric vessel is ligated at the level of the ileal and jejunal branches, and no reconstruction is performed. Upon follow-up, these patients did not develop any complications of obstructed venous flow. Although this is not common practice, it might be a suitable option for select patients who present with localized disease with isolated involvement of the distal superior mesenteric vein and the presence of collateral vessels.

POSTOPERATIVE CARE

Although perioperative mortality of patients undergoing the Whipple operation has declined significantly, postoperative morbidity remains high. The most frequent complications include delayed gastric emptying, postoperative pancreatic fistula, postpancreatectomy hemorrhage, and surgical site infections. The routine postoperative management of patients undergoing a Whipple operation without vascular reconstruction is detailed in another chapter.

The postoperative management of patients who undergo the Whipple operation with vascular resection is similar to that of patients not requiring a vascular resection. In particular for these patients, although systemic anticoagulation is not required, 300 mg of rectal aspirin is administered daily until the patient is tolerating a regular diet at which time it is switched to 81 mg daily of oral aspirin.

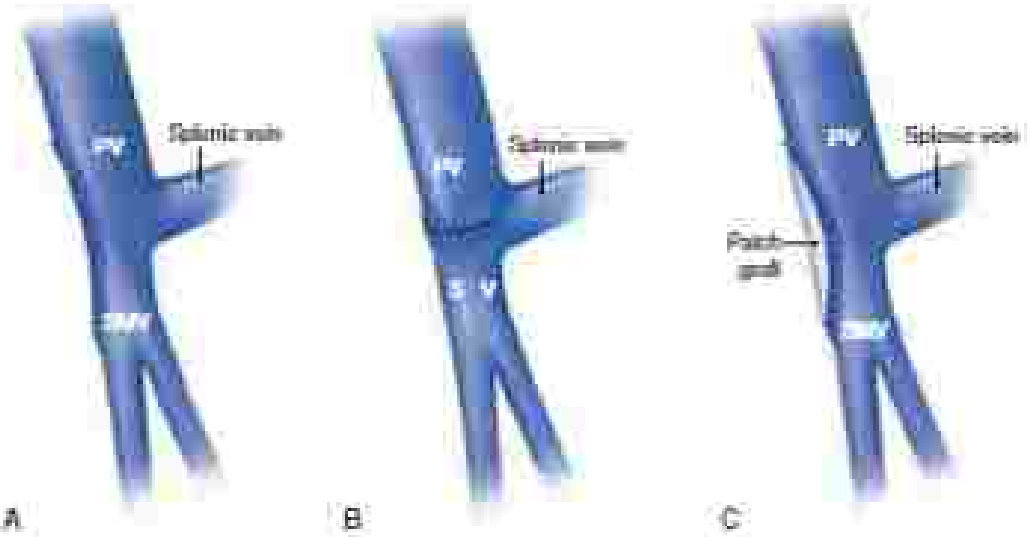

FIG. 7 Segmental resection of tumor and repair using (A) Primary venorrhaphy: longitudinal venorrhaphy. (B) Primary venorrhaphy: transverse venorrhaphy. (C) Patch venoplasty. *PV* portal vein; *SMV* superior mesenteric vein. (From Jagot AA, Black K, Ingraham A, et al. Pancreaticoduodenectomy with venous resection and reconstruction: current surgical techniques and associated postoperative imaging findings. Abdom Radiol (NY). 2019;44(1):119–129.)

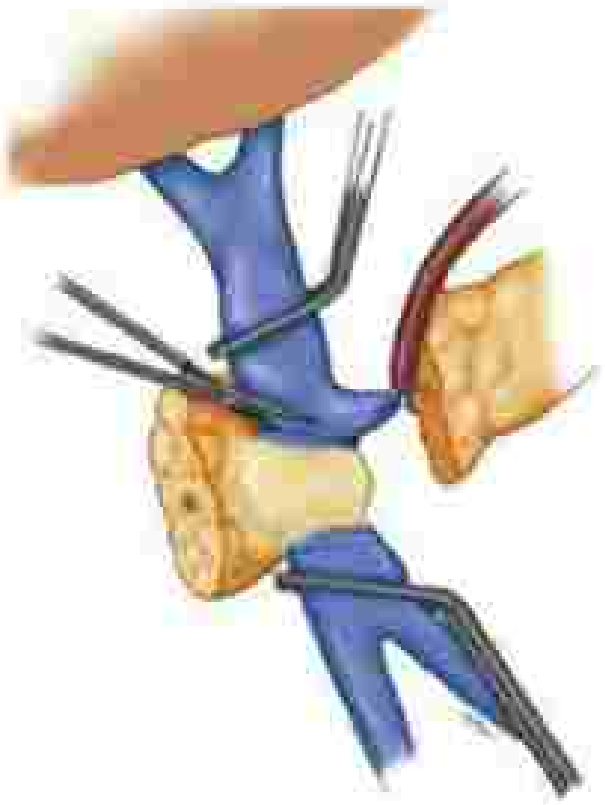

FIG. 8 Pancreatic tumor encasing the portal vein-superior mesenteric vein complex requiring segmental resection. (From Jagot AA, Black K, Ingraham A, et al. Pancreaticoduodenectomy with venous resection and reconstruction: current surgical techniques and associated postoperative imaging findings. Abdom Radiol (NY). 2019;44(1):119–129.)

Furthermore, the patient should be monitored for signs of thrombosis and graft occlusion. The most common signs of this are acute onset of ascites, oliguria, increased fluid requirement, and hypotension. Of note, the liver function tests may frequently be normal even with complete occlusion of the portal vein. If there is a suspicion for graft occlusion or thrombus, a duplex should be performed. In the event that the duplex is inconclusive because of presence of bowel gas or the dressing, a CT angiogram is warranted. For partial thrombosis and with no concern for a technical problem, systemic anticoagulation should be initiated. If complete occlusion exists and/or there is concern for a technical problem, the patient should return to the operating room for surgical thrombectomy and revision of the reconstruction.

POSTOPERATIVE APPEARANCE OF THE RECONSTRUCTED VENOUS VASCULATURE

One of the less frequently discussed aspects of vascular resection and reconstruction during a Whipple operation is the postoperative appearance of the reconstructed vasculature. A vast majority of patients who require these procedures are those that have malignant tumors of the pancreas. These tumors are at a high risk of recurrence; therefore, postoperative imaging is performed at regular intervals to rule out recurrence of disease. Interestingly, in patients undergoing a Whipple procedure with a concurrent vascular resection, aberrant or irregular appearance of the venous structures is common because of the new postoperative anatomy of the vessels.

Postoperative appearance of the venous vasculature was recently studied and defined by our group, and two distinct features of the vasculature were described that included changes to the appearance of the vasculature itself and identification of perivenous changes. Changes to the vasculature can be observed in approximately one half of all patients undergoing venous resections. These can be further classified into concentric smooth narrowing, eccentric irregular narrowing, or the presence of a thrombus (Fig. 10). The most frequent form is concentric smooth narrowing, whereas development of thrombus is a rare event. On the other hand, perivenous changes comprise perivenous fluid-like collections or perivenous soft tissue thickening that has a mass-like effect (Fig. 11). Perivenous changes are also frequently encountered in these patients, with perivenous fluid collections being more common of the two.

These changes observed on postoperative imaging overlap considerably with findings suspicious for the recurrence of disease. Interestingly, however, in the previously mentioned study on long-term follow-up, a majority of patients with these changes did not develop local recurrence, suggesting that these changes in fact are related to the surgically altered anatomy of the vasculature. We believe that a

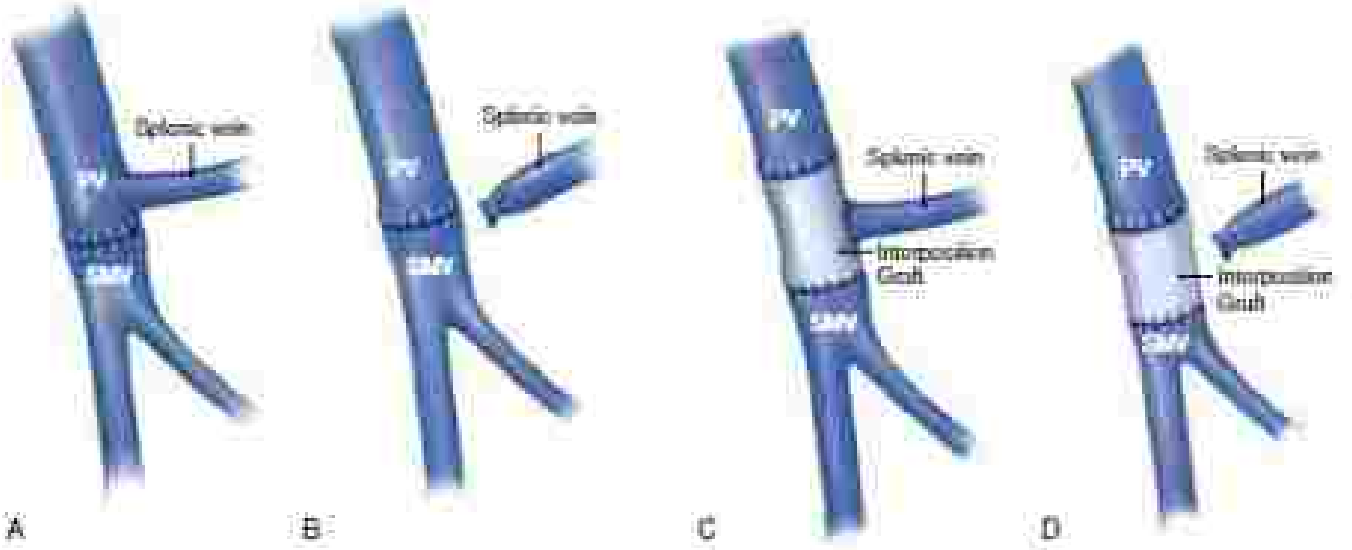

FIG. 9 Segmental resection of tumor and reconstruction with primary end-to-end anastomosis with (A) and without (B) preservation of the splenic vein. In cases of long segment resection, reconstruction can be performed with interposition graft, with (C) and without (D) preservation of the splenic vein. PV, portal vein; SMV, superior mesenteric vein. (From Jamil MA, Reich A, Segami J, et al. Pancreatoduodenectomy with venous resection and reconstruction: current surgical techniques and associated postoperative imaging findings. Abdom Radiol (NY). 2016;41(2):197–209.)

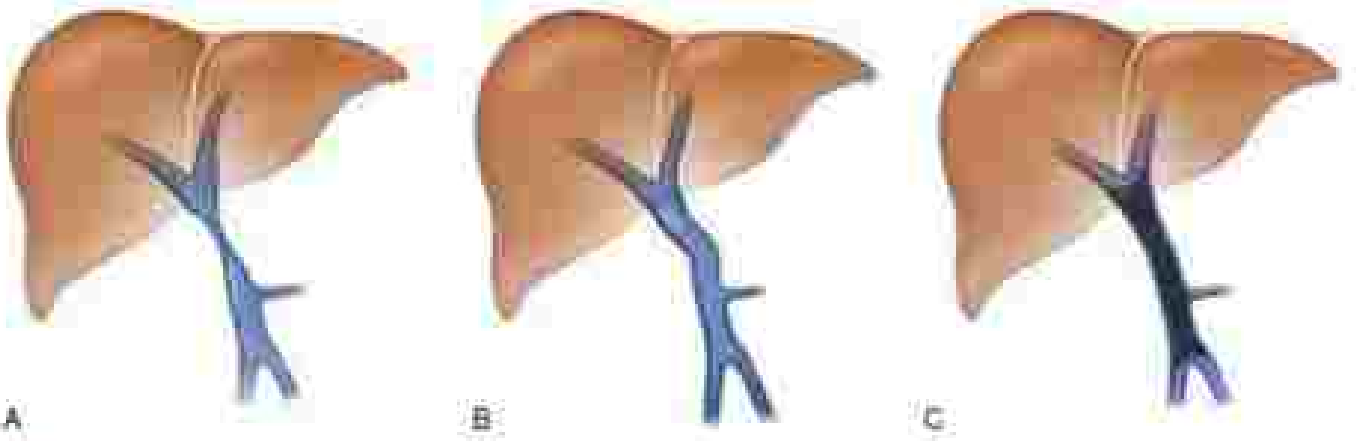

FIG. 10 Categories of postoperative portal vein (splenic mesenteric vein) complex changes. (A) Concentric smooth narrowing. (B) Eccentric irregular narrowing. (C) Venous thrombosis. (From Jamil MA, Reich A, Segami J, et al. Pancreatoduodenectomy with venous resection and reconstruction: current surgical techniques and associated postoperative imaging findings. Abdom Radiol (NY). 2016;41(2):197–209.)

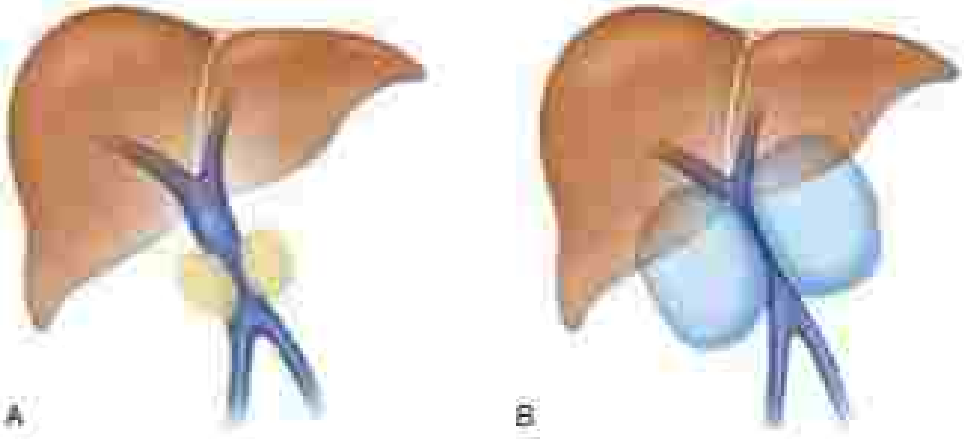

FIG. 11 Categories of peritoneal findings. (A) Peritoneal soft tissue thickening, which can have a mass-like appearance. (B) Peritoneal fluid collection. (From Jamil MA, Reich A, Segami J, et al. Pancreatoduodenectomy with venous resection and reconstruction: current surgical techniques and associated postoperative imaging findings. Abdom Radiol (NY). 2016;41(2):197–209.)

thorough knowledge of the postoperative appearance of the venous vasculature is important for all physicians involved in the care of these patients. If the radiologists, surgeons, or medical oncologists are not well versed in this area, there is a high risk of misdiagnosis of recurrence of disease, which in turn triggers a significant change in the management of these patients.

SUMMARY

With an increased utilization of effective systemic and locoregional therapies in the neoadjuvant setting, a significant proportion of patients with vascular involvement are now undergoing resection. Vascular resection and reconstruction add to the complexity of an already challenging surgical procedure; however, with appropriate preoperative imaging, thorough surgical planning, detailed knowledge of the available techniques, and surgical experience, these procedures can be performed safely. When performed by experienced surgeons at high-volume centers, outcomes similar to that of the standard Whipple operation can be achieved in patients undergoing these complex resections. The oncologic benefits of these procedures have been well established, and as these procedures become more common, patients who would have otherwise succumb to their disease will have a shot at undergoing curative resection. Last, changes in the postoperative appearance of the vasculature associated with altered vascular anatomy should be considered when evaluating these patients postoperatively to reduce the risk of misdiagnosis of recurrent disease.

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PALLIATIVE THERAPY FOR PANCREATIC CANCER

Ashley N. Knepline, MD, and Susan Tsai, MD, MHS

Patients with advanced pancreatic cancer often face myriad physical ailments. The overarching goal of palliative care is to improve in quality of life and alleviate pain and suffering for patients. Approaching patients about palliative care can be challenging because patients often have a misperception that palliative care is mutually exclusive from active cancer therapy. In reality, palliative care can be administered simultaneously with active cancer treatment and at times allows patients to return to a condition to be able to tolerate oncologic treatments. In other instances, focus on palliation of symptoms allows patients to achieve a better quality of life with their loved ones toward the end of life. Effective palliation of symptoms often requires consideration of the severity of symptoms while balancing the expected life expectancy and goals of care for the patient. Often, patients may present with multiple interrelated symptoms, which requires a multidisciplinary approach with the input of surgeons, medical oncologists, radiation oncologists, gastroenterologists, and radiologists to effectively address all symptoms. Guidance from palliative care specialists may further augment the development of a multidisciplinary, multimodal plan to comprehensively address symptoms while minimizing hospitalizations and ease the transition to end-of-life planning.

Because of the anatomic location, pancreatic cancers can affect adjacent structures through invasive growth and obstruction. Patients commonly experience gastric outlet obstruction from duodenal obstruction, distal biliary obstruction causing jaundice, and debilitating back or epigastric pain related to the tumor infiltration into the celiac plexus. In addition, debilitating ascites may occur either secondary to carcinomatosis or occlusion of the superior mesenteric vein/portal vein. Finally, patients with advanced pancreatic cancer have the highest rates of depression and suicide among all cancers. Effective counseling and medication can help to alleviate emotional pain and suffering. This chapter will provide an overview of palliative approaches for these problems.

INITIAL EVALUATION

Patients with advanced pancreatic cancer face difficult treatment decisions and open communication about goals of care will help patients to make sound, informed decisions. Fundamental questions which should be addressed with the patient and his/her family are summarized in Box 1. Understanding personal goals and preferences will help shape conversations about treatment recommendations and engage patients in shared decision-making. It is also important to elicit patient preferences for how information is communicated and what level of detail is suitable. Along with a foundational understanding, treatment goals should be revisited as necessary at future encounters. Longitudinal assessment of symptoms at the time of diagnosis and throughout the course of the treatment will help to identify and proactively address problems.

Patients with advanced pancreatic cancer are frequently monitored with imaging, such as a computed tomography (CT) scan of the chest, abdomen, and pelvis, and basic laboratory tests. Although these studies are obtained to assess treatment response, they should also be closely examined for impending complications. These may manifest as signs of current or impending biliary obstruction, bowel obstruction, ascites, tumor infiltration into the abdominal neural plexus (celiac axis), or significant portal venous narrowing/obstruction. In addition, routine assessment of pain, nausea, vomiting, abdominal distension, and cachexia can be helpful. Referral to palliative care services can facilitate addressing multiple symptoms. Notably, patients who are encouraged by palliative care specialists have been found to have decreased rates of intensive care admissions, emergency room visits, and repeated hospitalizations.

BILIARY OBSTRUCTION

More than 70% of patients with pancreatic cancer will present with biliary obstruction leading to jaundice and malabsorption. Jaundice can cause debilitating pruritus, abdominal pain, fatigue, weight loss, nausea, vomiting, and anorexia, which can be resolved with biliary decompression. Durable relief of biliary obstruction is necessary to improve quality of life and normalize liver function tests to allow initiation of chemotherapy. Several series have demonstrated that endoscopic retrograde cholangiopancreatography (ERCP) can

thorough knowledge of the postoperative appearance of the venous vasculature is important for all physicians involved in the care of these patients. If the radiologists, surgeons, or medical oncologists are not well versed in this area, there is a high risk of misdiagnosis of recurrence of disease, which in turn triggers a significant change in the management of these patients.

SUMMARY

With an increased utilization of effective systemic and locoregional therapies in the neoadjuvant setting, a significant proportion of patients with vascular involvement are now undergoing resection. Vascular resection and reconstruction add to the complexity of an already challenging surgical procedure; however, with appropriate preoperative imaging, thorough surgical planning, detailed knowledge of the available techniques, and surgical experience, these procedures can be performed safely. When performed by experienced surgeons at high-volume centers, outcomes similar to that of the standard Whipple operation can be achieved in patients undergoing these complex resections. The oncologic benefits of these procedures have been well established, and as these procedures become more common, patients who would have otherwise succumb to their disease will have a shot at undergoing curative resection. Last, changes in the postoperative appearance of the vasculature associated with altered vascular anatomy should be considered when evaluating these patients postoperatively to reduce the risk of misdiagnosis of recurrent disease.

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be safely and effectively performed in the vast majority of patients with malignant obstructive jaundice. Early complications after ERCP occur in 5% of patients and most commonly include ERCP-induced pancreatitis, infection, or bleeding. The most common delayed complication following biliary stenting to treat recurrent jaundice secondary to stent occlusion.

Self-expanding metal stents (SEMS) are clearly superior to plastic stents with regard to stent patency and stent-related complications. Because of the smaller lumen, plastic biliary stents are more likely to occlude from biliary sludge or bacterial overgrowth requiring frequent stent exchanges, whereas SEMS are more likely to be occluded with tumor ingrowth of the stent. In general, the patency of a plastic stent is proportional to the size of the stent, for example, an 8Fr stent will be patent for 8 weeks. In contrast, a 10 mm diameter SEMS will provide an equivalent drainage as nine 10Fr plastic stents, and therefore provide much more durable biliary drainage. Covered SEMS have become increasingly used and have demonstrated decreased rates of occlusion and therefore longer stent patency (Table 1). In addition to stent occlusion, another common complication of biliary stents is stent migration, which is more frequently seen with plastic and covered metal stents as opposed to uncovered SEMS.

Operative biliary bypass is an alternative strategy to allow for drainage of an obstructed biliary tree. There are several techniques that may be utilized for a biliary bypass. The most common and durable technique used is a retrocolic choledochojejunostomy with a Roux-en-Y reconstruction. Alternatively, a loop of jejunum may be used rather than a Roux-en-Y. This is a quicker operation and does not require a jejunojejunostomy but is associated with a higher incidence of cholangitis and is not preferred to the Roux-en-Y. If a patient has not had a prior cholecystectomy, a cholecystectomy should be performed in addition to the biliary drainage procedure, even in the absence of cholelithiasis or symptoms.

Resolution of biliary obstruction after endoscopic stent placement or surgical biliary bypass have been shown to be equivalent in several retrospective studies. In a series of 98 patients, 52 underwent surgical biliary bypass and 46 underwent placement of SEMS. Of the 52 patients undergoing surgical bypass, 38% developed perioperative morbidity and 7% with SEMS developed periprocedural complications. Recurrent biliary obstruction as a result of SEMS occlusion occurred in 40% of patients, whereas recurrent biliary obstruction was not identified in patients who underwent surgical bypass. However, the increased durability of a hepaticojejunostomy must be weighed against the potential for perioperative morbidity and an increased length of hospital stay (12 vs 3 days) when compared with SEMS. Biliary bypass has been shown to be more durable than SEMS placement, however, even when including procedure-related readmissions and repeat endoscopy for stent exchange. Biliary stent placement has also been associated with lower costs.

BOX 1 Questions Providers May Use to Engage Patients in Communicating Goals of Care

What is your understanding of your illness?
What are your hopes and fears?
What are your goals and priorities?
What outcomes are unacceptable to you?
What would a good day look like?

GASTRIC OUTLET OBSTRUCTION

Nausea and vomiting in patients with advanced pancreatic cancer can be due to mechanical and/or nonmechanical problems. An initial evaluation should include a thorough history and physical and radiographic studies to identify obstruction related either to the primary tumor (gastric outlet obstruction) or a metastatic deposit (malignant bowel obstruction). In the absence of a mechanical etiology, the symptoms may be related to malignant gastroparesis or to chemotherapy and may be best alleviated with pharmacologic agents. Patients with gastric outlet obstruction suffer from nausea, vomiting, anorexia, weight loss, and malnutrition. Clinical suspicion can be supported by the presence of a dilated stomach on CT scan, and may be confirmed by an upper gastrointestinal fluoroscopy or endoscopy to confirm the diagnosis (Fig. 1A). Traditionally, a gastrojejunostomy is performed to relieve the area of obstruction and palliate symptoms. Palliative gastrojejunostomy for malignant gastric outlet obstruction has been associated with a 30% rate of morbidity, but with advances in surgical treatment, the morbidity has decreased to approximately 10%. Gastrojejunostomy can be performed via an open or laparoscopic approach. Classically, a retrocolic gastrojejunostomy is performed by sewing the posterior wall of the stomach to a loop of jejunum in a stapled or handsewn side to side fashion. This approach is favored over a Roux limb to improve the emptying of the jejunal limb. Studies comparing efficacy of laparoscopic compared with open gastrojejunostomy are limited, however, current studies demonstrate a quicker return to oral intake with a laparoscopic approach and a trend towards decreased length of hospital stay.

More recently with the advent of endoscopic techniques, duodenal stenting has become an alternative strategy to manage malignant gastric outlet obstruction. Duodenal stenting has become a well-established technique to treat malignant gastric outlet obstructions (Table 2). A SEMS is endoscopically placed across a malignant stricture or area of narrowing. Duodenal stenting is typically associated with oral intake within 24 hours after placement, significantly faster than after an open bypass procedure. In a systematic review of 601

TABLE 1 Rates of Clinical Success and Complications Among Patients With Malignant Biliary Obstruction With Self-Expanding Metal Biliary Stents

Study	No. of Patients	Rate of Stent Occlusion (%)	Median Time to Uncovered Metal Stent Occlusion (mo)	Survival After Stent Placement (mo)
Fukuda et al, *BMC Gastroenterol*, 2007	84	65	6.6	6.7
Isayama et al, *Am J Gastrointest Endosc*, 2015	99	44	3.7	6.1
Kitano et al, *Am J Gastroenterol*, 2013	120	57	5.6	7.8
Yoon et al, *Dig Endosc*, 2013	107	34		6.8
Lee et al, *Gastrointest Endosc*, 2013	200	38	2e3	13.8
Matte et al, *Am J Gastroenterol*, 2016	58	21	7.0	
Dhir et al, *Dig Dis Sci*, 2013	84	14	8.3	

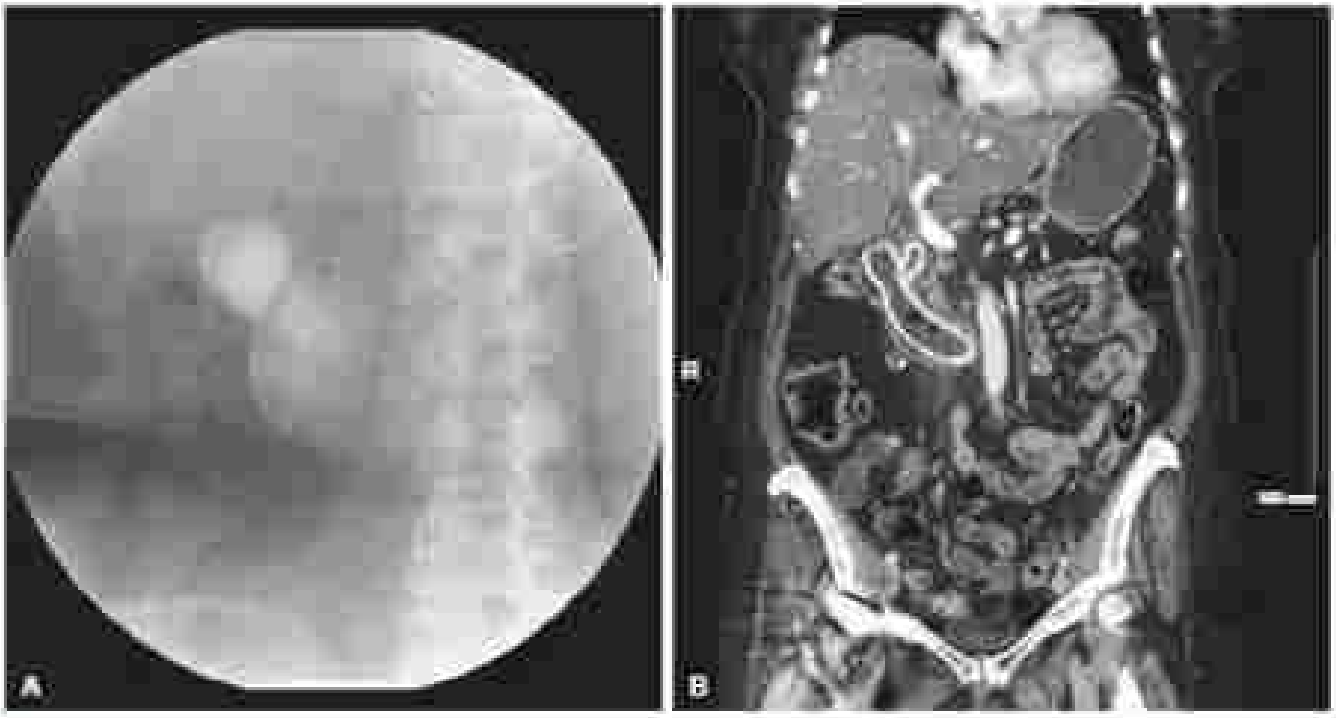

FIG. 1 Diagnosis and management of gastric outlet obstruction. (A) Upper gastrointestinal series demonstrating obstruction in the first portion of the duodenum. (B) Palliation with duodenal and biliary stenting.

TABLE 2 Rates of Clinical Success and Complications Among Patients With Malignant Gastric Outlet Obstruction Undergoing Duodenal Stenting

Study	No. of Patients	Median Survival (mo)	Clinical Success Rate (Tolerate Oral Intake) (%)	Complication Rate (%)
Ding et al. / Gastrointest Endosc 2013	94	3	90	5
Mutignani et al. / Endoscopy 2003	63	1.5	95	30
Dormann et al. / Endoscopy 2005	40	4	89	27
Mutter et al. / Am J Gastroenterol 2006	24	11	92	0
Graber et al. / Endoscopy 2007	31	2.5	84	11
Oh et al. / Gastrointest Endosc 2015	292	—	83	29

patients with malignant gastric outlet obstruction, duodenal stents were successfully placed in 97% of patients. Of the patients who underwent successful placement of a stent, 89% had a clinical success, defined as ability to tolerate soft or regular diet. Reintervention for recurrent symptoms, most commonly resulting from stent occlusion secondary to tumor infiltration, occurred in 18% of patients at a median of 115 days. This can often be managed with the placement of an additional covered SEMS within the existing stent. Other complications included stent migration which occurred in 5% of patients, and a major bleeding or perforation event which occurred in 1% of patients. If there is associated jaundice, biliary stenting should be performed before duodenal stent placement, as placement of a biliary stent after placement of a duodenal stent is technically difficult (Fig. 1B). The decision to perform duodenal stenting or surgical gastrojejunostomy depends on expected survival and goals of care. In patients who undergo duodenal stenting, rapid return of oral intake is possible, but the long-term risk of stent occlusion secondary to tumor ingrowth is high, especially after 4 months. Comparatively, rates of recurrent gastric outlet obstruction after undergoing gastrojejunostomy are quite low, estimated around 2%, but carry an added risk of perioperative morbidity and mortality.

PROPHYLACTIC BILIARY AND GASTRIC BYPASS

Palliation therapy implies that the patient is suffering from active symptoms. But, at times, palliative care decisions are made to prevent future complications in asymptomatic patients. The classic example of this is when patients who were thought to have operable disease are discovered at the time of surgery to have an unresectable pancreatic cancer. Among asymptomatic patients, future complications from local tumor extension results in duodenal obstruction in up to 20% of cases and biliary obstruction in 65% of cases. In a study of 87 patients undergoing exploratory laparotomy for resectable pancreatic cancer resection, patients that were found to be unresectable at time of operation were randomized into prophylactic hepaticojejunostomy or prophylactic hepaticojejunostomy with gastrojejunostomy. Hepaticojejunostomy with gastrojejunostomy was performed in 44 patients, and no patient developed subsequent symptoms of gastric outlet obstruction. In

contrast, 8 (10%) of the 83 patients undergoing hepaticojejunostomy alone developed symptoms of gastric outlet obstruction requiring intervention. Similarly, in a second smaller randomized study of 46 patients who had a nontherapeutic laparotomy, 29 patients underwent hepaticojejunostomy and 36 patients underwent hepaticojejunostomy with gastrojejunostomy. Gastric outlet obstruction occurred in 2 (6%) of the 36 patients who underwent double bypass compared with 12 (41%) of the 29 patients who underwent hepaticojejunostomy alone. Neither study identified increased morbidity, mortality, or difference in overall survival between the two surgical intervention arms; however, it is important to note that the overall perioperative morbidity and mortality from these two trials were 39% to 52% and 0% to 3%, respectively. This early experience supported the routine use of double bypass at the time of a nontherapeutic laparotomy for pancreatic cancer. The largest series of palliative double bypass included 583 patients from a single institution. The series reported a 14% major complication rate and a 1.6% overall mortality rate. In addition, 10% of patients required readmission within 30 days and recurrent biliary obstruction or gastric outlet obstruction occurred in 9% of patients.

Although concomitant prophylactic gastric and biliary drainage at the time of nontherapeutic laparotomy has been the standard practice for many years, more recent minimally invasive approaches of endoscopic stenting has led to a declining use of routine double bypass. Critics of routine surgical bypass at the time of a nontherapeutic laparotomy have reported that 98% of patients who do not receive a surgical bypass can be effectively palliated without an operation. In a study of 155 patients with advanced pancreatic cancer, only 4 patients required a future surgical intervention, and the median overall survival was approximately 6 months. Therefore, the authors argued that a prophylactic palliative operation has a detrimental impact on a patient's quality of life when less invasive treatments are available.

Ultimately, the decision regarding endoscopic versus surgical palliation requires knowledge about the (1) severity of symptoms, (2) expectation of patient's performance status, and (3) understanding of the patient's goals of care to best balance the durability of the intervention with respect to anticipated overall survival (Fig. 2). In the current era of multimodality chemotherapy, the median overall survival of patients with metastatic pancreatic cancer to 11 months with the multidrug regimen 5-FU, leucovorin, irinotecan, and oxaliplatin. Increasingly, patients are undergoing a diagnostic laparoscopy to rule out radiographically occult metastatic disease prior to resection. If patients are found to have radiographically occult metastatic disease and have symptoms of gastric obstruction, which have been inadequately managed with endoscopic therapy, then an open or laparoscopic gastrojejunostomy is indicated. Endoscopic management is usually successful in alleviating biliary obstruction, and therefore hepaticojejunostomy may be reserved for select patients who have been inadequately palliated with endoscopic stenting or for whom gastroduodenal obstruction prevents endoscopic access. In patients who are asymptomatic, emblematical approaches will likely be successful in palliating future symptoms and surgical bypass can be avoided. With expectant nonsurgical management, patients can avoid perioperative complications and receive systemic therapy for their metastatic disease with minimal delay.

Palliative Pancreaticoduodenectomy

A small volume of literature exists describing the benefits of palliative resection for pancreatic cancer. In such series, improved overall survivals were noted among patients who undergo palliative microscopic (R1) or macroscopic (R2) resections compared with patients who undergo palliative surgical bypass. It should be noted that many series which report a survival benefit for palliative pancreaticoduodenectomy include patients who had a R1 resection from an operation performed with curative intent. The survival of these patients, in whom a curative intent surgery was performed, is not surprisingly superior to patients with obvious metastatic disease or residual gross tumor. When curative intent patients are eliminated from the analysis, the survival benefit is lost. In a systematic review of four cohort studies which included 138 patients with pancreaticoduodenectomy performed for palliation has been associated increased risk of morbidity and mortality by 1.75 (95% CI, 1.35–2.26), $P < .0001$) and 2.98 (95% CI, 1.31–6.75, $P = .009$), respectively. Currently, there are no data to support palliative pancreaticoduodenectomy (R2 resection) for pancreatic cancer.

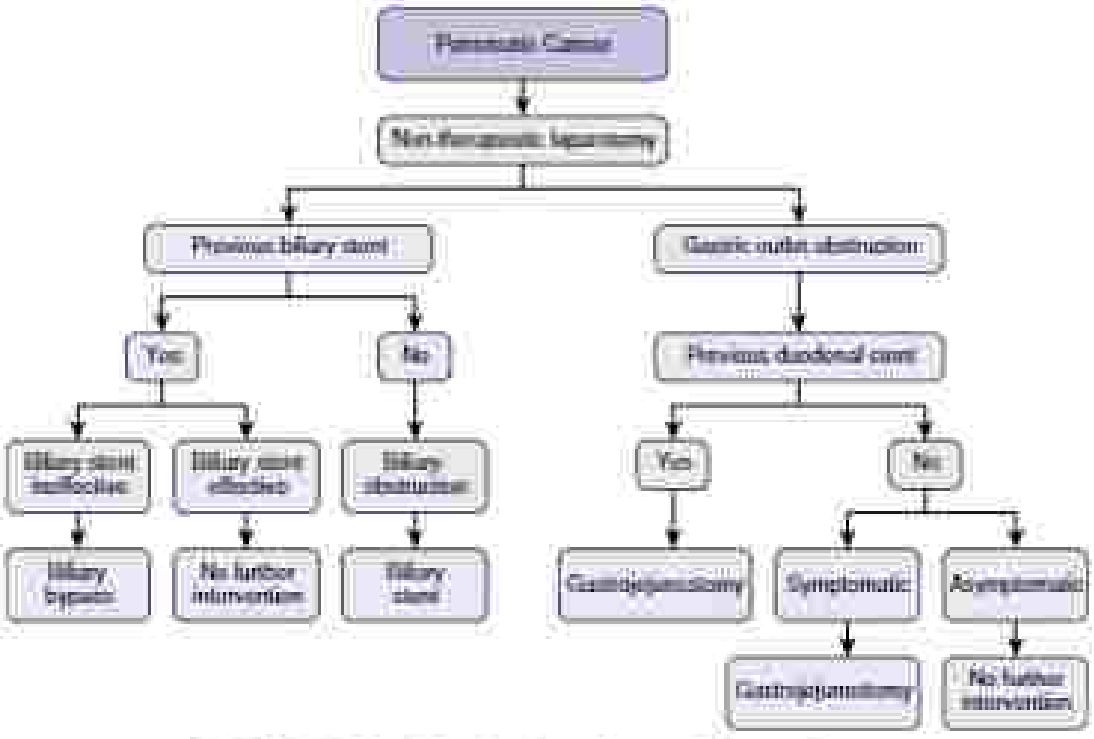

FIG. 1 Algorithm for palliation in patients with unresectable pancreatic cancer.

MALIGNANT BOWEL OBSTRUCTION

Malignant bowel obstruction resulting from peritoneal carcinomatosis is an ominous complication. These patients often suffer from severe, debilitating malnutrition and cancer cachexia which complicates their operative candidacy. In addition, most patients have concurrent malignant ascites, adding to the risk for postoperative complications, including wound dehiscence and seeding of the surgical incision causing local pain. Depending on the location of the obstruction, the success of endoscopic approaches may be limited, especially if the obstruction occurs within the mid to distal small bowel. Patients may find some alleviation of symptoms when abstaining from oral intake. Relief of nausea and vomiting may require gastric decompression with a nasogastric tube in the acute setting. In very select patients who have no ascites and very low volume disease, an operative exploration and surgical bypass may be considered. If patients are not candidates for surgical palliation, after a short interval (5–7 days), they may benefit from transitioning the nasogastric tube to a venting gastrostomy tube for long term palliation. If surgical or endoscopic intervention is not possible, pharmacologic therapy may provide some relief. Adequate pain control with opioids is critical either by intravenous or subcutaneous route in the acute setting and can be transitioned to equivalent transdermal doses when the patient has a stable opioid requirement. Antisecretory agents may reduce splanchnic blood flow, intestinal secretions, and cramping abdominal pain. Octreotide is considered the standard of care for malignant bowel obstruction and has been effective for palliation in prospective trials, with total daily doses ranging from 300 to 1200 mcg. In addition, haloperidol is effective in relieving nausea and vomiting in patients with malignant bowel obstruction. In our opinion, it is imperative to engage a palliative care specialist for these patients to aid in the transition to comfort care.

MALIGNANT ASCITES

Malignant ascites can lead to debilitating abdominal distension and early satiety. Ascites can develop as a result of portal hypertension or carcinomatosis. The etiology of the ascites can often be determined by the serum ascites albumin gradient (SAAG), with SAAG greater than 1.1 consistent with portal hypertension and nonperitoneal causes of ascites, while SAAG less than 1.1 is associated with carcinomatosis. Dietary sodium restriction and diuretics may be helpful in patients with ascites secondary to portal hypertension, but such measures are often ineffective in patients with carcinomatosis, with only 30% of patients seeing a benefit. Therapeutic paracentesis relieves symptoms, but repeated attempts are associated with increased complications, such as infection or bowel perforation. The ideal rate of fluid withdrawal is unknown, but large volume paracentesis of up to 5 L is usually safe. Significant improvement in abdominal pressure is experienced with a removal of 5 L of fluid, but this may be associated with hypotension, renal failure, hypoalbuminemia, and pulmonary embolism. Plasma expanders, such as albumin, have been effective in preventing circulatory collapse and should be considered in select patients based on symptoms. In patients with an anticipated survival of greater than 2 months, the placement of an indwelling pigtail or tunneled catheter to control ascites with drainage at home or in the clinic may be useful. In a meta analysis, tunneled catheters have a lower risk of infectious complications, than nontunneled (pigtail) catheters, which are associated with a 30% incidence of infection.

VASCULAR THROMBOSIS

The incidence of thromboembolic disease in pancreatic cancer is higher than in other malignant cancers and ranges from 10% to 20% in clinical trials and as high as 50% in autopsy series. Thrombosis can occur in the mesenteric veins resulting from tumor compression or in the peripheral veins because of the overall hypercoagulable state. Significant portal venous narrowing or thrombus should be treated with anticoagulation therapy when possible to prevent propagation of the thrombus to complete occlusion. Once mesenteric venous occlusion occurs, refractory ascites may develop, as does venous hypertension, resulting in small bowel edema, ileus, and in rare cases intestinal infarction. Low molecular weight heparin has been preferred over warfarin for anticoagulation for ease of management, but patients often struggle with long term repeated subcutaneous injections. With the advent of direct oral anticoagulants, patients with advanced pancreatic cancer have access to highly effective oral agents which require less monitoring.

TUMOR-ASSOCIATED PAIN MANAGEMENT

Patients with unresectable pancreatic cancer often suffer from tumor-associated abdominal and back pain resulting from direct tumor infiltration into the celiac ganglion. Effective pain management often requires opioid analgesia, which can be supplemented with additional adjunct analgesics for neuropathic pain as needed. Opioids are effective for nociceptive pain, but somewhat less effective for somatic or visceral pain. In addition, opioids have debilitating side effects including dizziness and sedation. More recently, the trend in pain management has been to optimize pain control with the lowest dose of opioids in combination with other adjunct analgesics to provide effective and consistent pain control.

Celiac plexus block has become increasingly used in treatment of pancreatic cancer related pain symptoms. A celiac plexus block involves injecting a 50% alcohol solution or other neuropetic agents into the celiac ganglion or splanchnic nerves under CT, endoscopic ultrasound, or fluoroscopic guidance. In the event a patient undergoes neoadjuvant treatment, celiac plexus block may also be performed at that time. More than 80% of patients experience improvement in pain control after celiac plexus block in blinded or sham studies, as measured by reduction of opioid requirements. Recently, a meta analysis identifying 358 patients undergoing celiac plexus block found improved pain scores at 4 and 8 weeks in patients undergoing celiac plexus block with narcotic therapy compared to patients receiving narcotic therapy alone. A meta analysis of 145 patients demonstrated relief in 90% of patients undergoing celiac plexus block at 3 months and relief persisted in 70% to 90% of patients long term. Short-term effects related to celiac plexus block include diarrhea, hypotension, and pain related to the procedure, which typically resolve with time celiac plexus block should be considered in the initial pain management plan for patients with pancreatic cancer and may be repeated in patients who demonstrated a prior benefit from neurolysis.

DEPRESSION

The rates of depression and suicide among patients with pancreatic cancer are the highest in any cancer population. Elevated levels of circulating cytokines such as interleukin-6 and tumor necrosis factor-α are thought to alter neurohormonal pathways in the brain causing depressive symptoms even before the diagnosis of cancer. Studies report that depression occurs in 25% to 50% of patients and has a significant impact on quality of life. Many symptoms of depression mimic symptoms associated with pancreatic cancer (fatigue, anorexia, weight loss), complicating the diagnosis of depression. However, asking a patient whether he or she has "felt depressed most of the time" is a validated tool with good sensitivity and specificity for identifying depression even among patients who are terminally ill. Antidepressants are effective in patients with advanced cancers and supportive counseling may help patients to strengthen coping strategies and help with anticipatory grief. Depression and anxiety often occur because of unaddressed fears of death or the symptoms that may arise in the process of dying. An early referral to a palliative care specialist can be beneficial to provide address concerns and focus on quality of life for these patients.

CONCLUSION

It is important for surgeons to understand how to improve the quality of life of patients with advanced pancreatic cancer. A multidisciplinary approach to symptom management in coordination with a palliative care specialist will prepare patients for the myriad physical and emotional challenges that occur. Frequent assessment of available imaging and proactive addressing of patient concerns will help providers to identify and manage symptoms more effectively. Clear communications about goals of care within the context of anticipated survival help to engage patients in shared decision making and allow providers to select the appropriate palliative treatment for each individual patient.

Suggested Readings

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Neoadjuvant and Adjuvant Therapy for Pancreatic Cancer

Brett L. Tchue, MD, and Charles M. Vollmer Jr, MD

Pancreatic ductal adenocarcinoma is an aggressive malignancy with low rates of long-term cure even after complete (R0) resection. The frequent and rapid development of systemic disease underscores the importance of multimodality treatment strategies. As such, chemotherapy is used for all stages of disease, including resectable, borderline resectable and locally advanced disease.

DEFINING THE CLINICAL STAGE OF DISEASE

The American Joint Commission on Cancer staging of pancreatic adenocarcinoma follows the Tumor, Node, Metastasis framework. Although this staging paradigm is prognostic of long-term survival, its dependence on postsurgical pathologic evaluation and its lack of definitional precision between resectable versus unresectable disease (i.e., T3 disease may classified as either) together limits its applicability in the preoperative setting. Rather, the National Comprehensive Cancer Network (NCCN) has endorsed the lexicography clinical staging based on the tumor relationship to the key vascular anatomy and the presence of extrapancreatic disease. Following a dedicated contrast-enhanced computed tomography (CT) scan (pancreatic protocol), tumors are classified according to the probability of achieving an R0 resection, and can be: (1) resectable, (2) borderline resectable, (3) locally advanced, or unresectable disease despite the absence of distant metastasis, and (4) demonstrated. The definitions for each are presented in Table 1. The NCCN guidelines forgo potentially vague terms such as "abutment" and "encasement" in favor of degrees of contact with the vessel wall, although abutment can be generally understood to represent involvement less than 180 degrees of vessel circumference without contour irregularity or thrombosis, whereas encasement denotes more than 180 degree involvement. Resectable pancreatic cancer (Fig. 1A) is defined by a primary tumor that does not contact any arterial vessel (celiac, hepatic, or superior mesenteric artery [SMA]) and does not contact the superior mesenteric vein/portal vein (SMV/PV), or contacts the SMV/PV less than 180 degrees without contour irregularity. Borderline resectable disease (Fig. 1B) is defined by limited tumor contact less than 180 degrees with the SMA or celiac artery, any contact (1–360 degrees) with the hepatic artery, or contact with the SMV/PV more than 180 degrees, SMV contour irregularity, or SMV thrombosis. The locally advanced category (Fig. 1C) includes more than 180-degree involvement of the SMA or celiac artery, or extensive involvement of the SMV/PV with no proximal and distal targets for vascular reconstruction. Extensive SMA involvement is considered unresectable because of the poor survival and higher morbidity and mortality expected following SMA resection. Acknowledging the limitations of cross sectional imaging to identifying micrometastases, this clinical framework is crucial to decisions regarding the sequencing of care.

Resectable Pancreatic Cancer

The clinical utility of multimodality therapy is well defined in the setting of resectable disease; yet, the timing of surgery relative to systemic therapy is an area of dispute and active research. Systemic chemotherapy has traditionally been administered after upfront surgery (i.e., in the adjuvant setting), although several institutions have championed the use of neoadjuvant therapy prior to surgical resection. Because complete surgical extirpation is the only opportunity for long-term cure, upfront surgery ensures that surgical resection can occur before the disease progresses to an unresectable state. Neoadjuvant therapy also requires a tissue biopsy, subjecting the patient to potential morbidity from unnecessary pretreatment endoscopic procedures. Jaundiced patients, as is common with pancreatic head lesions, will often require additional procedures for biliary drainage, with a small but attendant risk of complications. Last, neoadjuvant therapy may increase the burden of postoperative complications. Pancreatic fistula is one of the most common and clinically relevant morbidities after pancreatic resection, and accounts for one third of all mortalities after pancreaticoduodenectomy. Although the rate of pancreatic fistula may be less following neoadjuvant therapy, there is some evidence that fistula is associated with increased clinical burden in neoadjuvant cohorts. These data, which need to be confirmed more broadly, at least support that deconditioning from chemotherapy may lead patients to fail to promptly recover once a complication has occurred. In agreement, NCCN guidelines do not recommend the routine use of neoadjuvant therapy for those with clearly resectable disease without high-risk features (e.g., elevated CA 19-9, large tumor burden to the pancreas or surrounding lymph nodes, poor performance status) outside of a clinical trial.

In contrast, the primary benefits of neoadjuvant therapy include: (1) the early treatment of micrometastatic disease, which is common and can lead to early postoperative recurrences, (2)

CONCLUSION

It is important for surgeons to understand how to improve the quality of life of patients with advanced pancreatic cancer. A multidisciplinary approach to symptom management in coordination with a palliative care specialist will prepare patients for the myriad physical and emotional challenges that occur. Frequent assessment of available imaging and proactive addressing of patient concerns will help providers to identify and manage symptoms more effectively. Clear communications about goals of care within the context of anticipated survival help to engage patients in shared decision making and allow providers to select the appropriate palliative treatment for each individual patient.

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Neoadjuvant and Adjuvant Therapy for Pancreatic Cancer

Brett L. Eckel, MD, and Charles M. Vollmer Jr, MD

Pancreatic ductal adenocarcinoma is an aggressive malignancy with low rates of long-term cure even after complete (R0) resection. The frequent and rapid development of systemic disease underscores the importance of multimodality treatment strategies. As such, chemotherapy is used for all stages of disease, including resectable, borderline resectable and locally advanced disease.

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In contrast, the primary benefits of neoadjuvant therapy include: (1) the early treatment of micrometastatic disease, which is common and can lead to early postoperative recurrences, (2)

TABLE 1 National Comprehensive Cancer Network Definitions of Resectability

	Tumor-Artery Relationship	Tumor-Vein Relationship
Resectable	No radiographic contact between tumor and celiac, hepatic or superior mesenteric artery	No tumor contact with the SMV/PV, or <180 degrees without contour irregularity
Borderline resectable	Tumor contact <180 degrees with celiac or superior mesenteric artery, and/or tumor contact >180 degrees with hepatic artery	Tumor contact >180 degrees with the SMV/PV, or contour irregularity, or short segment thrombosis (amenable to resection)
Locally advanced	Tumor contact >180 degrees with celiac or superior mesenteric artery or aorta	Occlusion of the SMV/PV without suitable targets proximally and distally for vascular reconstruction
Disseminated	Evidence of peritoneal or distant metastasis	

SMV/PV, superior mesenteric vein/portal vein.

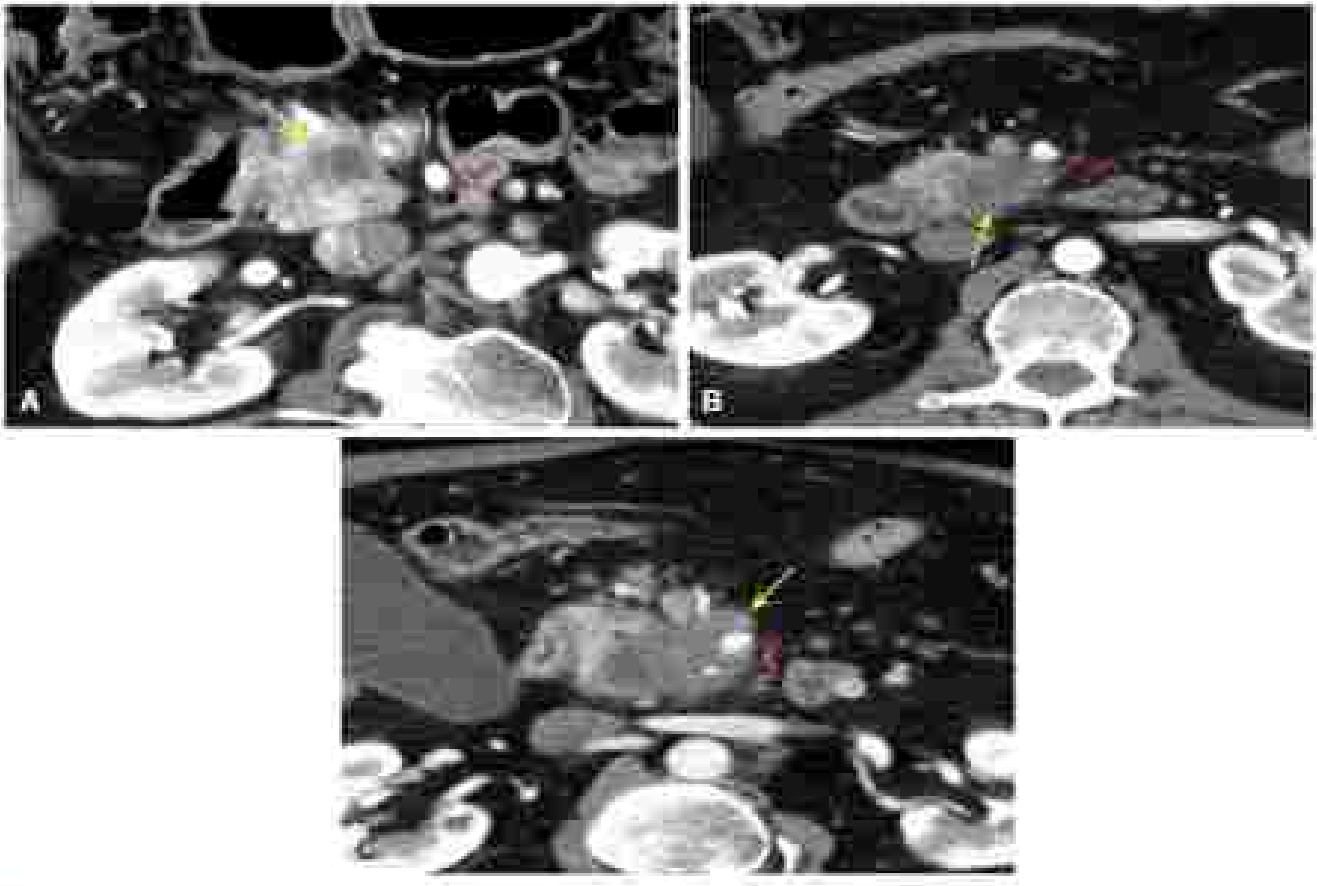

FIG. 1 Clinical staging is based on tumor-vessel contact. Contrast-enhanced axial computed tomographic images show the tumor (yellow arrow), superior mesenteric vein (SMV, blue arrowhead), and superior mesenteric artery (SMA, red arrow). (A) Resectable pancreatic cancer. Hypodense tumor is present in the pancreatic head with preservation of the fat plane between the pancreas and the SMV and without tumor abutment of the SMA. (B) Borderline resectable pancreatic cancer. Note the hypodense tumor that abuts both the SMV and the SMA. (C) Locally advanced pancreatic cancer. The hypodense tumor encases (>180 degrees) the SMA.

enhanced patient selection; (3) improved delivery and completion rates; and (4) enhanced efficacy of chemoradiotherapy (given the well oxygenated environment), with corresponding higher negative margin resection and lymph node negative rates. As many as 25% of patients will have metastatic disease discovered at operative exploration or during the postoperative recovery, thus negating any potential benefit derived from such morbid surgery. Instead, neoadjuvant therapy enriches the surgical population for those most likely to achieve a long-term cure. Additionally, postoperative morbidity influences the use and timing of adjuvant therapies, which are crucial to achieve the goal of long-term survival. More than half of all pancreaticoduodenectomy patients will suffer some postoperative morbidity, and prolonged postoperative recovery prevents the delivery of adjuvant therapy in nearly one quarter of patients. Neoadjuvant therapy ensures the delivery of some systemic therapy. Last, chemoradiotherapy has been associated with improved R0 rates in retrospective series. The benefits of each strategy (neoadjuvant vs. adjuvant) are summarized in Box 1.

At present, there is level I evidence to support the use of adjuvant therapy but no head-to-head randomized prospective data comparing adjuvant and neoadjuvant approaches. Established adjuvant chemotherapy regimens include monthly bolus 5-fluorouracil, which demonstrated superiority to observation alone in the European Study for Pancreatic Cancer (ESPAC)-1 trial; gemcitabine monotherapy following the results of the European Charité Onkologie 001 trial; and combination gemcitabine/capecitabine, which was superior to gemcitabine monotherapy in the ESPAC-4 trial. At present, there is level I evidence to support the use of adjuvant therapy but no head-to-head randomized prospective data comparing adjuvant and neoadjuvant approaches. Established adjuvant chemotherapy regimens include monthly bolus 5-fluorouracil, which demonstrated superiority to observation alone in the European Study for Pancreatic Cancer (ESPAC)-1 trial; gemcitabine monotherapy following the results of the European Charité Onkologie 001 trial; and combination gemcitabine/capecitabine, which was superior to gemcitabine monotherapy in the ESPAC-4 trial. Additionally, more aggressive regimens are the focus of currently enrolling and recently completed trials. The PRODIGE 24-GCCG PA-6 trial evaluating gemcitabine versus FOLFIRINOX in the adjuvant setting found significant improvements in overall survival with the multidrug regimen. Nab-paclitaxel/gemcitabine is superior to gemcitabine alone in the metastatic setting and is currently under evaluation in the adjuvant setting (APACT trial), and a trial has completed enrollment. The benefits of multidrug regimens will have to be balanced against increased treatment-related toxicities in a deconditioned postoperative patient, but we can expect increasing use of FOLFIRINOX when patient fitness allows. The relative efficacy of FOLFIRINOX versus nab-paclitaxel/gemcitabine has yet to be ascertained.

The role of adjuvant radiotherapy (RT) is less clearly defined. Both the Gastrointestinal Tumor Study Group 9173 trial and the European Organization for Research and Treatment of Cancer trial observed benefits for postoperative concurrent 5-fluorouracil plus external beam RT relative to observation. However, these results were not verified in the previously mentioned ESPAC-1 trial, which was a four-arm study that demonstrated a trend toward worse survival for the group receiving chemoradiotherapy. In these historical trials, split-course RT at lower doses (40 Gy) may have limited efficacy. The contemporary phase II European Organisation for Research and Treatment of Cancer 40013 trial evaluated gemcitabine-based chemoradiotherapy and observed that the addition of RT to gemcitabine alone improved local control, although without impacting disease-free or overall survival.

In the neoadjuvant setting, several phase I and II trials have demonstrated the safety and efficacy of many of the previously mentioned therapy regimens. Currently, there is no level I evidence defining the optimal neoadjuvant regimen, or how such therapies compare to their use in the adjuvant setting. PACT-15 (NCT01150630) was a three-arm, randomized, phase II/III trial comparing neoadjuvant gemcitabine, cisplatin, epirubicin, and capecitabine (PEX-C) to adjuvant gemcitabine monotherapy and adjuvant PEXG. As of this year, the study authors have decided not to continue with the phase III aspect of this trial, given ever-evolving adjuvant therapy standards. With 36 in the small cohort of treated patients (n = 36/arm), neoadjuvant therapy demonstrated promising efficacy (66% event-free at 1 year vs 38% event-free in the adjuvant PEXG group vs 23% event-free in the adjuvant gemcitabine group). Likewise, an interim analysis published in abstract form of the phase II/III ESPAC-5F trial comparing neoadjuvant gemcitabine-based chemoradiation with adjuvant gemcitabine-based chemoradiation demonstrated a survival benefit of upfront chemoradiotherapy (median survival, 23 months vs 11 months). Several recruiting trials comparing neoadjuvant with adjuvant therapy are ongoing (e.g., NEOPANC, NCT02047513, neoadjuvant nab-paclitaxel/gemcitabine vs adjuvant nab-paclitaxel/gemcitabine; PANACHE01/PRODIGE30, NCT02562089, neoadjuvant FOLFIRINOX or FOLFOX vs standard adjuvant chemotherapy; NorPACT, NCT02919982, neoadjuvant FOLFIRINOX and adjuvant gemcitabine/capecitabine vs adjuvant gemcitabine/capecitabine). In general, neoadjuvant therapy for resectable disease involves (1) the early initiation of chemotherapy (with or without RT); (2) restaging before surgical exploration, which occurs between 2 and 6 weeks after chemotherapy and 4 and 6 weeks after chemoradiotherapy; and (3) frequent use of additional chemotherapy (with or without RT) following postoperative recovery.

In summary, NCCN guidelines recommended the use of systemic therapies for all patients with resectable disease. Although the timing of such therapy can be justified in either the neoadjuvant or adjuvant setting, at present, neoadjuvant therapy is not yet considered a standard approach for patients with potentially resectable pancreatic cancer outside of the context of a clinical trial.

BOX 1 Potential Advantages and Disadvantages of Neoadjuvant Therapy

Advantages

- Ability to deliver systemic therapy to all patients
- Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of pretreatment and preoperative restaging who thereby avoid the morbidity of surgery
- Increased efficacy of radiation therapy, less radical production in a well-oxygenated environment
- Decreased radiation-induced toxicity to adjacent normal tissue because the radiated field is resected at the time of pancreatectomy
- Decreased rate of positive resection margins, superior mesenteric artery margin in particular
- Decreased rate of pancreatic fistula formation
- Potential for the tumor size to decrease, especially in borderline resectable tumors, which may facilitate surgical resection

Disadvantages

- Potential for complications from pretreatment endoscopic procedures (endoscopic ultrasound scan and fine-needle aspiration, and endoscopic retrograde cholangiopancreatography)
- Biliary stent–related morbidity, stent occlusion during systemic and therapy
- Disease progression obviating resectability, loss of a window of resectability may occur (rarely) in the borderline resectable patient
- Coordination of multiple physicians during the preoperative phase; the care handoff from surgeon to medical oncologist to radiation oncologist (as occurs with adjuvant therapy) is not possible in the neoadjuvant setting

Borderline Resectable Patients

In contrast to resectable disease, less controversy exists regarding the use of neoadjuvant therapy before attempted resection of borderline resectable disease. This category is defined by more advanced locoregional disease at higher risk for incomplete resection, obviating the oncologic benefit of surgical resection because patients who undergo a resection with a microscopically positive margin demonstrate long-term survival comparable to patients who do not undergo any operation. Moreover, although borderline resectable patients are apparently radiographically localized, they have a greater risk for subclinical distant metastases.

The current body of literature is limited by heterogeneity in regimens used and definitions of clinical resectability; nevertheless, many institutions have embraced neoadjuvant combination chemotherapy (with or without RT) for this scenario. The Alliance for Clinical Trials in Oncology Trial A021101 (NCT01821612) recently published the results of a prospective pilot trial using neoadjuvant FOLFIRINOX followed by capecitabine-based chemoradiation in borderline resectable patients, defined in strict accordance with current NCCN guidelines. Among the 33 patients enrolled, 15 (68%) completed neoadjuvant

therapy and proceeded to surgical resection, where 93% of patients underwent an R0 resection. Although not powered for a survival analysis, we notable that median survival for these patients was 21.7 months, which compares favorably to the 24 month survival observed in ESPAC 4 for gemcitabine monotherapy following upfront resection (for less advanced, resectable cancer). This year the Korean multicenter, randomized, controlled phase II/III trial (NCT01464957), which compared gemcitabine based chemoradiation in the neoadjuvant versus adjuvant setting for 50 borderline resectable patients was published. Among patients who underwent surgical resection, R0 resection rates were significantly improved with neoadjuvant therapy (82% vs 33%), which may explain the significant improvements observed in the intent-to-treat survival analysis (median, 21 vs 12 months). These encouraging results led to early termination of the trial.

Beyond enhanced resectability, neoadjuvant therapy can lead to pathologic complete response in a rare number of patients, which is independently predictive of long term survival. In the Korean trial described above, a complete pathologic response was observed in 12% of patients. In a contemporary cohort of borderline resectable and locally advanced patients treated at Johns Hopkins treated with chemoradiotherapy using either FOLFIRINOX or nab-paclitaxel gemcitabine based chemotherapy, a complete pathologic response was more common following FOLFIRINOX (13% vs 7%), suggesting that even greater gains may be expected than those observed with gemcitabine monotherapy in the Korean trial. In general, choice of systemic agents for neoadjuvant treatment has evolved from single-agent gemcitabine to combination therapies, such as FOLFIRINOX or gemcitabine/nab-paclitaxel, given their success in the metastatic and adjuvant setting, and ongoing randomized trials will provide much anticipated data on their efficacy.

Locally Advanced Patients

Locally advanced pancreatic cancer is unresectable, but no distinctly unresectable disease, usually because of interplay of the tumor with the critical local visceral vasculature. Similar to borderline resectable patients, initial management consists of chemotherapy with or without chemoradiotherapy. Although rare (~20%), certain patients with a significant response to therapy may become surgical candidates. These patients will receive a lengthy course of systemic therapy greater than those used in the neoadjuvant setting for resectable disease, and have no evidence of progressive disease by cross-sectional imaging at restaging and a stable/decreasing CA19-9) and good performance status. Given that complete pathologic response is rare with systemic therapy, and that complete surgical extirpation is considered the only means for cure, these patients may be referred from medical oncologists before consideration for maintenance chemotherapy. It is crucial that surgery be applied to such patients based on established criteria for resectability, recognizing that such patients have realized a robust survival benefit without surgery given their positive response to induction therapy.

Reported resection rates for locally advanced patients after neoadjuvant therapy have varied widely (1%–60%), where such population variability likely reflects heterogenous treatment schemes, imprecise definitions of locally advanced disease, and varying surgical capabilities of specific institutions (i.e., types of vascular reconstructions performed). In a recent multinational series from Memorial Sloan Kettering Cancer Center, including 101 patients with locally advanced disease treated with FOLFIRINOX with or without chemoradiation, 31% were converted to surgical candidates, of which one half underwent R0 resection. Hence, 16% underwent curative resection following aggressive multimodality therapy. Notably, the pattern of vascular involvement present at diagnosis varied between those who eventually proceeded to resection and those who did not. Involvement of the hepatic artery and unreconstructable venous involvement were commonly became resectable after neoadjuvant therapy as compared to involvement of the celiac axis, superior mesenteric artery, or multiple vessels.

Celiac artery involvement can be approached, if necessary, with celiac resection in carefully selected patients with tumors of the pancreatic body where the gastroduodenal artery maintains prograde hepatic arterial perfusion. SMA involvement (borderline resectable, <180 degrees; locally advanced, >180 degrees) can often be freely dissected in the plane between the SMA adventitia and the neural sheath. However, there are no data supporting more aggressive resection and reconstruction of the SMA. Similarly, complete 360 degree involvement of the SMA, which would require cutting through the tumor to separate it from the vessel, should be considered unreasonable in unoperable patients, other locoregional therapies include irreversible electroporation, radiofrequency ablation, stereotactic body radiation, and high intensity focused ultrasound.

FUTURE DIRECTIONS

Ongoing trials will clarify the role of multimodality chemotherapy regimens and their role in the neoadjuvant setting. Yet, poor long-term survival, despite aggressive surgery and multimodality therapy, demands the development of novel therapies. At least in the metastatic setting, numerous targeting therapies have been evaluated in clinical trials, but rarely with any benefit. Some failed

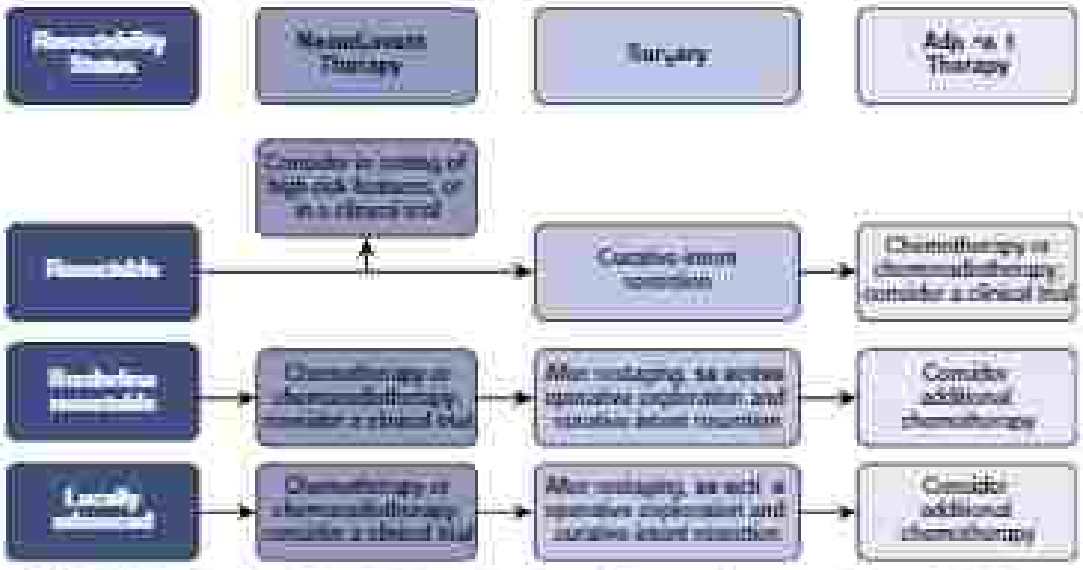

FIG. 1. Multimodality flowchart for the timing and use of systemic therapy and surgery stratified by clinical staging.

targeted therapies include antiangiogenic drugs (bevacizumab and aflibercept), multikinase inhibitors (sunitinib, sorafenib, axitinib, motesanib), anti-insulin-like growth factor 1 receptor antibodies (ganitumab and cixutumumab), and phosphatidylinositide 3-kinase inhibition (rigosertib). Such disappointments might be explained by both high tumor genetic heterogeneity and the influence of the inflammatory peritumoral stroma on signaling pathways and drug accessibility.

Immunotherapy has provided exciting results for several other cancer types, and may have an important role in the management of pancreatic cancer. Long-term survivors of pancreatic cancer have a higher frequency of neoantigens generated from mutations in the gene MUC16 (i.e., CA125) as well as robust T-cell responses (intratumoral and circulating) against mutant MUC16. Moreover, metastatic progression is associated with selective loss of *MUC16* neoantigenic clones. Several trials aimed to leverage the immune response against pancreatic cancer are underway.

Last, for the vast number of patients who do not respond to systemic therapy to the level of either standard or novel therapeutics, sensitive biomarkers are needed to measure therapy response and rapidly guide changes to alternative treatments. Repeat imaging at 2-month intervals, as is often performed, prohibits quick and reactive changes to potentially more effective therapy.

In conclusion, the past 5 decades have been instrumental to standardizing the definitions of clinical staging and establishing the benefit of adjuvant systemic therapy and more recently, the use of neoadjuvant chemoradiation in borderline resectable patients (summarized in Fig. 2). The wide adoption of the NCCN-sponsored clinical staging schema will ensure homogeneous patient populations that will clarify assessment of therapeutic response for novel therapies and/or treatment sequences.

Suggested Readings

Ang IT, Han Y, Lee G, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase II/III trial. Ann Surg 2018.

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Unusual Pancreatic Tumors

Elliot A. Asare, MD, MS; Douglas B. Evans, MD; and Susan Tsai, MD, MSHS

Symptomatic and incidental abnormalities of the pancreas have become much more common because of the frequent use of cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]). Most important for the surgeon, when faced with a new patient who has a pancreatic mass on imaging, is to construct a differential diagnosis, not simply proceed with biopsy or resection. Thoughtful creation of a differential diagnosis should always precede intervention. Patients with solid pancreatic masses, associated with atypical clinical presentations or unusual imaging characteristics may be diagnostically challenging and familiarity with less common pancreatic conditions is necessary for the development of a comprehensive differential diagnosis. This chapter will focus on unusual solid tumors of the pancreas and discuss optimal diagnostic and therapeutic approaches for their management. The combination of a careful patient history, thorough physical examination, analysis of specific laboratory results, and detailed review of all imaging studies will narrow the list of differential diagnoses even before a tissue biopsy is performed.

ACINAR CELL CARCINOMA

Acinar cell carcinomas (ACC) are rare and many surgeons may not see a single patient with this disease. In contrast to pancreatic ductal adenocarcinoma, ACC arises from the acinar elements of the exocrine pancreas, not ductal epithelium. As a result, ACCs often retain the exocrine characteristics of normal pancreatic acini and can produce digestive enzymes such as trypsin, chymotrypsin, and lipase. These tumors are more common among men (male to female ratio of 2:1) and usually occur in the sixth and seventh decades of life. Up to 50% of patients are asymptomatic at initial presentation; many others may complain of abdominal pain or weight loss. Approximately 10% of patients with ACC may present with a paraneoplastic syndrome caused by excessive pancreatic enzyme production, which is characterized by the presence of subcutaneous fat necrosis, bone infarcts, arthritis, and eosinophilia. Although no specific serum or plasma tests exist that are diagnostic for ACC, serum lipase levels are elevated in at least 25% of patients. Serum tumor markers, such as carbohydrate antigen (CA) 19-9, α-fetoprotein, and carcinoembryonic antigen are variably expressed. In our experience, serum lipase and α-fetoprotein are often elevated and, if so, can be quite helpful in assessing response to therapy (as well as disease recurrence for those patients who undergo a potentially curative operation).

ACCs may be noticeably large at presentation, even if within the pancreatic head as bile duct obstruction may be less common than with pancreatic adenocarcinoma. A large tumor in the pancreatic head without bile duct obstruction should raise the level of suspicion for an ACC or a pancreatic neuroendocrine tumor. Classic cross-sectional imaging findings (not present in all patients) include the presence of a large, exophytic, well-circumscribed mass with capsular enhancement but central hypodensity (Fig. 1A). The lesions can be entirely solid when small, but larger tumors often outgrow their blood supply and develop central areas of necrosis. ACC can occur anywhere in the pancreas and the incidence of tumors in the head is not appreciably greater than that of tumors in the body/tail. There may also be interval foci of calcifications although calcifications are not a distinguishing feature. Similar to pancreatic adenocarcinoma, ACCs are often metastatic at presentation with the liver being the most common site of metastasis. The radiographic differential diagnosis of ACC includes pancreatic ductal adenocarcinoma (Fig. 1B demonstrates how ACC can mimic the radiographic appearance of a typical adenocarcinoma), pancreatic neuroendocrine tumor, solid pseudopapillary tumors (SPT), pancreatoblastoma, and mucinous cystic neoplasms.

On histopathologic examination, pure ACCs have two predominant cellular patterns of growth: an acinar pattern consisting of cells growing in well-formed acini and a solid pattern characterized by sheets of cells that lack the prominent stromal component seen in pancreatic ductal adenocarcinoma. Classically the majority of ACCs will have coarse granular apical cytoplasmic staining for trypsin or chymotrypsin. In contrast to the staining pattern of pancreatic ductal adenocarcinoma, ACC generally stains negative for carcinoembryonic antigen and mucicarmine. Although fine-needle aspiration (FNA) biopsy can usually differentiate a pancreatic ductal

targeted therapies include antiangiogenic drugs (bevacizumab and aflibercept), multikinase inhibitors (sunitinib, sorafenib, axitinib, motesanib), anti-insulin-like growth factor 1 receptor antibodies (ganitumab and cixutumumab), and phosphatidylinositide 3-kinase inhibition (rigosertib). Such disappointments might be explained by both high tumor genetic heterogeneity and the influence of the inflammatory peritumoral stroma on signaling pathways and drug accessibility.

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Suggested Readings

Ang IT, Han Y, Lee G, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase II/III trial. Ann Surg 2018.

Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2016;34(21):2541–56.

Nimptsch U, Adam I-H, Ghaneh P, Hackert TH, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017;389(10073):1011–24.

Unusual Pancreatic Tumors

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Symptomatic and incidental abnormalities of the pancreas have become much more common because of the frequent use of cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]). Most important for the surgeon, when faced with a new patient who has a pancreatic mass on imaging, is to construct a differential diagnosis, not simply proceed with biopsy or resection. Thoughtful creation of a differential diagnosis should always precede intervention. Patients with solid pancreatic masses, associated with atypical clinical presentations or unusual imaging characteristics may be diagnostically challenging and familiarity with less common pancreatic conditions is necessary for the development of a comprehensive differential diagnosis. This chapter will focus on unusual solid tumors of the pancreas and discuss optimal diagnostic and therapeutic approaches for their management. The combination of a careful patient history, thorough physical examination, analysis of specific laboratory results, and detailed review of all imaging studies will narrow the list of differential diagnoses even before a tissue biopsy is performed.

ACINAR CELL CARCINOMA

Acinar cell carcinomas (ACC) are rare and many surgeons may not see a single patient with this disease. In contrast to pancreatic ductal adenocarcinoma, ACC arises from the acinar elements of the exocrine pancreas, not ductal epithelium. As a result, ACCs often retain the exocrine characteristics of normal pancreatic acini and can produce digestive enzymes such as trypsin, chymotrypsin, and lipase. These tumors are more common among men (male to female ratio of 2:1) and usually occur in the sixth and seventh decades of life. Up to 50% of patients are asymptomatic at initial presentation; many others may complain of abdominal pain or weight loss. Approximately 10% of patients with ACC may present with a paraneoplastic syndrome caused by excessive pancreatic enzyme production, which is characterized by the presence of subcutaneous fat necrosis, bone infarcts, arthritis, and eosinophilia. Although no specific serum or plasma tests exist that are diagnostic for ACC, serum lipase levels are elevated in at least 25% of patients. Serum tumor markers, such as carbohydrate antigen (CA) 19-9, α-fetoprotein, and carcinoembryonic antigen are variably expressed. In our experience, serum lipase and α-fetoprotein are often elevated and, if so, can be quite helpful in assessing response to therapy (as well as disease recurrence for those patients who undergo a potentially curative operation).

ACCs may be noticeably large at presentation, even if within the pancreatic head as bile duct obstruction may be less common than with pancreatic adenocarcinoma. A large tumor in the pancreatic head without bile duct obstruction should raise the level of suspicion for an ACC or a pancreatic neuroendocrine tumor. Classic cross-sectional imaging findings (not present in all patients) include the presence of a large, exophytic, well-circumscribed mass with capsular enhancement but central hypodensity (Fig. 1A). The lesions can be entirely solid when small, but larger tumors often outgrow their blood supply and develop central areas of necrosis. ACC can occur anywhere in the pancreas and the incidence of tumors in the head is not appreciably greater than that of tumors in the body/tail. There may also be interval foci of calcifications although calcifications are not a distinguishing feature. Similar to pancreatic adenocarcinoma, ACCs are often metastatic at presentation with the liver being the most common site of metastasis. The radiographic differential diagnosis of ACC includes pancreatic ductal adenocarcinoma (Fig. 1B demonstrates how ACC can mimic the radiographic appearance of a typical adenocarcinoma), pancreatic neuroendocrine tumor, solid pseudopapillary tumors (SPT), pancreatoblastoma, and mucinous cystic neoplasms.

On histopathologic examination, pure ACCs have two predominant cellular patterns of growth: an acinar pattern consisting of cells growing in well-formed acini and a solid pattern characterized by sheets of cells that lack the prominent stromal component seen in pancreatic ductal adenocarcinoma. Classically the majority of ACCs will have coarse granular apical cytoplasmic staining for trypsin or chymotrypsin. In contrast to the staining pattern of pancreatic ductal adenocarcinoma, ACC generally stains negative for carcinoembryonic antigen and mucicarmine. Although fine-needle aspiration (FNA) biopsy can usually differentiate a pancreatic ductal

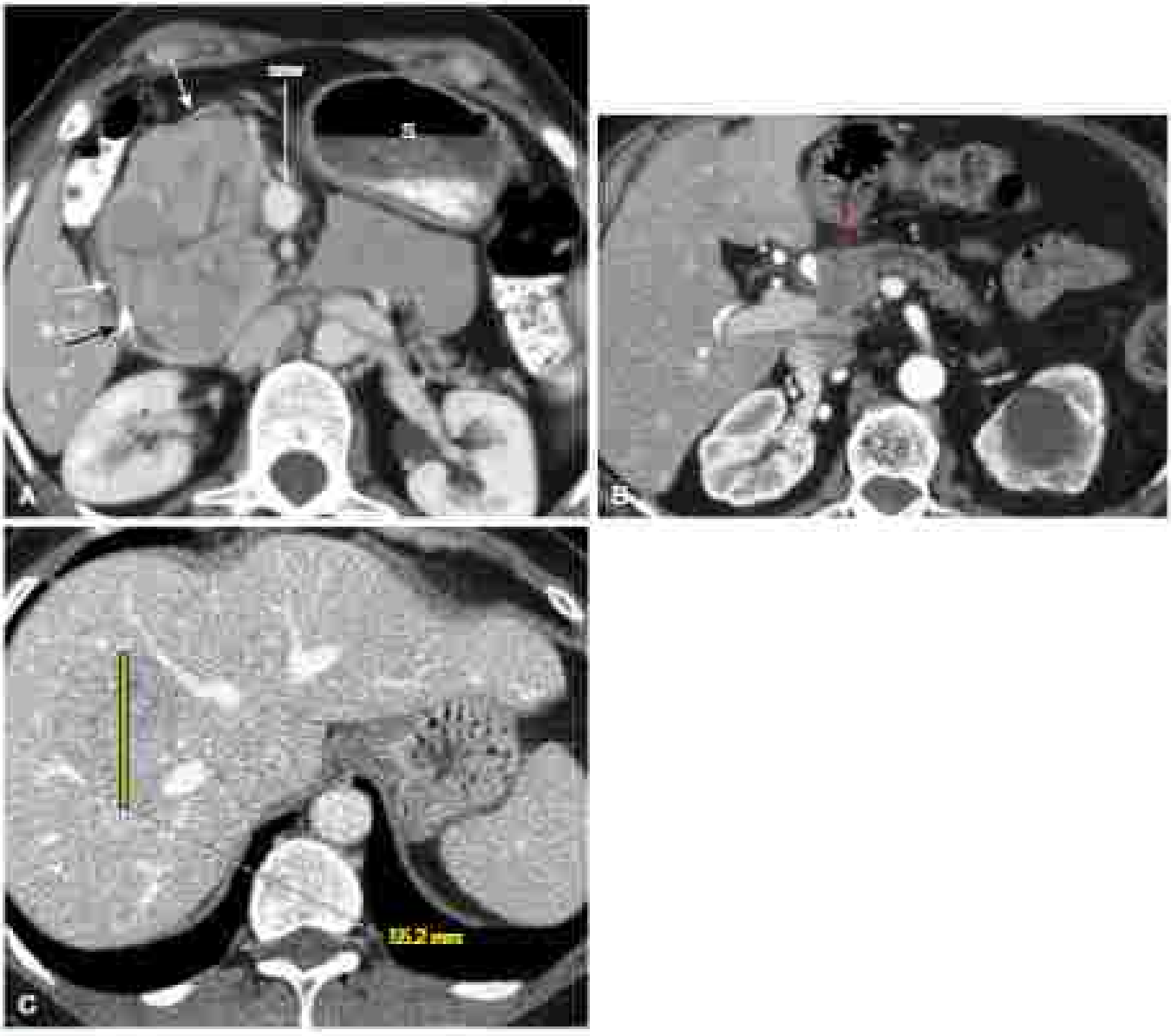

FIG. 1 (A) Axial image of a contrast-enhanced CT scan from a patient with a large acinar cell carcinoma demonstrating local compression of the duodenum (white arrow), causing gastric dilatation (S) and biliary obstruction, which required endoscopic stenting (black arrow identifies the plastic stent). (B) Axial image of a contrast-enhanced CT scan from a 79-year-old man who was believed to have pancreatic adenocarcinoma. The CT image is consistent with a diagnosis of adenocarcinoma of the pancreas. However, the correct diagnosis of ACC was made on review of biopsy specimens. This man developed metachronous lung metastases 4 years later and he died 6 years from the date of diagnosis from progressive metastatic disease confined to the chest. (C) Axial image of a contrast-enhanced CT scan, performed in 2011, demonstrating an ill-defined liver metastasis in a 51-year-old woman who underwent pancreaticoduodenectomy for a large acinar cell carcinoma in 2001. She received 4 months of systemic therapy followed by liver resection. She remains free of disease at her last surveillance evaluation in 2018. The patient featured in parts B and C demonstrates the unusual natural history that can be associated with ACC as compared with pancreatic adenocarcinoma. ACC, acinar cell carcinoma; CT, computed tomography; SMV, superior mesenteric vein.

adenocarcinoma from an ACC, the primary diagnostic dilemma is distinguishing between ACC and a well-differentiated pancreatic neuroendocrine neoplasm and pancreatoblastoma. ACC can have scattered neuroendocrine cells present in up to 40% of cells. Additional immunohistochemistry (performed on cytology specimens or core biopsies), if positive for synaptophysin and chromogranin A, would support a diagnosis of pancreatic neuroendocrine neoplasm. When neuroendocrine cells comprise greater than 30% of the tumor, it qualifies as a mixed acinar neuroendocrine carcinoma. At a molecular level, mutations in *ATM*, *BRCA2*, and *PALB2* have been identified similar to the experience with adenocarcinoma of the pancreas. However, key driver mutations present in pancreatic adenocarcinoma, including *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, were found to be infrequently mutated in ACC. Interestingly, the genetic mutations associated with the major types of pancreatic cancer are now known to be relatively distinct: pancreatic ductal adenocarcinomas are characterized by mutations in SMAD4, TP53, KRAS, and CTNNA; neuroendocrine tumors by mutations in *MEN1*, *DAXX*, *ATRX*, and the mTOR pathway; mucinous cystic neoplasms by mutations in RNF43; and intraductal papillary mucinous neoplasms by mutations in GNAS and RNF43. Although ACCs are microsatellite stable, they exhibit a high degree of chromosomal imbalances that may help distinguish

them from pancreatic ductal adenocarcinoma and neuroendocrine tumors. The different molecular alterations found in pancreatic tumors makes it possible to use DNA sequencing of a primary tumor or a metastatic biopsy when it proves difficult to classify the tumor solely by histopathologic criteria.

Treatment

Patients who have localized disease should undergo surgical resection if the tumor is operable. For all pancreatic tumors, operability is based on, and defined by, surgeon experience, especially with respect to patients who may require vascular resection and reconstruction at the time of pancreatectomy. In our experience, resection and reconstruction of the superior mesenteric-portal vein confluence, celiac artery, and/or the hepatic artery are procedures performed with reasonable frequency and therefore, very safe in properly selected patients. Such may not be the case at centers with less experience; operability needs to be defined based on surgeon and institution experience. Although ACC tumors are often large in size/dimension, they tend to be well circumscribed and may be amenable to complete surgical resection, in contrast to the uniformly infiltrative nature of adenocarcinoma of the pancreas. In a review of the National Cancer Database, the 5-year survival rate of 865 patients who underwent surgical resection for ACC was 36.2%. Survival durations from single institution series are even more favorable, with median survivals reported as high as 57 months for patients with localized disease who underwent complete surgical resection. Distant recurrence is the most common pattern of failure and, similar to pancreatic adenocarcinoma, liver and lung predominate. For this reason, adjuvant therapy would seem to be a logical alternative to surgery alone. However, there are few data available to guide the selection of adjuvant therapy after complete resection and therefore, many oncologists turn to molecular profiling of the resected specimen for clues to potential sensitivity to available chemotherapeutics. There are now a number of companies that provide this service in addition to the programs available in house at many larger centers. For patients with localized disease in whom the operation to remove the tumor may involve vascular resection/reconstruction, or when there is a concern for a positive margin, neoadjuvant therapy (chemoradiation) is quite reasonable to consider. Anecdotally, we have seen liver and lung recurrence after a long disease free interval (>5 years) in rare patients with ACC. In such situations, resection of a solitary metastasis may be considered in an otherwise healthy patient (Fig. 3C). This also allows for histologic confirmation of the diagnosis and molecular profiling as a guide to further systemic therapy.

SOLID PSEUDOPAPILLARY TUMORS

SPTs of the pancreas are also quite rare but, in contrast to ACC, they have low malignant potential. SPT have been associated with several other names, including Frantz tumors, Hamoudi tumors, and papillary cystic neoplasm. SPTs are well known for their high prevalence among women, most commonly occurring in the third decade of life and even earlier (mean age, 22 years; range, 2–85 years). The most common presenting symptoms and signs (if present) include abdominal pain and/or the presence of an abdominal mass on physical examination. In the asymptomatic patient, tumors may be discovered as a palpable mass on routine physical examination or as an incidental finding on imaging for an unrelated complaint. Serologic tests are often of little value with CA19-9 being rarely elevated.

On CT imaging, SPTs can range from being completely cystic to completely solid; in our experience, a pure cystic SPT is uncommon because the cystic portion is secondary to necrotic degeneration of the primary tumor. They frequently demonstrate peripheral enhancement and central calcification and are characteristically large (often much larger than seen in Fig. 1), heterogeneously enhancing lesions with solid and cystic components. On MRI, SPTs have a low signal intensity on T1-weighted images and a high intensity on T2-weighted images. Although SPTs can occur throughout the pancreas, they are perhaps slightly more common in the pancreatic tail. When they occur in the pancreatic head, they can attain large size in the absence of bile duct obstruction, similar to ACC and pancreatic neuroendocrine tumors. However, SPT can grow into the wall of the superior mesenteric or portal vein; it would be a mistake to operate on a large SPT of the pancreatic head and assume that a narrowed superior mesenteric or portal vein could be successfully separated from the tumor; venous resection/reconstruction may be required. The radiographic differential diagnosis of a SPT should include other cystic neoplasms including mucinous neoplasms or serous cystadenomas, and intraductal papillary mucinous neoplasms, as well as a pancreatic neuroendocrine tumor. However, age is important, in a young woman younger than age 30, SPT and pancreatic neuroendocrine tumor would be most likely. In the absence of an inherited endocrinopathy (such as MEN1 or VHL), an IPT would be most likely. In a young woman younger than age 20, SPT would clearly be the most likely diagnosis as even in MEN1, a large pancreatic neuroendocrine tumor would be uncommon under the age of 20. FNA biopsy may be useful when routine imaging is inconclusive and diagnostic uncertainty exists, however, because of the tumor's largely necrotic composition, FNA biopsy may often be nondiagnostic.

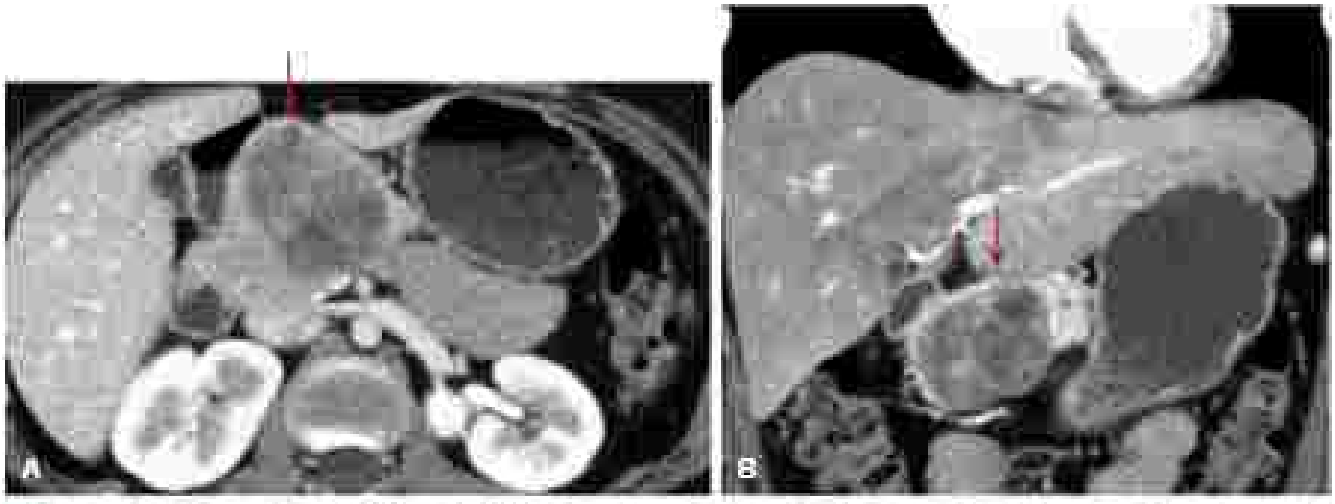

FIG. 3. (A) Axial and (B) coronal images of a contrast-enhanced computed tomography scan from a patient with a solid pseudopapillary tumor (arrows) of the neck of the pancreas with solid and cystic characteristics.

Some defining histologic features of SPTs include the presence of solid cellular hypervascular regions without gland formation, and the presence of branching papillary fronds with fibrotic and degenerative pseudopapillae. Cells stain positively for neuron-specific enolase, CD10, and keratins, chromogranin, synaptophysin, and endocrine pancreatic enzymes are generally not expressed. SPTs often stain positive for progesterone receptors, whereas estrogen receptor positivity is more variable. There are no histologic characteristics that appear prognostic for patients with SPTs. The genetic profile associated with SPT is different from adenocarcinoma, most notably for an absence of *KRAS*, *GNAS*, and *SMAD4* mutations. Almost all SPTs harbor alterations in the APC/β-catenin pathway resulting from a mutation involving *CTNNB1* (exon 3). Nuclear accumulation of β-catenin has been described in 95% of SPTs and 74% of tumor specimens (cyclin D1, a downstream effector of β-catenin). Interestingly, *BCL9*, a β-catenin stabilizing gene, is significantly decreased in SPT, which may help attenuate the protumorigenic effects of overactivation of the Wnt/β-catenin pathway. In addition, genes involved in the Hedgehog and androgen receptor signaling pathways, as well as genes involved in epithelial mesenchymal transition have been shown to be activated in SPT.

Treatment

Surgical resection is recommended for all patients with localized SPT. Although these tumors may be extremely large and can invade critical vasculature, most tumors are usually amenable to complete resection if the operating team is comfortable with resection and reconstruction of the superior mesenteric and/or portal vein. Arterial resection/reconstruction is required much less often. Pancreaticoduodenectomy or distal pancreatectomy can be performed with en bloc resection of involved adjacent organs when indicated. Recurrence is very uncommon; these authors have seen only one patient who had metastatic disease and, in that patient, it was present at the time of diagnosis. We have not seen a patient with SPT who developed a metachronous recurrence following a potentially curative operation. Although recurrence rates are low, long-term surveillance is felt to be important because of the young age of most all patients at the time of diagnosis. Given the excellent survival rates following surgical resection alone, adjuvant systemic therapy is not routinely used. If metastatic disease occurs (very rare), the most common sites include liver, mesentery, and peritoneum. The management of such very patients is anecdotal and for those with single site recurrence, surgery may be a reasonable approach.

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is a form of pancreatitis characterized by obstructive jaundice with or without a pancreatic mass, lymphoplasmacytic infiltration, and fibrosis of the pancreas, and a therapeutic response to corticosteroids. The incidence of AIP is unknown, but it has become less frequently found on pathologic examination of surgical specimens following operations for presumed cancer; the diagnosis of AIP is rarely being made more often without surgical resection of the pancreas. Patients with AIP often present with painless jaundice that can mimic pancreatic ductal adenocarcinoma and is due to inflammation and narrowing/stricture of the distal common bile duct. In addition, other common symptoms of AIP include weight loss and abdominal pain but usually in the absence of cachexia and pain requiring narcotic medication. Similar to patients with adenocarcinoma, many of those with AIP are diabetic with impaired glucose tolerance.

AIP is currently classified into two subtypes. Type 1 AIP is associated with an elevation in serum immunoglobulin G4 (IgG4) levels and radiographic evidence of extrapancreatic involvement such as Sjögren syndrome, rheumatoid arthritis, primary sclerosing cholangitis, retinal pseudotumor, and inflammatory bowel disease. Extrapancreatic organ involvement can occur before, synchronous with, or after the diagnosis of AIP and type 1 is more common in older men. Biopsy of extrapancreatic sites can be helpful in making the diagnosis because the affected organs often demonstrate the characteristic lymphoplasmacytic infiltrate rich in IgG4 positive cells. In contrast, type 2 AIP is seen in the absence of elevated IgG4 levels and associated autoimmune disease is limited to inflammatory bowel disease, which is found in approximately 20% of patients. There is also an age predilection to type 2 AIP. Serum IgG4 is the single best serologic marker of AIP with a sensitivity of 80% in patients with type 1 AIP, but only 17% in those with type 2 AIP. IgG4 elevation above twice the upper limit of normal is strongly suggestive of AIP in the setting of obstructive jaundice.

The classic features of AIP on CT or MRI include a diffusely enlarged, sausage shaped pancreas with homogenous attenuation and no visible pancreatic duct. However, when the predominant area of involvement is the pancreatic head and ampulla/papilla, the imaging characteristics can be more challenging (Fig. 3). In contrast to alcohol induced pancreatitis, AIP is not associated with ductal dilation, calculi, and pseudocyst formation. Importantly, although AIP may involve a stricture of the pancreatic duct, the upstream dilation characteristic of pancreatic ductal adenocarcinoma is rarely observed.

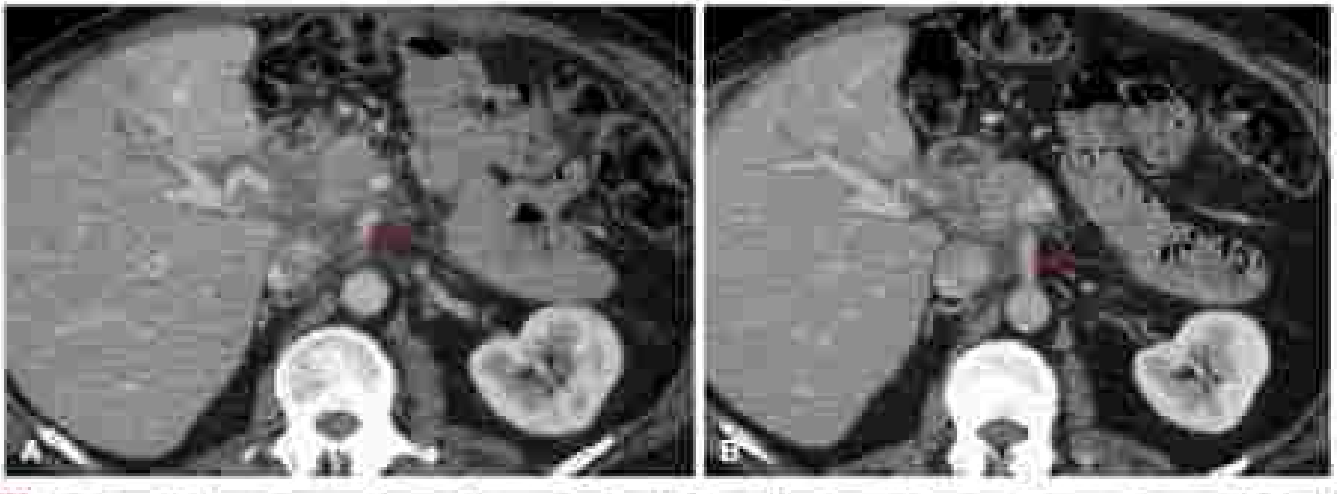

FIG. 3 Axial images of a contrast-enhanced computed tomography scan from a 53-year-old man proven to have type 1 autoimmune pancreatitis before (A) and after (B) steroid treatment. Image taken at the level of the superior mesenteric artery (arrow). Biopsy showed lymphoplasmacytic inflammation and a positive immunohistochemical stain for immunoglobulin G4.

However, occasionally, AIP may present as a focal mass-forming lesion in the pancreas that can be easily confused with pancreatic ductal adenocarcinoma; in such cases, the diagnosis is usually made by the pathologist after the involved pancreas has been surgically excised. Recently, international consensus diagnostic criteria were developed for type 1 and type 2 AIP, which incorporate the findings from radiographic imaging (including ductal imaging with magnetic resonance cholangiography or endoscopic retrograde cholangiopancreatography) as well as serologic and histopathologic data.

Type 1 AIP may not require a histologic diagnosis when the typical clinical, radiographic, and laboratory criteria are present, but since type 2 AIP is often seronegative and lacks other organ involvement, definitive diagnosis requires a pathologic biopsy specimen. Type 1 AIP has three essential features: (1) lymphoplasmacytic infiltrate surrounding small-sized interlobular pancreatic ducts, (2) fibrosis centered around the ducts and veins affecting predominantly the peripancreatic adipose tissue, and (3) obliterative phlebitis affecting the pancreatic veins. Immunostaining often demonstrates abundant (>10 cells/high power field) IgG4 positive cells. Type 2 AIP differs from type 1 by less prominent fibrosis, phlebitis, and the lack of IgG4 positivity. In type 2 AIP, lymphoplasmacytic infiltrates may result in obliteration of the pancreatic duct lumen, in contrast to type 1 AIP, in which the ductal epithelium is generally spared. The diagnosis of AIP (especially type 2) can be difficult, short of removing part of the pancreas as no single diagnostic test is sufficient. A correct diagnosis, made short of removing the pancreas, relies on a combination of cytology/histology of biopsy specimens, cross-sectional and endoscopic imaging, serologic findings, and a detailed clinical history. In general, the diagnosis of AIP requires a multidisciplinary team consisting of a radiologist, pathologist, surgeon, and gastroenterologist with expertise in the disease.

Treatment

AIP is highly responsive to corticosteroid therapy and when this does not occur quickly (in weeks), an alternate diagnosis (especially adenocarcinoma) should be considered. Although AIP can resolve spontaneously, treatment with corticosteroids has been associated with rapid reversal of jaundice, diabetes, and exocrine dysfunction usually within 2 to 4 weeks of starting treatment. The resolution of bile duct obstruction shortly after starting corticosteroids confirms the diagnosis. The International Consensus Diagnostic Criteria for Autoimmune Pancreatitis recommends a trial of 0.6 to 1 mg/kg per day of prednisone for a period of 2 weeks followed by imaging and interval assessment of CA 19-9 levels. If the diagnosis of AIP is correct, the bile duct stricture and gland enlargement should improve with steroid therapy. On clinical and radiologic improvement, the prednisone can be tapered by 5 to 10 mg/day every 1 to 2 weeks until a daily dosage of 20 mg, then decreased by 5 mg every 2 weeks. Because clinical relapse can occur in up to 30% of patients, some have advocated a more prolonged taper or the administration of low dose maintenance prednisone. In Japan, prednisone (2.5–7.5 mg/day) is administered for up to 3 years, which has demonstrated a lower relapse rate in type 1 AIP. Patients with type 1 AIP who experience a rapid decrease in serum IgG4 levels have a low probability of relapse. If corticosteroids are ineffective in disease relapse, other immunologic therapies, including rituximab and azathioprine, have been used. Surgery is reserved for situations where diagnostic uncertainty exists. If the diagnosis of AIP cannot be confirmed and the pancreas has been biopsied more than once, surgical resection of the pancreas (involved segment, Whipple's or distal pancreatectomy) is the most logical approach. If the pancreas (and the patient) are operable/resectable and a trial of steroids is preferred despite diagnostic uncertainty, we would reimage in 3 to 4 weeks and in the absence of improvement, proceed to surgery. If the involved segment or entire pancreas is deemed not resectable because of local anatomy, and AIP is suspected but not confirmed, then a trial of corticosteroids is quite reasonable. If there is no response to corticosteroids, repeat biopsy should be performed. One of the most difficult clinical situations involves a patient with an inoperable pancreas tumor in which the differential diagnosis includes both AIP and adenocarcinoma and the diagnosis cannot be established despite multiple attempts at endoscopic ultrasound (EUS)-guided or percutaneous biopsy and a trial of corticosteroids. In this situation we would not start empiric chemotherapy (patient may not have cancer), but rather, perform a comprehensive reassessment in 4 to 6 weeks and consider rebiopsy at that time. If the correct diagnosis is, in fact, inoperable pancreatic cancer, such a treatment delay will be of little clinical significance and with time, the diagnosis will become apparent.

PRIMARY PANCREATIC LYMPHOMA

Lymphomas involving predominantly the pancreas are extremely rare and can occur exclusively in the pancreas (primary pancreatic lymphoma [PPL]), via direct extension from adjacent peripancreatic lymphadenopathy (secondary pancreatic lymphoma), or originate from lymph nodes distant from the pancreas. PPL is defined by the World Health Organization as "an extranodal lymphoma arising in the pancreas with the bulk of the disease localized to the site, contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the pancreas with treatment directed to this site." PPL is predominantly non-Hodgkin's lymphoma of B-cell phenotype and diffuse large B-cell lymphoma is the most common histological subtype. PPL accounts for less than 2% of extranodal lymphomas. Currently, no specific biochemical markers aid in the diagnosis of PPL. Elevated serum lactate dehydrogenase and β2-microglobulin levels in the setting of a normal CA 19-9 may provide a clue to the diagnosis of PPL. PPLs predominantly occur in men (7:1) and usually present in the fifth to sixth decade of life. Common presenting symptoms include abdominal pain, and symptoms such as fever, night sweats, chills, weight loss, jaundice, and gastric or duodenal outlet obstruction resulting from the bulk of disease.

In patients with PPL, CT or MRI demonstrates the presence of a large mass that focally involves the head of the pancreas (Fig. 4) or occasionally a more diffuse form that is infiltrative and can mimic the appearance of acute pancreatitis. As one would expect, patients with PPL often present with significant lymphadenopathy involving the peripancreatic lymph nodes and most notably, the retroperitoneal lymph nodes below the renal vein in the paraaortic location. The involved lymph nodes lack central necrosis or calcifications and the pancreatic duct is rarely dilated despite what appears to be a large

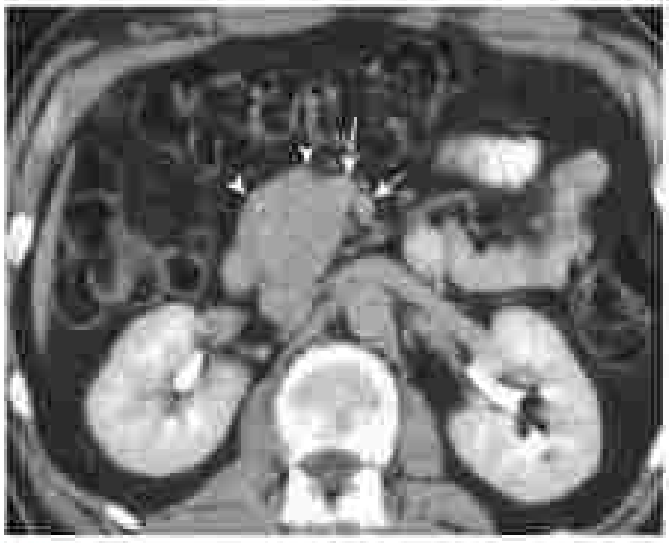

FIG. 4. Axial image of a primary pancreatic lymphoma involving the head of pancreas (white arrowheads) and the hypodense appearance of the mass (arrowheads) and the adjacent abutment of the superior mesenteric vein (long arrow) and proximity to the superior mesenteric artery (short arrow).

pancreatic tumor. Also, narrowing or occlusion of the superior mesenteric or portal veins is rarely present in most patients despite the bulky tumor size. PPLs are said on diffusion-weighted postcontrast magnetic resonance scans with uptake patterns that may be focal nodular, diffuse, or segmental. Such findings prompt biopsy, either with either EUS-FNA (small or core biopsy needle) or percutaneous core biopsy technique. Cytopathologic features include large malignant lymphocytic nuclei, prominent nucleoli, and a background of necrosis. Immunohistochemical stains that are positive in pancreatic endocrine neoplasms, such as synaptophysin, are generally negative in PPL. The use of flow cytometry may be limited by the cellularity of some fine-needle aspirate specimens; therefore, core needle biopsy is usually preferred when the diagnosis of PPL is suspected.

Treatment

The standard of care in the management of PPL is chemotherapy alone, which provides excellent control of symptoms, including jaundice, as well as long-term remission. PPL is most commonly treated with a multidrug regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone. Complete remission can be expected with multidrug therapy in the majority of patients with large B-cell lymphoma. However, recurrence is common in patients older than age 60. The use of an anti-CD20 antibody, rituximab, and cyclophosphamide, doxorubicin, vincristine, and prednisone has been associated with improved response rates of up to 80% in diffuse large B-cell lymphoma. Other regimens include cyclophosphamide, vincristine, and prednisone and methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin. Laparotomy should be reserved for patients in whom the diagnosis is uncertain despite percutaneous or endoscopic biopsy often in the setting of biliary obstruction/endoscopic stenting or for therapeutic purposes (palliative surgery) in the setting of gastrointestinal hemorrhage or gastric outlet obstruction.

METASTATIC RENAL CELL CANCER

Metastatic lesions to the pancreas are also very rare and the vast majority of patients thought to have a metastasis to the pancreas actually have metastases to peripancreatic lymph nodes. The one exception is renal cell cancer (RCC), which metastasizes to the pancreatic parenchyma. Synchronous metastases can occur in up to 25% of patients with RCC and metachronous metastases may occur in up to 40% of all patients with a history of RCC. RCC metastases to the pancreas may present after an extended disease free interval from nephrectomy, and we have seen an accidental patient with a disease free interval of 20 years. This emphasizes the importance of long term follow up for patients with RCC after initial resection. There are no differences in the frequency of pancreatic metastases based on the laterality of the primary tumor and metastases from RCC can occur anywhere within the pancreas; there is not a preferred location (head vs body or tail). Interestingly, many patients have solitary metastases (based on CT/MRI imaging), which are usually asymptomatic (>60%) and identified during follow up surveillance. Occasionally, a metastasis from RCC can erode into the duodenum and cause gastrointestinal hemorrhage (because they are highly vascular tumors) or obstruct the splenic vein resulting in gastroesophageal varices and anemia, melena, or hematemesis. In patients with more widespread disease, abdominal pain, weight loss, or jaundice may be the presenting complaint. Many patients also have intrapancreatic metastases; therefore, a thorough staging evaluation should be performed in patients with suspected or biopsy-proven metastatic RCC to the pancreas (to include an MRI of the brain).

CT is the first test for the evaluation of presumed RCC metastases to the pancreas and is often diagnostic in the absence of a biopsy. The classic hypervascular tumor may demonstrate a central area of low attenuation on the arterial phase (Fig. 5) in a patient with a history of prior surgery for a large RCC is diagnostic. The imaging characteristics can be similar to pancreatic neuroendocrine tumors but this is a clinical dilemma only in patients with VHL who underwent prior nephrectomy for RCC. In contrast to the hypervascularity of RCC metastasis to the pancreas, pancreatic ductal adenocarcinoma is hypodense on the arterial phase of CT imaging. In the majority of patients with a history of RCC, the CT findings are diagnostic, and there is no need for a pancreatic biopsy. However, a tissue biopsy may be helpful if there is a concern over the diagnosis on imaging. Positive immunohistochemical staining for CD10 and PAX8 can be used to distinguish between metastatic RCC and other tumors, such as clear cell carcinoma of the pancreas, clear cell pancreatic endocrine tumor, and the solid variant of serous cystadenoma.

Treatment

In general, surgery is applied only to patients with isolated pancreatic metastases from RCC (uni- or multifocal); those with synchronous extrapancreatic metastases are usually not considered for surgical treatment in the absence of pancreas-associated complications such as bleeding or biliary/gastric outlet obstruction. Patients with isolated RCC metastases to the pancreas who undergo surgical resection may experience a long disease free survival. In a systematic review that identified 321 patients with resected RCC metastases to the pancreas, the 5-year disease free survival and overall survival were 37% and 73%, respectively. However, with improvements in systemic therapies (targeted agents, immunotherapy) to include innovative clinical trials, patients with metastatic RCC may experience prolonged survival without surgery. In addition, antiangiogenic agents such as bevacizumab, sunitinib, and sorafenib, have shown promising results in metastatic RCC, necessitating the need for a multidisciplinary approach to the management of these patients.

CONCLUSIONS

The major diagnostic concern in patients with a pancreatic neoplasm, either suggested or clearly demonstrated on cross-sectional imaging, is pancreatic ductal adenocarcinoma. Remember that most patients with adenocarcinoma of the pancreas will also have an elevation in serum levels of CA19-9 and/or an elevation in hemoglobin A1c (often in the setting of weight loss). For patients with a symptomatic or asymptomatic pancreatic mass, accurate staging with CT or MRI is usually followed by EUS with FNA biopsy. Although EUS-FNA biopsy has become very safe in experienced hands, it should not be used to replace a detailed patient history, physical examination, focused laboratory evaluation and a thorough review of all imaging studies. Rather, pancreatic biopsy should be used in conjunction with all available clinical and laboratory information to arrive at an accurate diagnosis and stage of disease. If the diagnosis is not adenocarcinoma, a thorough understanding of rare and unusual pancreatic neoplasms is important to develop the correct treatment plan. Surgery is the cornerstone of therapy for SPT, ACC, and isolated RCC metastases (especially those with a long disease free interval) if the tumor is operable. For those patients with tumors that are inoperable from the superior mesenteric or portal vein (on preoperative imaging), surgery should only be undertaken if the operative team has experience with venous resection and reconstruction at the time of pancreatectomy. Similarly, if the tumor appears to encase the celiac artery or common hepatic artery, arterial resection and reconstruction may be necessary, such tumor vascular relationships are accurately delineated on preoperative imaging and should not be an unexpected finding at the time of laparotomy. Most important, patients with diagnoses as discussed in this chapter will often live many years even without surgery, mandating that surgery associated mortality be close to zero and morbidity be managed safely. This can be achieved by referral of patients to specialty centers (often referred to as high volume centers) when indicated.

Finally, it is important to remember that medical therapy is the obvious choice for patients with ATP and PPL when the diagnosis can be accurately established. Usually this is possible without an operation (open or laparoscopic).

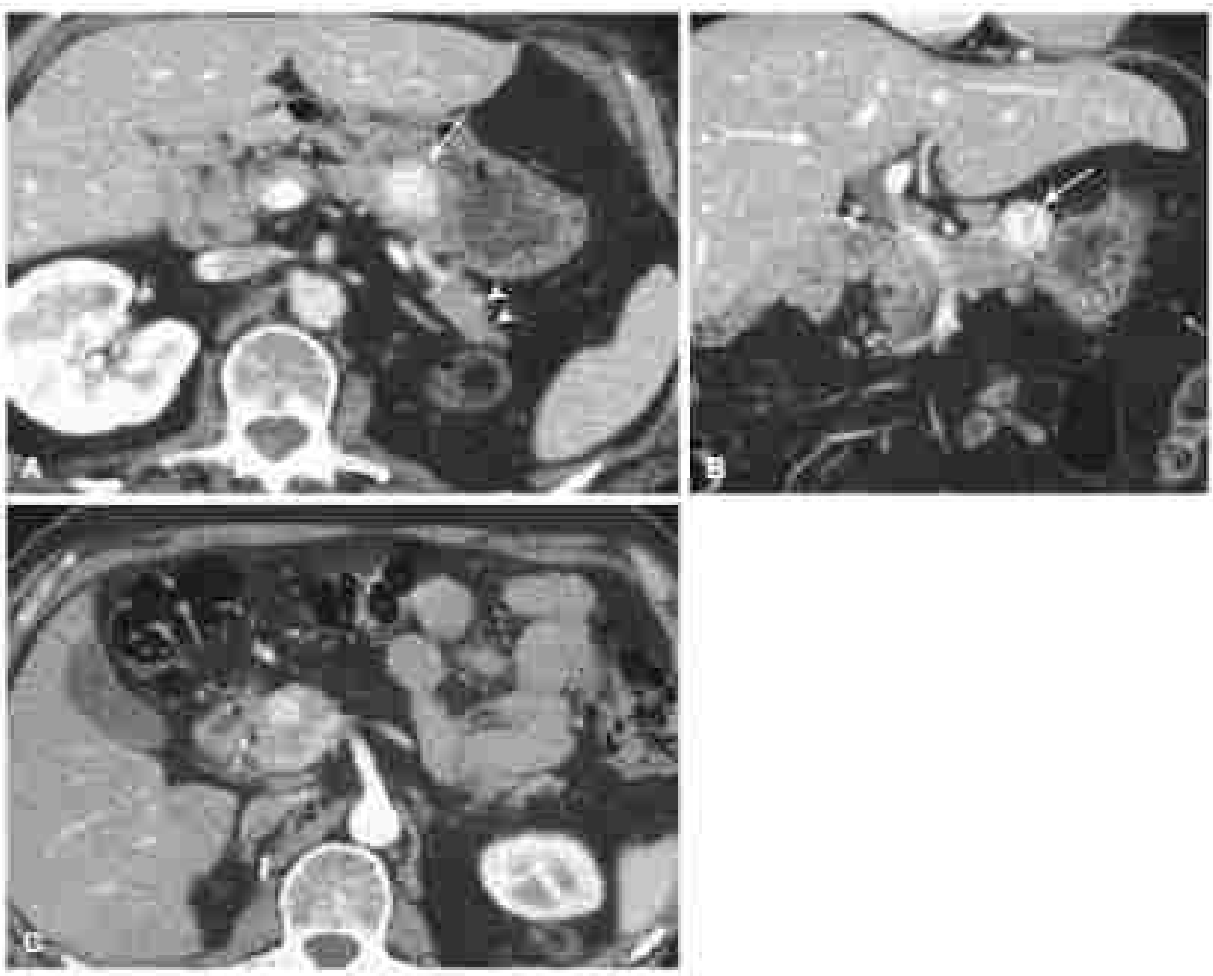

FIG. 1 (A, C) Axial and (B) coronal images of a contrast-enhanced computed tomography scan from a patient who underwent a left nephrectomy for renal cell carcinoma 15 years prior and then developed a metachronous metastasis to the pancreatic body. Note the characteristic bright enhancement of the metastatic lesion (arrow) on arterial phase imaging as well as the posterior displacement of the pancreas (arrowheads) because of the absence of the left kidney.

Suggested Readings

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Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas were first described in Japan in 1980 and have been increasingly identified over the past 30 years because of the advances of cross-sectional abdominal imaging and its more frequent use in the evaluation of various abdominal complaints. At the Massachusetts General Hospital (MGH) approximately 25% of pancreatic resections are for IPMNs. Based on autopsies, it is suspected that IPMN lesions are found in up to 2% to 3% of the general population. Furthermore, IPMNs are more prevalent in older individuals, with about 10% of individuals older than 70 years being identified with an IPMN. Historically, IPMNs were thought to occur more frequently in men; however, more recent studies and our experience at MGH has been that there is most likely no sex difference in IPMN prevalence. This chapter reviews IPMN characteristics, risk of malignancy, and management recommendations.

CLASSIFICATION OF THE TYPES OF IPMN LESIONS

There are two distinct types of IPMN lesions and these include main duct (MD) IPMN and branch duct (BD) IPMN. Mixed-type IPMN lesions are a third type that include features of MD IPMN and BD IPMN (Fig. 1). IPMNs are categorized as MD IPMN if the main pancreatic duct has segmental or diffuse dilation that is greater than 5 mm without other causes of obstruction. Conversely, BD IPMNs are defined as having a pancreatic cyst that is more than 5 mm in size that communicates with a nondilated main pancreatic duct. Mixed-type IPMN lesions are characterized as having a pancreatic cyst that communicates with a dilated main pancreatic duct. Most IPMNs are identified incidentally when patients are undergoing cross-sectional imaging for abdominal complaints, most often abdominal pain. Although most IPMN lesions are incidentally found using a multidetector computed tomography (MDCT) or a magnetic resonance imaging (MRI), the best imaging modality in the initial workup of a suspected IPMN is a pancreas-protocol MDCT scan of the abdomen and pelvis (Fig. 2). This includes an arterial contrast phase and a portal venous contrast phase that favors imaging of the pancreas.

After a lesion has been identified as being suspicious for an IPMN, the decision must be made to either proceed with observation, diagnostic intervention, or resection. The decision on how to proceed depends on the type of lesion and other characteristics that have been classified as high-risk stigmata and worrisome features. This classification scheme and management recommendations are based on the International Association of Pancreatology (IAP) 2006 Sendai consensus guidelines that were subsequently updated to the IAP 2012 Fukuoka consensus guidelines. These guidelines were most recently revised in 2017, and they are now known as the revised IAP 2012 Fukuoka consensus guidelines.

A distinct feature of IPMN lesions are papillary projections in the pancreatic ductal system. Based on the morphology of these projections, IPMNs are categorized into epithelial subtypes or phenotypes. There are four distinct epithelial phenotypes: intestinal, gastric, pancreatobiliary, and oncocytic. This categorization is important because these phenotypes are associated with tubular, colloid, and oncocytic invasive malignancy with varying degrees of survival.

CLINICAL PRESENTATION

At our institution, the majority of patients (57%) were asymptomatic at the initial time of presentation. Of those patients who were managed with surveillance, 83% were asymptomatic at the initial time of presentation and only 10% of patients progressed to have symptoms at the 6-month mark. Among patients who underwent surgical resection, about 50% had symptoms at presentation that included abdominal pain (43%), weight loss greater than 10 pounds (29%), acute pancreatitis (12%), and jaundice (9%). Additionally, about 34% of patients who underwent resection at MGH had a diagnosis of diabetes mellitus, and these patients had an adjusted twofold elevated risk of having high-grade dysplasia and invasive carcinoma.

FAMILY HISTORY

Although there are currently no clear genetic disorders that are associated with IPMN lesions, at MGH, 11.9% of all patients with an IPMN lesion had a family history of pancreatic cancer. Despite this finding, a family history of pancreatic cancer was not associated with type (MD IPMN, BD IPMN, or mixed-type IPMN), epithelial subtype, or presence of malignancy. Among these same patients, however, there was an associated increase in the incidence of concurrently occurring pancreatic ductal adenocarcinoma (PDAC) (13.1% vs 2.9%, $P = .02$) and extrapancreatic malignancies (35.6% vs 20.1%, $P = .03$). The Johns Hopkins experience has reported that a family history of pancreatic cancer was an independent risk factor for recurrence of IPMN after initial resection, and that it carried a fourfold increased risk of developing a recurrence.

MD-IPMN

MD IPMN lesions usually occur in the sixth decade of life, and they are more often associated with symptoms, with more than 50% presenting with abdominal pain, weight loss, jaundice, or pancreatitis. About 50% of all MD IPMN lesions are intestinal epithelial phenotype. These express MUC2, which produces a thick mucin that may lead to obstruction of the main pancreatic duct and subsequent pancreatitis. Intestinal epithelial phenotype IPMN lesions are associated with high-grade dysplasia and invasive carcinoma and most often progress to colloid carcinoma. Colloid carcinomas have a median survival of 95 months after resection and are more indolent than tubular carcinomas, which have a reported postresection survival of about 26 months. Additionally, colloid carcinomas are associated with GNAS mutations. Oncocytic epithelial phenotype is associated with MD IPMN, but it is only seen in 2% of all IPMN lesions. These lesions are indolent and if they transform into invasive malignancy their median survival has been reported to be approximately 132 months, which is much more favorable than colloid or tubular carcinomas.

According to the revised IAP 2012 Fukuoka consensus guidelines, all MD IPMNs with main duct dilation of more than 10 mm, jaundice, or mural nodules should be considered for surgical resection if the patient is an appropriate surgical candidate. The reasoning behind this recommendation is the increased risk for high-grade dysplasia and invasive carcinoma. The risk of identifying high-grade dysplasia in a resected MD IPMN specimen at MGH is about 52%, and the reported risk of invasive carcinoma ranges from 16% to 70%.

BD-IPMN

The majority of the pancreatic cysts identified in cross-sectional abdominal imaging are suspected to be BD IPMN lesions. The most common epithelial phenotype found among BD IPMN lesions is gastric epithelial subtype (63%), which does not commonly undergo malignant transformation. When malignant transformation does occur, however, BD IPMN lesions transform into tubular carcinomas.

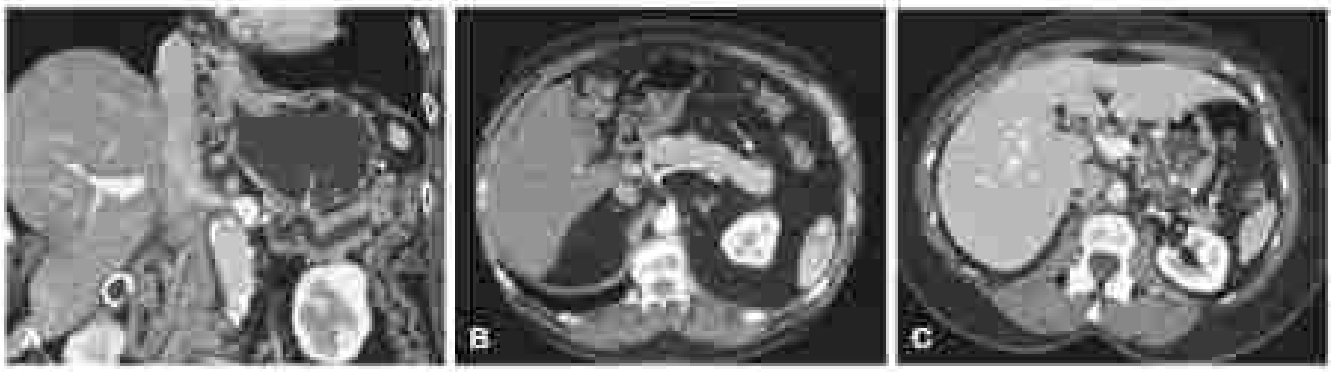

FIG. 1. (A) Sagittal multidetector computed tomography image showing main duct intraductal papillary mucinous neoplasm with focal dilation (arrow) of the main pancreatic duct. (B) Axial multidetector computed tomography image showing a small cystic lesion in the pancreatic tail (arrow) consistent with branch duct intraductal papillary mucinous neoplasm. No dilation is observed in the main pancreatic duct. (C) Mixed-type intraductal papillary mucinous neoplasm on computed tomography scan. There is notable diffuse dilation of the pancreatic duct in the head and body of the gland (arrowheads) and multiple small branch duct lesions throughout the body and tail (arrow).

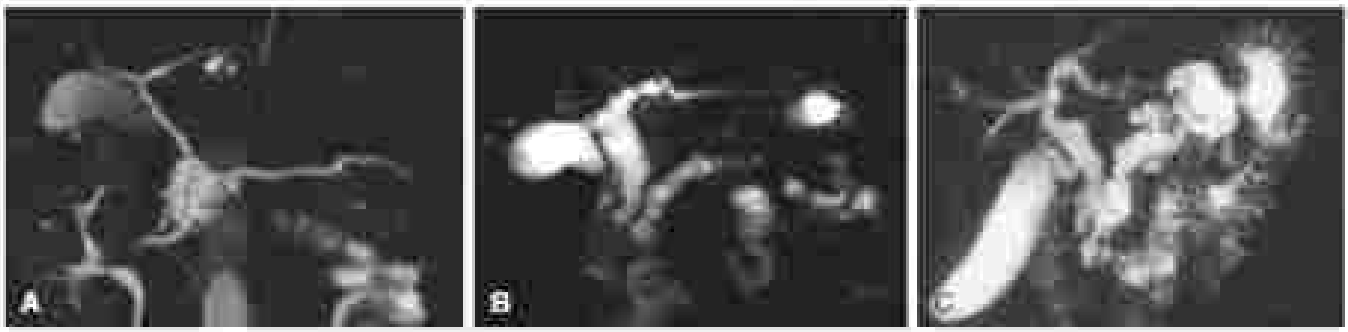

FIG. 2. Radiographic appearance of (A) branch duct, (B) main duct, and (C) mixed-type intraductal papillary mucinous neoplasms. (*From* Tanaka M, Fernández-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17(5):738–53.)

which are more aggressive tumors. Despite being a more aggressive form of invasive cancer, the 5-year survival of invasive BD-IPMN is still more favorable than pancreatic ductal adenocarcinoma (55% vs 37%).

Pancreatobiliary type epithelial phenotype IPMNs are more often seen in BD-IPMN lesions than in MD-IPMN lesions and are also associated with tubular carcinoma (Fig. 2); however, pancreatobiliary type is difficult to distinguish from gastric type. Overall, the risk of invasive carcinoma associated with BD-IPMN ranges from 9% to 12%, whereas the risk of high-grade dysplasia is about 15% to resected BD-IPMNs.

MIXED-TYPE IPMN

By definition, mixed-type IPMN lesions include dilation of the main pancreatic duct and cystic lesions arising from branches of the main pancreatic duct. At our institution, the risk of high-grade dysplasia and invasive carcinoma for mixed-type IPMN tumors is about 31% and 28%, respectively. This is notably higher than for BD-IPMN, but lower than what has been reported for MD-IPMN. Although recent data have shown that the degree of main duct dilation may play a prognostic role in predicting how mixed-type IPMN lesions behave, the revised IAP 2012 Fukuoka consensus guidelines recommend consideration for surgical resection of mixed-type IPMN with main duct dilation larger than 10 mm, jaundice, or mural nodules and if the patient is an appropriate surgical candidate.

IAP Guidelines for BD-IPMN Lesions

The revised IAP 2012 Fukuoka consensus guidelines provide recommendations on how to proceed when a BD-IPMN lesion is identified. These guidelines are based on the presence or absence of high-risk stigmata and worrisome features. According to the previous IAP 2006 Sendai consensus guidelines, surgical resection should be considered for a BD-IPMN lesion if the patient is evaluated to be an appropriate surgical candidate and if any of the following criteria were met: any symptomatic cyst, asymptomatic cyst that was greater than 3 cm in size, main pancreatic duct dilation that was greater than 6 mm in diameter, or presence of mural nodules within the cyst.

The revised IAP 2012 Fukuoka consensus guidelines were brought forth because many patients were undergoing pancreatic resections for benign IPMN lesions (Table 1 and Fig. 4). The revised IAP 2012 Fukuoka consensus guidelines categorized IPMN characteristics into high-risk stigmata and worrisome features. Surgical resection should be considered for a BD-IPMN lesion if the patient is identified as being an appropriate surgical candidate and if any of the following high-risk stigmata are present: obstructive jaundice in a patient with a cystic lesion of the head of the pancreas, enhancing mural nodule greater than or equal to 5 mm, or main pancreatic duct greater than or equal to 10 mm in diameter. If high-risk stigmata are not present, then management recommendations depend on the presence of worrisome features. Worrisome features include pancreatitis, a BD-IPMN cyst greater than or equal to 3 cm in size, enhancing mural nodule smaller than 5 mm, thickened and/or enhancing cyst wall, main pancreatic duct measuring 5 to 9 mm in diameter, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA19-9, and cyst growth rate greater than or equal to 5 mm over 2 years. If worrisome features are present, then the recommendation is to perform an endoscopic ultrasound (EUS) and fine needle aspiration (FNA) biopsy to further investigate the BD-IPMN. Surgical resection should be considered if

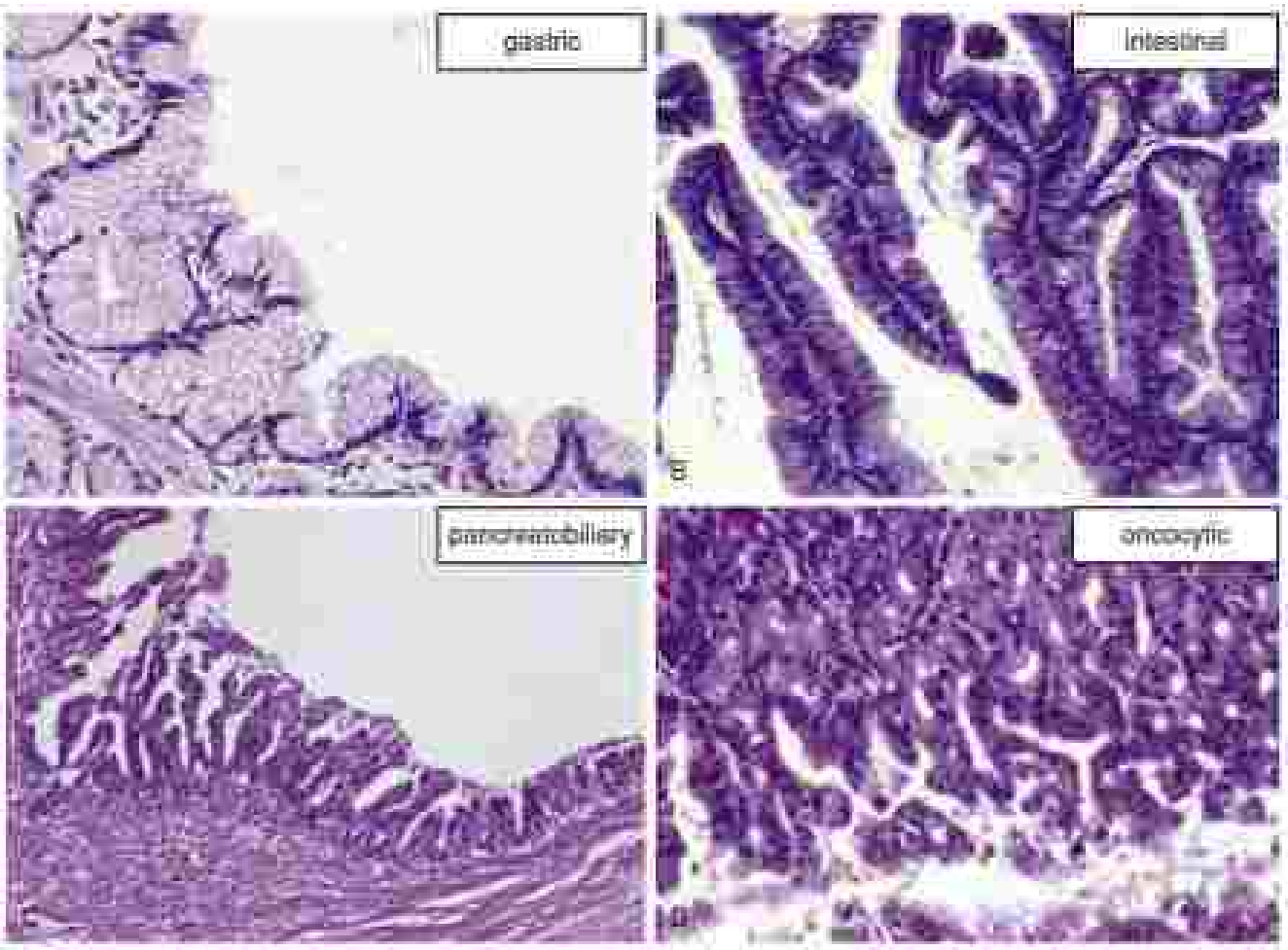

FIG. 1 The four histologic classifications of intraductal papillary mucinous neoplasm are (A) gastric, (B) intestinal, (C) pancreatobiliary and (D) oncocytic. (From Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012;12(3):183–97.)

the patient is an appropriate surgical candidate and if any of the following are present during the EUS with FNA: mural nodule, suspicion for involvement of the main pancreatic duct, or cytology from the FNA biopsy that is suspicious or positive for malignancy.

FIELD-DEFECT CONCEPT

The field-defect concept refers to the phenomenon that a patient may have an IPMN in one location in the pancreas and concomitantly have PDAC at a different site of the pancreas. The reported incidence of concomitant PDAC has ranged from 4% to 11%. In addition to concomitant PDAC, patients may have synchronous and multifocal lesions. Independent predictors of concomitantly occurring PDAC are worsening diabetes mellitus and abnormal serum CA19-9. Furthermore, it is important to note that IPMNs can histopathologically range from low grade dysplasia, which can be considered to be similar to adenomas, to high grade dysplasia and invasive carcinoma. Because of the field defect concept, multiple IPMN lesions with varying degrees of dysplasia and presence of invasive carcinoma can be present concurrently. As such, each suspicious lesion should be maximized; multifocality and cyst specific pancreatectomy should be performed rather than total pancreatectomy.

ELEVATED SERUM CA19-9

The revised IAP 2012 Fukuoka consensus guidelines now includes elevated serum CA19-9 as a worrisome feature. This is based on recent findings from a meta-analysis of 15 studies that included 1639 patients and found that elevated serum CA19-9 was significantly predictive of detecting invasive carcinoma in IPMN lesions (pooled sensitivity of 52% and specificity of 88%, respectively). We have found that among resected BD IPMN at MGH, an elevated serum CA19-9 of 100 units/mL or higher had the highest predictive accuracy for detecting invasive carcinoma (93%), when compared with the standard cutoff of 37 units/mL (83%). However, there is no evidence to support a diagnostic cutoff of serum CA19-9 for detecting high grade dysplasia.

IMAGING MODALITIES

Many patients will be diagnosed with an IPMN based on CT imaging performed for the workup of abdominal pain or as part of the workup for another abdominal reason or pathology. If contrast was used, the portal venous phase was most likely not captured, and if it was captured, it was most likely suboptimal. All patients with a known or suspected IPMN should undergo a pancreas protocol MDCT scan or a gadolinium-enhanced with magnetic resonance cholangiopancreatography (MRCP). A pancreas protocol MDCT captures the arterial and portal venous phase and provides the best images of the pancreas. At MGH, MDCT includes negative oral contrast with water and intravenous contrast administration. The amount of IV contrast is weight dependent and is given via bolus at about 3 to 4 mL/s. There is a 50 second delay from when the contrast injection starts to when the arterial phase is captured. The portal venous phase, also referred

TABLE 1 International Association of Pancreatology Consensus Guidelines for Management of BD-IPMNs

	Recommendations
2006 SENDAI GUIDELINES	
Symptomatic cyst >3 cm Asymptomatic cyst >3 cm Main pancreatic duct >6 mm in diameter	Surgical resection should be considered if any are present in a patient who is an appropriate surgical candidate
REVISED 2012 FUKUOKA GUIDELINES	
High-Risk Stigmata	
Obstructive jaundice in a patient with cystic lesion of pancreatic head Enhancing mural nodule ≥5 mm Main pancreatic duct >10 mm	Surgical resection should be considered if any are present in a patient who is an appropriate surgical candidate
Worrisome Features	
Pancreatitis Cyst ≥3 cm Enhancing mural nodule <5 mm Thickened/enhancing cyst walls Main duct size 5–9 mm Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy Lymphadenopathy Increased serum level of CA19-9 Cyst growth rate >5 mm over 2 years	EUS with FNA might be performed to further characterize the BD-IPMN
If Detected on EUS or FNA:	
Definite mural nodule(s) ≥5 mm Suspicious for main duct involvement Suspicious or positive cytology for malignancy	Surgical resection should be considered

BD-IPMN, branch duct intraductal papillary mucinous neoplasm; *EUS*, endoscopic ultrasound; *FNA*, fine needle aspiration.

to as the mature abdominal phase, is captured after a 75-second delay after the start of contrast injection. Of note, the MDCT should ideally be performed in a dual energy manner. An MRI/MRCP however, might be preferred over a pancreas protocol MDCT because of the lack of radiation exposure, which becomes important when considering that many patients will require long-term IPMN surveillance. Additionally, an MRI/MRCP has been reported to have superior contrast resolution and better delineation of septations, mural nodules, and communication with the main pancreatic duct, when compared with a pancreas protocol MDCT. The accuracy rate of MDCT and gadolinium enhanced MRI to detect high grade dysplasia and invasive carcinoma in IPMN lesions ranges from 75% to 86%.

Although an EUS is an additional imaging modality to survey IPMN lesions, we argue against its use as a surveillance imaging modality. An EUS should be performed to further characterize a BD-IPMN with worrisome features, as previously discussed. Using EUS as a routine long-term follow-up imaging surveillance modality carries risks because of its invasive nature. Although EUS is able to delineate main duct involvement and can detect mural nodules within the pancreatic cyst, it has also been reported to erroneously identify mucin globules as mural nodules. One way to avoid this erroneous identification is to perform a contrast-enhanced EUS, which allows for better discrimination between mucin globules and mural nodules by detecting blood flow signal in mural nodules (sensitivity, 69%; specificity, 92.2%; and accuracy, 75.9%).

EUS AND FNA OF CYST FLUID

EUS with FNA has become an important diagnostic procedure when evaluating IMPN lesions, and in particular BD-IPMNs. EUS with FNA can sample the cyst fluid and biopsy solid or nodular cyst components. Approximately 70% of IPMN lesions have an elevated carcinoembryonic antigen (CEA) in their cyst fluid. Although a cyst fluid CEA level of 192 ng/mL has been found to be associated with IPMNs, cyst fluid CEA cannot distinguish between benign and malignant cysts. In addition to elevated CEA in the cyst fluid, there will also be mucin and, typically, an elevated amylase level.

Other important information that can be obtained from cyst fluid is cytologic and molecular analyses. Although these are more operator-dependent because they are complex to perform and they commonly are limited by indeterminate samples because of insufficient sample volume or cross-contamination with gastric or duodenal wall cells, cyst fluid cytologic and molecular analyses can identify common mutations and high grade atypia or malignant cells. The most common mutations that are associated with IPMN lesions are *GNAS* and *KRAS*; however, identification of these common mutations does not confirm the presence of malignancy. The majority of IPMN lesions (66%) have *GNAS* mutations. *KRAS* mutations in the cyst fluid are found in about 50% of IPMN lesions; however, *KRAS* mutations are also found in mucinous cystic neoplasms. From 45% to 96% of IPMN lesions have either *GNAS* or *KRAS* mutations in their cyst fluid.

Although the presence of *GNAS* and/or *KRAS* mutations does not confirm malignancy, mutations in these two genes are implicated in the progression pathway of IPMN lesions transforming into invasive IPMN malignant lesions. When comparing the presence of *GNAS* versus *KRAS* mutations to colloid versus tubular carcinomas, *GNAS* mutations are more frequently associated with colloid carcinoma (89% vs 52%, $P = .0003$) and *KRAS* mutations are most frequently associated with tubular carcinoma (89% vs 52%, $P = .01$). *KRAS* mutations are also seen in PDAC.

ROLE OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

In current practice, endoscopic retrograde cholangiopancreatography (ERCP) is not routinely used in the diagnostic work-up of an

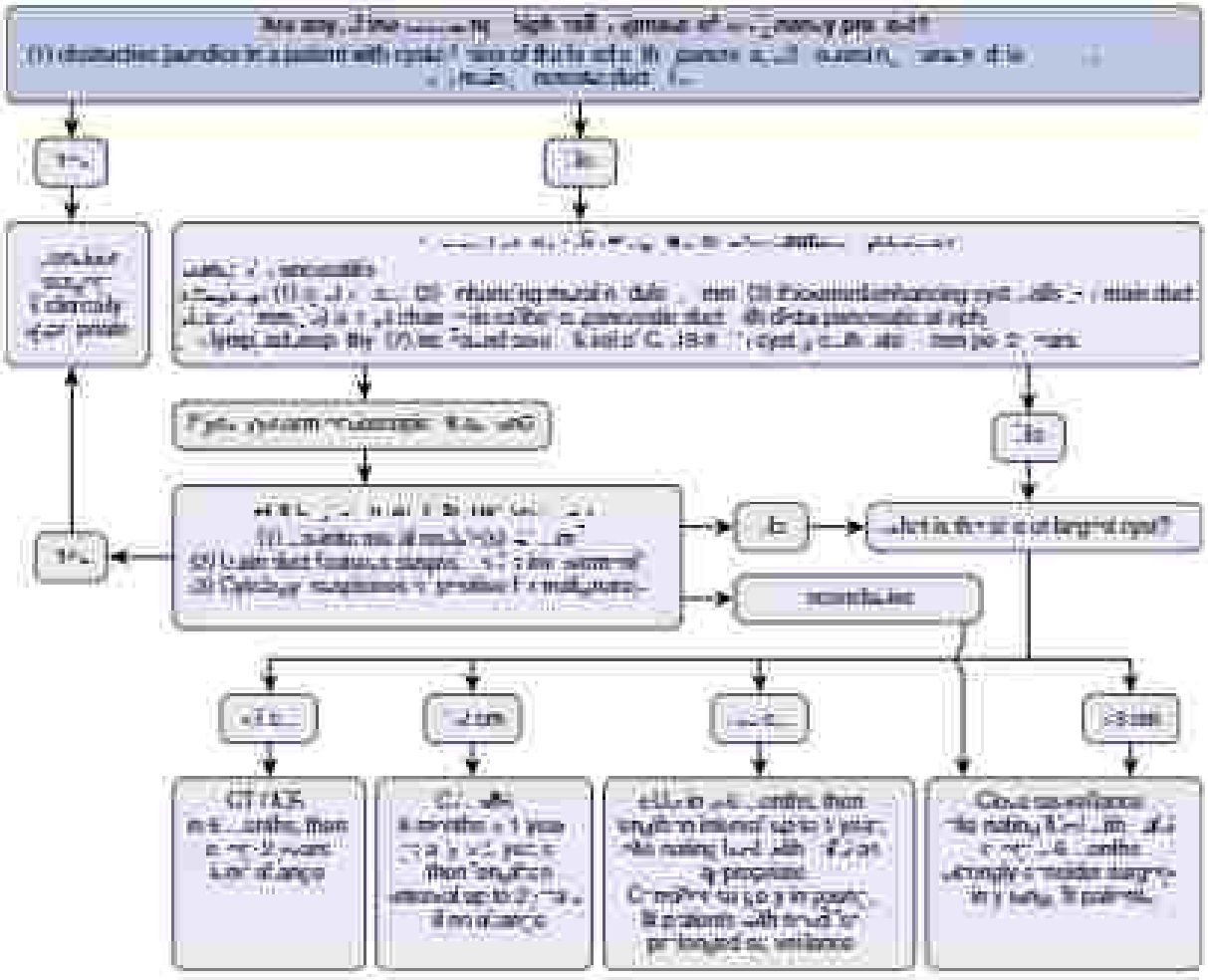

FIG. 4 Algorithm for the management of suspected intraductal papillary mucinous neoplasm (IPMN). Patients may be referred for evaluation of pancreatic cystic lesions or for evaluation of symptoms (eg, abdominal pain, weight loss, new-onset diabetes mellitus, or pancreatitis). Patients with findings suspicious for pancreatic cancer (eg, obstructive jaundice, a pancreatic mass, or dilated pancreatic duct) should undergo pancreatic protocol computed tomography (CT) or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) to evaluate for IPMN. Patients with findings suspicious for IPMN (eg, cystic lesion communicating with the pancreatic duct) should undergo endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) and MRCP to further characterize the lesion and evaluate for worrisome features or high-risk stigmata. Patients with main duct IPMN, mixed-type IPMN, or branch duct IPMN with worrisome features or high-risk stigmata should undergo surgical resection. Patients with branch duct IPMN without worrisome features or high-risk stigmata can undergo surveillance. Surveillance intervals are based on the 2017 International Consensus Fukuoka guidelines for management of IPMN of the pancreas. (From Tanaka M, Fernández-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738–753.)

asymptomatic IPMN lesions. EUS with FNA and MRCP are more routinely used since they can identify IPMN lesions and provide information about their malignancy potential without the invasiveness of an ERCP and its postprocedure risk of acute pancreatitis. However, when ERCPs were routinely used in the workup of patients with IPMN lesions, about 25% of patients would have the pathognomonic finding of a bulging ampulla, or a fish-mouth appearance, which extrudes thick mucin. ERCP may be necessary if patients present with obstructive jaundice resulting from an IPMN lesion and therefore need a sphincterotomy and possible stent placement. In this setting, an ERCP would be diagnostic and temporarily therapeutic.

MANAGEMENT

The most important classification when considering management recommendations is whether the lesion is a MD IPMN, BD IPMN, or mixed-type IPMN lesion. Second, the presence of high-risk stigmata and worrisome features is the next layer of classification that plays an important role in management recommendations. Next, we will summarize recommended management strategies based on the type of IPMN lesion and whether high-risk stigmata or worrisome features are present.

LESIONS THAT SHOULD BE RESECTED

All MD IPMN, mixed-type IPMN, and BD IPMN lesions with high-risk stigmata features should be considered for surgical resection. Preoperatively deciding the extent of the pancreatic resection may prove difficult because of the nature of IPMN lesions and how they present on imaging. Oftentimes, there is no discrete tumor that can be identified in a MD IPMN or mixed-type IPMN. Instead, there may only be the presence of a focal dilated area and either a distally or proximally dilated pancreatic duct. The presence of nodular components should raise the suspicion of a site of local malignancy or an adjacent malignancy. After an initial preoperative decision has been made regarding the extent of pancreatic resection (Whipple resection, extended Whipple resection, middle pancreatectomy, distal pancreatectomy, or total pancreatectomy), the surgeon must plan on sending pancreatic margins for frozen section to pathology to ensure that high-grade dysplasia or invasive malignancy is not being left behind. This is important because invasive malignancy spreads microscopically along the duct, and at times without any macroscopic evidence. Conversely, low- or moderate-grade dysplasia may be left in situ because all patients with a history of an IPMN, even following resection, should undergo routine surveillance. Intraoperative ultrasound has not been found to be useful in identifying the extent of malignant

spread of an IPMN lesion. At MGH, in the presence of pancreat[illegible] [illegible] the pa[illegible] [illegible] IPMN [illegible] the setting of [illegible] 404 patients, 58% [illegible] than 3% [illegible] 25% [illegible] [illegible]

[illegible] MD IPMN [illegible] alternatives [illegible]

Lesions That Should Undergo Further Work-Up With EUS and FNA Biopsy

BD IPMN lesions with worrisome features should be further investigated with an EUS and FNA biopsy [illegible] [illegible] appropriate surgical candidate [illegible] during the [illegible] mural nodule, suspected involvement of the main pancreatic duct, or cytology that is suspicious or positive for malignancy.

LESIONS THAT SHOULD UNDERGO FOLLOW-UP

BD IPMN lesions without high-risk stigmata or worrisome features should be followed with surveillance imaging. Small lesions that are between 0 and 2 cm should have a pancreas protocol MDCT or MRCP performed after an initial interval of 6 months. If the IPMN lesion is stable in size and appearance, then the surveillance interval can be lengthened to 1 year. IPMN lesions that are larger than 2 cm on MRCP and EUS should be performed every 3 to 6 months to establish a baseline and to confirm that the lesion is stable in size and in features. Once a baseline is established, then follow-up imaging interval length can be prolonged as appropriate. Another approach is to have a uniform surveillance program for all lesions that fall under the category of necessitating surveillance. This approach could take the form of surveillance with imaging, MRCP or MDCT, every 6 months for 1 year. If the lesion remains stable in size and in features during that 1 year period, then the follow-up interval can be increased to once a year for 3 years. Once again, if the IPMN lesion remains stable in size and in features, then the follow-up interval can be increased to 2 years.

APPROACH TO MULTIFOCAL BD-IPMN

Indications for resection of multifocal BD IPMNs with high-risk stigmata or worrisome features are the same as for unifocal BD IPMN lesions. The operative approach would favor a segmental resection in cases where all cysts are located in the same pancreatic region. However, BD IPMNs located in separate regions of the pancreas should be individually evaluated to assess which, if any, have high-risk stigmata or worrisome features and thus warrant surgical resection. When possible, a segmental resection of the lesion that has the highest oncologic risk is favored.

SURVIVAL AFTER RESECTION OF AN IPMN LESION

The distinction between noninvasive versus invasive disease when treating IPMN lesions is paramount since it has significant effects on survival. Noninvasive would be considered to be low- and high-grade dysplasia, despite the latter being considered to be equivalent to carcinoma in situ. In our experience, the 10-year specific survival after complete resection of a noninvasive IPMN is greater than 95%; however, we have found that survival is significantly decreased after resection for an invasive IPMN with 5-year and 10-year overall survival rates of 47% and 34%, respectively.

GUIDELINES FOR FOLLOW-UP AFTER RESECTION OF IPMN LESIONS

Because of the field defect concept seen in IPMN lesions, patients who undergo resection of an IPMN still need continued surveillance of the remaining pancreas because of the risk of developing new IPMN lesions and/or carcinomas in the remaining pancreas. Approximately 17% of patients who underwent a resection of a noninvasive IPMN lesion developed a new or progressive IPMN lesion on surveillance imaging. A different study found that recurrence in the remnant pancreas differed depending on whether the resection margin of a noninvasive IPMN was positive or negative. If the resection margin was positive the risk of recurrence was [illegible]% versus 2% if the resection margin was negative. The median time to recurrence of a noninvasive IPMN has been found to be about 4 years.

Nevertheless, there is currently a debate about whether the resection margin status of a noninvasive IPMN is associated with subsequent recurrence of an IPMN or development of invasive carcinoma. The Johns Hopkins experience reported that there was no difference in the development of a new IPMN lesion in patients who had a positive resection margin when compared to patients who had a negative resection margin (27% vs 22%, P = nonsignificant). The Memorial Sloan Kettering experience reported that dysplasia of any degree at the resection margin was an independent predictor of recurrent disease in the remnant gland, but not at the resection margin (odds ratio, 2.9; P = .02). However, they reported that dysplasia of any degree at the resection margin was not significantly associated with development of invasive disease. At the MGH, a positive resection margin after resection of a main duct IPMN lesion was significantly associated with survival in a multivariate analysis (hazard ratio, 2.6; P = .044).

SUMMARY

The incidence of IPMNs is increasing because of the rising use of MDCT and MRI in the workup of abdominal complaints. There are two main types of IPMN, MD IPMN and BD IPMN, and a third type that includes MD IPMN and BD IPMN features, which is known as mixed type IPMN. In addition to being categorized into types, IPMN lesions are also categorized into histologic epithelial subtypes. Depending on the type of IPMN and the histologic epithelial phenotype, these lesions have varying degrees of association with malignancy. The revised IAP 2012 Fukuoka consensus guidelines provide management recommendations depending on the type of IPMN. All MD IPMN, BD IPMN, and mixed type IPMN lesions with high-risk stigmata should be considered for surgical resection. Furthermore, BD IPMN with worrisome features should be considered for surgical resection if EUS with FNA biopsy shows a mural nodule, is suspicious for involvement of the main pancreatic duct, or shows cytology that is suspicious or positive for malignancy. Last, routine surveillance with MDCT or MRCP is important for all patients with IPMN, regardless of whether they undergo resection or do not initially meet criteria for resection.

Suggested Readings

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Management of Pancreatic Islet Cell Tumors Excluding Gastrinoma

Dmitriy S. Fedorov, MD, Ph.D., and Jeffrey A. Ramsey, MD

The incidence of pancreatic neuroendocrine tumors (pNETs) is steadily increasing. They comprise 3% of all pancreatic tumors and autopsy studies indicate that between 3% and 10% of people will have pNETs, suggesting that many are small and often asymptomatic. pNETs comprise a heterogeneous group of tumors that secrete signals in each area of the pancreas (head, body, and tail). Some pNETs occur in association with familial disorders, for example, pNETs in the setting of multiple endocrine neoplasia type 1 (MEN-1). The majority (80%–85%) of pNETs, however, occur sporadically. These tumors typically show an indolent course and are difficult to diagnose with a mean time from presentation of symptoms to diagnosis of 6 years. Management of pNETs generally includes a combination of medical and surgical therapy.

CLINICAL PRESENTATION AND ASSOCIATED SYNDROMES

pNETs are found throughout the pancreas and may be single or multiple. They are always multiple when they are present in patients with MEN-1. Patients may present with symptoms from a hormone-secreting or functional pNET that secretes excessive uncontrolled amounts of a hormone that results in a specific syndrome. The two most common pNET functional syndromes are Zollinger-Ellison syndrome (ZES) from excessive secretion of gastrin and hyperglycemia from excessive secretion of insulin. ZES is described in detail in another chapter of this text so it will not be discussed here. Pancreatic NETs can also present with a large mass that causes pain or bleeding if they invade into a blood vessel or obstruct the splenic vein and cause gastric varices. Occasionally the patient will have no symptoms and the tumor is seen as a mass in the pancreas on an abdominal computed tomography (CT) or magnetic resonance imaging (MRI) that was done for another reason. This is particularly true with non-functional pNETs. Nonfunctional pNETs still secrete chromogranin A or pancreatic polypeptide, but they do not secrete a hormone that causes a specific clinical syndrome. Tumor mass and response to therapy of pNETs can be assessed by measuring serum chromogranin A levels and or pancreatic polypeptide. Pancreatic polypeptide and chromogranin A levels correlate with tumor mass and extent of disease, increasing levels suggest more tumor volume. Size greater than 2 cm, intratumoral calcium deposits, and a solid rather than a cystic pNET each portend a more aggressive malignant tumor and should be noted. Malignant pNETs metastasize to lymph nodes and liver. They are shown to decrease survival when metastatic, but they are still indolent, and surgery should still be considered especially if all pNET can be excised.

If functional, patients usually display symptoms related to excessive hormone secretion that allow the smart clinician to make the diagnosis. Examples are Whipple's triad for insulinoma, fasting hypoglycemia, weight gain, and altered mental status with or without seizures with amelioration of symptoms following administration of glucose. In glucagonoma, patients have a rotund red pruritic rash called necrolytic migratory erythema in intertriginous areas plus diabetes, stomatitis, hyperaminoacidemia, and weight loss. In patients with vasoactive intestinal polypeptide (VIP) secreting tumors (VIPoma), severe secretory (watery) diarrhea (>10 stools per day) is present that is associated with hypokalemia, achlorhydria (WDHA syndrome), and hypercalcemia. Secretory diarrhea means that the diarrhea persists even when the patient is made nothing by mouth. The diarrhea cannot be effectively controlled with only intravenous electrolyte replacement therapy. It is best managed with Sandostatin injections that decrease VIP secretion and greatly ameliorate the diarrhea. pNETs can also secrete adrenocorticotropic hormone (ACTH), which causes severe hypercortisolism that is difficult to manage medically with standard medications such as antihyperglycemics, ketoconazole, and metyrapone so subsequently may require laparoscopic bilateral adrenalectomy.

CLINICAL WORKUP

Initially, a complete history and physical examination is performed. For insulinoma, laboratory studies include a diagnostic 72 hour provocative fast measuring insulin and glucose levels at the time of observed neuroglycopenic symptoms. Measuring C-peptide and proinsulin levels is also indicated. The diagnosis is confirmed if the glucose level is below 45 mg/dL, insulin greater 5 mIU/mL, and there are elevated serum levels of C-peptide and proinsulin. The neuroglycopenic symptoms should be ameliorated with either oral or intravenous administration of glucose. For glucagonoma, studies include elevated serum levels of glucagon, elevated fasting glucose levels, and markedly decreased fasting serum amino acid levels. For VIPoma, the diagnosis is made by increased serum VIP levels. For ACTHoma, elevated serum levels of ACTH and cortisol are measured. For somatostatinoma, patients have type 2 diabetes, steatorrhea, and cholelithiasis. Another important component of the clinical work up is to exclude MEN-1. MEN-1 is an autosomal dominant inherited disease with a prevalence of 2 to 3 per 100,000 people, caused by a gene mutation in chromosome 11 (11q13) that encodes for the menin protein. The syndrome is characterized by primary hyperparathyroidism, pNETs (either functional, most commonly gastrinoma, or nonfunctional), and pituitary adenoma. It is best excluded by measuring serum calcium and parathyroid hormone levels as primary hyperparathyroidism is usually the first manifestation of MEN-1.

Preliminary imaging to localize pNET often includes pancreatic protocol CT scan with intravenous contrast or MRI with luminal or gadolinium (Fig. 1), although occasionally with hormone secreting tumors, a mass may not be not localized using standard diagnostic

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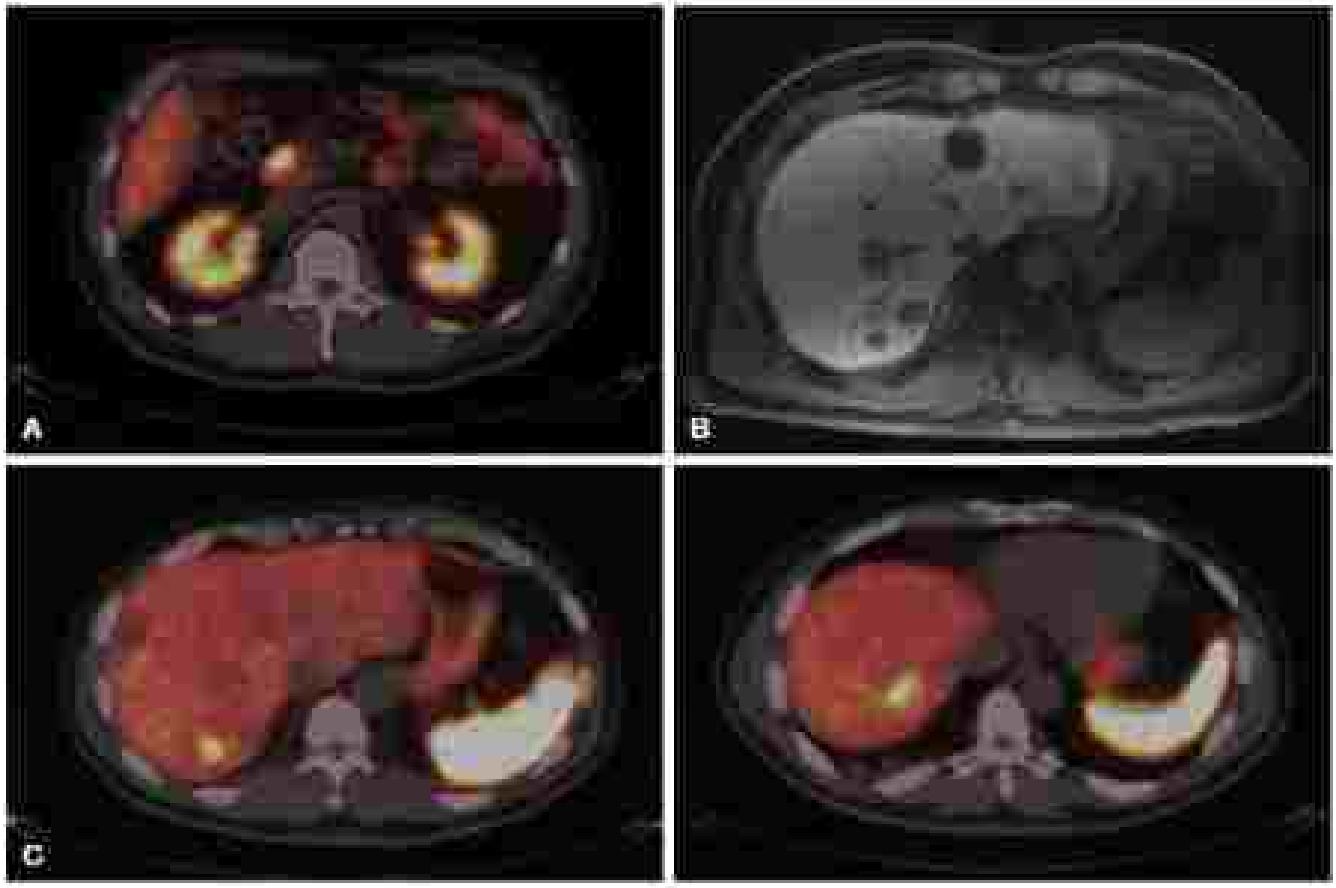

FIG. 1. (A) DOTATOC positron emission tomography scan showing a primary 3-cm pancreatic neuroendocrine tumor in the head of the pancreas. (B) Liver magnetic resonance imaging of the liver in the same patient suggesting multiple tiniest liver metastases such that the patient was thought to be unresectable and he was given everolimus for 3 months without benefit. (C) The same DOTATOC scan as seen in (A) showed only two liver metastases and both were located in the posterior portion of the right lobe. Because of the resectable pancreatic neuroendocrine tumor found on the DOTATOC scan, the patient underwent Whipple's procedure with right posterior segmentectomy and was disease free.

imaging. Somatostatin receptor scintigraphy (Octreoscan) has previously been used to image pNETs. It has been an effective imaging modality for most pNETs except insulinoma. Now, 68Gallium Dotatate (DOTA) positron emission CT imaging has replaced Octreoscan because it is more sensitive and specific for pNETs. This scan is used to localize the primary tumor and to evaluate for distant metastases (Fig. 1). It has dramatically improved imaging for pNETs and is able to detect small, previously unseen tumors. Endoscopic ultrasound can also be used to localize pNETs and lymph node metastases. pNETs appear nonfocal on ultrasound compared with the more echodense pancreas. Primary gastrinomas are most commonly localized to a triangle located around the head of the pancreas including the duodenum, whereas the remainder of the pNETs, including insulinoma, are uniformly distributed throughout the entire pancreas. For small insulinomas (not visualized on CT or MRI), endoscopic ultrasound and calcium angiogram are useful studies to localize a small pNET insulinoma. Calcium angiogram localizes the insulinoma to a region of the pancreas that can be extensively explored with intraoperative ultrasound during surgery. Intraoperative ultrasound facilitates removal of the insulinoma by not only identifying it, but by determining its relationship to the pancreatic duct.

For nonfunctional pNETs, it is important to realize which tumors are potentially malignant and warrant definitive surgery. pNET tumor size has been one of the best determinants of malignant potential. pNETs greater than 2 to 3 cm in diameter have a 60% probability of liver metastases and are considered more malignant. These need to be removed in a more aggressive way, including regional lymph nodes and therefore require definitive resection, including Whipple's pancreaticoduodenectomy for tumors in the head of the pancreas and distal pancreatectomy with splenectomy for tumors in the body or tail. There is controversy about the value of surgery for small nonfunctional pNETs. Small (<1 cm) nonfunctional pNET tumors in the elderly (>65 years) found incidentally on CT or MRI for another indication can safely be watched with serial imaging delaying surgery for an observed increase in size. Other indicators of a more malignant pNET are the presence of calcifications and hypoenhancement on arterial phase CT. Most pNETs are hyperenhancing on arterial CT, but when they are not enhancing their behavior is found to be more aggressive and warrant surgical resection.

CLINICAL MANAGEMENT

When a pNET is diagnosed, it is important to begin symptomatic management immediately, even during the work up. Somatostatin analogs inhibit secretion of most of the relevant hormones and are useful for the management of all functional NETs except insulinoma. For glucagonoma, the necrolytic migratory erythema can be ameliorated with somatostatin analogues. Diarrhea and blood chemical abnormalities in VIPomas are also ameliorated with somatostatin analogues. Lanreotide is currently preferred over Sandostatin LAR because it is administered subcutaneously and binds to more somatostatin receptors than Sandostatin. For insulinoma, medical management generally involves careful maintenance of blood glucose with frequent food intake until surgical resection can be implemented.

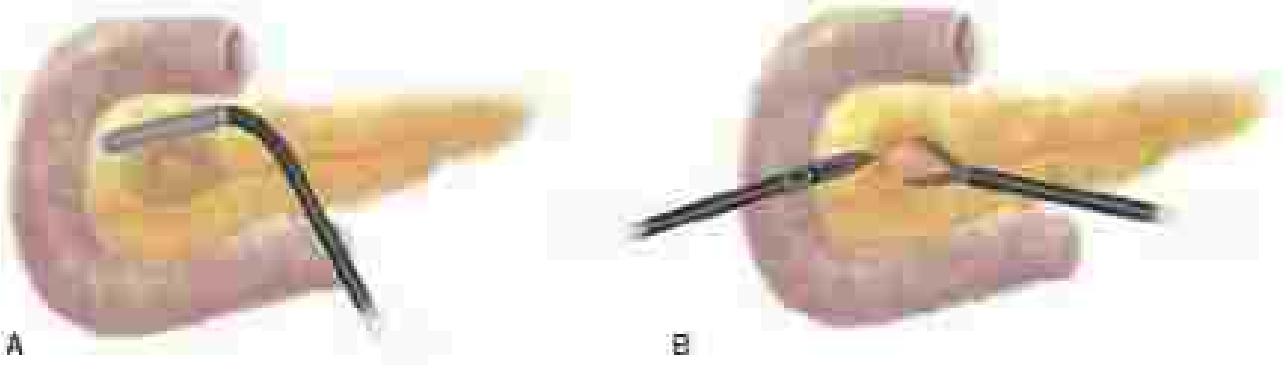

FIG. 2 For patients with well-localized insulinoma (pancreatic neuroendocrine tumor) seen on the preoperative imaging studies, we recommend laparoscopic enucleation of the pancreatic neuroendocrine tumor (pNET). (A) The location of the pancreatic neuroendocrine tumor is identified intraoperatively with a 10-MgHz transducer and its relationship to the pancreatic duct is elucidated. (B) It is enucleated using the harmonic scalpel to dissect the pancreatic parenchyma with the goal of remaining right on the capsule of the tumor.

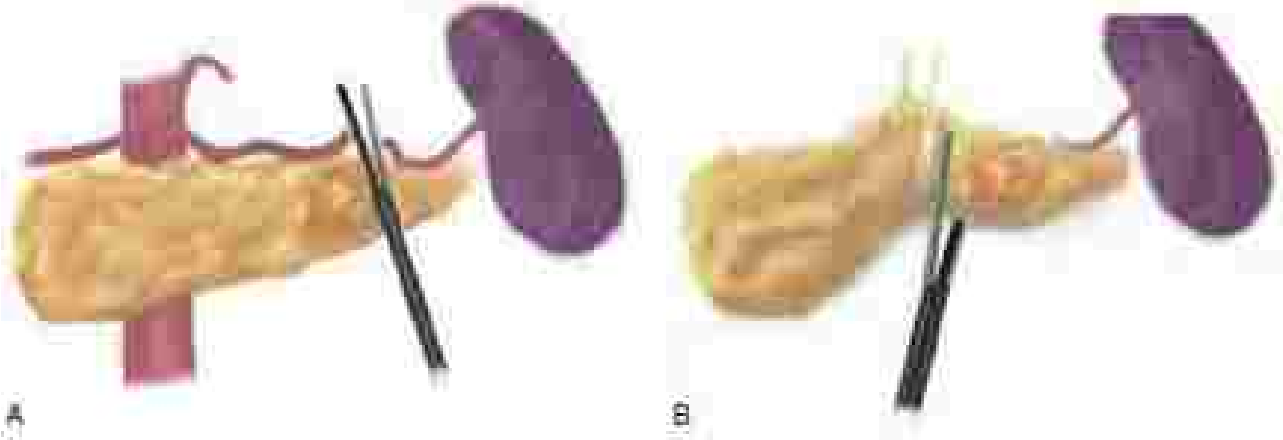

FIG. 3 (A) Division of the splenic artery with a vascular load stapler during laparoscopic distal pancreatectomy. (B) Division of the distal pancreas with umbilical tape in preparation for division of the distal pancreas. Peri-Strips are used to minimize the margin of leakage from the divided pancreatic duct.

Cornstarch mixed with a glucose solution can be administered at bedtime so that the patient can sleep all night and does not develop hypoglycemia while sleeping.

For localized pNETs, surgery is the mainstay of treatment. In the pancreas, NET resection can involve enucleation, distal pancreatectomy or Whipple pancreaticoduodenectomy, depending on the size, type and location of the pNET (body/tail of the pancreas and relationship to the pancreatic duct). Because insulinomas are almost always benign and smaller than 2 cm, enucleation is the procedure of choice. This can be done either laparoscopically (if the tumor is well localized on the preoperative studies, Fig. 2) or open (if not well localized). Intraoperative ultrasound with a 10 MgHz transducer applied to the pancreas is the intraoperative localization study of choice (Fig. 2A). pNETs in the setting of MEN-1 are almost always multiple so tumors in the body and tail are resected with distal pancreatectomy, whereas tumors in the head of the pancreas are enucleated. For laparoscopic enucleation, the patient is positioned with the left side up at 45 degrees. Four to five trocars can be used. We use the harmonic scalpel for dissection of the pancreas around the tumor (Fig. 2B). When you get in the appropriate plane on the capsule of the tumor, the dissection is smooth and bloodless. Care should be taken not to handle the tumor too much because if the capsule is interrupted, little seeds of even a benign insulinoma can implant and cause local recurrence. For distal pancreatectomy, a laparoscopic approach is generally pursued unless the tumor is clearly aggressive and very malignant (involving the splenic vein, stomach, or colon mesentery) (Fig. 3). This is performed using four trocars: periumbilical for the camera, two subcostal ports on the left, and one on the right for instruments. The spleen can either be preserved (Warshaw's procedure, in which blood flow is maintained to the spleen via the short gastric vessels while the splenic artery and vein are taken and divided) or sacrificed at the time of distal pancreatectomy. We divide the splenic vessels using a vascular stapler endoGIA 30 mm 4cl tip stapler with a tan load (Fig. 3A). Then we elevate the pancreas using an umbilical tape and divide the pancreatic tissue proximal to the mass using a 45-mm endoGIA stapler with a black load and Peri-Strips, which help to prevent any leakage from the divided pancreatic duct (Fig. 3B). We divide the pancreas slowly with the stapler to not crush it, such crushing may cause pancreatic leakage postoperatively. Large pNETs (>3 cm) in the head of the pancreas usually require a Whipple's pancreaticoduodenectomy.

Surgery can have a role, even in the setting of metastatic disease. Surgical resection of liver metastases either alone concomitantly as with the pancreatic surgery or as a separate second procedure has been applied to liver metastases with good results and subsequently long term survivals of 40% to 70% at 10 years in various reports. Therefore, accurate staging of the liver is imperative and the presence of liver metastases does not preclude aggressive resection of the primary tumor. A common strategy in liver-sparing surgery that means the use of intraoperative ultrasound to identify all liver

tumors. Wedge resection of tumors that are near the surface of the liver and ablation of tumors within the center of the liver. This has been recently facilitated with microwave ablation that is faster and easier to do than radiofrequency ablation (RFA). Microwave ablation only requires positioning the probe in the center of the lesion, whereas RFA requires multiple overlapping applications. Microwave is still even effective for tumors near a major intrahepatic blood vessel, however, with RFA, if a tumor is near a hepatic vein there is cooling that reduces the effectiveness of the procedure.

The patient in Fig. 1 is a real-time example of the sense of the discussed principles. This patient presented with a 5 cm nonfunctional pancreatic neuroendocrine tumor in the head of the pancreas. Preoperative MRI and CT suggested that he had multiple bilobar liver metastases, so he was treated preoperatively with everolimus; however, this patient had no response to treatment and his primary tumor increased in size. During his chemotherapy he had a DOTA scan that demonstrated much less liver tumor than anticipated on conventional imaging. He only had two liver pNET metastases in the posterior sector of the right lobe (Fig. 1C). Simple cysts were the other liver lesions seen on MRI (Fig. 1B). He underwent a pylorus-preserving Whipple's pancreaticoduodenectomy with right posterior sectorectomy and currently he is disease-free and doing well postoperatively. This demonstrates the importance of DOTA scans to carefully stage the extent of pancreatic neuroendocrine tumor and the potential value of aggressive surgery in these patients even with liver metastatic disease.

Further, management of liver disease may also involve medical therapy and/or liver-directed therapies. With regard to the latter, radioembolization with radionucleotide microspheres, embolization, or chemoembolization can be used. Peptide receptor radiotherapy (PRRT) involves coupling a somatostatin analogue by a linker to a radionuclide emitting beta radiation particle, most commonly ^{177}Lutetium ([^{177}Lu-DOTA^0-Tyr^3] octreotate). Lutetium-based therapy is available at a number of hospitals worldwide and most recently now in the United States, marketed under the name Lutathera. It is generally reserved for metastatic pNET disease and has been shown to be beneficial in clinical trials. A recently published phase III trial using ^{177}Lu-Dotatate for pNETs showed significantly extended progression-free survival compared with control (high-dose octreotide) and had limited toxic side effects. The somatostatin analogue targets the ^{177}Lu-Dotatate to the tumor, where it can be internalized and the radiation can then destroy the tumor. Positive DOTA imaging is a prerequisite criterion for PRRT.

Systemic medical therapies are indicated in the setting of metastatic disease that is clearly progressive on imaging despite use of somatostatin analogs. These include vascular endothelial growth factor inhibitors, and more recently mammalian target of rapamycin (mTOR) inhibitors, such as everolimus, which were introduced with the discovery that many NETs contain mutant genes in the PI3K/Akt/mTOR pathway. Sunitinib, a small-molecule receptor tyrosine kinase inhibitor, is also being used in cases of metastatic progressive pNET.

SUMMARY

With the increasing incidence of pNETs and the opportunity for potential cure if early diagnosis and surgery are undertaken, understanding the presentation and key diagnostic and therapeutic goals related to pNETs is important for surgeons. Part of the diagnosis involves consideration of associated inherited disease syndromes such as MEN 1. Several new diagnostic and treatment technologies have recently been introduced, such as DOTA scanning, PRRT, and mTOR inhibitors, which assist in locating these tumors and managing more advanced disease, respectively. Minimally invasive surgical methods can increasingly be used to remove these tumors. Aggressive resection of metastatic and locally advanced tumor is indicated because studies have shown that the prognosis is still excellent.

SUGGESTED READINGS

Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: a prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore). 2013;92(3):135–181.

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INTRAOPERATIVE RADIATION FOR PANCREATIC CANCER

Amol K. Narang, MD, and Joseph M. Herman, MD, MSc

Although intraoperative radiation therapy (IORT) for pancreatic cancer has a long history of inquiry, improvements in systemic control with multiagent chemotherapy have increased the enthusiasm for aggressive local therapy, including more frequent exploration and attempts at radiation dose escalation. As such, there has been renewed enthusiasm surrounding the potential use of IORT. Indeed, IORT provides an opportunity for the focused delivery of high doses of radiation while shielding radiosensitive structures that often limit the dose of external beam radiation therapy (EBRT). Nevertheless, considerable challenges exist surrounding the development of a successful IORT program. Beyond the need for a shielded operating room and delivery system, successful administration of IORT requires a coordinated effort between the radiation oncology and surgery teams. As such, it is critical that surgeons interested in administering IORT have an in-depth understanding of both the scientific and technical underpinnings of this treatment modality.

REVIEW OF EXISTING LITERATURE

Early exploration of IORT for pancreatic cancer came from Japanese investigators. In the 1970s, Kyoto University investigators described their experience with IORT for locally advanced disease, in which doses of 20 to 40 Gy resulted in improvements in tumor-related pain. These findings subsequently prompted investigators at the Massachusetts General Hospital (MGH) and the Mayo Clinic to further study IORT for pancreatic cancer in both the unresectable and

tumors. Wedge resection of tumors that are near the surface of the liver and ablation of tumors within the center of the liver. This has been recently facilitated with microwave ablation that is faster and easier to do than radiofrequency ablation (RFA). Microwave ablation only requires positioning the probe in the center of the lesion, whereas RFA requires multiple overlapping applications. Microwave is still even effective for tumors near a major intrahepatic blood vessel; however, with RFA, if a tumor is near a hepatic vein there is cooling that reduces the effectiveness of the procedure.

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Intraoperative Radiation for Pancreatic Cancer

Amol K. Narang, MD, and Joseph M. Herman, MD, MSc

Although intraoperative radiation therapy (IORT) for pancreatic cancer has a long history of inquiry, improvements in systemic control with multiagent chemotherapy have increased the enthusiasm for aggressive local therapy, including more frequent exploration and attempts at radiation dose escalation. As such, there has been renewed enthusiasm surrounding the potential use of IORT. Indeed, IORT provides an opportunity for the focused delivery of high doses of radiation while shielding radiosensitive structures that often limit the dose of external beam radiation therapy (EBRT). Nevertheless, considerable challenges exist surrounding the development of a successful IORT program. Beyond the need for a shielded operating room and delivery system, successful administration of IORT requires a coordinated effort between the radiation oncology and surgery teams. As such, it is critical that surgeons interested in administering IORT have an in-depth understanding of both the scientific and technical underpinnings of this treatment modality.

REVIEW OF EXISTING LITERATURE

Early exploration of IORT for pancreatic cancer came from Japanese investigators. In the 1970s, Kyoto University investigators described their experience with IORT for locally advanced disease, in which doses of 25 to 40 Gy resulted in improvements in tumor-related pain. These findings subsequently prompted investigators at the Massachusetts General Hospital (MGH) and the Mayo Clinic to further study IORT for pancreatic cancer in both the unresectable and

resectable setting. In 1984, MGH reported outcomes among unresectable patients treated with IORT and 50RT, noting high rates of pain improvement and a median survival of 8–9 months. Three years later, Mayo investigators retrospectively reported outcomes among resected patients who received either postoperative EBRT alone or IORT followed by postoperative EBRT, noting higher rates of 1- and 2-year local control in patients who received both modalities. Since then, encouraging data have been reported in both the unresectable and resectable settings, as outlined below.

IORT for Unresectable Disease

Multiple subsequent series, including reports from Mayo and Japan, further explored IORT in the locally advanced setting, suggesting improvements in local control with the use of both IORT plus EBRT compared with EBRT alone. These findings prompted a multiinstitutional US study through the Radiation Therapy Oncology Group, namely report 8505, in which locally advanced pancreatic cancer patients were treated with IORT to 20 Gy followed by 50.4 Gy of EBRT. Unfortunately, median survival in this cohort was only 9 months, which dampened enthusiasm for the role of IORT.

Since then, however, other institutions have published positive long-term results with the use of IORT, with MGH reporting the most robust experience. An analysis of long-term outcomes among 104 locally advanced patients who were treated at MGH with IORT between 1978 and 2010 showed decent outcomes, particularly among well-selected patients with smaller tumors, with a 2-year overall survival of 16% and with a small fraction of patients (3%) experiencing long-term survival more than 5 years. These findings have renewed interest in IORT as a component of therapy for locally advanced pancreatic cancer, particularly with more patients with more advanced disease now undergoing attempted exploration in an era of better systemic control with multiagent chemotherapy.

IORT for Resected Disease

Following the results of the Mayo study of resected patients, the National Cancer Institute conducted a small, randomized trial of 24 patients comparing resection alone to resection with IOHDR. Patients in the IORT arm experienced improvements in local control and survival. Since then, subsequent institutional reports (see the Suggested Readings) have also suggested improvements in local control with the administration of IORT.

The most modern experience with IORT in the postoperative setting comes from MGH, where investigators recently reported outcomes among patients with borderline resectable or locally advanced patients who were managed with a modern regimen of upfront multiagent systemic therapy (primarily FOLFIRINOX or gemcitabine/nab-Abraxane), chemoradiation to a median dose of 50.4 Gy, and surgical exploration with or without IORT. The report analyzed 86 patients who made it through the neoadjuvant regimen without progression, of whom 41 successfully (48%) underwent resection, 18 (22%) had unresectable disease, and 9 (13%) had metastatic disease. Among the 41 patients who underwent resection, 22 were treated with IORT to a dose of 10 Gy. Patients treated with IORT experienced improved survival without additional toxicity or complications. Furthermore, unresectable patients who were treated with IORT to a dose of 15 Gy experienced an encouraging median survival of 24.8 months.

PATIENT SELECTION

As reflected in the literature, well-established guidelines for use of IORT for pancreatic cancer are lacking. Nonetheless, institutional data support consideration of IORT in instances when close or positive margins are expected at the time of resection or when disease may be unresectable, both of which are frequent scenarios with pancreatic cancer. Certainly, the decision to consider IORT should be discussed in a multidisciplinary setting, and its potential use should be defined ideally from the outset of therapy. Importantly, it is unlikely that intraoperative radiation alone is sufficient to achieve immortal doses for either gross or microscopic disease, and as such, IORT should be used in combination with either preoperative or postoperative radiation therapy. Although postoperative radiation can be considered with the use of surgical clips for guidance of radiation fields, preoperative radiation is often preferred for a number of reasons, including the following.

1. Better definition of the intact tumor target in the preoperative setting as compared to the often ill-defined surgical bed in the postoperative setting.
2. Displacement of bowel by the intact tumor in the preoperative setting compared with filling of the surgical bed by bowel in the postoperative setting.
3. Improved oxygenation of target tissue in the preoperative setting, rendering the target potentially more radiosensitive compared with the postoperative setting.
4. Removal of irradiated tissue with the preoperative approach.

EQUIPMENT

IORT can be administered using multiple devices, including Linac-based electron beam radiation therapy (IOERT), low-energy photons, low-dose-rate brachytherapy, or high-dose-rate (HDR) brachytherapy. Each of these modalities are viable strategies with their own relative merits. HDR-based IORT delivers a more concentrated dose at the surface of the target with sharp fall off, which may be optimal for a surgical cavity/margin, whereas IOERT delivers a more homogenous dose of radiation to a greater depth. A significant advantage of an HDR-based technique lies in its method of delivery through use of customized applicators that can allow delivery of radiotherapy to irregular surfaces compared with the rigid cone applicators that are required for IOERT or IOMT with low-dose photons. At our institution, we have primarily used an HDR technique to take advantage of the flexible applicators, and so the technique described in this chapter will primarily focus on the administration of HDR-based IORT. Newer applicators that allow the delivery of low-dose-rate brachytherapy such as the Contura are also under investigation.

As noted, HDR-based IORT requires the use of a sterile flap applicator along with an HDR-based afterloader system. The Freiburg Flap is the applicator used at our institution and consists of silicone balls that are 1 cm in diameter and that are connected to each other to form a flexible planar sheet, through which 4Fr catheters can be inserted. The size and shape of the Freiburg Flap can be customized at 1-cm intervals based on the dimensions of the target site. The afterloader system used at our institution is the Nucletron system by Elekta; however, other applicators and afterloader systems are available.

TECHNIQUE

The first step of HDR-based IORT is for the surgeon to try to retract as much radiosensitive normal tissue such as bowel (see Normal Tissue Toxicity section) out of the field and protect these structures by placing lead shields in front of them. Subsequently, the surgeon and radiation oncologist should jointly identify the high-risk surgical bed and/or gross disease. The target area is measured to inform the size of the applicator. The target area can also be marked out with a marking pen to aid in accurate positioning of the applicator. Once the dimensions of the applicator have been finalized and the prescription dose and depth have been selected, the radiation oncologist's physics team can subsequently begin developing the radiation plan, which primarily consists of determining the amount of time that the radioactive source will spend in each dwell position. While the radiation plan is being developed, the radiation oncologist can preselect an applicator that is closest in size to the desired size. If an exact match is not available, the applicator can be cut to the appropriate size. Before proceeding further, it is a good idea to place

FIG. 1 Freiburg flap in surgical bed connected with catheters to afterloader (not visualized).

FIG. 2 Packing over the Freiburg flap to ensure stability.

the applicator to the surgical field to ensure that the dwell dimensions are optimal and that the applicator fits well into the surgical field. Additionally, the entrance route of the catheters from the afterloader into the surgical cavity and subsequently into the applicator should also be considered to ensure that the catheters will not be kinked due to sharp angling.

Thereafter, 6Fr catheters are thread through the applicator and secured on either side of the applicator. The catheters are subsequently labelled in numeric order. It is helpful to place labels on the catheters both at a point near the applicator (in our institution, we use the labels as one of the mechanisms of securing the catheters to the applicator) as well as at a point a distance away from the applicator. These labels are critical because they allow accurate identification of the catheters even after the applicator can no longer be visualized once packing has been placed.

At this point, the applicator and catheters can be positioned into the surgical field in the location that had been previously defined (Fig. 1). Wet lap sponges can be packed on top of the applicator to help ensure its stability (Fig. 2). If needed, sutures can also be considered to further secure the applicator in place. Additional lead shields can be placed to minimize radiation dose to surrounding structures, with 3 mm of lead roughly reducing the dose by 70%. Of note, it is important to remember to cover lead shields with wet gauze to minimize backscatter dose. Distance from the applicator also helps reduce radiation dose, with the prescribed dose dropping to 70%, 50%, and 35% at 1, 2, and 3 cm, respectively.

Thereafter, the catheters are connected to the after loader, and a dry run is performed without a radiation source to ensure that there are no kinks or other obstacles to successful delivery. The room is evacuated, and appropriate video surveillance of the patient is confirmed. Radiation delivery can subsequently commence. Total treatment time is dictated by the prescription dose, the size of treatment area, and the activity of the source. At our institution, we use an ^{192}Ir source, which has a half life of 73 days.

DOSING

Given that IORT consists of high doses of radiation administered at one time, the biological effective dose of a given IORT prescription dose is significantly higher than an equal EBRT dose administered in a fractionated manner. Conversion factors between IORT and fractionated EBRT doses are primarily derived from in vitro data and animal studies and therefore must be interpreted with some caution. Nevertheless, Table 1 provides helpful estimates for IORT dose conversions. In general, multiplication of an IORT dose by 2.3 to 2.5 yields a rough estimate for an equivalent fractionated EBRT dose to tumor, whereas multiplication of an IORT dose by 3 yields a rough estimate for an equivalent fractionated EBRT dose to normal tissue.

TABLE 1 Conversion Estimates Between IORT and EBRT Doses

IORT Dose	EBRT Tumor Dose	EBRT Normal Tissue Dose (Acute)	EBRT Normal Tissue Dose (Late)
10 Gy	17 Gy	30 Gy	30 Gy
15 Gy	31 Gy	37 Gy	45 Gy

EBRT, external-beam radiation therapy; IORT, intraoperative radiation therapy.

NORMAL TISSUE TOXICITY

Data describing normal tissue toxicity from IORT come primarily from canine models. In general, EBRT for pancreatic cancer will approach the radiation tolerance of bowel, so great effort should be made to limit any further bowel exposure from IORT to minimize the risk of late bowel toxicity such as obstruction, ulceration, perforation, or fistula. Sites used for anastomotic creation should be avoided in particular. As opposed to HDR brachytherapy, IORT may allow for minimization of dose to anastomotic sites.

Dose to the ureter, although usually less relevant to the treatment of pancreatic cancer, should also be minimized because excessive dose to the ureter can result in ureteral stenosis. In canine models, IORT doses above 10 Gy in combination with EBRT doses of 50 Gy led to significant risk of luminal stenosis. Although typical IORT prescription doses tend to be below 10 Gy, effort should still be made to shield the ureter.

Vascular structures have a higher radiation tolerance compared with bowel and ureter. Nevertheless, at high IORT and EBRT doses, clinically significant luminal hyperplasia and medial wall fibrosis have been described, with the potential for subsequent complications including arterial thrombus. Although these risks tend to be less apparent at the IORT and EBRT doses used in the abdomen, caution should nonetheless be taken, particularly if the patient has received prior courses of radiation.

Last, patients should be counseled on the risk of neuropathy, which tends to occur with IORT doses in excess of 15 Gy. For pancreatic IORT, the effect on wound healing should be less relevant compared with IORT in more superficial sites, with modern series from MGH showing no increase in wound complications in patients receiving IORT.

CONCLUSIONS

IORT represents a potential treatment option for decreasing local recurrence in pancreatic patients with resected or unresectable disease, particularly when administered as a boost in combination with other preoperative or postoperative EBRT. Successful delivery of IORT requires a joint effort between the surgical oncologist and radiation oncologist to ensure appropriate targeting and minimization of radiation exposure to surrounding structures. In the era of contemporary multiagent systemic therapy leading to better systemic control, IORT can serve as a tool to provide more durable local control for this disease.

Suggested Readings

Abe M, Takahashi M. Intraoperative radiotherapy: the Japanese experience. *Int J Radiat Oncol Biol Phys*. 1988;2:863–868.

Call S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1950 to 2010. *Cancer*. 2013;119:4196–4204.

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Nishimura S, Nakacho M, Ohta H, et al. Intraoperative radiotherapy for advanced carcinoma of the pancreas. *Cancer*. 1994;74:2375–2384.

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Pancreas Transplantation

Joseph R. Scalea, MD

Pancreas transplantation is the only diabetes treatment that restores normal glucose homeostasis without the complications of severe hyperglycemia or hypoglycemia. Furthermore, pancreas transplantation may stabilize if not improve diabetic complications. Pancreas transplantation has been referred to as a diabetes cure. It is an elegant, technically challenging operation typically performed along with a kidney transplant. The most recent data suggest that combined kidney and pancreas transplantation is the ideal treatment for patients with diabetes and end-stage kidney disease.

HISTORY AND NATIONAL TRENDS

Diabetes mellitus was frequently fatal before the Nobel prize–winning work of Banting and Best. With the knowledge that insulin was critical to survival, success with the first kidney transplant in 1954 began interest in transplantation of the pancreas. Pancreas transplantation was first successfully performed in 1966 at the University of Minnesota by Kelly and Lillehei. A great deal of effort was expended by pioneers of pancreas transplantation to overcome initial poor outcomes. As technical improvements took hold, so too did improvements in pharmacologic immunosuppression, allowing the practice of pancreas transplantation to blossom into the early 1990s. In 2006, the United States saw a peak of volume in pancreas transplant procedures. During that year, nearly 1000 combined kidney pancreas transplants were performed. Despite dramatic improvement in patient and graft survivals, surgical volumes began to decrease. The reasons for decreased volumes are multifactorial but include a lack of appropriate training. As such, this chapter will focus on standard techniques for pancreas transplantation that can be safely performed by competent residents and fellows under appropriate guidance.

INDICATIONS

With rare exception, pancreas transplantation is performed for patients with diabetes mellitus. The vast majority of patients who undergo pancreas transplantation are type 1 diabetic. (Table 1); however, it is now recognized that type 2 diabetics may enjoy excellent outcomes after pancreas transplantation. The most basic tenet of assessing a patient's candidacy for pancreas transplantation is a determination of whether insulin produced by the transplanted pancreas will benefit the recipient. Presuming medical clearance, patients with classic type 1 diabetes are ideal candidates for the operation. Patients who produce large amounts of insulin, as is typically determined by C-peptide level, are likely not ideal candidates for pancreas transplantation.

C-peptide is a molecule produced from the enzymatic cleavage of pro-insulin and is produced in equimolar amounts to insulin. C-peptide level has been adopted by the transplant community as a diagnostic tool for the assessment of type 1 versus type 2 diabetes. Insulin (and thus, C-peptide) levels are downregulated after exogenous insulin administration. Further, insulin and C-peptide levels are increased after eating; thus, timing of C-peptide measurement is potentially important. In Scandinavia, however, where type 1 diabetes is two to three times more common than it is in the United States, population studies have shown that random C-peptide level measurement is an acceptable test for diagnosing type 1 diabetes. According to the United Network for Organ Sharing, a C-peptide level of less than 2.0 classifies patients as having type 1 versus type 2 diabetes.

Diabetes Type 1 and 2

Our understanding of type 1 and type 2 diabetes is changing; however, it is important to recognize that to the most basic physiology, diabetes is a spectrum of disease. The traditional model of diabetes development suggesting that a patient's finite number of islets are destroyed by autoimmune responses initiated by an inflammatory event (e.g., cocksackievirus, cow's milk), is now thought to be incomplete. More recently, in the modern model, we recognize diabetes as a complex process of autoimmunity and sensitivity of beta cells to inflammatory injury, which over a variable period, leads to loss of insulin production and absence of insulin and C-peptide production. It is also thought the development and timing of islet antibodies are associated with time of diabetes onset and perhaps diabetes type. Classic type 2 diabetes generally refers to insulin resistance and is associated with the metabolic syndrome. Nonetheless, patients with type 2 diabetes now enjoy similar graft survivals when compared with patients with type 1 diabetes.

Diabetes "Type 1.5"

Patients may have findings of both type 1 and type 2 diabetes. These patients may be diagnosed as having diabetes 1.5 or latent

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Diabetes "Type 1.5"

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TABLE 1 Operation, by Percentage, Performed for Each Diabetes Type

Attribute	Value	Interpretation
Operation	Diab Type	% for Years 2010–2014
SPK	1	91
	2	9
PAK	1	95
	2	4
PTA	1	85
	2	4

PAK, pancreas after a kidney transplant; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney.
Data source: SRTR Publication Publication Publication of 1,0 and new 1,0 cases from 2005 to 2014 as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). Rev Diabet Stud. 2016;13(1):3–16.

autoimmune diabetes of the adult (LADA). As many as 20% of patients diagnosed with type 2 diabetes, may be more accurately diagnosed as having LADA, or type 1.5 diabetes. LADA shares genetic similarities with type 1 and type 2 diabetes and is likely the most common form of autoimmune diabetes in general. Patients with diabetes 1.5 are diagnosed later in life, when compared with type 1, but earlier than for type 2 diabetes. Many of these patients are good candidates for pancreas transplantation. For example, these patients may have detectable C-peptide, but a low body mass index and an insulin requirement of less than 0.5 units/kg per day. For the purposes of this chapter (and for understanding a patient's potential candidacy for pancreas transplantation), it is important to assess physiology, rather than simply relying on a diagnosis of type 1 or type 2. Selected attributes of candidacy for pancreas transplantation are shown in Table 2.

Other Elements of Candidacy

Pancreas transplantation is not performed for pancreatic cancer. Pancreas transplantation was initially considered only for young patients (age <40 years). However, chronologic age alone should no longer determine candidacy. In rare cases, patients with pancreatic exocrine deficiency can be transplanted with a pancreas for nutritional and digestive benefits. These patients make up less than 1% of those transplanted. Pancreatogenic diabetes, or type 3c diabetes (e.g., pancreatic resection, cystic fibrosis, chronic pancreatitis) is also an indication for pancreas transplantation. Seven percent of patients transplanted with a pancreas received the organ not for diabetes but as part of a multivisceral transplant operation (liver + small bowel, etc.).

RECIPIENT WORKUP

Because approximately 80% of pancreas transplant recipients also have kidney failure (or a prior kidney transplant), pancreas transplant candidates uniformly fall into the highest preoperative cardiac risk category according to the revised Lee classification (also known as the revised cardiac risk index). For this reason, pancreas transplant candidates frequently require pretransplantation coronary artery architecture assessment, using computed tomography (CT) imaging or coronary angiography. At my center, pancreas transplant candidates undergo CT imaging and calcium scoring by the Agatston method. If the score is greater than 360, patients are referred for left heart catheterization. Historically, pancreas transplant candidates

TABLE 2 Attributes of Candidacy for Pancreas Transplantation

Factor	Candidacy
BMI	
<18	Likely favorable, nutrition consult
18–30	Favorable
30–35	Likely favorable
>35	Potential candidate, rule out significant insulin resistance
C-PEPTIDE	
<2.0	Favorable
2.0–10.0	Likely favorable
>10.0	Potential candidate, rule out significant insulin resistance
AGE (Y)	
<18	Select cases are reasonable
18–65	Favorable
>65	Potentially unfavorable, address cardiac status aggressively
IDDM	
Yes	Favorable
No	Not a candidate
CORONARY CALCIFICATION	
Mild	Favorable
Moderate	Likely a candidate, aggressive cardiac clearance
Severe	Potential candidate, unfavorable, aggressive cardiac clearance
INSULIN DOSE	
<0.5 U/kg/day	Favorable
0.5–1.0 U/kg/day	Likely favorable
>1.0 U/kg/day	Potential candidate, may indicate significant insulin resistance, address BMI

BMI, body mass index; IDDM, insulin-dependent diabetes mellitus.

have a more than 10% rate of cardiovascular complications after surgery, but this can be minimized with a rigorous workup and with careful patient selection.

Atherosclerosis is a systemic, inflammatory process. Thus, just as patients with diabetes are at risk for coronary disease, pancreas transplant candidates are at high risk for calcifications and luminal narrowing of the iliac arteries. CT imaging of the iliac arteries should be performed in advance of transplantation. It is also important to assess microvascular diabetic complications. Diabetic intestinal dysmotility and gastroparesis can be particularly challenging after surgery because the recipient jejunum is used to drain the exocrine secretions of the transplanted pancreas. Patients with severe pretransplantation gastroparesis may experience prolonged ileus after surgery. This complicates recovery because these patients may have difficulty taking, absorbing, and retaining appropriate levels of important medications such as tacrolimus or mycophenolate mofetil.

TABLE 3 Percentage of Pancreas Transplants Performed With and Without a Kidney

Operation	2017*	2005–2014†
SPK	79%	74%
Solitary pancreas	21%	26% (17% PAK, 9% PTA)

*Organ Procurement and Transplantation Network data (accessed June 2018).

†Gruessner AC, Gruessner RW. Pancreas transplantation of US and non-US cases from 2005 to 2014 as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). Rev Diabet Stud. 2016;13(1):30–38.

PAK, pancreas after a kidney transplant; PTA, pancreas transplantation alone.

OPERATION TYPES

The most common form of pancreas transplantation is simultaneous pancreas and kidney (SPK) transplantation (Table 3). Solitary pancreas transplantation in the form of a pancreas after a kidney transplant or pancreas transplantation alone (PTA) are also performed. All forms of transplantation require potentially nephrotoxic immunosuppression, and thus PTA has slowly fallen out of favor. If a diabetic patient already requires a kidney transplant, the immunosuppression required for the kidney (and thus the pancreas) is a foregone conclusion. On the other hand, there is a potential risk of kidney failure in patients who undergo PTA. Accordingly, PTA is reserved for type 1 diabetic patients with impeccable kidney function but who have fragile diabetes not manageable with insulin alone. The most common indication for pancreas transplant alone is hypoglycemic unawareness.

TECHNICAL PANCREAS TRANSPLANTATION

Pancreas transplantation consists of three parts. These are: (1) donor organ procurement, (2) donor pancreas preparation, or the "back table" operation, and (3) pancreas transplantation. Again, the vast majority of pancreas transplantations are performed along with a kidney transplantation (described elsewhere in this text). Perhaps unlike other forms of organ transplantation, a great deal of time and effort is required for donor pancreas procurement as well as back table organ preparation. Very little dissection and back table preparation are required for hearts, lungs, kidneys, and variably for livers. However, the dissection alone during pancreas recovery surgery can exceed 60 minutes and the back table procedure frequently takes 120 minutes.

Part 1: Donor Organ Procurement

A midline laparotomy provides access to the abdominal organs. A sternotomy allows access to the chest, but also improves abdominal exposure. Occasionally, recovery teams will also make a transverse cruciate incision at the level of the umbilicus, depending on the visualization required and the instruments available.

First, the surgeon focuses on gaining access to the aorta and the inferior vena cava. To do so, the surgeon mobilizes the right colon and the hepatic flexure. The cecum is elevated, and the peritoneal attachments are divided from lateral to medial. This dissection is limited to the superior mesenteric artery (SMA). Next, a Kocher maneuver is performed to gain access to the vena cava and to the left renal vein, which is present in 95% of patients. Once complete, the right colon should be a mid line structure. A moist towel is then used to bundle the intestines, improving surgical ergonomics. Once bundled, medical students typically enjoy retracting (spiritual) while standing on the donor's left. This gives the primary surgeon, on the patient's right, easy access to the aorta and the inferior vena cava.

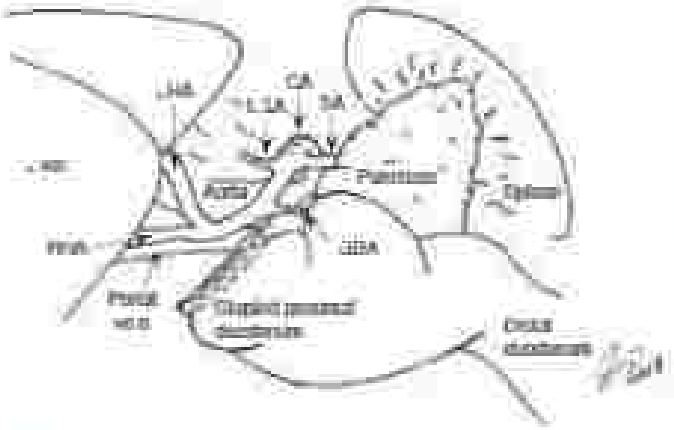

FIG. 1 Surgeon's view of the pancreas and liver during recovery. The surgeon will find the splenic artery at the superior aspect of the body of the pancreas. The splenic artery (SA), the gastroduodenal artery (GDA), the portal vein, and the bile duct (not pictured) need to be divided to separate the liver from the pancreas. *CA*, celiac axis; *LGA*, left gastric artery; *LHA*, left hepatic artery; *RHA*, right hepatic artery.

The aorta is then dissected inferior to superior, beginning at the bifurcation, and the inferior mesenteric artery is divided between heavy silk sutures. The dissection is carried out to the level of the SMA, taking care to identify and mobilize the left renal vein, which is less than 1 cm from the SMA, just anterior to the aorta.

Either before or immediately after the dissection of the aorta and left renal vein, the recovering surgeon will prepare the distal aorta for cannulation. Due to done early in the recovery because if the donor becomes hemodynamically compromised, the organs can be flushed quickly. Thus, the aortic bifurcation is dissected circumferentially. Heavy ligatures, or umbilical tapes, are used instead of heavy silk suture or vessel loops because the entire aorta will need to be ligated later in this case. Once the ligatures or umbilical tapes are placed beneath the bifurcation, the ends are tagged with Mixter tips, and focus is redirected toward completion of the organ recovery dissection.

By convention, the liver is addressed first. The liver dissection is important in the context of pancreas recovery for two reasons: (1) the splenic artery, which arises from the celiac trunk, supplies the tail of the pancreas; and (2) the potential for a replaced right hepatic artery (10%–20% incidence) most commonly arises from the proximal SMA, just beneath the pancreas. The SMA supplies the pancreatic head.

The splenic artery must be divided (after cross clamp) to separate the liver from the pancreas. As the liver surgeon dissects free the common hepatic artery, toward the aorta, the splenic artery will be identified at the superior aspect of the body of the pancreas. It will course inferiorly, and typically orthogonal to the common hepatic artery (Fig. 1). The splenic artery should be dissected free approximately 1 cm from its takeoff of the celiac axis to (after cross clamp) safely divide it without affecting the liver's blood supply. In general, the length of the divided splenic artery that accompanies the pancreas is unimportant, because the inflow to the pancreas will be reconstructed on the back table using donor iliac artery.

The pancreas is addressed after the liver dissection. There are several ways to approach the pancreas. We begin with the spleen. The spleen is recovered en bloc with the pancreas, and the transplanting surgeon removes it on the back table. Notably, a small number of donors are asplenic as a result of trauma, or for medical reasons. This should not preclude donation but should raise a flag of concern that anatomic abnormalities may disallow safe pancreas recovery.

The surgeon, standing on the right, grasps the spleen and gently retracts medially. Cautery is used to incise the posterolateral peritoneum. This should be bloodless because there are no named vessels in

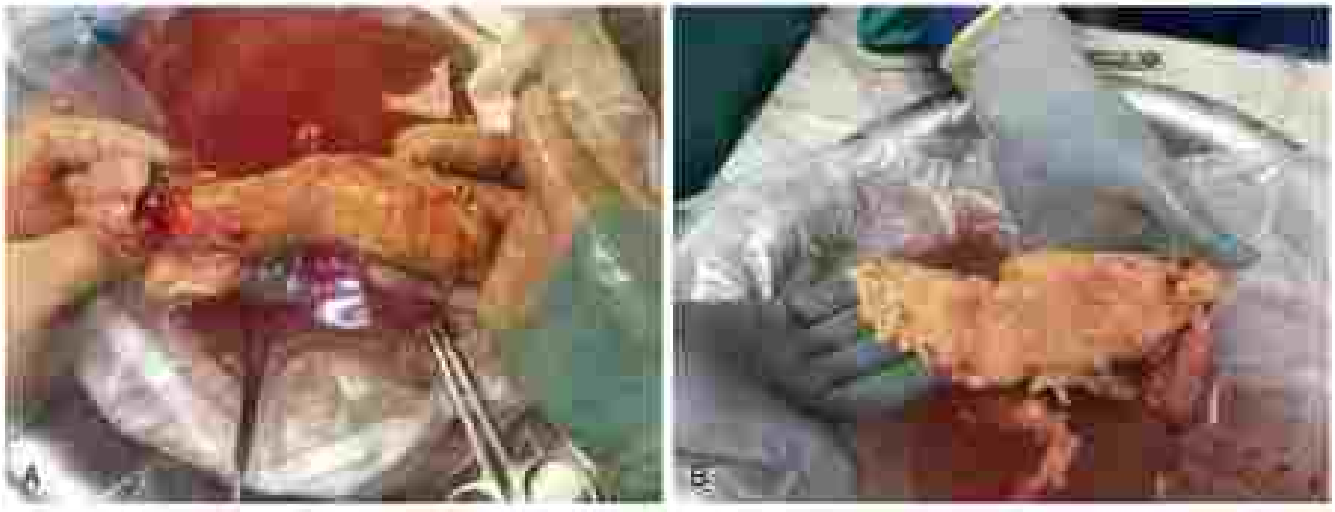

FIG. 2. (A) Normal pancreas. (B) Fatty pancreas.

thin tissue. The dissection is continued both superiorly and inferiorly. The splenocolic ligament is divided as well, and the spleen is then mobile.

With the mesentery flat, the gastrocolic ligament, at the inferior aspect of the stomach, is divided. The division of multiple small branches of the left gastroepiploic artery can be performed with energy devices or between ties. Division of the gastrocolic ligament provides access to the anterior aspect of the pancreas. At this point, the spleen and pancreatic tail are mobile enough to begin posterior dissection.

Next, the surgeon divides the gastrosplenic ligament as well as the short gastric vessels. This may require ties and is frequently difficult in a donor with a high body mass index. Next, the spleen is progressively elevated, and the avascular plane between the pancreas and the retroperitoneum is divided, using cautery. This is critical because the splenic vein can be injured if the surgeon is in the wrong plane. The splenic vein should accompany the pancreas and the adrenal should remain in the donor. If done well, this too is bloodless. Moving lateral to medial, the limit of the dissection is the SMA.

The stomach is then divided proximal to the pylorus. On occasion, as in Fig. 1, the surgeon may feel comfortable dividing the proximal duodenum distal to the pylorus. Before division, the surgeon requests that the organ recovery staff infuse into the donor's nasogastric tube the pancreas recovery cocktail that includes antibiotics and antifungals. Next, two green loads of large TA stapler are used to divide the stomach. The stomach is then retracted cephalad, and the remaining soft tissue between the lesser curvature and the pancreas, in addition to the right gastric artery, are divided. The stomach is then tucked up and out of the way into the left upper quadrant for the remainder of the case.

At this point, the pancreas is free with the exception of the portal vein, the SMA, splenic artery, and the proximal jejunum with its mesentery. The bile duct will have been divided by the liver surgeon. Once the recovery teams are ready, the distal aorta is ligated, and the aortic cannula is inserted and tied with umbilical tapes. A portal infusion cannula is then frequently placed into the inferior mesenteric vein (IMV). Some pancreas transplant surgeons prefer an IMV cannula be placed, but rather portal flush directly through the portal vein. The reason for this is that, theoretically, IMV flushes may cause pancreatic edema. However, in my experience, IMV placement has little or no effect on the pancreas and is safer and easier than a portal flush. With cannulae in place, 30,000 units of heparin are administered. Three minutes later, the aorta is clamped in the chest, and the retrograde aortic infusion of University of Wisconsin (UW) solution commences.

The liver is removed first. To do so, the splenic artery is divided immediately before division, the pancreatic portion of the splenic artery should be tagged with a 5-0 or 6-0 Prolene stitch because it may retract into the soft tissues of the pancreas and become cumbersome to identify on the back table. The portal vein is divided with scissors at the coronary vein. The jejunum is stapled with a GIA blue. Next, the small bowel mesentery is divided with a vascular load. The SMA is divided with scissors. The pancreas is passed off the field and assessed for transplantability. The pancreas should be stored in UW solution at 4°C. There are data to suggest that other preservation solutions, such as histidine-tryptophan-ketoglutarate, are unsafe for pancreas preservation. The gland should be transplanted in less than 12 hours (24 hours maximum) for the optimal results. The pancreas should pass the Oglaten test to ensure transplantability. To pass the test, the pancreas should be supple enough to hang gently over the surgeon's index finger. Whereas a high-quality pancreas will easily bend, the firm, fatty pancreas will remain stiff.

If the donor has a replaced right hepatic artery, the liver surgeon should divide the SMA (with the pancreas surgeon holding retraction) above the level of the replaced right as it exits the SMA. Enough distal artery on the SMA should accompany the liver such that a Hartert's reconstruction (covered elsewhere) can be performed. Replaced right hepatic arteries should not preclude pancreas recovery unless the takeoff of the replaced right hepatic artery is deep within the pancreatic parenchyma.

Part 2: Back Table Preparation

The pancreas is nearly always accompanied by the spleen. The first maneuver on the back table is to remove the spleen. The splenic artery and vein are large and require heavy ties. The smaller vessels can be ligated with small clips, energy devices, or ties. One center prefers silk ties.

Young donor pancreata are typically free of fat (Fig. 2A). Older, heavier pancreas donors may have peripancreatic fat, which needs to be removed from the tail and body of the pancreas (Fig. 2B). Small vessels in this tissue should be addressed. Conservatively, fatty pancreata should be avoided, but with short cold ischemia times they are likely reasonable for the right recipient.

The proximal intestine inclusive of the pylorus is removed by resecting. The staple line is oversewn with interrupted silk 3-0 sutures or running 3-0 Prolene. Similarly, the distal duodenum is also resected, such that the remaining duodenal C loop is approximately 6 to 12 cm in length. Too much redundant donor intestine is not useful and may become problematic postoperatively. The distal staple line is

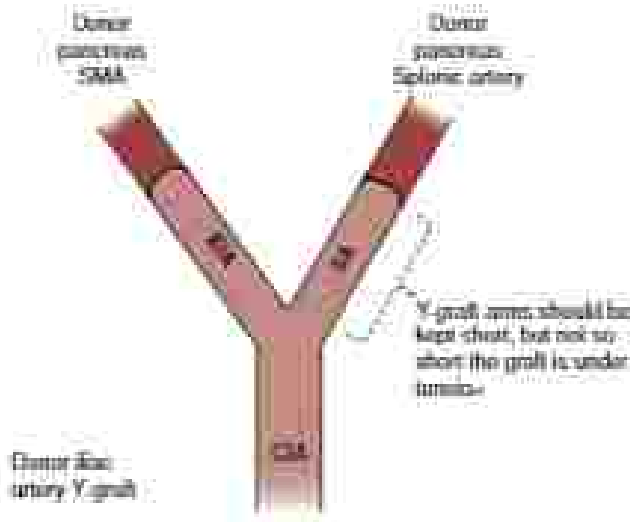

FIG. 3 Donor iliac artery Y-graft. The donor superior mesenteric artery is sewn to the donor external iliac artery and the donor splenic artery is sewn to the donor internal iliac artery. The graft is portioned through the donor Y-graft common iliac artery (CIA). EIA, external iliac artery; IIA, internal iliac artery; SMA, superior mesenteric artery.

reservoir with interrupted silk sutures as well. In the authors' experience the purpose of oversewing is for hemostasis rather than leak prevention. Depending on the recovery team, the transplanting surgeon may also desire to oversew or to reinforce the small bowel mesentery. This is a frequent source of bleeding after reperfusion.

The blood supply to the transplanted pancreas is dual via the SMA and splenic arteries. Thus, the arterial inflow requires reconstruction on the back table. To do so, the iliac arterial system is recovered from the pancreas donor. The iliac artery is referred to as a Y-graft. The external iliac artery typically has a smaller diameter than the external, and is thus sewn to the splenic artery, end to end, using a 6-0 or 7-0 Prolene. Thereafter, the external iliac artery is sewn end to end with the SMA, using a 6-0 or 7-0 Prolene. Each arm of the Y should be short (Fig. 3), to avoid unnecessary decreases in resistance to flow as well as kinking after implantation. These anastomoses are large and represent a good opportunity to teach residents and fellows.

The prudent surgeon will leak test the pancreas, paying special attention to the lymphatic and ganglial tissue between the arms of the Y graft. There are frequently small vessels in this area which can be incredibly difficult to manage after reperfusion.

Part 3: Transplantation of the Pancreas

There are several ways to perform a simultaneous pancreas and kidney transplant. For example, the pancreas can be transplanted before or after the kidney. Both organs can be placed unilaterally (usually on the right), or with the pancreas on the right and the kidney on the left. In rare situations, the pancreas is placed on the left. My standard approach is for the pancreas to be placed on the right (before the kidney) and the kidney on the left. This involves dissection of both iliac systems, which is important because if the patient needs a future transplant, neither side is virgin. The benefit of the unilateral approach is that the left side is untouched and is open for a future organ if required. In solitary pancreas transplantation, the pancreas is usually placed on the right.

A pancreas transplant is typically performed through a midline incision. Gibson incisions can be used in this case because the peritoneum needs to be accessed to complete the bowel anastomosis. It is important to make sure the incision allows access to the bladder for an SPK. Thus, the incision frequently descends right to the level of the pubis. In heavier patients, it is best to use a full laparotomy incision (i.e., to the xiphoid) because it can be quite challenging to retract epithelial fat to the side.

First, the right colon is fully mobilized to include the hepatic flexure. In thinner patients, a bit less mobilization is required. A partial Kocher's maneuver may be required so that the surgeon will have access to the anterior surface of the inferior vena cava. The peritoneal attachments beneath the colon are divided to the SMA, as was done in the donor operation. A Steinmann pin (metal lap pad unfolded and rolled up like a cigar) is then placed at the base of the mesentery, and a moist towel is used to cradle the intestines. The intestines are then retracted to the left upper quadrant, usually with a large malleable or the Bookwalter retractor or with Martin arms.

The right common iliac artery is dissected free, as is the anterior surface of the inferior vena cava. The two vessels are separated. The separation of the right common iliac artery from the vena cava and right common iliac vein can be precarious, so the surgeon should proceed cautiously. During this step of the operation, the recipient's native ureter and gonadal vein should be retracted laterally. Meticulous hemostasis of the retroperitoneum should be achieved prior to transplanting the pancreas, because it can be challenging to see the retroperitoneum after the gland is in place.

The pancreas, in an ice filled bag, is held outside the wound, upside down, and head up. The pancreas is positioned upside down for ease of access to the portal vein. A cantomy is fashioned and the vein flushed with heparinized saline. The portal vein is then sewn to the inferior vena cava using two running 6-0 Prolene stitches. For a pediatric pancreas, a 7-0 Prolene may be used in all cases, because the size of the anastomosis is substantial. In my experience, a shouldered approach to the backwall of the pancreatic portocaval anastomosis is more hemostatic. A bull dog is then placed across the donor portal vein, and the Satinsky clamp is removed to ensure hemostasis of the anastomosis before the artery is sewn.

Proximal and distal control of the common iliac artery are obtained with Debarty (or other) vascular clamps. An arteriotomy is fashioned and the blood vessel flushed with heparinized saline. A single 6-0 Prolene suture is typically used to fashion a running end-to-side anastomosis.

Before reperfusion, the surgeon should communicate with the anesthesia staff. The cold UW fluid in the pancreas can lead to arrhythmias in the recipient after reperfusion. The reperfusion event is generally more substantial than observed with a kidney transplant, but far less so than with a liver transplant. The pancreas is reperfused by first releasing the portal venous bull dog clamp. Large bleeders, if present, are dealt with thereafter, the distal followed by the proximal arterial clamps are released.

Next, a loop of small bowel 40 cm distal to the ligament of Treitz is identified. A side to side, handsewn donor duodenum to recipient jejunum anastomosis is performed. The outer layer is completed with narrowly spaced 3-0 silk sutures. The inner, full thickness layer is generally completed using a double armed 3-0 PDS suture. Hemostasis is achieved by carefully rotating the pancreas back and forth. Small bleeders between the arms of the arterial Y graft can be challenging to see and manage. For these, interrupted 7-0 Prolene repair stitches are ideal.

If an SPK is being performed, and the pancreas is transplanted first, urethral obstruction of inflow and outflow of the pancreas should be avoided while repositioning the ureters for the kidney transplant. The end to side venous anastomosis is performed first, using running 6-0 Prolene suture. Next, an end to side arterial anastomosis is performed using a single running 6-0 or 7-0 Prolene suture. The organ is then reperfused. The arterial anastomosis is performed second to stasis and is completed with 6-0 PDS suture. Most kidney transplant ureteroneocystostomies are performed over a ureteral stent.

Technical Caveats of Pancreas Transplantation

Portal-Venous Drainage

In the procedure described previously, the venous outflow of the pancreas was portocaval. This, however, differs from native anatomy

whereas the venous effluent from the pancreas undergoes first pass metabolism in the liver. During this process, as much as 50% of circulating insulin are removed from the bloodstream. This is potentially important, because systemically drained pancreas recipients may have hyperinsulinemia. Dr. Stephen T. Bartlett helped popularize the technique and showed that portal drainage may yield a lower rate of rejection, perhaps as a result of antigen clearance through the liver.

For portal venous drainage, the portal vein of the donor pancreas can be sewn to the superior mesenteric vein (SMV) of the recipient. This technique is best used in thinner patients, in whom the mesentery is not particularly thick. The SMV is identified in the small bowel mesentery, to the right of midline. Small branches of the SMV may need to be controlled (but not ligated) for sufficient access and visualization. The portal vein is sewn end to side using running Prolene suture. The pancreas will sit high in the mesentery. As a result, the iliac artery Y graft is longer to reach the recipient common iliac artery.

Bladder Drainage of Exocrine Secretions

Bladder drainage was popularized in the mid-1980s by a pioneer of pancreas transplantation, Dave Sollinger. The use of bladder drainage allowed for safe management of pancreatic exocrine secretions in the early postoperative course. Further, bladder drainage allowed for diagnosis of rejection via urinary amylase. However, long-term complications such as bicarbonate loss and cystitis led to the eventual adoption of enteric drainage as the superior technique. Accordingly, many centers stopped routinely performing bladder-drained pancreas transplants in the mid-1990s. The technique, which is not technically dissimilar from enteric drainage requires that the pancreas be placed head-down, as opposed to head-up, as were described previously. Many of the patients who underwent bladder drainage of the pancreas were converted successfully to enteric drainage in the years after their pancreas transplants.

Transmesenteric Pancreas Transplantation

Full mobilization of the right colon can be avoided by performing a transmesenteric approach to the right iliac vessels. Although this minimizes the dissection of the right colon, a transmesenteric approach may require an extension of the donor portal vein using donor iliac vein. Some surgeons are wary of donor portal vein extensions as they may be prone to thrombosis.

Duration After Circulatory Death Versus Brain Dead Donors

Duration after circulatory death (DCD) implies that a person is not brain dead at the time of organ allocation. Thus, life support for these donors is withdrawn, and only once the patient is declared deceased can the organs be removed. In the DCD scenario, the blood pressure and heart rate decrease at variable rates during which time donor organs may experience ischemic damage. The use of pancreata from DCD donors is not worse than for brain dead donors. Surgically, organs are removed rapidly during DCD procurement to minimize surgical tissue injury. Thus, ensuring that the pancreas is recovered quickly (less than 30 minutes of warm ischemia time, and expeditiously after aortic cross clamp) while free from technical injury is important.

Stapled Versus Hand-Sewn Anastomoses

The duodenojejunostomy described previously does not tend to be handsewn. Described by Prudell et al, a stapled duodenoenterostomy can be performed by inserting an EEA stapler through one end of the donor duodenum. Thereafter, the open end can be itself stapled using a GIA stapler. Other stapled techniques have also been described.

Robotic Pancreas Transplantation

The techniques described previously are open. Minimally invasive techniques are challenging in transplantation, because at some point, an incision big enough to allow for organ insertion is required. Nonetheless, robotic minimally invasive SPK has been done and with encouraging results. These techniques are particularly helpful when the recipients are obese. A portion of the benefit for minimally invasive techniques is attributed to a reduction in wound complications after surgery.

Perioperative Management

Pancreas transplant patients are at risk for bleeding, reperfusion injury, thrombosis, and infection. The surgeon should closely monitor recipient blood counts in the hours after surgery. Reperfusion injury severity is reflected in serum amylase and lipase elevation, which may reach 20 to 30 times the upper limit of normal. Lipase should begin to clear rapidly (~12–24 hours), presuming adequate renal function. Pancreas transplantation is associated with a higher rate of thrombosis than with other solid organs. Rapid blood sugar elevation may indicate thrombosis. To avoid thrombosis, care providers at the author's institution are directed to maintain mean arterial pressure above 75 mm Hg in the 72 hours after surgery. In addition, aspirin 81 mg on postoperative day 1 is initiated if bleeding has not occurred. If there is concern for thrombosis, a bedside ultrasound is likely sufficient to make the diagnosis. Infection may occur in the first several weeks after pancreas transplantation. Retroperitoneal abscesses are particularly troublesome because they sit atop the aorta and inferior vena cava, and adjacent to the pancreatic T graft.

RESULTS

In the initial series, fewer than 10% of pancreas transplants survived a year. In the most recent studies, 1 year SPK patient survival rates are 97.4%. In addition, 1 year pancreas graft survival rates are 91.3% and 1 year SPK kidney graft survival rates are 95.5%. The increases in pancreas graft survival were driven, in part, by reduced rates of technical graft loss. High resolution immunologic testing has reduced the rate of rejection, which remains higher after pancreas transplantation than for kidney transplantation alone. There is not 100% concordance with rejection in the kidney versus the pancreas when the recipient undergoes SPK, and biopsy of both organs may be necessary to diagnose rejection.

Pancreas transplantation is superior to exogenous insulin with regard to glucose control. SPK is associated with longer patient survival than for kidney transplantation alone, regardless of whether the kidney alone donor was living or deceased. This finding is likely explained by very high quality organs for SPK donors, when compared with most kidney transplant alone donors (particularly deceased donors). Nonetheless, the elimination of diabetes for patients with kidney failure also contributes to prolonged patient and kidney graft survivals. Pancreas transplantation dramatically improves the quality of life for recipients. As a care provider, there are few experiences more gratifying than telling a patient's family their loved one's diabetes is gone.

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Islet Autotransplantation for Chronic Pancreatitis

Charles G. Rickert, MD, PhD; Ji Lei, MD, MSc, MBA; and James F. Markmann, MD, PhD

In the United States, chronic pancreatitis (CP) currently affects approximately 42 in 100,000 individuals, resulting in $635 million in direct inpatient hospital costs. The disease is an irreversible, fibrotic condition of the pancreas resulting from long standing inflammation, which often results in disabling abdominal pain. The initial manifestation of CP in approximately 80% of patients is abdominal pain, often after eating, which radiates to the back and is relieved by sitting forward. It may be accompanied by nausea and vomiting. Throughout the course of the disease, it can progress from intermittent discomfort to continuous pain. Twenty percent of patients will first present with symptoms related to deficiency of endocrine or exocrine function, including severe malnutrition or the development of diabetes mellitus. However, overt diabetes is usually only a factor of late term disease or in patients with a family history of type 1 or type 2 diabetes mellitus. Beyond these symptoms directly related to the inflammation of the pancreas, CP can also result in splenic vein thrombosis, bile duct and duodenal obstruction, pseudocyst formation, ascites, pleural effusion, and pancreatic cancer.

The treatment options for this disease aim at reduction of pain and compensation of pancreatic insufficiency. Initial management focuses on medical therapy and lifestyle changes—cessation of inciting behavior, such as alcohol intake and smoking, eating small meals, and supplementing with medium chain triglycerides. Pain management is initially attempted through suppression of pancreatic exocrine secretion by providing exogenous supplement pancreatic enzymes. Many patients will ultimately rely on some combination of narcotic analgesia, nonsteroidal antiinflammatory drugs (NSAIDs), and low dose tricyclic antidepressant, typically amitriptyline. Some patients will undergo endoscopic decompression via pancreatic duct stent placement.

Operative management is generally considered for patients with medically refractory disease or when pancreatic cancer is suspected. The operative approach selected to treat this disease depends on the location and extent of the pancreatic inflammation. The approaches can be classified as decompression, denervation, and resection—partial or total. Decompression, for example through a Puestow procedure, can be highly effective in patients with refractory pain and a large, dilated pancreatic duct (>8 mm). Initial pain relief of operative decompression appears to be similar to endoscopic approaches, however, 5-year follow up suggests that surgery may be superior for long term management of pain. Denervation is performed by disruption of the celiac ganglion or splanchnic nerves through open or thoracoscopic operative approaches. Overall efficacy of this approach is still an active area of study.

Resection of inflamed pancreatic tissue is often utilized once other alternatives have been exhausted, due to the loss of pancreatic tissue and risk of both exocrine and endocrine pancreatic insufficiency. In a healthy individual, only about 20% of the normal pancreas is required to provide adequate function. However, in CP, much of the pancreas may be nonfunctional, and even a small loss of tissue may result in exocrine insufficiency or diabetes mellitus. Thus great care must be taken in determining which operation will lead to the best outcome for the patient. Operations to remove pancreatic tissue include pylorus preserving and nonpreserving pancreaticoduodenectomy (Whipple), Beger procedure, distal pancreatectomy, and total pancreatectomy (TP). Distal pancreatectomy is most limited in efficacy and reserved for disease that is limited to the body and tail of the pancreas. The Whipple operation provides additional pain relief, even with disease in the tail, secondary to denervation. Total pancreatectomy is the most complete removal of the inflamed tissue and has been shown to improve pain control when other options fail. This operation obligatorily results in exocrine and endocrine insufficiency. Autologous islets, purified from the removed pancreas, provide a potential means of avoiding the endocrine insufficiency of TP. Thus, for the proper patients, TP with islet autotransplantation (TP-IAT) provides the best opportunity for pain relief with minimized sequelae. While TP alone for CP has been performed since the 1940s, Sutherland and colleagues at the University of Minnesota first performed the pancreatectomy with the islet autotransplantation in 1977. Since then, it has expanded with nearly 20 centers now offering the operation. The University of Minnesota recently reported their 500th TP-IAT operation.

PATIENT SELECTION AND PREOPERATIVE EVALUATION

CP is a multifactorial disease that results in both loss of pancreatic function and severe abdominal pain. Proper workup of this disease requires careful assessment of the patient's symptoms, laboratory values, and radiographic findings. For most chronic pancreatitis patients, disease progression occurs over years and, therefore, extensive evaluation and monitoring has occurred prior to referral for surgical assessment. Typically, patients are referred for TP only after failure of less invasive surgical or endoscopic therapies. Delayed

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In the United States, chronic pancreatitis (CP) currently affects approximately 42 in 100,000 individuals, resulting in $635 million in direct inpatient hospital costs. The disease is an irreversible, fibrotic condition of the pancreas resulting from long standing inflammation, which often results in disabling abdominal pain. The initial manifestation of CP in approximately 80% of patients is abdominal pain, often after eating, which radiates to the back and is relieved by sitting forward. It may be accompanied by nausea and vomiting. Throughout the course of the disease, it can progress from intermittent discomfort to continuous pain. Twenty percent of patients will first present with symptoms related to deficiency of endocrine or exocrine function, including severe malnutrition or the development of diabetes mellitus. However, overt diabetes is usually only a factor of late term disease or in patients with a family history of type 1 or type 2 diabetes mellitus. Beyond these symptoms directly related to the inflammation of the pancreas, CP can also result in splenic vein thrombosis, bile duct and duodenal obstruction, pseudocyst formation, ascites, pleural effusion, and pancreatic cancer.

The treatment options for this disease aim at reduction of pain and compensation of pancreatic insufficiency. Initial management focuses on medical therapy and lifestyle changes—cessation of inciting behavior, such as alcohol intake and smoking, eating small meals, and supplementing with medium chain triglycerides. Pain management is initially attempted through suppression of pancreatic exocrine secretion by providing exogenous supplement pancreatic enzymes. Many patients will ultimately rely on some combination of narcotic analgesia, nonsteroidal antiinflammatory drugs (NSAIDs), and low dose tricyclic antidepressant, typically amitriptyline. Some patients will undergo endoscopic decompression via pancreatic duct stent placement.

Operative management is generally considered for patients with medically refractory disease or when pancreatic cancer is suspected. The operative approach selected to treat this disease depends on the location and extent of the pancreatic inflammation. The approaches can be classified as decompression, denervation, and resection—partial or total. Decompression, for example through a Puestow procedure, can be highly effective in patients with refractory pain and a large, dilated pancreatic duct (>8 mm). Initial pain relief of operative decompression appears to be similar to endoscopic approaches, however, 5-year follow up suggests that surgery may be superior for long term management of pain. Denervation is performed by disruption of the celiac ganglion or splanchnic nerves through open or thoracoscopic operative approaches. Overall efficacy of this approach is still an active area of study.

Resection of inflamed pancreatic tissue is often utilized once other alternatives have been exhausted, due to the loss of pancreatic tissue and risk of both exocrine and endocrine pancreatic insufficiency. In a healthy individual, only about 20% of the normal pancreas is required to provide adequate function. However, in CP, much of the pancreas may be nonfunctional, and even a small loss of tissue may result in exocrine insufficiency or diabetes mellitus. Thus great care must be taken in determining which operation will lead to the best outcome for the patient. Operations to remove pancreatic tissue include pylorus preserving and nonpreserving pancreaticoduodenectomy (Whipple), Beger procedure, distal pancreatectomy, and total pancreatectomy (TP). Distal pancreatectomy is most limited in efficacy and reserved for disease that is limited to the body and tail of the pancreas. The Whipple operation provides additional pain relief, even with disease in the tail, secondary to denervation. Total pancreatectomy is the most complete removal of the inflamed tissue and has been shown to improve pain control when other options fail. This operation obligatorily results in exocrine and endocrine insufficiency. Autologous islets, purified from the removed pancreas, provide a potential means of avoiding the endocrine insufficiency of TP. Thus, for the proper patients, TP with islet autotransplantation (TP-IAT) provides the best opportunity for pain relief with minimized sequelae. While TP alone for CP has been performed since the 1940s, Sutherland and colleagues at the University of Minnesota first performed the pancreatectomy with the islet autotransplantation in 1977. Since then, it has expanded with nearly 20 centers now offering the operation. The University of Minnesota recently reported their 500th TP-IAT operation.

PATIENT SELECTION AND PREOPERATIVE EVALUATION

CP is a multifactorial disease that results in both loss of pancreatic function and severe abdominal pain. Proper workup of this disease requires careful assessment of the patient's symptoms, laboratory values, and radiographic findings. For most chronic pancreatitis patients, disease progression occurs over years and, therefore, extensive evaluation and monitoring has occurred prior to referral for surgical assessment. Typically, patients are referred for TP only after failure of less invasive surgical or endoscopic therapies. Delayed

criteria for TP IAT remain an area of active research and discussion; however, most centers adhere to the consensus guidelines established at PancreasFest 2012 (Box 1). When evaluating patients for TP IAT, it is generally recommended that a multidisciplinary team, consisting of pancreatic surgeon, transplant surgeon, endocrinologist, gastroenterologist, psychologist, social work, and nursing, evaluate the patient for optimal planning of the procedure.

Evaluation of a potential patient must begin with careful assessment of the patient's disease process. When considering any procedure performed to alleviate pain, it is important to first ensure that the patient's symptoms are the result of the disease targeted by the procedure. When considering a TP combination that the pancreas is the source of pain is particularly important because the pancreatectomy will result in loss of any residual pancreatic function. The IAT is utilized to abrogate the loss of endocrine pancreatic tissue, but the graft will be less than 100%, and thus the glucose control may worsen postoperatively.

Taking a careful history is important to understand the underlying etiology of the CP and extent of endocrine dysfunction preoperatively. The etiology can give insight into whether the CP is large or small duct, which can indicate whether a decompressive operation (e.g., Puestow or Frey) or more limited resection may be warranted. Individuals with a history of genetic risk factors for recurrent acute pancreatitis or CP, such as mutations in *CFTR* (cystic fibrosis transmembrane conductance regulator), *SPINK1* (serine protease inhibitor Kazal type 1), or *PRSS1* (cationic trypsinogen), should warrant careful consideration and potentially earlier intervention because of their lifetime risk of pancreatitis and pancreatic cancer. The patient should also be assessed for symptoms of hepatic disease and portal hypertension, as marked portal hypertension is a contraindication for intraportal infusion of islets. Additionally, history of systemic symptoms concerning for pancreatic neoplasm would warrant a more extensive workup. A complete patient history can also be valuable to understand comorbidities and social factors that may significantly impact perioperative care.

Laboratory testing for both exocrine and endocrine functioning should be performed pre-operatively. This includes glucose tolerance test, HbA1C, C-peptide, and fecal elastase measurement. Complete blood count, electrolytes, and liver function tests are also ordered. Most patients with longstanding CP will have some degree of glucose intolerance. The degree of intolerance is indicative of the number of functional islets present in the pancreas. The success of the IAT is highly dependent on the number of islets. Therefore, understanding the degree of islet dysfunction preoperatively will be important when discussing expectations with the patient and planning how to manage postoperative diabetes. There is no generally accepted threshold for pancreatic endocrine function that will dictate whether attempted IAT is appropriate. However, it is generally accepted that an elevated A1c portends poor glycemic control post TP IAT, and the absence of islet function, indicated by the lack of C-peptide production, is a contraindication to TP IAT. Many centers are now advocating for earlier referral, before other surgical interventions that will reduce residual islets, for TP IAT to increase the likelihood of achieving long-term glucose control without need for supplemental insulin.

Radiographic studies for chronic pancreatitis often consist of computed tomography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, and/or endoscopic ultrasound. For operative planning, imaging to particularly valuable for assessing the extent of fibrosis (diffuse vs localized), ductal diameter, and evidence of neoplasm. Evidence of head- or tail-dominant disease may indicate that a nonlocal resection is warranted. If the ductal diameter is more than 5 mm, a decompression operation should be considered. Assessment for potential neoplasm is of the utmost importance because neoplastic disease could dramatically impact the extent of pancreatic resection and whether IAT is an option.

If splenectomy is anticipated as part of the pancreatectomy, appropriate preoperative vaccinations should be administered to reduce the risks of overwhelming postsplenectomy sepsis. These vaccinations included pneumococcus, meningococcus, and *H. influenza* type B.

BOX 1 Summary of Guidance Statements from PancreasFest 2012

Inclusion

1. The primary indication for TP IAT is to treat intractable pain in patients with impaired quality of life due to chronic pancreatitis or recurrent acute pancreatitis in whom medical, endoscopic, or prior surgical therapy have failed.

Exclusion

1. TP IAT should not be performed in patients with active alcoholism, active illicit substance use, or untreated/uncontrolled psychiatric illness that could be expected to impair the patient's ability to adhere to complicated medical management. Patients with poor support networks have a relative contraindication due to the cost and complexity of managing diabetes and pancreatic exocrine replacement therapies.
2. TP IAT should not be performed in patients with specific medical conditions, including C-peptide negative diabetes,[a] type 1 diabetes,[a] portal vein thrombosis, portal hypertension, significant liver disease, high-risk cardiopulmonary disease, or known pancreatic cancer.

Evaluation

1. The severity, frequency, and duration of pain symptoms, narcotic requirements, disability/impaired quality of life, residual islet function, rate of disease progression, and age of the patient should be considered in timing of the procedure.
2. Patients who meet inclusion criteria and who are not excluded should be evaluated by a multidisciplinary team, who will review alternative interventions, assess the likelihood of success in reducing pain and preventing or minimizing diabetes, follow the patient through the procedure and provide guidance for long-term care.
3. Evaluation should include confirming that pancreatitis is the primary diagnosis, determining that the pain is of pancreatic origin, monitoring for the presence of diabetes, assessing ß-cell mass (by C-peptide), and assessing the patency of the portal venous system, evaluating for liver disease, and determining the nutritional status.

Follow-up

1. Life-long monitoring for diabetes mellitus shall be performed at least annually and should include self-monitored blood sugar, fasting blood glucose, and hemoglobin A1c. These patients may be followed for ß-cell mass (by C-peptide).
2. Life-long pancreatic enzyme replacement therapy is mandatory. Nutritional monitoring should include assessment of macrocytosis, weight maintenance, and fat-soluble vitamin levels on an at least an annual basis.
3. A physician experienced in pain management should be part of the patient's care team following hospital discharge to assist with the tapering of narcotic medications.

[a]Candidate for total pancreatectomy alone. From Sellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology. 2014;14(1):22–36.

The evaluation process thus is focused on establishing that the patient has severe pain, which would likely improve from total removal of the pancreas, and that none of the contraindications are present (Box 1). Nearly every patient evaluated for a TP should be considered for IAT as well.

PROCEDURE: TOTAL PANCREATECTOMY, ISLET ISOLATION, PURIFICATION, INTRAPORTAL ISLET INFUSION

Definitive operative management of chronic pancreatitis by TP-IAT consists of three connected procedures: (1) TP; (2) islet isolation and purification; (3) infusion of purified islets into the portal circulation (Box 2).

Total Pancreatectomy

The operative approaches for TP for chronic pancreatitis vary between centers and include the traditional TP with splenectomy, as well as splenic preserving and pylorus preserving procedures. As opposed to TP for pancreatic cancer, the removal of the pancreas as part of TP-IAT necessitates minimization of warm ischemic time to ensure the greatest viability of the islets of Langerhans. For this reason, the ligation of the vascular flow to the pancreas is performed only after complete mobilization and preparation for removal, regardless of the specific TP procedure utilized. Early attempts to perform duodenal sparing procedures have been largely abandoned because of the longer warm ischemic time.

The typical approach involves taking down of the hepatocolic and hepatocolic ligaments to mobilize the transverse colon, entry of the lesser sac with direct assessment of the pancreas, medial mobilization of the pancreas and duodenum via Kocher maneuver and small bowel transection, mobilization of the body and tail of the pancreas with spleen, and finally, ligation of the pancreatic and splenic vasculature to undertake. It is also important to avoid injuring the gastric vasculature to decrease the risk of postoperative delayed gastric emptying. Some centers have developed laparoscopic approaches for the TP. The specimen is removed and immediately placed on ice and perfused with cold preservation solution.

Restoration of enteric continuity is achieved through the creation of a hepaticojejunostomy and end to side gastrojejunostomy (or duodenojejunostomy if pylorus preserving resection is performed). The proximal portion of the ligated bowel is mobilized and advanced to a retrocolic fashion and end to side anastomosis of the biliary system to the jejunum is performed. Depending on the site of the small bowel resection, this anastomosis may be between the biliary system and segments three or four of the duodenum. Antecolic gastrojejunostomy is then performed. Alternatively, some centers prefer a Roux-en-Y reconstruction. Additionally, some surgeons may elect to place gastrostomy and jejunostomy tubes during the operation to ensure postoperative nutrition and venting, if necessary for delayed gastric emptying postoperatively. A Blake drain is placed at the hepaticojejunostomy to monitor for possible leak and lymphatic drainage.

The open operative field is covered by a moist, saline soaked drsesing to maintain sterility during islet processing. During this time, patient temperature, electrolyte balances, and blood glucose levels should be closely monitored, and an insulin infusion started immediately after pancreatic resection to maintain serum glucose of 100 to 120 mg/dL. Multiple animal studies have demonstrated that hyperglycemia is detrimental to transplanted islet engraftment, and, therefore, euglycemia may be important for initial graft survival. Some centers prefer to close the abdomen after reconstruction of the gastrointestinal system, with planned percutaneous intraportal islet delivery.

Removal of the pancreas as a single specimen with intact pancreatic capsule allows for single duct infusion of collagenase and protease during the islet processing procedure (see later in the chapter) with more effective distention of the pancreas. Some centers prefer to remove the pancreas in two sections by first removing the distal pancreas and sending that portion to begin processing prior to removal of the head of the pancreas. The specific approach to pancreatic removal is dictated by the degree of pancreatic inflammation and fibrosis and any previous decompression or resection procedures. Studies have shown that between 10% and 20% of TP-IAT patients had previously had distal pancreatic surgery prior to TP-IAT. Regardless, the surgeon should adhere to the principle of decreasing warm ischemia by maintaining the vasculature until complete mobilization of the pancreas and immediate cold perfusion after removal.

BOX 2 Overview of TP-IAT Procedure

Total Pancreatectomy

1. Inspection and mobilization of the pancreas
2. Ligation of vasculature just prior to removal
3. Cold perfusion immediately after removal
4. Drain and gastrostomy/jejunostomy tube placement, if necessary
5. Close monitoring and control of blood sugars during islet isolation

Islet Isolation and Purification

1. Cannulation of pancreatic duct
2. Perfusion
3. Digestion
4. Purification
5. Quality assessment

Intraportal Islet Infusion

1. Catheter placement, splenic, umbilical, mesenteric, directly to portal vein
2. Systemic heparinization
3. Infusion of digested pancreatic islets
4. Portal circulation pressure monitoring; maintain below 20–25 mm Hg

Islet Isolation/Purification

The quality of islet preparation from the removed pancreas often determines whether the IAT will have the desired result of minimizing or eliminating the need for exogenous insulin after the TP. The key factors for success of the IAT are the underlying health of the pancreas, the optimization of islet preparation to minimize ischemic time and unnecessary handling, and the careful monitoring of the pancreas digestion to ensure maximal islet yield without significant enzymatic injury of the islets. With to the best-case scenario, the patient will not require exogenous insulin, often the goal is to provide the maximum number of recoverable islets to protect against life-threatening labile diabetes mellitus.

The processing of the pancreas begins in the operating room with removal of nonpancreatic tissue, including fat and the splenic vasculature that is often closely apposed to the pancreas. Depending on the comfort of the surgeon, the pancreatic duct may also be cannulated with a large bore angiocatheter prior to transport to a specialized islet processing facility (Fig. 1A, B). If any concern for local infection, once the pancreas has been cleared of nonpancreas tissue, it will be decontaminated using a solution containing povidone-iodine, Hank's buffered salt solution and cefazolin. An alternate broad spectrum antibiotic may be utilized depending on the patient's allergy history.

The decontaminated pancreas is then placed onto a perfusion tray in a tissue culture hood. Using an automated or manual perfusion system, the pancreas will be inflated with an enzyme mixture of collagenase and protease (Fig. 1C). Total perfusion takes approximately 10 minutes, with a goal of distending the pancreas while not

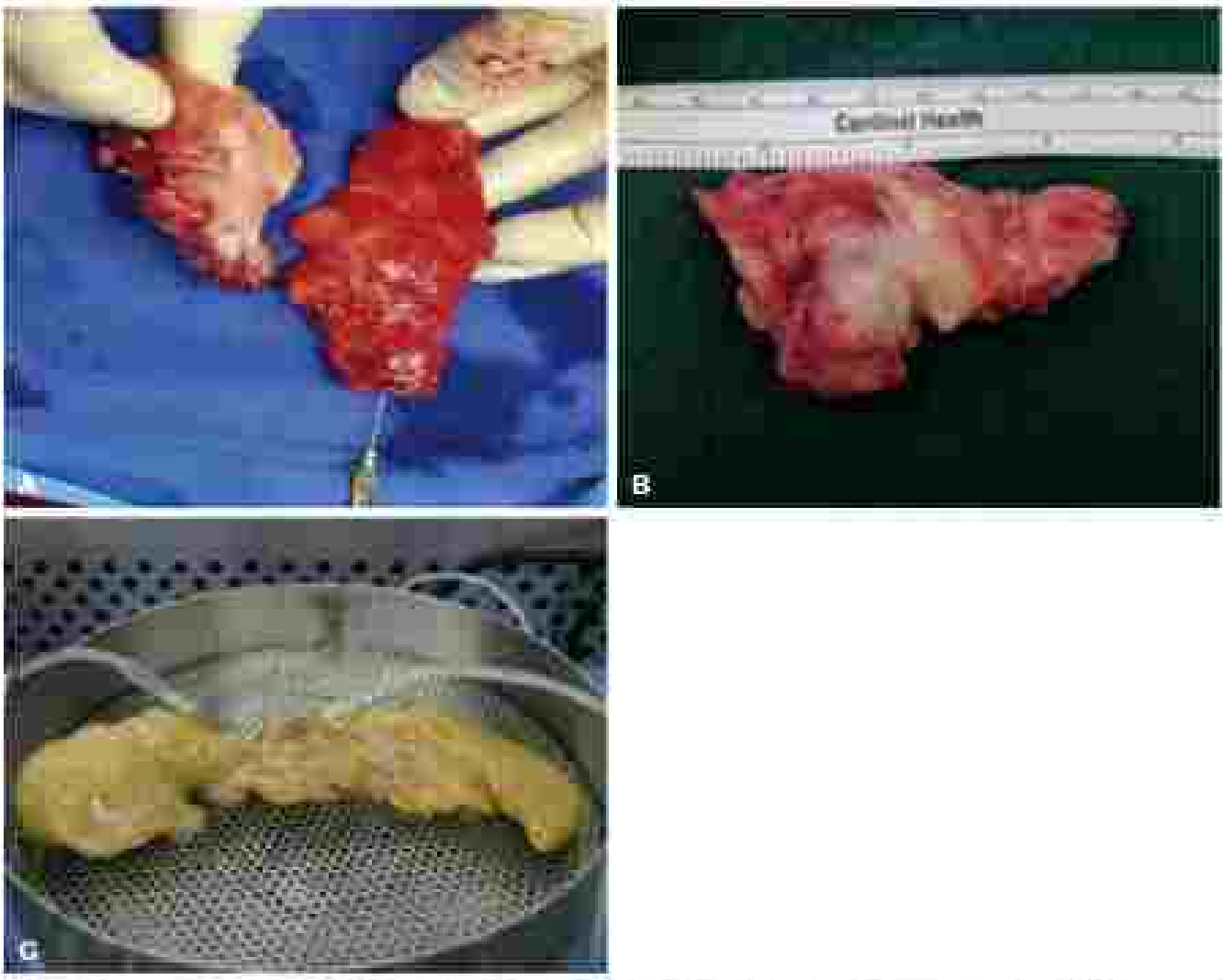

FIG. 1 (A) Whole pancreatectomy—chronic pancreatitis, severe fibrosis. (B) Partial pancreatectomy—post Whipple. (C) Representative gravitic perfusion unit from chronic pancreatitis sample.

causing rupture of the pancreas capsule. In the setting of a severely fibrotic pancreas, where it is not possible to cannulate or infuse the pancreatic duct, multiple injections of enzyme mixture into the interstitium may be the only alternative. Further modification for digestion of a severely fibrotic pancreas include increasing the volume of enzymes, lengthening the digestion, and pulsating enzymes. After perfusion, the pancreas is sectioned into 10 to 12 cubes and placed into a filtered digestion chamber (Fig. 2A–B). Tissue is digested in a 37°C enzyme solution with manual or mechanical agitation. Small samples are assessed every 2 to 5 minutes by microscopy to determine the degree of islet disaggregation, size of exocrine tissue (which can impact ability to deliver sample intraportally), and proportion of islets still imbedded in exocrine tissue. Once the sample is deemed sufficiently digested (Fig. 2C), the enzymatic reaction is stopped through cooling, dilution, and addition of high concentration albumin.

After digestion, the volume of pancreas tissue is measured to determine whether the amount could be safely infused into the portal system. It is generally accepted to target a volume of less than 20 mL for an average adult recipient. For pediatric patients, the University of Minnesota team has recommended 0.20 mL/kg. If the volume of pancreatic tissue greatly exceeds this amount, there are two options. (1) Traditionally, centers have infused as much tissue as feasible based on the capacity of the liver as measured by a rise in portal pressures. If portal pressures rise more than 15 to 20 mm Hg and fail to fall after halting the infusion and observation for 5 to 10 minutes, the infusion is aborted. Any remaining tissue can be injected into the peritoneal cavity or some have injected it into the wall of the stomach. (2) The alternative is to purify the preparation using techniques perfected and standardized in recent clinical trials. Although this adds a few hours to the procedure, we favor this approach. It reduces the risk of portal vein thrombosis by the reduction of tissue volume. Purification is achieved through continuous density gradient centrifugation. For IAT, the goal for purification is to maximize the number of islets while decreasing the exocrine tissue to achieve a safe volume. Because the diseased pancreas often has greatly reduced islet recovery from the digested tissue, it is important to preserve as many as possible. Given that the purification will decrease the yield of islets, the goal of purification is to reduce the volume to an acceptable level while maximizing the maximum number of islets.

Finally, the purified islets are counted, and the yield is expressed as islet equivalents (IEQ). The islet preparation is tested for overall quality using fluorescein diacetate (FDA) and propidium iodide to assess islet cell viability (Fig. 2D). Additionally, endotoxin, Gram stain, and bacterial cultures are performed. The culture data will not be available until post-transplant and can be utilized to guide antibiotic therapy, if necessary. The prepared islets are resuspended in approximately 250 mL of buffered solution, placed in an infusion bag (Fig. 3A) and stored at room temperature to be transplanted within 4 hours.

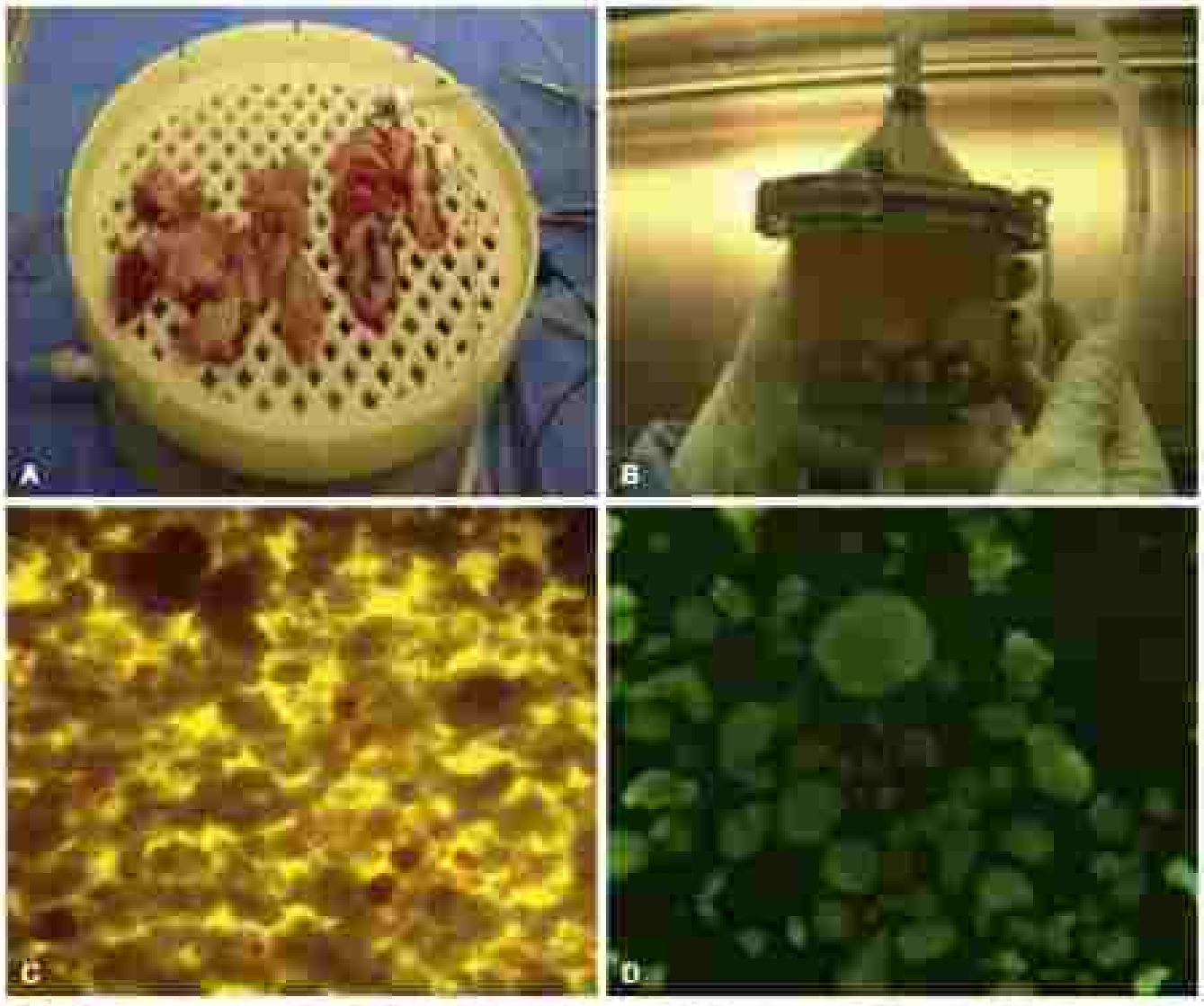

FIG. 2 (A) Traditional pancreas preparation. (B) Closed digestion chamber with partially digested pancreas. (C) Microscopic analysis of pancreatic digestate material. Individual islets exist and with dispersion. Necrotizing tissue is secretive pancreas material. (D) Quality control of isolated islets. Fluorescein diacetate viability assay shows living islets fluorescing green.

Islet Infusion

Islet infusion is carried out through intraportal delivery of the digested and purified islet preparation. It carries the risk of increasing portal hypertension and potential portal vein thrombosis. Studies in animal models have demonstrated alternative sites may be a viable option in the future, but no human clinical studies have demonstrated an alternative site that results in efficient islet survival and restoration of glycemic control.

In the setting of TP, access to the portal circulation for islet delivery is often easily achieved through the splenic vein, umbilical vein, or by directly accessing the portal vein. Alternatively, a catheter may be placed into a mesenteric vessel (Fig. 3B) or access achieved through a fluoroscopically aided percutaneous approach, which is typically utilized by centers that clear the abdomen prior to islet infusion.

The absolute volume of pancreatic tissue that can be delivered via intraportal infusion is highly dependent on the size of the liver and the degree of steatosis. For an average sized healthy liver, up to 20 mL of pancreatic tissue can often be safely tolerated. However, because of the challenges of making an accurate estimate, it is important to transduce intraportal pressure throughout the infusion. A three-way stopcock is attached to the infusion line and connected via transducer tubing to a pressure monitor, which allows for pausing of the islet infusion and assessment of intraportal pressure every 2 to 5 minutes (Fig. 3B). Multiple studies have demonstrated that islets can be safely infused when the intraportal pressure is maintained below 20 to 25 mm Hg. When the intraportal pressure is noted to rise above 20 mm Hg, the infusion is held and the pressure continuously monitored. Often, after a short pause, the infusion can resume once a decrease of portal pressure is noted. Systemic heparinization is started immediately prior to islet infusion and continued postoperatively to decrease the risk of portal vein thrombosis. We often give additional heparin boluses if the portal pressure rises above 20 and is slow to fall.

Once portal pressure has risen above ≥5 mm Hg and does not decrease with resting, additional intraportal infusion must be abandoned. Remaining islet preparation should not be discarded and should be placed in an alternative site. Most centers prefer to place the remaining islet preparation into the gastric submucosa or omentum pouch. No definitive evidence has demonstrated a benefit from placement of islets in an alternative site, but theoretically, even a small amount of islet survival may be beneficial.

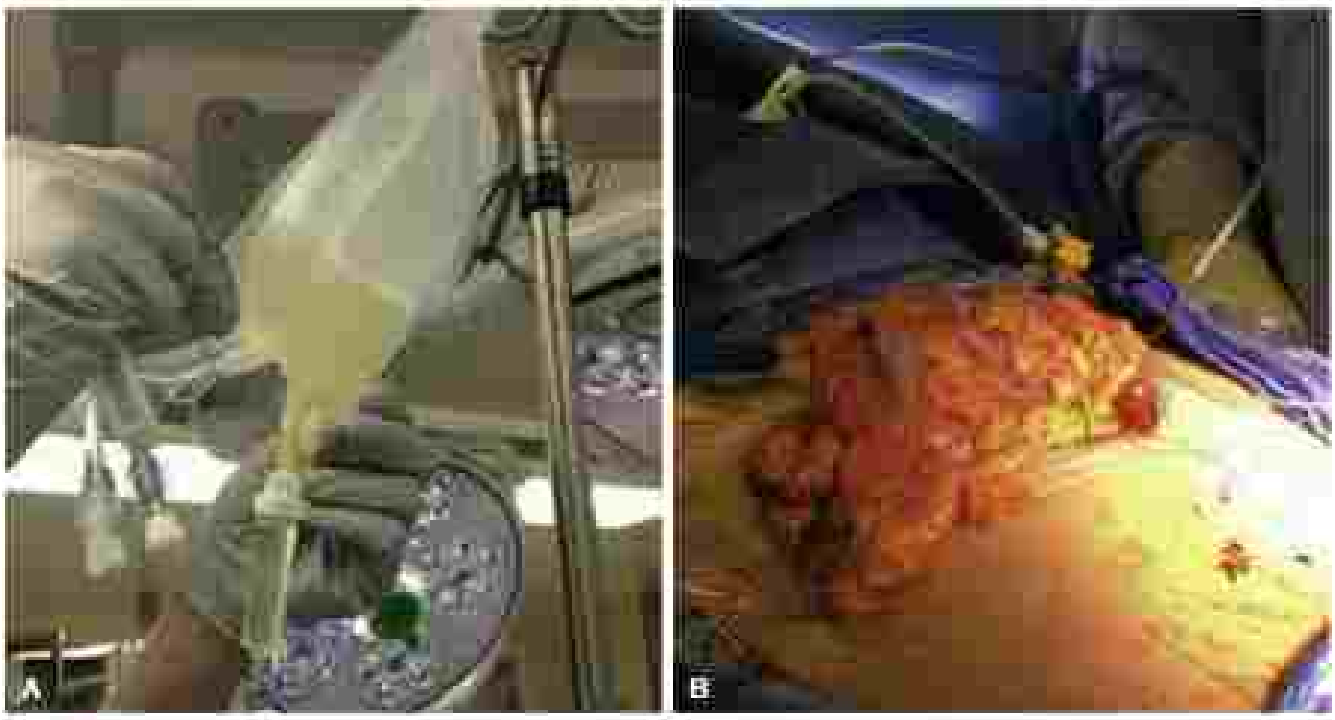

FIG. 3 (A) Ollier axes for infusion. (B) Infusion of line through micrometer site. Three-way stopcock to allow for pressure monitoring.

POSTOPERATIVE MANAGEMENT

In addition to standard postpancreatectomy care, TP IAT patients require very tight glycemic control. The transplanted islets are avascular and rely on diffusion of oxygen and nutrients during the immediate postoperative period. Maintenance of tight glucose control via insulin infusion decreases metabolic activity of the islets and prevents undue stress and apoptosis. Typically, an insulin infusion is utilized to maintain blood sugars at or below 120 mg/dL. Patients are routinely kept on insulin therapy for up to 3 months to decrease the metabolic burden on the transplanted islets and allow for proper engraftment and revascularization. After this period of time, insulin will be weaned to assess for the islets' ability to control blood glucose.

Pain management postoperatively can be challenging given the high likelihood of opiate tolerance secondary to long-standing chronic pain. For this reason, it is recommended to utilize available pain specialists and set up a multimodal pain management plan using ketamine, gabapentin, NSAIDs, lidocaine, benzodiazepines and epidural or paravertebral catheters as necessary.

Early enteral nutrition is important for aiding in wound healing. If enteral tube feeding access is in place, elemental tube feeds should be started at a low rate on postoperative day 1. Tube feeds will be continued until oral nutrition has been well tolerated. Delayed gastric emptying and gastroparesis are common postoperative complications and can be addressed by gastrostomy tube venting. If put in place, gastrostomy and jejunostomy tubes are typically kept in place for 4 weeks. Depending on clinical progress, clear liquid diet is often delayed until approximately postoperative day 10.

Most centers utilize standard perioperative antibiotics, regardless of the results of bacterial culture sent during islet isolation. These culture results, however, are used to guide antibiotic choice if the patient shows evidence of active infection.

Systemic heparinization is continued postoperatively to prevent portal vein thrombosis and liver function tests are monitored daily. Anticoagulation is often continued until postoperative day 30 using enoxaparin on discharge.

Length of stay is approximately 5 to 8 days. Prior to discharge, patient pain management and nutrition must be clearly established and an appropriate insulin regimen in place.

OUTCOMES

The 40 years of experience with TP and islet autotransplantation has established this procedure as a definitive treatment for medically refractory CP, for which other endoscopic or more limited operative management have been ineffective or deemed unsuitable. Studies looking at both pain control as well as endocrine function have established TP IAT as providing highly effective pain management with improved control of blood glucose levels and protection from life-threatening brittle diabetes found in TP alone patients.

TP has long been documented as an effective treatment to control the pain associated with CP, with historical data going back over 50 years showing significant pain relief in greater than 70% of patients. The largest single center outcome study for TP IAT is from the University of Minnesota, with outcomes for over 13 years of postoperative monitoring and includes more than 500 patients in their report. They have demonstrated pain improvement in 85% to 92% of patients, and roughly 40% being narcotic free at 2 years post TP. Importantly, nearly all individuals that had a complete pancreatectomy after a previous Whipple operation reported improvement in pain scores. Furthermore, based on the 36-item Short Form Health Survey, 94% report an improvement in their quality of life, with the highest percentage of improvement among individuals who achieved pain control and insulin independence. Follow-up surveys demonstrated that additional quality of life improvement happened during the second year post-operatively. A large study from the University of Cincinnati has shown 58% of patients with minimal change CP, who underwent TP IAT, achieved narcotic independence. The Cincinnati team has also demonstrated improvements in quality of life at 5 and 10 years of follow up. Other work from centers in Leicester and Alabama has had similar results, with typically 50% to 80% of patients becoming opiate independent. Unfortunately, data show that 10% to 30% of patients will see little to no improvement in pain or quality of life. Overall success of weaning off opiates is likely dependent on several poorly understood factors, but high pre-operative opiate use is associated with persistent postoperative narcotic requirement. Persistent pain has also been associated with pancreas divisum, previous Whipple, more than three previous stents, and body mass index greater than 30.

Patients with TP alone are at high risk for severe, life-threatening type 3c pancreatogenic diabetes with studies showing that up to 77% of TP alone patients experience severe problems with diabetes control. Furthermore, the lack of both insulin producing β cells and glucagon producing α cells greatly disrupts glucose homeostasis and can result in unpredictable responses to exogenous insulin and dangerous hypoglycemic emergencies. The use of IAT has dramatically decreased the rates of diabetes and hypoglycemia unawareness in pancreatectomy patients. Based on large scale studies, approximately 10% to 40% of individuals will achieve insulin independence, with the largest single center study showing approximately 30% of patients independent, 39% with partial islet function, and 27% requiring regular insulin therapy at 3 years post IAT. Importantly, while there is some initial decrease in islet function over the first 3 years, the University of Minnesota reports that among patients for whom they have 10 year follow up, a third remain insulin independent. The longest insulin independence post IAT has been reported to be more than 18 years. Based on C-peptide production, some degree of islet function is found in approximately 90% of TP IAT patients and the vast majority maintain a HbA1C below 7.0%. The success rate correlates very closely with the number of islets transplanted. With more than 5000 IEQ/kg, insulin independence rates are as high as 75% at 3 years, while only 12.5% of patients achieve insulin independence if less than 2500 IEQ/kg are transplanted. The cause of decreased islet isolation is linked to the degree of pancreatic damage from inflammation and fibrosis, and whether there has been any previous resection.

Overall complication rates for TP IAT have been reported in approximately 50%, with mortality rates of 1.4% to 6%. Most common complications reported in major series include pneumonia (18%), delayed gastric emptying (9%), deep venous thrombosis (9%), wound infection (9%), pulmonary embolism (7%), urinary tract infection (7%). The Minnesota series reports a 15.9% rate of reoperation in the immediate postoperative setting, most commonly for bleeding (9.5%). This rate of reoperation for bleeding is significantly higher in patients who had a final portal pressure of more than 25 cm water (18.4 mm Hg), which suggests that the bleeding complication is related to systemic hypertension and/or increased pressure in the portal system. Long term survival for TP IAT has been documented at 90% at 5 years and 62% at 20 years.

The use of TP IAT has been expanded to treat select pediatric patients with chronic pancreatitis, most with genetic risk factors. TP IAT in pediatric patients has achieved narcotic independence in 90%, which was stable for at least 10 years. Insulin independence was achieved in 41.3% of patients. Younger patients (<8 years) had significantly higher rates of insulin independence at 82%, and 100% of these patients became narcotic independent. In these young children, hospitalizations decrease from an average of 5 per year preoperatively to 0.35 per year postoperatively. Mean follow up to this young cohort is only 2.2 years, so longer follow up will be needed to establish the overall success of this procedure in very young children.

Due to the demanding requirements of establishing an islet isolation lab adherent to good manufacturing practice standards, efforts at some institutions have been made to utilize remote islet processing centers for the isolation. Multiple small single-center studies have demonstrated that TP IAT using a remote processing site can be comparable to local processing in achieving insulin independence, with results varying between 33% and 88%.

SUMMARY AND FUTURE DIRECTIONS

Total pancreatic resection with islet autotransplantation has been established as an effective treatment for pain associated with chronic pancreatitis and able to abrogate the severe glucose intolerance that results from TP alone. In patients who have failed to achieve relief from less invasive measures, TP-IAT may provide the only option for long term pain control. Numerous studies have demonstrated that it leads to overall improvement in quality of life for the patients and abrogates the potential risks from labile diabetes. The procedure is now widely accepted as a standard of care for appropriate patients and most insurance companies cover this treatment. However, because of the complexity of the operation and the requirement for a highly specialized processing facility and expert processing team, it is not universally available, and significant work needs to be undertaken to ensure that it is available to more individuals.

A recent workshop led by the National Institute of Diabetes and Digestive and Kidney Diseases identified several research and policy areas to be addressed, including standardization of patient selection, national registry to monitor outcomes, need to better understand the disease process of CP, and optimal timing for operative care. Furthermore, enhancement of intrahepatic islet survival and alternative engraftment sites are key areas of active research.

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Total Pancreatectomy With Islet Autotransplantation

Nadeged T. Fachiche, MD, Christi Walsh, BS, MSN, Vikash K. Singh, MD, MSc, and Martin A. Makary, MD, MPH

Chronic pancreatitis (CP) is a challenging clinical syndrome that may present with minimal symptoms or with severe debilitating pain, endocrine and exocrine insufficiency, and radiographic findings at presentation that may not correlate with symptoms. In addition, the diagnosis can be clouded by other conditions that can mimic CP, including functional gastrointestinal disorders, emotional dysmotility, and opioid use disorder. This chapter will briefly review the etiologies and management of CP, with a focus on total pancreatectomy with islet autotransplantation (TPIAT) as a therapeutic modality for select patients. Given that the procedure commits patients to eventual insulin dependence and indefinite pancreatic exocrine supplementation, patient selection for TPIAT versus other hybrid procedures should be exercised very judiciously.

CHRONIC PANCREATITIS

CP encompasses a group of etiologically distinct fibro-inflammatory processes that result in irreversible pathological and structural damage to the pancreas. Progressively diffuse parenchymal and pancreatic fibrosis combined with ductal strictures ultimately lead to decreased endocrine and exocrine function; however, severe debilitating abdominal pain is the most common clinical presentation and indication for therapeutic intervention.

EPIDEMIOLOGY AND RISK FACTORS

The incidence of CP in the United States is about 4 per 100,000 persons per year and has been reported to be as high as 200 per 100,000 in parts of Asia and Europe. Males are twice as likely to be diagnosed. CP is a clinical syndrome with multifactorial etiology. Classification systems such as the toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and severe acute pancreatitis, obstructive, provide a method of organizing the most common risk factors (Fig. 1). However, this classification scheme has limitations (e.g., acute recurrent pancreatitis is a common pathway to CP in multiple etiologies) and is undergoing revision to focus on the pathophysiology of CP from the early to later stages of disease.

Chronic alcoholic pancreatitis features progressive parenchymal and interlobular fibrosis as well as ductal dilation and intraductal calculi believed to result from recurrent insults caused by direct toxicity from alcohol metabolites and associated increased oxidative stress.

Chronic obstructive CP results from either extrinsic or intrinsic ductal obstruction by calculi, cysts, or strictures. Postobstructive ductal dilation and uneven parenchymal fibrosis are often noted.

Genetic alterations have been identified as an etiology in up to 30% of patients with idiopathic CP. Hereditary CP is caused by a gain of function mutation of the cationic trypsinogen gene (*PRSS1*). Affected patients present with CP within the first 2 decades of life have an accelerated disease progression, and a 22% increased risk of developing pancreatic cancer by the age of 70 years, although developing pancreatic cancer before age 50 is rare with this mutation. Autosomal recessive mutation of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene responsible for cystic fibrosis is the most common cause of CP in children. Impaired cellular transport of chloride in epithelial cells leads to overconcentration of physiologic secretions and subsequent inflammation in organs such the lungs and pancreas. Recent studies have linked minor mutations in the *CFTR* genes with idiopathic chronic pancreatitis. Genetic alteration of the *SPINK1* gene coding for a potent antitrypsin serine protease acts synergistically with other risk factors leading to earlier onset and increased severity of CP.

Acute recurrent pancreatitis (ARP) features recurring episodes of self-limiting acute pancreatitis as defined by the presence of two of the following: epigastric pain radiating to the back, lipase or amylase level three times the normal levels, and radiographic findings suggestive of pancreatitis. ARP can cause a substantial decrease in the quality of life even in the absence of CP. ARP progresses to CP in 8% to 15% of cases and is highest in subjects with a history of alcohol use and idiopathic etiologies. In two-thirds of patients, the etiology of ARP can be identified. Alcohol abuse and genetic alteration of the *PRSS1*, *SPINK1*, and *CFTR* genes have all been implicated in the pathogenesis of ARP.

Idiopathic CP, for which no clear etiology can be ascertained, affects 10% to 30% of patients.

PATHOPHYSIOLOGY

Regardless of etiology, all the subtypes of CP share a common final pathway characterized by diffuse and near complete destruction of

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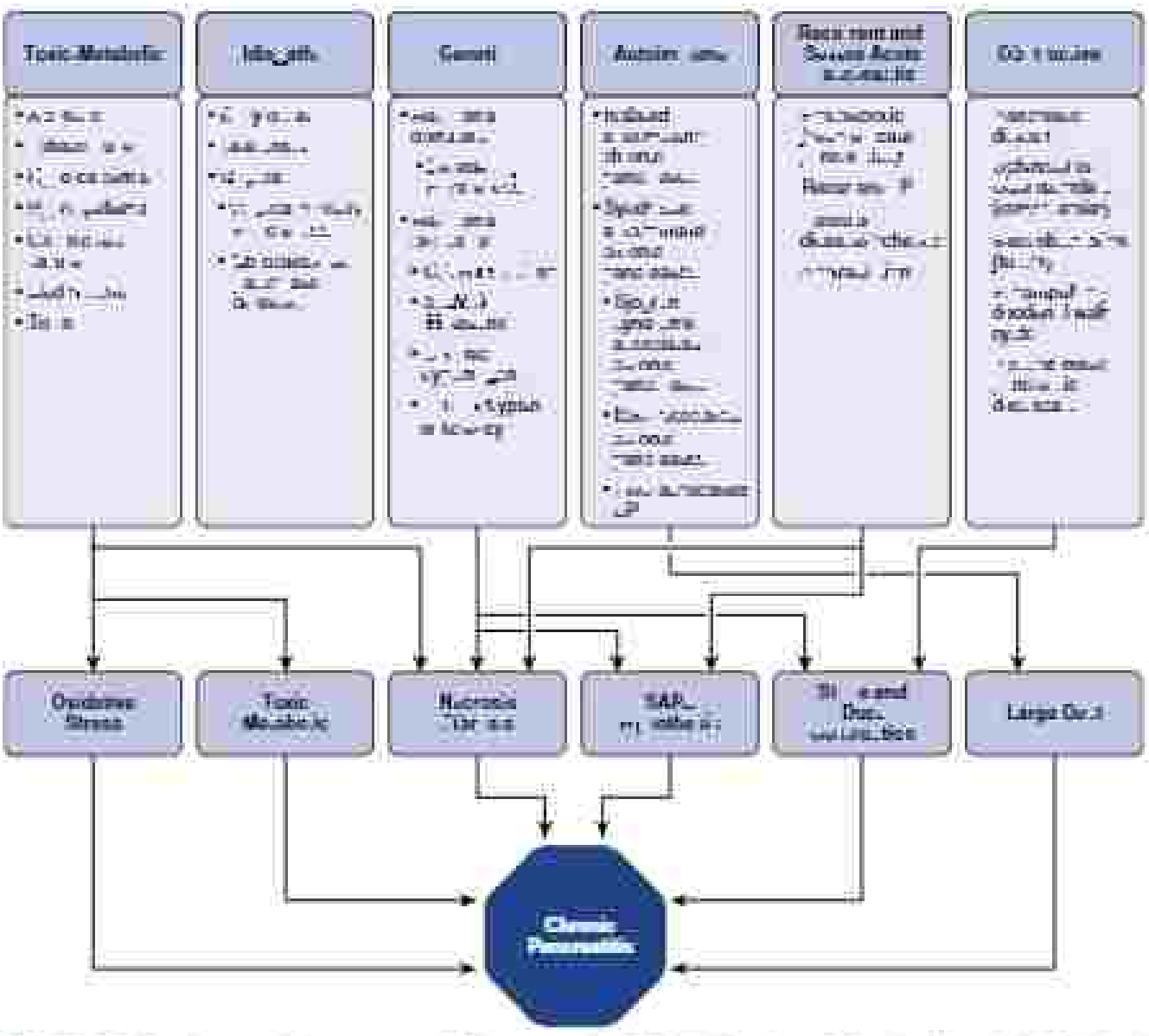

FIG. 1 TIGAR-O classification system. AP, acute pancreatitis; CP, chronic pancreatitis; IBD, irritable bowel disease; PBC, primary biliary cirrhosis; SAP, recurrent acute pancreatitis event.

acinar and islet cells. Acinar destruction leads to exocrine insufficiency because the decreased secretion of fat-digesting enzymes causes steatorrhea and fat soluble vitamin deficiency. Similarly, endocrine dysfunction and resulting diabetes mellitus set in with the destruction of 90% of islet cells. The mechanisms of pain in CP are not fully elucidated. New evidence challenges the long held dogma ascribing pain to increased intraductal pressure and resulting parenchymal ischemia. Recent studies suggest that chronic pain in CP is the result of a complex interplay between peripheral sensitization resulting from activation of pancreatic nociceptors by proinflammatory mediators, pancreatic neuropathy caused by peripheral inflammation of intrapancreatic nerves, and alterations in the central pain mechanisms leading pancreatic hyperalgesia.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with CP present with severe epigastric pain as the main symptom in 70% to 90% of cases. The pain is often associated with episodes of acute pancreatitis, which may become more and more frequent over several years. Over time, pain may also progress to be chronic and occur between episodes. Although some patients have recurrent acute pancreatitis that progresses to CP, others may have a slowly developing form of the disease that was previously known as late-onset idiopathic CP. These patients may have pathogenic mutations not involving trypsin pathways of disease, for example, the unfolded protein response. A clear lipase elevation associated with each episode of acute pancreatitis is a prerequisite for making the diagnosis, although over time, increasing pancreatic fibrosis results in less amylase and lipase secretion from the pancreas. Lipase is the test of choice for acute chemical pancreatitis but is less reliable for the diagnosis of CP. Amylase testing is redundant and a wasteful addition to a lipase value.

Patients often describe the pain as severe, postprandial epigastric pain radiating to the back, which is relieved by leaning forward or sitting upright. In about 20% of patients, however, CP can be painless. Steatorrhea, insulin deficiency, and malnutrition are additional symptoms, mostly seen in advanced disease.

A thorough history and physical examination combined with imaging studies such as abdominal ultrasonography, computed

tomography scan, and magnetic resonance cholangiopancreatography are typically sufficient to establish both diagnosis and etiology. Imaging features of CP include parenchymal atrophy, ductal dilation, and calcifications. Laboratory evaluation of pancreatic function is adjunctive. Tests measuring the levels of trypsin and fecal elastases may shed light on the patient's baseline pancreatic insufficiency.

The psychosocial issues of patients with chronic pancreatitis are important. As with inflammatory bowel disease, which may affect a patient's mental health, patients with CP are often falsely accused of having a history of alcoholism. We find that CP from alcohol abuse is a small minority of patients that present with chronic pain, and we do not offer these patients a TPIAT based on the experience from the University of Alabama Birmingham, which shows that this subgroup had the poorest outcomes following the procedure. These patients occasionally are candidates for a hybrid Frey procedure.

MANAGEMENT

For most patients with CP, therapeutic interventions are at relieving intractable abdominal pain and palliating exocrine and endocrine insufficiency. Medical and endoscopic interventions for the treatment of chronic pain can sometimes be successful in patients with minimal to moderate disease. Historically the tenets of surgery for chronic pain in CP relied on a simplistic assessment of the etiology of pain and the location of the disease. A Whipple procedure can be ideal for disease localized or dominant in the pancreatic head and a distal pancreatectomy can be ideal for disease localized in the tail. A hybrid procedure such as a duodenal preserving pancreatic head resection (Frey, Beger, and Berne) is our procedure of choice for patients with large duct disease or symptoms resulting from obstructing stones. We limit a lateral pancreaticojejunostomy (Puestow) to patients with ductal obstruction resulting from a pancreatic duct stricture because symptoms can sometimes be due to pressure caused by obstructed pancreatic ducts. We rarely perform a Puestow procedure because the Frey procedure has been shown in large studies to have superior outcomes, most likely because it more completely opens the gland's ductal system. The Puestow and other hybrid procedures can also be performed as a fallback procedure if an operation appears too high risk at the time of surgery.

Of note, a Frey or TPIAT procedure is contraindicated in any patients with a pancreas mass concerning for cancer, and generally we proceed straight to a TPIAT procedure in patients with a PRSS1 gene mutation (hereditary pancreatitis) as well as other pathogenic mutations. Given that benign masses such as chronic pseudocysts are common in patients with chronic pancreatitis, an intraoperative biopsy may be warranted during a Frey procedure. As a minimum, we send the excavated pancreatic head from a Frey procedure for a rapid frozen pathology analysis to rule out cancer given the increased risk of cancer in patients with CP.

A Whipple procedure may not exclude the option of a future TPIAT because pancreatic islets are more concentrated in the tail.

TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION

Total pancreatectomy as a definitive cure for CP is typically decision of last resort, reserved for patients in whom CP has been refractory to all other interventions, and in whom quality of life and the ability to lead a productive life is profoundly compromised because of pain and recurrent acute pancreatitis. Historically, the high morbidity of the procedure, which invariably guaranteed lifelong insulin dependence from surgically induced diabetes mellitus, and pancreatic exocrine replacement therapy for exocrine insufficiency, was a deterrent for both surgeons and patients. Combining total pancreatectomy with islet cells transplantation offered hopes of thwarting the postoperative development of diabetes mellitus. Since the first autologous islet cell transplantation by Sutherland et al. in 1977, TPIAT has gained wider acceptance owing to continued surgical innovation and improved outcomes over the past 4 decades.

Indications

Recently published selection criteria by our institution sought to minimize the effect of the low sensitivity and specificity of diagnostic tools such as endoscopic ultrasound, static magnetic resonance cholangiopancreatography, and endoscopic pancreatic function testing. Our recommendations are summarized in Table 1. TPIAT should be considered for carefully selected patients in whom chronic debilitating pain is unrelated despite maximal medical, endoscopic, and surgical interventions, and who meet the following criteria:

1. CP with chronic abdominal pain and one of the following:
   a. Calcification on imaging
   b. Moderate to severe ductal changes based on the Cambridge criteria
   c. ARP
   d. Pathology confirmed CP at prior surgery
2. Confirmed diagnosis of ARP with impaired quality of life
3. Confirmed hereditary or genetic CP with items 1 or 2

Patient Selection

Careful patient section is essential for successful outcomes after TPIAT. Poorer outcomes have been reported in patients with active alcohol or illicit substance abuse, poorly controlled psychiatric illnesses, chronic abdominal pain exceeding 5 years in duration, and inadequate support systems. Also, many patients with CP may also have undiagnosed or undertreated opioid use disorder, which could cloud the decision-making process. For these reasons, TPIAT is contraindicated in these select patients.

It is imperative that every patient who chooses to have a TPIAT be fully prepared for lifelong severe insulin-dependent diabetes and pancreatic enzyme supplementation. Also, he or she should also be fully aware that these complications are a certainty with a variable time to onset, and that their chronic pain may not improve. Virtually all patients will develop diabetes after surgery with a variable time to onset, and the islet autotransplantation is intended to delay the onset. Islet cells rarely have long-term (10 plus years) adequate insulin-producing function where insulin injections are not required.

Patients without preoperative diabetes or those with minimal preoperative insulin requirement, ARP, and those with concurrent CFTR, PRSS1, or SPINK mutations are more likely to have better outcomes. At our institution, patients are selected based on a consensus decision to recommend TPIAT by attending physicians in a multidisciplinary pancreatitis clinic. Over the decades, our criteria have narrowed for TPIAT given a high complication rate. Using a multidisciplinary approach ensures a careful and exhaustive review of the patient's clinical and surgical history. We also require multiple clinic visits before surgery because having the procedure is a major decision for the patient. Baseline pain assessment using a visual analog pain scale (0–10), baseline exocrine and endocrine function, as well as overall health status, are considered.

Additionally, all patients undergo preoperative evaluations by their primary care and the anesthesiology service. Ultimately, we do not proceed with a TPIAT unless the patient meets our narrow clinical criteria and a patient is willing to trade severe morbid and enzyme dependence for a chance of pain improvement.

Technique

Since Dr. John Cameron first performed the TPIAT operation at Johns Hopkins in the late 1970s, advances in minimally invasive pancreatic tumor as well as in islet isolation and transplantation have lessened the technical challenges of TPIAT. At our institution, laparoscopic total pancreatectomy is now our procedure of choice for select patients and is associated with reduced postoperative pain and wound complications. Open TPIAT is reserved for cases in which a laparoscopic approach would be either unsafe or technically challenging. About 60% of TPIAT operations we perform are done laparoscopically. We have a rule of

conversion is open of about 10%, usually after a rapid inspection of the scar tissue with a laparoscope. Thirty percent are scheduled open, and we also use the robot for some cases depending on surgeon preference.

OPERATING ROOM SETUP

As previously reported, we use a dedicated operating room equipped with an islet isolation laboratory, which allows immediate processing of the resected pancreas within the operative room while gastroduodenectomy and hepatojejunostomy are performed. This step eliminates transfer time from outside facilities while minimizing cold ischemia time.

Laparoscopic Total Pancreatectomy

Crucial to islet yield and successful isolation is to preserve pancreatic perfusion for as long as possible before resection to minimize warm ischemia time. We achieve that objective by sequentially resecting the head and body and reserving the ligation of the vascular supply for last.

1. Following entry into the peritoneum using standard port placement, the lesser sac is accessed through the gastrocolic ligament.
2. The gastroduodenal artery is skeletonized and divided distally (Fig. 1).
3. The portal vein is dissected from above the pancreas, and the superior mesenteric vein is dissected from below.
4. A tunnel behind the pancreatic neck is created, and the stomach is divided just proximal to the pylorus using a laparoscopic stapling device with green or black loads.
5. A cholecystectomy is performed, and the common bile duct divided.
6. The neck of the pancreas is cautiously divided, avoiding injuries to the portal vein and the superior mesenteric vein. This step facilitates the division of the superior mesenteric artery margin, allows a staged removal for the back table team, and enables easy cannulation of the pancreatic duct for collagenase infusion into the duct.
7. Next, we perform a Kocher maneuver to free the ligament of Treitz from the right side, marching distally on the duodenum. After approximately 20 cm of jejunum are delivered to the right side of the ligament of Treitz, the jejunum is divided with a laparoscopic stapling device with a white load (2.5 mm).
8. The small bowel mesentery is then divided in the proximal direction to the uncinate and along the superior mesenteric artery margin until the head of the pancreas is free. It is then extracted through the umbilicus by extending the 12 mm port slightly.
9. The specimen is passed to the laboratory team to isolate the gastroduodenal artery with cellugenase and to clean off the pancreas head.
10. Next, the body and tail of the pancreas are mobilized along with the spleen. The splenic vessels are divided, beginning when possible with the splenic artery followed by the splenic vein. Following extraction, in a similar fashion to the head, the body and tail are perfused, chunked, and dissected into small pieces before processing by the islet laboratory personnel.
11. Next, hepatojejunostomy reconstruction is done using a novel technique pioneered by our team and previously reported, in which the anastomosis is done with a single layer of 4-0 barbed suture anteriorly with interrupted barbed sutures and suture clips.
12. The gastrojejunostomy is then performed in an antecolic retrogastric manner along the posterior wall of the stomach in a stapled side-to-side technique with a laparoscopic stapler.
13. To reduce bile acid reflux, a Braun's jejunojejunostomy is sometimes added to the procedure.

Intraoperative Laboratory Isolation of Pancreatic Islets

For pancreas digestion and autologous islet isolation, we use a modified version of the Ricordi protocol. On the back table in the operating room, the resected specimen is flushed through the gastroduodenal artery and the tail through the splenic arteries with cold University of Wisconsin solution. The pancreatic duct is cannulated and distended with a pressurized mixture of collagenase and thermolysin. The pancreas is then sectioned into 1- to 2 cm^3 pieces, placed in a 600 mL digestion chamber and transferred to a Ricordi islet isolator. Following digestion, the mixture of islets and acinar tissue is collected, washed, and resuspended in 5% human serum albumin supplemented with 70 U/kg of heparin. Final islet counts can be determined using an automated islet counter or a standard manual counting method.

Autologous Islet Infusion

Once the islet solution is ready for autotransplantation into the liver, a metal, hollow-bore, 16-gauge needle with intravenous tubing attached is placed through a 12 mm port site. From within the peritoneal cavity, laparoscopic instruments are used to place the needle into the portal vein (Fig. 3). Once the infusion is completed, the needle is subsequently removed, and direct pressure is applied to the puncture site of the vein to achieve hemostasis. During infusion, the portal vein

FIG. 2 Division of the pancreas along the portal vein and superior mesenteric artery. Gastroduodenal artery is clipped with the white clips at the top of the image.

FIG. 3 Laparoscopic islet autotransplantation infusion into the portal vein.

pressure is continuously monitored using a Transonic vascular flow probe with the aim of keeping it below 15 to 20 mm Hg. Of note, for all advanced laparoscopic pancreas procedures, a 9in. 10 blade scalpel and Mayo scissors are always kept on the Mayo stand in case a rapid conversion to an open procedure is necessary.

Postoperative Care and Follow-up

Postoperatively, patients are admitted to a surgical intensive care unit for monitoring and administered intravenous insulin infusion and dextrose containing intravenous fluids for tight glucose control. After a successful transition to subcutaneous insulin injections, patients are discharged when deemed stable. Unless contraindicated, patients are kept on insulin regimens in an attempt to rest the newly transplanted islets. Insulin requirements following are assessed during each postoperative visit.

TPIAT has one of the highest intrinsic complication rates of any elective operation. Readmission rates can be as high as 50%, and some of the complication management is related to opioid use disorder that may be undiagnosed before surgery.

Complications

Acute endocrine insufficiency is ubiquitous immediately following surgery and is managed with insulin drips and glycemic control measures.

Delayed gastric emptying is very common and affects up to one-half of the patients after TPIAT and could be a rule preoperative dysmotility from chronic opioid use; for most patients, prokinetics and probiotics are an effective therapy.

Portal venous thrombosis/thrombus and resulting portal hypertension are less frequent with the advent of PVP monitoring intraoperatively.

OUTCOMES

Chronic Pain

Four decades of data have demonstrated that TPIAT has been effective in relieving preoperative pain and improving quality of life in the majority of the carefully selected patient. A recent cohort study of 61 patients having undergone TPIAT from 2011 to 2015 conducted at our institution revealed that 89% of patients experienced resolution of their preoperative pain. Interestingly, 83% developed new characteristic abdominal pain and discussed opioid use was noted in only 66% of patients, underscoring the complexity of managing chronic abdominal pain. Furthermore, ARP (odds ratio, 11.66; 95% confidence interval, 1.47 to 92.36; $P = .02$) was independently associated with resolution of preoperative abdominal pain on multiple logistic regression.

Endocrine Insufficiency

The advent of islet autotransplantation has significantly reduced the morbidity of total pancreatectomy. Most series report insulin independence in 25% to 40% of patients with a bigger portion of patients left with manageable insulin requirements. Recently published outcomes by our group reflect these findings. In a prospective cohort of 76 patients having undergone TPIAT, 29% were insulin independent at 1 year. However, all the patients with preoperative findings of impaired glucose metabolism remained dependent within the same period, underscoring the importance of comprehensive patient education preoperatively.

CONCLUSION

In carefully selected patients in whom CP is debilitating and has been refractory to medical interventions, TPIAT can be an effective option. We recommend a Frey hybrid procedure, which does not involve islet autotransplantation, when patients meet clinical criteria, such as large duct disease without a genetic mutation.

BOX 1 Indications and Contraindications for Total Pancreatectomy

Indications

1. Documented CP
2. Chronic abdominal pain with one of the following:
   - Calculi, multiple
   - Main duct >7 mm in diameter changes on CT, MRCP, or ERCP
   - Ductal __ stricture __ and CP on pathology or imaging
   - ...
3. ARP with impaired QOL
   - ... in the setting of acute pancreatitis with ... abnormal imaging and no evidence of a treatable etiology
4. Documented hereditary/genetic pancreatitis with other indications 1 or indication 2

Contraindications

5. Alcoholic/smoking etiology
6. Active substance addiction/abuse
7. Duration of pain <3 years
8. Opioid use >3 years unless patient can successfully wean off and initiate centrally acting drugs (e.g., gabapentinoids) before surgery
9. Poorly controlled psychiatric comorbidity
10. Medical noncompliance

ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; HGP, hereditary genetic pancreatitis; QOL, quality of life.

SUGGESTED READINGS

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SPLENECTOMY FOR HEMATOLOGIC DISORDERS

[illegible]

The spleen is a lymphoid organ that [illegible] and immune [illegible] allows [illegible] hematologic disorders [illegible] the main reasons for elective splenectomy. Hypersplenism (symptoms related to splenomegaly and decreased blood counts related to sequestration of blood elements) [illegible] is a common complication and is the most frequent splenic [illegible] splenomegaly [illegible] have normal pain, early satiety, [illegible] and abdominal distention. In addition, splenectomy should be considered for patients with true [illegible] splenomegaly [illegible] for hematologic conditions rarely leads to a cure of the underlying hematologic disorder, [illegible] may be beneficial for the resolution of hematologic abnormalities and improving symptoms [illegible] hematologic diseases that require splenectomy may be treated [illegible] limited to red blood cell [illegible], platelet, lymphoproliferative, and myeloproliferative disorders [illegible].

[illegible] PRIMARY IMMUNE HEMOLYTIC ANEMIA

[illegible] Hemolytic Anemia

Autoimmune hemolytic anemia [illegible] is secondary to antibodies directed against one or several components of the RBC surface. [illegible] should be suspected in patients with anemia, reticulocytosis, elevated lactate dehydrogenase, low haptoglobin, and indirect hyperbilirubinemia. According to the immunochemical characteristics, AIHA can be classified as warm [illegible] or cold [illegible] based on the results of direct agglutination test (DAT). If the DAT is positive for immunoglobulin G (IgG), IgM, or IgA and complement, and then the diagnosis is most precise by WAIH. Conversely, if the DAT is positive for complement and alone, then [illegible] is more likely the diagnosis. In WAIH, polyclonal IgG sometimes IgA autoantibodies, usually directed toward Rh antigens, form a light coat over RBCs that are removed by the spleen. The peak incidence of WAIH occurs between the ages of 20 and [illegible] but it can occur at any age. In children, the disease is often self-limited, occurring after a viral infection and resolving in 1 to 3 months. Initial treatment with corticosteroid therapy (prednisone, 1 mg/kg per day) usually results in improved hemoglobin levels within several days, and remission occurs in 80% of patients. Children generally respond better to steroid therapy than adults. The steroid dose is tapered gradually to the lowest dose needed to control hemolysis. More recently, this [illegible], a monoclonal antibody directed against the CD20 antigen on the surface of mature B lymphocytes, has replaced the other second line medications and it is often associated with a complete response in both the adults and children. Splenectomy should be reserved to older patients who are corticosteroid resistant, for corticosteroid dependent patients who require high doses of corticosteroids, for patients who fail to achieve remission within 3 weeks, or for those who cannot maintain acceptable hemoglobin levels. A response rate of 60% to 80% is usually seen within the first 2 weeks after surgery. Approximately 10% of patients will require postoperative low dose steroids [illegible] to maintain adequate hemoglobin concentrations. In Cold [illegible] monoclonal IgM autoantibodies are active at lower temperatures, usually between 0°C and 20°C, resulting in intravascular complement-mediated hemolysis. In these patients, RBCs are removed by the liver, rather than the spleen. Cold [illegible] makes up [illegible] to 25% of AIHA. This disorder is usually associated with infections, such as mycoplasma pneumonia or with lymphoproliferative disorders. Treatment consists of avoiding cold temperatures, which can prevent an acute hemolytic crisis. Corticosteroid therapy is ineffective and contraindicated because of the risk of infections. Alkylating agents such as chlorambucil and cyclophosphamide have been successfully used for treatment along with plasmapheresis. Splenectomy is also not indicated because of the intravascular location of the hemolysis. Currently, rituximab is the only treatment that has proven long-term response.

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is characterized by the presence of spherocytes on peripheral blood smear, hemolysis, anemia, and increased RBC clearance by the spleen. HS is the most common congenital anemia, prompting splenectomy with a prevalence of 1 in 5000 people in Europe and North America. The disorder is also common in Japanese and African populations. HS, also known as Minkowski-Chauffard disease, is an inherited disease resulting from a genetic mutation encoding red cell membrane components alpha I-spectrin (α-[illegible]), beta-spectrin (β-[illegible]), ankyrin (ANK-1), and band 3 anion transport protein (EPB3). However, some less common variants are inherited through an autosomal recessive pattern (protein 4.2). Membrane protein mutations lead to the destabilization of the lipid bilayer, with subsequent release of lipids from the membrane surface and consequent sphering of the RBCs. Spherocytes have decreased deformability, which impairs their passage through the splenic pulp and increases osmotic fragility; therefore, spherocytes are prematurely destroyed in the spleen. HS may manifest as a mild or severe form. In mild forms, patients may be asymptomatic or suffer only mild jaundice. Patients with more severe forms may present with anemia, jaundice, splenomegaly, and cholelithiasis. Peripheral blood smear demonstrates spherocytes and reticulocytes. Splenectomy is curative for the majority of patients with severe forms and is indicated in the presence of growth retardation, skeletal changes, symptomatic hemolytic disease, anemia induced organ dysfunction, leg ulcers, or development of extramedullary hematopoietic tumors.

BOX 1 Hematologic Disorders for Which Splenectomy May Be [illegible]

Red Cell Membrane and Hemolytic Disorders

[illegible]
Autoimmune hemolytic anemia

[illegible]
Hereditary spherocytosis
Hereditary elliptocytosis
Hereditary pyropoikilocytosis
Hereditary stomatocytosis
Hereditary xerocytosis

[illegible]
Thalassemia
Sickle cell anemia

[illegible]
Pyruvate kinase deficiency
Glucose-6-phosphate dehydrogenase deficiency

Platelet Disorders

Immune thrombocytopenia
Thrombotic thrombocytopenic purpura

Lymphoproliferative and Myeloproliferative Disorders

Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Hairy cell leukemia
Chronic lymphocytic leukemia
Chronic myelogenous leukemia
Primary myelofibrosis

Miscellaneous Disorders

Gaucher's disease
Amyloidosis
Sarcoidosis
Felty's syndrome

Preoperative abdominal ultrasonography should be performed for patients undergoing surgery, and cholecystectomy should be taken into account for patients with gallstones. Splenectomy is usually delayed until the age of 5 years to decrease the risk of overwhelming postsplenectomy infection (→ 794). There may be a role for partial splenectomy in younger children as some studies have shown clinical improvements with splenic function preservation.

Hereditary Elliptocytosis

Hereditary elliptocytosis (HE) is a rare disorder that results from mutation of the RBC membrane skeleton proteins spectrin, protein 4.1R, and glycophorin C. HE has a prevalence of 1 to 5 per 10,000 in the United States. Inheritance usually follows an autosomal dominant pattern, and the disorder is more common in people of African and Mediterranean descent. The true incidence is unknown because of the wide variety of clinical presentations. Most patients with the dominant inheritance are asymptomatic with a mild compensated anemia or no anemia at all. Affected cells are morphologically characterized by ovalocytes, elliptocytes, or rod-shaped cells. These cells are much more deformable than spherocytes, and patients have a less severe clinical course. In contrast, the rare autosomal recessive form can lead to severe hemolysis. Patients with mild HE, who are asymptomatic and without evidence of hemolysis, do not require treatment. Patients with chronic hemolysis may require blood transfusions and daily folic acid. Splenectomy is curative and indicated for patients with symptomatic anemia.

Hereditary Pyropoikilocytosis

Hereditary pyropoikilocytosis (HPP) is an autosomal recessive hemolytic anemia with microspherocytosis and thermal instability. HPP represents a subtype of HE, arising from the same molecular defects. Patients with HPP usually have a common HE mutation from one parent and a milder subclinical defect in spectrin from the other parent. The disease usually is seen as anemia and jaundice in newborns and infants. Splenectomy is curative and indicated for patients with severe anemia.

Hereditary stomatocytosis (Hydrocytosis) and Xerocytosis (Pseudohydrocytosis)

Hereditary stomatocytosis and xerocytosis are rare autosomal dominant hemolytic anemias characterized by a variable clinical course. In stomatocytosis, the underlying defect leads to increased erythrocyte permeability and volume. Stomatocytes have a mouth-shaped area with central pallor. In xerocytosis, there is a decrease in intracellular cation content and cell volume, and patients present with target cells and spherocytic cells on peripheral blood smear. For cases of severe hemolysis, splenectomy may improve symptoms but does not fully correct the hemolysis. In these patients, the role for splenectomy should be considered carefully because they can develop severe complications, such as hypercoagulability, leading to catastrophic thrombosis episodes, and chronic pulmonary hypertension. Fortunately, most patients have a mild clinical course and do not require surgical intervention.

Thalassemia

Thalassemia is an autosomal recessive genetic disease characterized by reduced production of alpha-globin protein for alpha-thalassemia and beta-globin protein for beta-thalassemia. The clinical manifestations associated with thalassemia arise from quantitatively imbalanced accumulation of globin subunits and inadequate hemoglobin production. The beta subtype is the most common form of thalassemia in the United States and occurs mainly in patients of Italian and Greek descent. Patients who have the heterozygous form of β-thalassemia (thalassemia minor) are usually asymptomatic with microcytosis and mild anemia. The homozygous form (thalassemia major or Cooley's anemia) is much more severe. Patients are usually asymptomatic until age 6 months because of the presence of fetal hemoglobin, they then develop severe hemolytic anemia, abdominal swelling, growth retardation, tetralogy, jaundice, pallor, splenomegaly, pigmented gallstones, and skeletal abnormalities. Laboratory values show a severe microcytic anemia with nucleated RBCs, acanthocytosis, and poikilocytosis. Patients may also have mild neutropenia and thrombocytopenia. Treatment requires monthly lifelong transfusions of RBCs, in association with iron chelators to avoid iron overload. Splenectomy is reserved for patients with increased blood transfusions in the setting of hypersplenism. Patients requiring more than 100 to 200 mL/kg/yr of RBCs are possible candidates for splenectomy. Usually, a 25% to 50% reduction in transfusion requirements is expected after splenectomy.

Sickle Cell Anemia

Dyspnocytosis (sickle cell anemia) is another autosomal recessive genetic disease resulting from an anomaly of the hemoglobin β chain that leads to the formation of hemoglobin S, which polymerizes under hypoxemic stress, inducing a characteristic sickle deformation in the shape of red cells. Sickle cells cause stasis and vascular occlusion, leading to tissue ischemia, severe pain, and chronic organ tissue damage. Exacerbations of symptoms are referred to as sickle cell crises. Management of this disease relies on general measures, such as hydration and transfusions, to prevent vaso-occlusive events and related complications. Patients who are homozygous for the disorder

have sickle cell disease, and many suffer autosplenectomy by an early age as a result of multiple infarcts. Therefore, splenectomy is rarely indicated but should be considered in the following situations: (1) after a major acute sequestration crisis, which is an absolute life-threatening emergency that requires transfusion; (2) hypersplenism, causing abdominal pain and increased transfusion requirements; and (3) splenic abscess, a rare but classic complication, enhanced by repeated infarctions. Acute splenic sequestration has high mortality, up to 15%, and is characterized by massive splenomegaly, acute exacerbation of anemia, and hypovolemia. This is primarily treated with restoration of blood volume and RBC mass, but recurrence is common. Splenectomy should be considered to prevent further episodes.

Pyruvate Kinase Deficiency

Pyruvate kinase deficiency (PKD) is the most common genetic defect causing congenital nonspherocytic hemolytic anemia. PKD is an autosomal recessive disease that occurs when a defect in the glycolytic pathway results in deficiency of adenosine triphosphate. RBCs are less deformable and often are destroyed in the spleen, leading to splenomegaly. Hemolysis can be exacerbated by acute infections and pregnancy. Patients with PKD have mild to severe anemia and splenomegaly. Clinically, these patients have mild symptoms resulting from the elevated levels of 2,3-DPG in RBCs, which result in a right shift of the hemoglobin–oxygen dissociation curve. This means that affected individuals have an increased capacity to release oxygen into tissues, enhancing oxygen delivery. Treatment is symptomatic, and splenectomy is only rarely indicated for patients with the severe hemolytic variants of PKD.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase deficiency is widespread (about 400 million people worldwide are carriers). X-linked genetic disease of the glutathione pathway, which leads to damage of RBCs by toxic oxygen products. It causes acute hemolytic accidents after oxidative stress (acute infections, certain medications, and fava beans), or, rarely, chronic hemolytic anemia. In adult patients, glucose-6-phosphate dehydrogenase deficiency does not usually require transfusion, except during severe hemolytic crises; management focuses on the avoidance of trigger food and medications. Splenectomy is not indicated, except in patients with severe hypersplenism, which requires transfusion dependency.

PLATELET DISORDERS

Immune Thrombocytopenia

Immune thrombocytopenia (ITP; formerly idiopathic/immune thrombocytopenic purpura) is an autoimmune disease caused by one or several antiplatelet antibodies directed against platelet glycoprotein complexes (GPIIb/IIIa, GPIb/IX). ITP leads to platelet destruction by the reticuloendothelial system in the spleen. In addition to humoral immunity, there is a component of cell-mediated immunity involved in this process. This condition is characterized by isolated thrombocytopenia with a platelet count that falls below 100,000/mm^3. Specific therapy is indicated when platelet count is less than 30,000/mm^3, but is also related to bleeding risk, presence of comorbidities, and risks of trauma.

Primary ITP is a diagnosis of exclusion as other illnesses, such as human immunodeficiency virus infection, systemic lupus erythematosus, antiphospholipid antibody syndrome, hepatitis C virus, and lymphoproliferative disorders, can cause secondary ITP. In addition, some medications and drugs may elicit similar immune-mediated platelet destruction (cocaine, antibiotics, antihypertensives, anti-inflammatories, heparin, quinidine, and abciximab). The prevalence of ITP in adults is about 5 per 100,000 people, occurring nearly twice as frequently in women. There is an approximately fourfold increase in prevalence in adults older than 65 years of age. Most patients with ITP are asymptomatic, whereas symptoms occur when platelet counts drop below 20,000/mm^3. Symptoms include bruising, purpura, petechiae, bleeding from the oral mucosa, epistaxis, menorrhagia, and gastrointestinal bleeding. Less than 1% of patients experience intracerebral hemorrhage, the most severe complication. The prevalence of ITP in children is approximately 12 per 100,000 in girls and 9 per 100,000 in boys. Children may present with a sudden onset of petechiae or purpura, usually days to weeks after an infectious disease. In the pediatric population, ITP is usually self-limited, with more than 70% remission within 6 months; the risk of intracerebral hemorrhage is less than 0.2%. Observation is a possible treatment option as long as the platelet count is greater than 20,000/mm^3. Conservative treatment is also reasonable in adults with platelet counts above 30,000/mm^3. However, patients who exhibit persistent thrombocytopenia or platelet counts below 30,000/mm^3 (20,000/mm^3 in children), should start corticosteroid therapy.

First-line treatment consisting of oral corticosteroids (typically prednisone) leads to complete remission in 10% to 30% of patients; high-dose corticosteroids (usually dexamethasone) leads to complete remission in 40% to 80% of patients. The standard initial dose is 1 to 2 mg/kg/d of prednisone for 2 to 4 weeks followed by a steroid taper. Several second-line therapy options are available including azathioprine, cyclosporine, cyclophosphamide, danazol, or dapsone, none of which has been shown to be superior to other therapies. More recently, new medications have been introduced. Rituximab, by its immunosuppressant effect, decreases the production of antiplatelet antibodies leading to a response in approximately 60% of patients and complete remission in about 40% of patients. Synthetic thrombopoietin receptor agonists have been recently developed. The two main medications used today, romiplostim and eltrombopag, lead to high rates of complete response, but relapses are frequent. Intravenous immunoglobulin (1 mg/kg/d for 1 to 2 days) can be considered for patients who would benefit from a rapid increase in platelet count (i.e., in the setting of bleeding or in preparation for an invasive procedure) or for those who are unable to tolerate steroids. Splenectomy has long been considered as the treatment of choice in the wake of corticosteroid failure because patients respond in 65% of cases with a durable 5-year response, without additional treatment in 60% of patients. Splenectomy is indicated for refractory thrombocytopenia, relapses requiring multiple cycles of therapy, or in patients who have experienced side effects of medical treatment. If perioperative platelet transfusion is needed, transfusion should be withheld until the splenic artery has been ligated. Several studies have reported that splenectomy can be safely performed, with minimal bleeding risk, even in patients with platelet count below 10,000/mm^3.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a severe form of thrombotic microangiopathy characterized by the association of mechanical hemolytic anemia, peripheral platelet consumption, and microthrombosis involving different organs. TTP is a disorder in which a deficiency of the ADAMTS13 protein leads to increased platelet aggregation and subsequent microvascular thrombosis. The interaction between von Willebrand factor (vWF) and platelets is usually controlled by the ADAMTS13 protein, which cleaves von Willebrand factor and prevents platelet aggregation. TTP may occur spontaneously but is often precipitated by different factors such as chemotherapeutic agents (gemcitabine, mitomycin C, or calcineurin inhibitors), quinine, cyclosporine, clopidogrel, ticlopidine, hematopoietic stem cell transplantation, or pregnancy. The annual incidence of TTP is 4 to 10 cases per million. TTP is characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, fever, neurologic complications, and renal failure. Patients have petechiae (most commonly on the lower extremities), fever, myalgia, and fatigue. Neurologic symptoms include headache, mental status changes, seizures, and even coma. Patients can develop congestive heart failure or

cardiac arrhythmias. TTP is suspected with unexplainable hemolytic anemia and thrombocytopenia in the setting of elevated lactate dehydrogenase and bilirubin, a negative Coombs test, and a peripheral blood smear demonstrating schistocytes, nucleated RBCs, and basophilic stippling. Initial therapy consists of daily plasma exchange. Plasmapheresis is carried out with a goal of exchanging 1.5 plasma volumes. Approximately 70% of patients will respond to this therapy. Platelet transfusions are generally not recommended because of the risk of severe clinical deterioration. Rituximab (anti-CD20 antibody) and glucocorticoids are second-line therapies. Until the 1970s, splenectomy was the only treatment modality for TTP. Now, splenectomy is reserved for refractory thrombocytopenia or relapses. When combined with high-dose steroid therapy, splenectomy has been shown to improve disease-free interval; however, the response rate is only 40%.

LYMPHOPROLIFERATIVE AND MYELOPROLIFERATIVE DISORDERS

Hodgkin's Lymphoma

Hodgkin's lymphoma is a malignant neoplasm of lymphoreticular cell origin that usually affects young adults in their second and third decades of life. Primary treatment consists of chemotherapy and/or radiation. Historically, splenectomy was performed as part of a staging laparotomy that included lymph node sampling and liver biopsy. Now, staging laparotomy has been replaced by imaging modalities such as computed tomography (CT) and positron emission tomography. Splenectomy may be beneficial for patients who develop splenomegaly and related thrombocytopenia.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma represents the most common primary neoplasm with splenic involvement occurring in 65% to 80% of cases. Splenectomy is indicated for symptoms related to massive splenomegaly and cytopenia resulting from splenic sequestration. Splenectomy may be helpful to assist with diagnosis and to determine appropriate therapy. This may occur in situations in which patients have failed therapy or when inadequate tissue is available for proper histologic or cytometric analysis. There are some subtypes of non-Hodgkin's lymphoma that involve the spleen more than others. Splenic marginal zone lymphoma represents a particular entity of indolent B-cell lymphoma in which the spleen is often the only organ macroscopically involved. Marginal zone lymphomas require strict surveillance and the indications for splenectomy should be discussed in symptomatic patients. However, splenectomy in these patients has been shown to lead to partial or complete remission because the spleen is the site of lymphoma origin. The discovery of isolated splenomegaly without any obvious etiology calls for complete work up, which leads to two possible scenarios: (1) splenomegaly remains isolated without a clear diagnosis of hematologic disease and splenectomy should be considered for diagnostic purposes. The alternative to splenectomy is a CT guided biopsy, which is diagnostic in 80% to 90% of cases. (2) When definitive diagnosis has been established, splenectomy might be part of the therapeutic strategy. However, in case of splenic mantle cell lymphoma, follicular lymphoma or diffuse large B-cell lymphoma, the indications for splenectomy are quite limited.

Hairy Cell Leukemia

Hairy cell leukemia is a rare disease, representing 2% of all leukemias. Patients have fatigue, left upper quadrant abdominal pain, fever, infections, and/or coagulopathy. The disease is characterized by B-lymphocytes that possess cytoplasmic projections from the cell membrane ("hairy cells"). This is an indolent disease that commonly occurs in the fifth decade of life with splenomegaly (80% to 90% of patients), pancytopenia, neoplastic peripheral mononuclear cells, and bone marrow infiltration. Pancytopenia is caused by hypersplenism and replacement of bone marrow by leukemic cells. In the past, splenectomy was considered the standard of care with a 40% to 70% improvement in the hematologic cell lines for up to 10 years. Recently, treatment with purine analogs, such as pentostatin and cladribine, has replaced splenectomy as primary therapy. These agents have patient response rates of 92%, with a complete remission rates of 80% and a 40% 10-year survival. Splenectomy is currently reserved for cases of incomplete response to first-line therapy, persistent splenomegaly in the absence of bone marrow involvement, traumatic splenic rupture, and severe bleeding.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia represents a B-cell leukemia in which there is progressive accumulation of functionally impaired lymphocytes. Chronic lymphocytic leukemia usually arises after the fifth decade of life and is more common in men than in women. Splenic infiltration is common and can lead to severe splenomegaly and cytopenias from hypersplenism. Splenectomy is indicated to relieve symptoms associated with massive splenomegaly, such as abdominal pain, distension, and early satiety. Splenectomy for the treatment of severe thrombocytopenia and anemia, in the setting of secondary ITP or AIHA, has a 50% to 70% hematologic response rate and has been shown to improve survival.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a disorder resulting from an abnormal proliferation of granulocytes. Ninety-five percent of CML patients have a chromosomic translocation between chromosomes 9 and 22 [t(9;22)] leading to fusion of the breakpoint cluster region and Abelson leukemia virus gene. CML may occur in childhood but it is mainly found in adults with a mean age of 45 years. Diagnosis is commonly made during the chronic phase, which is characterized by splenomegaly in 40% of patients. Despite medical therapy, the disease can progress to an accelerated phase with development of fever, night sweats, weight loss, bone pain, increased white blood cell count, and splenomegaly. An acute blastic crisis with splenomegaly and hypersplenism can occur, resulting in severe anemia, bleeding, and infections. Current first-line therapy is with imatinib, a tyrosine kinase inhibitor. Bone marrow transplantation or interferon-alpha can be used in cases of poor response or relapse. Splenectomy has not shown any survival benefit in the early chronic phase or before bone marrow transplantation, but it may be offered as palliative treatment in patients with severe symptoms due to splenomegaly and hypersplenism.

Primary Myelofibrosis (Myelofibrosis With Myeloid Metaplasia)

Primary myelofibrosis (PMF) is a chronic malignant hematologic disorder that results in hyperplasia of abnormal myeloid precursor cells leading to marrow fibrosis and extramedullary hematopoiesis in the liver and spleen. This can lead to significant splenomegaly, cytopenia, and portal hypertension secondary to sinusoidal thrombosis. PMF is prevalent in patients with history of radiation or toxic industrial agent exposure. It is more common in men than women, with an average age of 65 years. Splenectomy is indicated for patients who develop hemolysis requiring significant transfusions, thrombocytopenia, symptomatic splenomegaly, recurrent splenic infarctions, hypercatabolic symptoms (anorexia, fatigue, fever, night sweats, weight loss), and portal hypertension with refractory ascites and variceal hemorrhage. Splenectomy in progressive myelofibrosis with myeloid metaplasia has a considerable risk of morbidity (15%–30%) and mortality (10%) and should be performed in select patients only. Splenectomy in patients with progressive myelofibrosis with myeloid metaplasia has been associated with hemorrhage, infection, leukocytosis, severe thrombocytosis (18%–60%), progressive hepatomegaly (12%–39%), fatal hepatic failure (7%), and leukemic

transformation (11%–20%). The appropriate use of palliative splenectomy in PMF can result in improved quality of life for patients who are unresponsive to conventional treatment. Perioperative use of platelet-lowering agents such as hydroxyurea, interferon alpha, aspirin, and anagrelide has been shown to reduce thrombotic complications. Ligation of the splenic vein at its confluence with the superior mesenteric vein has been described to improve hepatic flow and decrease portal vein thrombosis. Compensatory massive hepatic enlargement can be treated with low-level radiation and chemotherapy.

MISCELLANEOUS DISORDERS

Amyloidosis

Amyloidosis is a common disorder that results in extracellular deposition of insoluble fibrillar proteins in tissues and organs. Hepatosplenomegaly may occur in 25% of patients, and severe splenomegaly is seen in approximately 10% of individuals. Splenectomy is indicated for symptomatic splenomegaly. In addition, patients with severe hepatic dysfunction may develop coagulopathy associated with factor X deficiency. In these patients, splenectomy may improve factor X levels. Perioperative administration of factor VIIa is important to control bleeding in patients undergoing surgery. However, splenectomy does not modify the ultimate course of the disease.

Gaucher's Disease

Gaucher's disease is a glycolipid storage disease resulting from a deficiency of beta-glucosidase (glucocerebrosidase). This leads to deposition of glucocerebroside in the reticuloendothelial system with severe organomegaly, pulmonary infiltration, and bone marrow infiltration. Patients can have anemia, thrombocytopenia, osteopenia, bone pain, osteonecrosis, and massive hepatosplenomegaly. Splenectomy is indicated for severe and symptomatic splenomegaly and refractory cytopenia. Partial splenectomy has been advocated in children with Gaucher's disease to preserve splenic function. The spleen is a reservoir for storage material; therefore, splenectomy can result in redistribution and deposition in other organs causing severe bone disease (twofold increased risk of osteonecrosis) and worsening of lung and kidney function.

Felty's Syndrome

Felty's syndrome includes rheumatoid arthritis, neutropenia, and splenomegaly in 85% of cases this disease is associated with an HLA DR4 antigen. Patients present with chronic infections as a result of neutropenia, especially when neutrophils are below 0.5×10^9/mm^3. First-line treatment consists of low-dose methotrexate or disease-modifying antirheumatic drugs. Granulocyte colony-stimulating factor may be used for treatment failures, in cases of increased infection risk, or before surgery. Splenectomy is indicated when medical treatment fails and usually results in 80% hematologic response rate. Unfortunately, infectious complications may still occur and do not always correlate with granulocyte counts.

Sarcoidosis

Sarcoidosis is a noncaseating granulomatous disease. Although 90% of patients have primary lung involvement, it can affect every organ in the body. Primary splenic sarcoidosis is very rare, and splenic involvement is often found as part of a multiorgan disease. Up to 40% of patients with sarcoidosis have splenomegaly and 3% have massive splenomegaly. Treatment is usually conservative and includes corticosteroids or methotrexate. Indications for splenectomy include: splenomegaly and hypersplenism, intractable pain, and exclusion of a neoplastic process. Splenectomy does not alter the course of sarcoidosis but has been shown to improve refractory hypercalcemia.

FIG. 1 Accessory spleen.

Idiopathic Splenomegaly

In the setting of splenomegaly without a clear cause, splenectomy has a diagnostic and therapeutic role. Studies have revealed a 40% to 70% occurrence of lymphoma in this patient population. Most of these patients do not exhibit any signs of malignancy or lymphadenopathy. Tissue obtained through splenectomy may be the only way to perform appropriate histopathologic and cytologic diagnosis. When hypersplenism is present, splenectomy can alleviate symptoms of splenomegaly and correct cytopenia.

Preoperative Considerations

Preoperative imaging with ultrasound and/or CT scan is critical for operative planning. CT provides information regarding anatomic relationships, spleen size, vascular anatomy, presence of accessory spleens (Fig. 1), perisplenic lymphadenopathy, and inflammation. The normal spleen measures about 11 cm in length. Moderate splenomegaly, from 14 to 25 cm, should be noted in preoperative planning. Massive splenomegaly, greater than 25 cm length, may change preoperative and intraoperative strategy (Fig. 2). Although not indicated for routine total splenectomy, preoperative splenic artery embolization can be useful in patients with massive splenomegaly to prevent excessive blood loss in the setting of severe thrombocytopenia, or in patients who do not wish to receive blood transfusions. In addition, embolization helps reduce the splenic tissue hypercoagulopathy. Timing is important because patients can develop significant pain from infarcted splenic tissue; we suggest performing angiographic embolization within 24 hours before surgery. A broad-spectrum antibiotic prophylaxis should be administered at the time of induction of anesthesia and continued postoperatively for at least 24 hours. Low-molecular-weight heparin should be administered subcutaneously before induction of anesthesia and should be continued postoperatively for up to 1 month as prophylaxis for splanchnic thrombosis. The use of an orogastric or nasogastric tube can reduce gastric distension and improve visualization and dissection of the short gastric vessels along the greater curvature of the stomach. Blood products must be available intraoperatively, especially platelets for patients with severe thrombocytopenia. Prophylactic platelet transfusions are typically given only when the platelet count is below 50,000 and the platelets are administered only after the splenic artery has been ligated. If patients have been treated with chronic corticosteroids, stress dose steroids should be administered with a rapid taper postoperatively. In elective cases, it is recommended to vaccinate patients against encapsulated organisms (haemophilus influenzae B, polyvalent pneumococcus, and meningococcus vaccines) 2 weeks before splenectomy. If splenectomy is emergent, the patient should be vaccinated postoperatively.

FIG. 1 Massive splenomegaly in a patient who underwent splenectomy for complications of a deep open cut wound.

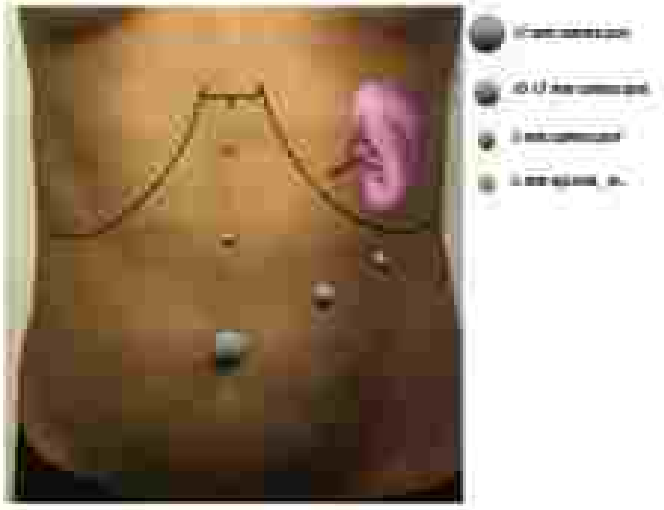

FIG. 2 Laparoscopic splenectomy, anterior approach.

Surgical Procedure

Laparoscopic splenectomy has become the standard approach for performing splenectomy in patients with hematologic disorders. The laparoscopic approach provides the advantages of shorter length of stay, decreased postoperative pain, and decreased morbidity. Recent studies have shown a trend toward shorter operative times that are comparable to open splenectomy in cases of normal or moderately enlarged spleens. Most data show comparable detection of accessory spleens that can result in disease recurrence in cases of autoimmune hematologic disorders. However, laparoscopic splenectomy is not a forgiving procedure. Methodical control of the hemostasis is the key for success. The splenic parenchyma is fragile, has a rich blood supply, and is particularly vulnerable to capsular tear and hemorrhage. Understanding the variation of splenic anatomy is essential for a safe intraoperative management. Much of the controversy surrounding laparoscopic splenectomy involves the size of the spleen. The normal adult spleen measures up to 11 cm in length and weighs approximately 80 to 300 g. Moderate splenomegaly generally is defined as a spleen that is 11 to 25 cm, and massive splenomegaly represents a spleen that is more than 25 cm. We believe that laparoscopic splenectomy can be performed safely in patients with splenomegaly. Factors to be considered should include medical comorbidities, indication for surgery, blood counts, coexisting coagulopathy, and history of previous splenic embolization. The hand-assisted laparoscopic approach may be useful for inexperienced surgeons to shorten the learning curve and to allow rapid control of hilar vessels and assistance with retraction. Nevertheless, open surgery should never be considered a failure and may be the safest approach in some cases. Laparoscopic splenectomy can be performed with the patient in lateral decubitus position or supine. A bean bag can be used to facilitate positioning for surgeons who prefer the right lateral decubitus approach. A split leg bed can be helpful when the patient is supine; this also allows the surgeon to stand between the patient's legs. For the anterior approach, port placement generally includes a 12-mm periumbilical camera port, and three to four additional ports in a V-shaped placement adjacent to the left upper quadrant, with the initial port for the camera at the base of the V. One line of the V extends from the initial port to the xiphoid process; the other line of the V extends from the initial port to the most lateral left subcostal region. Two dissection ports are placed, one near the midline and one along the lateral V line. A 10- to 12-mm port at this location may be preferable because it is likely the port for introduction of an endoscopic stapler or Endocoby device. An additional port for retraction is placed further lateral at the anterior axillary line (Fig. 2). If a fifth port is necessary for retraction, it is placed in the subxiphoid region. Access to the abdomen can be gained using a Veress needle, an optical trocar, or an open approach depending on the surgeon preference. The patient is then placed in reverse Trendelenburg and tilted slightly to the right. For patients with large liver or splenomegaly, a self-retaining liver retractor, such as the Nathanson device with fan clamp, can facilitate visualization. For the lateral approach, the position is similar to that used for posterolateral thoracotomy and/or laparoscopic left adrenalectomy. Patients are initially positioned supine on a beanbag. Once general anesthesia is established and the airway is secured, the operative team repositions the patient in lateral decubitus with the right side down. The kidney rest is raised, and the operating table is flexed. The goal is to maximize the working space between the left costal margin and the left anterior superior iliac spine. The umbilicus is avoided, and the first port is positioned approximately one-third the distance from the umbilicus to the splenic hilum. After securing access to the peritoneal cavity, typically three additional ports are placed along the costal margin. Depending on the splenic size and body habitus, it may be necessary to place the trocars inferiorly or medially. A 10- to 12-mm port, capable of accommodating an endostapler or large Endocoby device, is typically placed in the left subcostal anterior axillary line. A 5-mm port is placed in the left subcostal region in the midaxillary line. A fourth port, usually 5 mm, is placed in the far left lateral subcostal position. Occasionally, an additional port is required for retraction toward the midline, near the xiphoid process (Fig. 4). The abdomen is explored, paying careful attention to identify any accessory spleens. The liver should also be inspected for signs of cirrhosis. The splenocolic ligament is mobilized and divided with an energy device. This allows for further mobilization and inferior retraction of the splenic flexure of the colon. The gastrosplenic ligament and the short gastric vessels then are divided using an ultrasonic energy device, endoscopic metallic clips, or bipolar energy device. This dissection should be carried up to the level of the left crus, and the stomach can be retracted to the right. The splenorenal ligament then is dissected to identify the splenic artery and splenic vein within the splenic hilum (Fig. 5). These structures then are divided using a vascular load on an endoscopic linear stapling device. The splenophrenic ligament is divided last because it maintains cephalad/lateral retraction of the spleen during dissection of the hilar vessels. The spleen is then placed into an endoscopic bag and morcellated. After extraction, the splenic bed, hilum, and greater curvature of the stomach should be inspected thoroughly to ensure hemostasis. At this point, the abdomen should be examined again for splenunculi or accessory spleens. The most common locations for splenunculi are the gastrosplenic ligament and greater omentum. For open splenectomy, a midline or left subcostal incision may be used. The midline incision may be preferable to patients with massive splenomegaly or with a narrow costal margin.

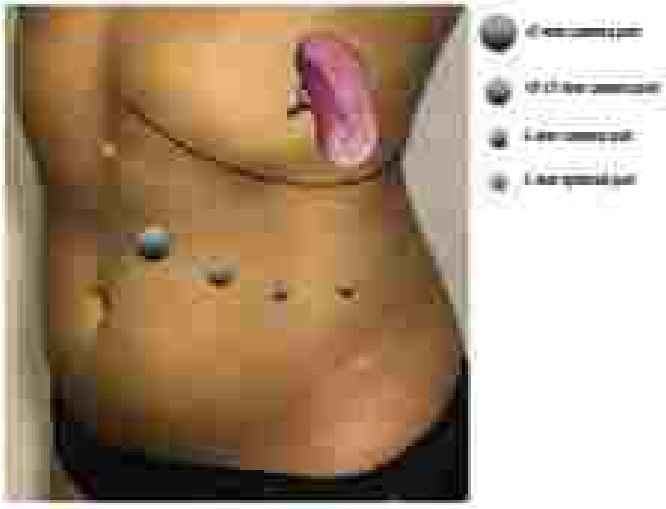

FIG. 4 Laparoscopic splenectomy lateral approach.

FIG. 5 Laparoscopic view of splenic vein ligation.

Postoperative Management and Complications

Postoperative care following a laparoscopic splenectomy is a straightforward process, provided that the procedure is uneventful. Orogastric tubes and urinary catheters are removed immediately after the operation and routine postoperative chest radiograph is not required. However, patients should be monitored for hemorrhage, atelectasis, and infection in the early postoperative period. The most common site of hemorrhage at reexploration is from the undersurface of the diaphragm. Deep vein thrombosis prophylaxis is continued postoperatively with pneumatic sequential compression devices and heparin or enoxaparin, unless contraindicated. A diet is restarted as tolerated. Typical length of stay is 1 day, although many series report average length of stay of 2 to 3 days. Infectious complications include subphrenic abscess and OPSI. All patients undergoing splenectomy should be counseled regarding their increased lifetime risk of infections. If patients were unable to receive preoperative vaccinations, they should be vaccinated 2 weeks after surgery. Vaccinations should be withheld for 3 months after surgery in patients who have been treated with immunosuppressive agents. Patients should receive booster vaccinations every 5 years for pneumococcus and meningococcus. Prophylactic antibiotics have been recommended for at least 2 years in children but generally are not used in adults. Penicillin is the agent of choice (Box 3). In patients with penicillin allergies, trimethoprim-sulfamethoxazole or erythromycin may be used.

BOX 2 Guidelines for OPSI Prophylaxis

Incidence of OPSI

- [illegible] 2 years after splenectomy (4.2% to 9.9%) [illegible] 5.0%)
- Risk factors: Age < 5 years, [illegible] malignancy, [illegible] > suppression

Vaccination and Antibiotic Prophylaxis Recommendations

[illegible] children

- Haemophilus influenzae type B, pneumococcus, meningococcus 2 wk preoperatively (elective cases) or at discharge or 2 wk postoperatively
- If [illegible] received [illegible] immunosuppressive therapy, vaccines 3 mo after treatment
- Booster vaccinations for pneumococcus, meningococcus every 5 yr
- If [illegible] vaccine antibody titers can be followed for need of a booster dose
- [illegible] neither monitoring titers. Fail-save to immunocompromised patients

- Antibiotic prophylaxis
- [illegible] children [illegible] penicillin
- Amoxicillin, lactic acid tablets for [illegible] sensitivity in children [illegible]
- Children [illegible] 5 yr of age [illegible] recommended

[illegible] 2.0 mL/kg [illegible]

The risk for OPSI is higher in children younger than age 5 and within the first 2 years after surgery but does carry a lifelong risk. Risk factors for OPSI include age (14% in children younger than 5 years vs 6.5% in children older than 5 years), splenectomy for a hematologic disorder, and history of immunosuppressant therapy.

PSI has a reported fatality rate of 50%. Streptococcus pneumoniae, Neisseria meningitidis, H. influenzae type B, and group A streptococcus account for most of the severe infections. Escherichia coli, Capnocytophaga species, and intraerythrocytic parasites also pose a risk. Patients typically have an upper respiratory infection that rapidly proceeds to sepsis and multisystem organ failure. An early and aggressive treatment with broad-spectrum antibiotics and supportive measures can be lifesaving. Other postoperative complications include thrombocytosis, leukocytosis, pneumonia, pleural effusion, pancreatitis, pancreatic fistula, venous thrombosis, injury to adjacent organs, and hyperplenism resulting from the presence of a retained accessory spleen. Thrombocytosis can occur postoperatively with a peak at 3 weeks. Antiplatelet therapy is indicated with thrombotic complications or when platelet levels reach 1 million. Patients with an accessory spleen often have an absence of Howell-Jolly bodies, and target cells in the peripheral blood and may require reexploration for accessory spleens or refractory anemia/thrombocytosis. Portal vein or mesenteric vein thrombosis can be a serious complication of splenectomy. Postsplenectomy splanchnic venous thrombosis has been reported in 20% to 50% of patients undergoing splenectomy, with higher rate for laparoscopic splenectomy. For this reason, patients should be maintained on prophylaxis with low molecular weight heparin for 4 weeks. Risk factors for thrombosis include myeloproliferative disorders, hemolytic anemias, long spleens with manipulation, postoperative thrombocytosis, hypercoagulable state, and splenomegaly. Patients present with vague abdominal pain and distention, fever, liver, and nausea and can develop intestinal infarction and portal hypertension. In the setting of splanchnic venous thrombosis, systemic anticoagulation is required, which leads to effective thrombolysis in more than 90% of patients, if promptly treated.

CONCLUSION

Splenectomy remains an important tool for the treatment of a wide range of acquired, congenital, and neoplastic hematologic disorders. Splenectomy can also serve as a diagnostic tool in the setting of idiopathic splenomegaly. To ensure a safe perioperative course, management of patients undergoing splenectomy requires careful preoperative preparation and postoperative management.

Suggested Readings

Arnold C, Matthews JB. Minimally invasive surgical and image-guided interventions for splenic [illegible] the future [illegible] Surg Clin North Am. 2010;90:[illegible]

[illegible] splenectomy. Surg Clin North Am. 2010;90:[illegible]

[illegible] splenectomy. Surg Clin North Am. 2010;90:[illegible]

Management of Cysts, Tumors, and Abscesses of the Spleen

Anna Lee B. Mann, MD, and Peter Mac A. Villa, MD

Typically found incidentally on imaging, cysts and tumors of the spleen are uncommon entities. When symptomatic, they may be life threatening and warrant surgery. The incidence of splenic abscesses is decreasing with increasing awareness and administration of antibiotics. Splenic abscesses continue to be a source of significant morbidity in affected patients. This chapter describes the presentation and management of the numerous cysts, tumors, and abscesses of the spleen. We focus primarily on laparoscopic splenectomy as the gold standard operative intervention.

SPLENIC CYSTS

There are several known classification systems for splenic cysts. Cysts are categorized as primary (true) or secondary (false) cysts. Secondary splenic cysts are the most common, accounting for 90% of all splenic cysts. They usually are described as developing in the posttraumatic or postinfectious setting, the latter most commonly resulting from mononucleosis or tuberculosis. Another subcategorization is nonparasitic versus parasitic cysts. Parasitic cysts are the most common worldwide and are frequently related to echinococcal infections. This can easily be determined by the presence of calcifications or daughter cysts on imaging with positive serologies. Anaphylaxis, shock, and death have been described after spillage of echinococcal cyst contents, so care must be taken in handling these cysts during surgery. Congenital cysts are usually benign and are subdivided into epidermoid, dermoid, and endodermoid or simple cysts. The epidermoid subtype accounts for 90% of primary nonparasitic cysts.

There is no evidence-based determinant of a threshold for the watch and wait approach management of asymptomatic cysts, although most would advocate intervention when cysts are larger than 5 cm. Further diagnostic testing or biopsies are unnecessary and can often cause increased morbidity. When symptomatic, patients will most frequently report vague upper abdominal pain from capsular distention or mass effect on adjacent organs but may also report nausea, vomiting, early satiety, or diarrhea. Cysts that are either enlarging, symptomatic, or larger than 5 cm should be considered for intervention (Fig. 1). The risk of rupture and infection increase with increasing size, with hemoperitoneum or intraabdominal abscess being the greatest source of morbidity and possible mortality.

Total splenectomy is still considered by many as the gold standard for management of nonparasitic splenic cysts; however, a growing body of evidence is developing that favors organ preservation. Partial splenectomy, when technically feasible, may be superior to total splenectomy because of the benefit of maintaining the immunologic function of the spleen. Thus, the life-threatening complication of overwhelming postsplenectomy sepsis is prevented.

Other spleen preserving management strategies have been described and include percutaneous drainage, cyst fenestration, and marsupialization. Percutaneous drainage has been shown to have a high risk of recurrence. The risk of recurrence decreases with injection of sclerosing agents such as alcohol and tetracycline. Percutaneous drainage has also been described as an adjunct to decrease cyst size preoperatively. This may cause increased adhesions to the left upper quadrant adding complexity to the surgery, however.

Cyst fenestration, in which the anterior cyst wall is unroofed and the contents drained, is effective but also has a high rate of recurrence. Omental flaps may be placed in the region of the cyst and have been shown to decrease recurrence rates slightly. There is no consensus on the amount of cyst wall that needs to be removed for a successful fenestration with low rates of recurrence. A similar procedure, cyst marsupialization, in which the cyst wall is separated from the splenic parenchyma in its entirety, has the lowest rate of recurrence but has the significant complication of bleeding. This hemorrhage is often controlled effectively with electrocautery and hemostatic agents. Marsupialization is recommended for superficial splenic cysts that are easily accessible.

Splenic Peliosis

Splenic peliosis is a rare benign condition that has been reported and is better described in the liver. Sinusoidal dilatation leads to the appearance of multiple blood-filled "cystic" cavities scattered within the splenic parenchyma in the periarteriolar red pulp. Rupture of these cavities may lead to hemorrhagic shock and subsequent death. Risk factors for peliosis include HIV, cytotoxic steroid usage, oral contraceptives, and chronic hematologic disorders, including Hodgkin's lymphoma and multiple myeloma. In most of these cases, both the liver and spleen are involved. Isolated splenic involvement is extremely rare and often presents as hemoperitoneum. Management is total splenectomy even when peliosis is detected incidentally to eliminate the risk of hemorrhage.

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Suggested Readings

Antiel C, Matthews JB. Minimally invasive surgical and image guided interventional approaches to the spleen. *Gastrointest Surgery of the Abdominal Tract*. 8th ed. 1603–1621.

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Management of Cysts, Tumors, and Abscesses of the Spleen

Anna Liveris, MD, and Peter Muscarella II, MD

Typically found incidentally on imaging, cysts and tumors of the spleen are uncommon entities. When symptomatic, they may be life threatening and warrant surgery. The incidence of splenic abscesses is decreasing with increasing awareness and administration of antibiotics. Splenic abscesses continue to be a source of significant morbidity in affected patients. This chapter describes the presentation and management of the numerous cysts, tumors, and abscesses of the spleen. We focus primarily on laparoscopic splenectomy as the gold standard operative intervention.

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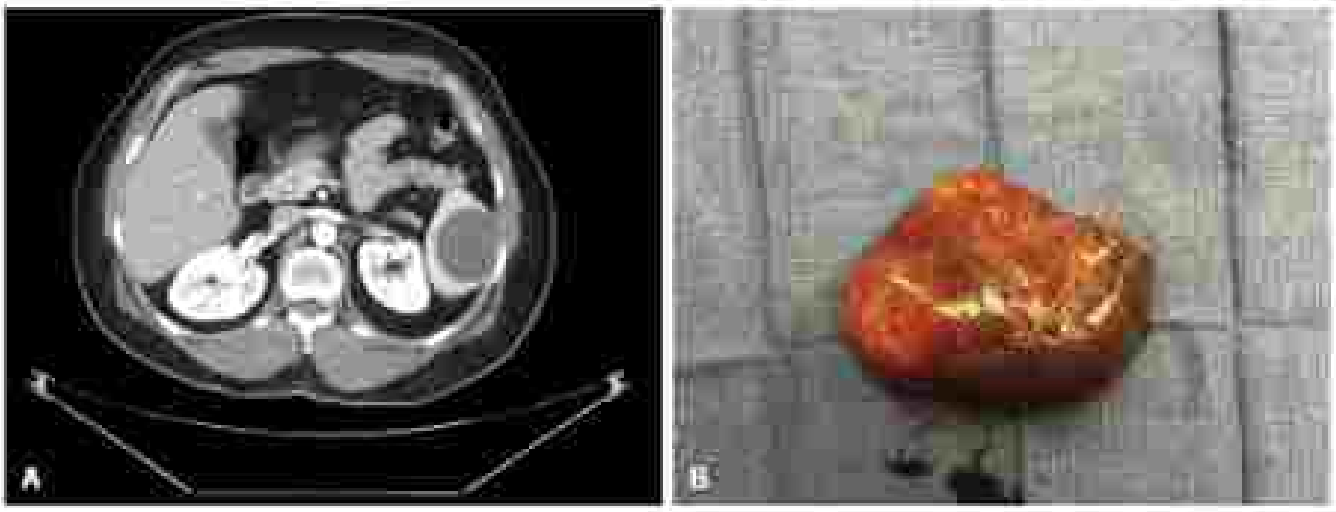

FIG. 1 (A) Patient with a symptomatic splenic cyst found on computed tomography. (B) The spleen was removed with the cyst intact.

BOX 1 Splenic Neoplasms

Benign tumors
- Hemangioma
- Lymphangioma
- Hamartoma
- Littoral cell angioma

Malignant tumors
- Lymphoma
- Angiosarcoma

Nonvascular, nonhematopoietic tumors
- Inflammatory pseudotumor
- Mesenchymal tumors

Metastatic tumors

SPLENIC TUMORS

Primary splenic neoplasms are rare entities that can be categorized by their tissue of origin (Box 1). Lymphoid neoplasms arise from the white pulp, whereas vascular neoplasms arise from the red pulp. In addition to this categorization, primary neoplasms can be more readily divided into benign and malignant tumors. Benign tumors include hemangioma, lymphangioma, hamartoma, and littoral cell angioma. Malignant tumors include lymphoma and angiosarcoma. Other tumors such as lipoma and inflammatory pseudotumors have been described but are exceedingly rare with very few reports in the literature. Secondary neoplasms also occur within the spleen with melanoma, breast, lung, ovary, colon, stomach, and pancreatic neoplasms all being reported as metastasizing to the spleen.

Benign Tumors

Hemangioma

The most common benign tumors of the spleen are hemangiomas. Most patients are asymptomatic, and the tumors are found incidentally on imaging. Most are smaller than 2 cm in size and solitary, although multiple and diffuse lesions can be noted rarely with hemangiomatosis and generalized angiomatosis syndromes. Splenic hemangiomas come in two varieties: capillary and cavernous, the latter being the more common. These two patterns have slightly different appearances on imaging. On ultrasound, hemangiomas appear as echogenic lesions with cavernous lesions showing a more complex nature. On computed tomography, punctate peripheral calcifications are characteristic. Hemangiomas larger than 3 cm have an associated risk of bleeding and may be considered for complete or partial splenectomy.

Lymphangioma

Splenic lymphangiomas are benign and slow-growing neoplasms that are more commonly found during childhood. As with hemangiomas, these lesions may be unifocal or part of a systemic lymphangiomatosis syndrome involving multiple organs. Unlike hemangiomas, they can appear multiloculated, lobulated, and cyst like. In children, they still often present as a palpable abdominal mass because they tend to be larger in size. Lymphangiomas detected in adulthood are typically incidental on imaging and patients remain asymptomatic. Three histologic subtypes are capillary, cavernous, and cystic. These entities are hypoechoic on ultrasound and hypodense on computed tomography. They are more common in a subcapsular location and may have enhancing septa and peripheral rim calcification (Fig. 2). The current standard of management for suspected splenic lymphangiomas has traditionally included splenectomy, although splenic preservation with partial splenectomy is increasingly being used.

Hamartoma

Characterized by malformation of the red pulp without organized lymphoid follicles, splenic hamartomas are rare benign lesions. They are usually small in size and discovered incidentally on imaging but can rarely present as a large mass or diffuse splenomegaly. Most patients are asymptomatic, but spontaneous splenic rupture has been reported to associations with this entity particularly in larger masses. Ultrasonography depicts a well-circumscribed homogenous solid mass, whereas computed tomography demonstrates early enhancement with intravenous contrast and uniform delayed enhancement of an isodense mass. With larger hamartomas, more heterogeneous contrast uptake and prolonged retention of contrast may be seen likely because of stagnation within the red pulp sinusoids. Imaging, though suggestive of a diagnosis, is not always definitive and percutaneous biopsy is warranted when feasible. If biopsy is not possible, splenectomy is indicated for definitive diagnosis and management.

Littoral Cell Angioma

The cells lining the red pulp, known as littoral cells, may give rise to a benign vascular neoplasm of the spleen known as littoral cell angioma. This entity was first described in 1991 and has been characterized by diffuse nodular involvement of the spleen. As such, patients may present with splenomegaly and signs of hypersplenism, including anemia, fatigue, and bleeding. Splenic rupture and hemoperitoneum have also been described. Noncontrast computed tomography shows multiple nodular masses of varying size. Following contrast administration, the masses appear hypodense on the early portal phase, returning to an isodense appearance on the delayed phase.

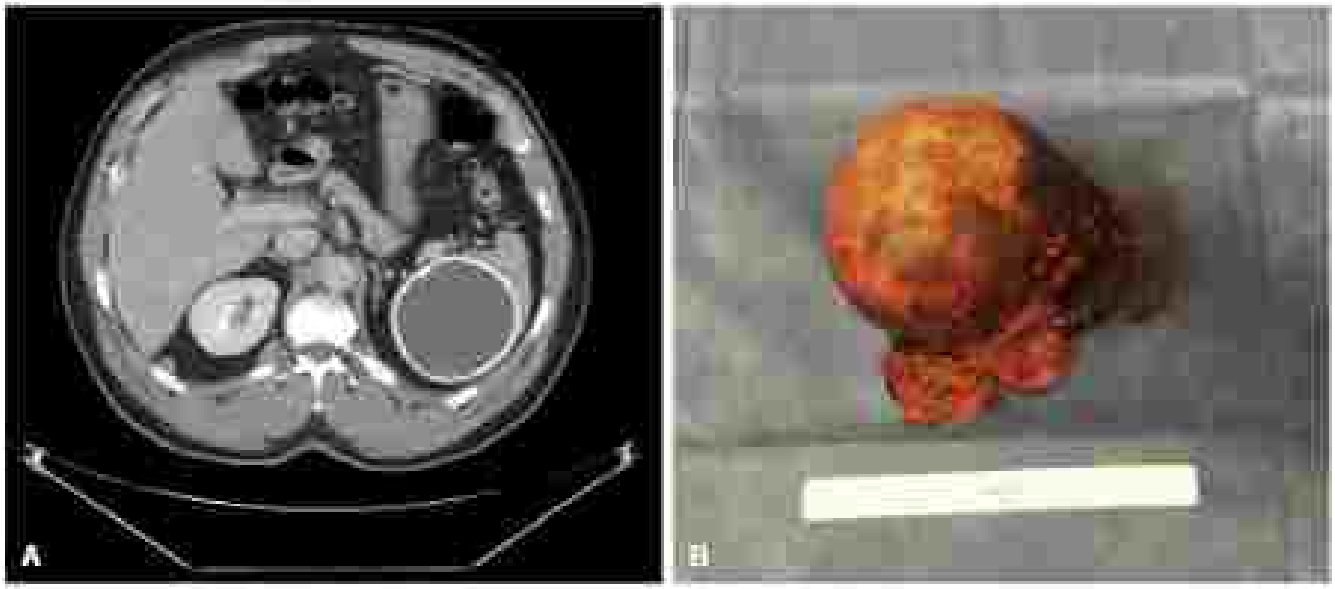

FIG. 2. (A) A large (>6 cm) cavitary splenic lesion was seen on computed tomography. (B) An thin cavitary wall is noted on the surgical specimen after splenectomy.

because of the risk of splenomegaly and hypersplenism, splenectomy is advocated for when littoral cell angiomas are detected. Confirming the diagnosis, pathologic specimens have shown small vascular channels lining cystic spaces with papillary projections on histology.

Malignant Tumors

Lymphoma

The most common primary malignant tumor of the spleen is lymphoma. Primary splenic lymphoma accounts for less than 1% of all lymphomas and usually represents non-Hodgkin's B cell lymphoma. Despite this, secondary involvement of the spleen with lymphoma is far more common than primary disease. Splenomegaly is the most common finding on examination for primary splenic lymphomas and is present in more than two-thirds of cases. Diagnostic criteria have classically included disease limited to the spleen and hilar nodes without recurrence after splenectomy. Thin needle aspiration and core needle biopsy have been avoided in the past resulting from concerns that puncture of the hypervascular, fragile spleen may lead to hemorrhagic complications. This has been disproved in most recent studies and is considered safe practice.

Of special note, splenic marginal zone lymphoma is a slow-growing subtype that almost always presents with splenomegaly. It is associated with hepatitis C virus infection. Treatment has traditionally been splenectomy but more recently rituximab monotherapy has been found to be efficacious as the initial treatment of this subtype of primary splenic lymphoma. The prognosis is good with appropriate treatment with an estimated 5-year overall survival of 80% to 95%.

Angiosarcoma

The most common primary nonhematopoietic malignant neoplasm of the spleen is the rare angiosarcoma. Also known as hemangiosarcoma, these tumors tend to be highly aggressive and carry a poor overall prognosis. Patients often present with advanced disease, already having splenomegaly and evidence of metastasis, most commonly to the liver. Spontaneous splenic rupture is the presenting finding in a quarter of patients diagnosed with this neoplasm. Multiple complex heterogeneous and hypervascular masses are seen on imaging. Calcifications are rarely noted. As with lymphoma, biopsy had been avoided in the past from concerns for bleeding but has now been considered safe when care is taken. Treatment is with splenectomy when feasible.

Other Nonvascular, Nonhematopoietic Splenic Tumors

Inflammatory pseudotumor is an uncommon benign tumor of the spleen. The etiology is unclear but is likely related to an inflammatory reparative response to traumatic or infectious injury. Usually an incidental finding on imaging, patients are frequently asymptomatic but may present with symptoms from mass effect. On computed tomography, these pseudotumors appear as a hypodense mass with delayed contrast enhancement and central scarring. If the patient is symptomatic, or there is question of the diagnosis, splenectomy should be performed. Pathology will confirm the diagnosis by the presence of spindle cell proliferation and plasma cells.

Mesenchymal tumors such as fibroma, fibrosarcoma, lipoma, angiomyolipoma, leiomyosarcoma, and malignant fibrous histiocytoma have been described in the literature and are very rare. Apart from the characteristic presence of fat in lipoma, there are no specific pathognomonic features on imaging with these neoplasms. Patients are frequently asymptomatic and the diagnosis is made after splenectomy.

Metastatic Tumors

Overall splenic involvement in metastatic disease is uncommon. Splenic metastases are found in less than 10% of all untreated malignancies. There are numerous theories for why the spleen is seemingly protected from metastases. These include the lack of afferent lymphatics, the sharp angle of the splenic vessels, and antitumor activity of the splenic lymphoid tissue itself. Hematogenous spread is the most likely route when splenic metastases do occur. The most common primary malignancies to metastasize to the spleen are melanoma, breast, lung, and ovarian cancers.

Rarely, metastases from colon, stomach, and pancreas primaries are also found. Though infrequent, these latter tumors may spread via direct invasion into the spleen. Diffuse infiltration is rare. More commonly, metastatic disease is seen as solitary or multiple masses. Radiologic findings vary with the primary neoplasm. Cystic and necrotic degeneration can occur, particularly with melanoma. Calcifications may be noted with mucinous adenocarcinomas. Carcinomatosis and pseudomyxoma peritonei may manifest as serosal implants on the splenic surface, also visualized as splenic margin scalloping.

SPLENIC ABSCESS

Abscesses of the spleen are uncommon complications of other underlying infectious processes. They most frequently occur via hematogenous spread in the presence of bacteremia or fungemia but can also happen by contiguous spread. Clinically, splenic abscess has been associated with endocarditis, although urinary tract infections and gastrointestinal infections have also been implicated. Patients most commonly present with fever and left upper quadrant pain, often with signs of sepsis. People at high risk for splenic abscess include those who are immunosuppressed (e.g., HIV, diabetes, hemoglobinopathies, amyloidosis, Felty syndrome, abnormalities of the spleen such as cysts, intravenous drug abusers). Those patients with HIV are at the highest risk. Diagnosis is best made using ultrasonography or computed tomography.

Antibiotic therapy should be tailored to cover the most frequently cultured organisms. Gram-positive cocci, including *Staphylococcus* species and *Streptococcus* species, and gram-negative enteric organisms, *Salmonella* species in particular, are most common isolates. In the immunocompromised, coverage for *Mycobacterium* species and *Candida* species should also be considered, especially for those who may present in septic shock.

Definitive management of splenic abscesses with percutaneous drainage has had good success in most recent studies. Patients most likely to achieve complete resolution with percutaneous or image-guided drainage are those with unilocular abscesses. For patients who fail to improve clinically, have multiloculated abscesses, or incomplete resolution after initial drainage, splenectomy is indicated.

SURGERY

Aside from surgery for splenic trauma, surgery is most commonly complicated by bleeding and infection. Given these risks, preoperative planning is of considerable importance and should be performed in every patient. The gold standard of surgical management remains laparoscopic splenectomy. Laparoscopic splenectomy provides the advantages of shorter length of stay, decreased postoperative pain, and decreased morbidity as compared with open splenectomy. The latter still occurs predominantly in the setting of trauma and large malignant tumors not amenable to removal laparoscopically. Other spleen-preserving methods are briefly described earlier in this chapter.

Preoperative Considerations

Preoperative imaging is imperative for operative planning. Computed tomography and ultrasonography are both acceptable options for assessing splenic size. The former may be preferred because it provides better visualization of the anatomic relationships and anatomy, including the presence of accessory spleens and hepatolienopathy. Other factors to be considered in the preoperative assessment include medical comorbidities, splenic size, blood counts, coexisting coagulopathy, history of previous splenic irradiation, or percutaneous manipulation.

Appropriate preoperative antibiotics are given to cover skin flora prior to making skin incision. Despite the risk of bleeding, there is also a risk of splanchnic thrombosis after manipulation of the splenic vessels such that we routinely administer low molecular weight heparin before induction of anesthesia and continue this postoperatively for up to 1 month as prophylaxis. Gastric decompression with an orogastric or nasogastric tube can reduce gastric distention and can improve visualization, particularly when the short gastric vessels are dissected along the greater curvature.

Blood products should be available intraoperatively, particularly in patients with severe thrombocytopenia. After ligation of the splenic artery, platelets are transfused only as needed and not routinely required. In the elective setting, patients are vaccinated against encapsulated organisms (haemophilus influenzae B, polyvalent pneumococcus, and meningococcus vaccines) 2 weeks before splenectomy to minimize the risk of overwhelming postsplenectomy sepsis. If the splenectomy is emergent, the patient should be vaccinated before discharge from the hospital.

Laparoscopic Splenectomy

The spleen is located high in the left upper quadrant of the abdomen and protected by the lower ribs. In a normal, healthy adult it weighs approximately 80 to 300 g and measures 10 to 12 cm in greatest dimension. Laparoscopic splenectomy can be performed safely in patients with splenomegaly, even in cases where the spleen is greater than 20 cm in length. The major limitation in our experience has been the size of the retrieval device. The hand-assisted laparoscopic approach may be a useful adjunct for selected patients with splenomegaly because it allows for rapid control of hilar blood flow.

In the case of massive splenomegaly, preoperative splenic artery embolization with absorbable gelatin powders may also be useful and may allow laparoscopic resection where it previously was not possible. This technique may also be advantageous in the setting of severe thrombocytopenia to minimize excessive blood loss. We do not routinely perform this adjunct because embolization may cause severe pain and ischemia, making patient selection crucial.

For a laparoscopic splenectomy, the patient is placed in either right lateral decubitus or the supine position with a bump under the left side. If the supine position is selected, a split-leg bed can be useful to facilitate dissection when the surgeon stands in between the legs. Access to the abdomen can be gained using either a closed or open technique based on surgeon preference and patient factors. Further port placement generally includes a 5 mm periumbilical camera port, a 5 mm right upper quadrant port, a 5 mm left upper quadrant port, and a 12 mm left sided port placed inferolateral to allow for an endoscopic stapling device. Exposure of the spleen is facilitated by placing the patient in reverse Trendelenburg with the left side up. If required, a Nathanson liver retractor may be placed through a 5 mm incision between the xiphoid process and the left costal margin. The abdomen should be explored at this point to assess for the presence of accessory spleens or splenunculi. The most common locations are the gastrosplenic ligament and greater omentum.

The dissection begins with the inferior attachment of the spleen, the avascular splenocolic ligament. This is mobilized and divided with an energy device and allows for inferior retraction of the colonic splenic flexure of the colon. The gastrosplenic ligament, containing the short gastric vessels, is then divided using an energy device. This dissection should be carried up to the level of the left crus and the stomach can be retracted to the right. Care is then taken while mobilizing the posterior attachment of the spleen, the lienorenal ligament, to identify the splenic artery and splenic vein within the hilum. These structures are then divided with an endoscopic linear stapling device. Care should be taken to avoid injury to the tail of the pancreas in this area. The splenophrenic ligament is the last attachment to be divided as it maintains cephalad and lateral retraction of spleen during division of the hilar vessels.

The spleen is then placed into an endoscopic retrieval bag. The edges of the bag are then brought through the lateral trocar site and the spleen is morcellated using ringed forceps. This piecemeal extraction should be avoided if malignancy is suspected. A hand-assisted laparoscopic approach can still be utilized in this situation by creating a small upper midline laparotomy or a small Pfannenstiel incision. If this is not possible, open splenectomy via a midline or left subcostal incision should be considered. Before closure, the surgical bed is again inspected carefully for hemostasis. Drains are not placed routinely unless there is suspicion for pancreatic injury.

Postoperative Management and Complications

In the early postoperative period, monitoring for hemorrhage is of the utmost importance. The most common site of hemorrhage

al recuperation to the undersurface of the diaphragm. Infectious complications are also common, with subphrenic abscess the most common in the early postoperative state. Overwhelming postsplenectomy infection is a potentially fatal complication with a reported 50% mortality rate. It is usually a late occurrence with most cases occurring greater than 2 years after splenectomy, but they can occur at any time in the patient's postoperative course. Patients typically present with symptoms of an upper respiratory infection that is rapidly progressive to sepsis with multiorgan failure. A high index of suspicion is required and early and aggressive treatment with broad-spectrum antibiotics is necessary. Children younger than 5 years are at highest risk. Vaccinations are critical for prevention with booster vaccines necessary every 5 years for pneumococcus and meningococcus. Despite this, overwhelming postsplenectomy infection is exceedingly rare, and most surgeons cannot recall ever treating a case.

Other postoperative complications include thrombocytosis, leukocytosis, pneumonia, pancreatitis, pancreatic fistula, venous thrombosis, and hypersplenism resulting from the presence of a missed accessory spleen. Reactive thrombocytosis is observed frequently, can occur immediately, and peaks at 3 weeks. Antiplatelet therapy is reserved for patients with thrombotic complications or when platelet counts reach 1 million. Hypersplenism from missed accessory spleens can be treated with selective embolization but may require reexploration if the patient fails and is symptomatic.

Portal or mesenteric vein thrombosis is well described after ligation of the splenic vein. It has been reported in up to 50% of postsplenectomy patients with higher rates with laparoscopic approaches as compared to open. Risk factors include a long splenic vein stump, postoperative thrombocytosis, hypercoagulable state, myeloproliferative disorders, hemolytic anemias, and preoperative splenomegaly. Patients will often present with vague abdominal pain, distention, and fever. Ultimately, if untreated, intestinal ischemia and portal hypertension can occur. Given these potentially devastating outcomes, patients can be maintained on prophylactic doses of low molecular weight heparin for 4 weeks postoperatively.

CONCLUSION

Splenic cysts, tumors, and abscesses, although uncommon, are potentially life-threatening entities of which every surgeon should be aware. Diagnosis is almost always made on imaging, particularly cross-sectional. In the symptomatic patient, surgery is indicated as definitive management to prevent life-threatening rupture with hemoperitoneum. Abscesses may be percutaneously drained with image guidance if amenable. Splenic salvage with partial splenectomy or other techniques may be considered if neoplastic lesions are small and there is no question of malignancy. Laparoscopic splenectomy continues to be the gold standard of treatment for any questionable splenic mass.

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SPLENIC SALVAGE PROCEDURES

Yuan-Laur Larry Lee, MD, MS, and David [illegible], MD, FACS

Splenic injury represents the most common solid organ injury after blunt abdominal trauma in adults, and the second most common in children. Though splenectomy remains the definitive management of splenic injury, removal carries a variety of attendant risks, both immediate and remote. Splenic salvage, then, offers an attractive alternative when resources and the clinical situation permit.

RATIONALE FOR SALVAGE

The spleen performs a variety of hematologic and immunologic functions; its absence therefore exposes patients to potential risk, the most well characterized being overwhelming postsplenectomy infection (OPSI). Splenic macrophages are responsible for phagocytosis of opsonized pathogens, whereas resident lymphocytes play a crucial role in humoral immunity through antibody and cytokine synthesis. Splenectomy thereby reduces immunologic responsiveness until these assets can be redeveloped. Unsurprisingly then, OPSI is most common in the years immediately following splenectomy, although risks persist through the patient's lifetime. Despite this process being classically associated with encapsulated organisms, asplenism is associated with increased susceptibility to infections from nonencapsulated pathogens as well, including gram-negative bacteria and even protozoans. Vaccination, therefore, does not confer complete protection. At greatest risk are patients at the extremes of age, warranting a greater interest in salvage in these vulnerable populations.

The current availability of vaccines to encapsulated organisms has potentially aided in the fight against OPSI, although definitive data are lacking. Patients who undergo splenectomy for trauma are at a lower risk of OPSI than those whose spleens are removed for hematologic or oncologic indications. The unpredictable nature of trauma, the relatively suboptimal immunologic state for vaccination experienced in the immediate postsplenectomy period, and the high incidence of poor compliance is further motivation for splenic salvage.

The spleen also serves as a hematologic filter, removing senescent cells from circulation. Splenectomy therefore allows damaged cells and cellular debris to circulate, which may lead to elevated platelet viscosity, platelet activation, endothelial activation, and a general trend toward pro-coagulability. Asplenism therefore has been associated with venous thromboembolism, stroke, myocardial infarction, and pulmonary hypertension, though these sequelae are more commonly identified in patients undergoing splenectomy for hematologic disease. Additionally, loss of splenic elimination leads to leukocytosis and thrombocytosis, which can complicate interpretation of laboratory data in patients with complex presentations. The immunologic functions of the spleen may also have protective functions against malignancy. This risk, although historically described in populations undergoing splenectomy for staging purposes, has more recently been identified following traumatic splenectomies as well. Consequently, the benefits of splenic salvage are lifelong when preservation can be accomplished safely.

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Splenic Salvage Procedures

Yuan-Laui Larry Lee, MD, MS, and David T. Efron, MD, FACS

Splenic injury represents the most common solid organ injury after blunt abdominal trauma in adults, and the second most common in children. Though splenectomy remains the definitive management of splenic injury, removal carries a variety of attendant risks, both immediate and remote. Splenic salvage, then, offers an attractive alternative when resources and the clinical situation permit.

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NONOPERATIVE INTERVENTION

The American Association for the Surgery of Trauma (AAST) grading scale remains the most common rubric for categorizing splenic injury severity (Table 1). In the absence of other indication for laparotomy, injuries of grades I and II, absent contrasting risk factors or concomitant injuries, can generally be managed successfully with observation in the vast majority of situations. Serial hemoglobin or hematocrit measurements alongside hemodynamic monitoring in an intensive care unit setting allow for recognition of potential deterioration and conversion to more aggressive interventions as indicated. Higher grade injuries do not necessitate operative intervention, but greater failure rates and the potential for complications with grade III or higher injuries, angioembolization may be beneficial if a nonoperative strategy is pursued in these patients (Fig. 1). Similarly, though not explicitly delineated in the AAST scale, the presence of vascular findings such as active contrast extravasation, or pseudoaneurysms on initial imaging increase the risk of failure and generally benefit from more aggressive intervention.

Hypotension unresponsive to transfusion, peritonitis, or significant transfusion requirement are generally considered failure, requiring salvage angiographic or operative intervention. Transfusion thresholds vary in practice; there are those who set a threshold of any transfusion needed as an indication for operative intervention. Typically, transfusion as a threshold for operative intervention range from more than 2 to 4 units of packed red cells. Failure rate of nonoperative management for injuries of any grade is approximately 10%, and can be as high as 75% in grade V injuries. Selective management practice for splenic injuries varies greatly between adult and pediatric populations, likely secondary to the greater concern for the development of OPSI in children. Pediatric patients are more likely to undergo greater transfusion amounts than adults in the attempt to salvage the injured spleen.

TABLE 1 American Association for the Surgery of Trauma Splenic Injury Grades

Grade	Characteristics
I	<10% subcapsular hematoma <1 cm laceration
II	10%–50% subcapsular hematoma 1–5 cm intraparenchymal hematoma 1–3 cm laceration without trabecular vascular involvement
III	>50% subcapsular hematoma >5 cm intraparenchymal hematoma >3 cm laceration or trabecular vascular involvement
IV	Laceration involving vasculature with >25% devascularization
V	Shattered spleen Hilar laceration with splenic devascularization

Modified from Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). J Trauma. 1995;38:323–24.

Angioembolization

Splenic angioembolization has become a mainstay of selective management of blunt splenic injury, allowing avoidance of operative morbidity and preservation of splenic tissue while decreasing vascular inflow to control hemorrhage. Hemorrhage control is achieved in 85% to 95% of patients referred for angioembolization; however, typical operative fluoroscopic suites notwithstanding, the presence of labile hemodynamic instability is a contraindication to angioembolization because of limited resuscitative capabilities in most angiographic suites.

Additional considerations include resource availability, operator expertise, and anatomic suitability; vascular injury such as intimal dissection or perforation during angiography is an uncommon but potentially catastrophic complication of endovascular therapy. Nonetheless, this strategy, when appropriate, allows avoidance of the morbidities of laparotomy as well as limiting aspleric or hyposplenic consequences.

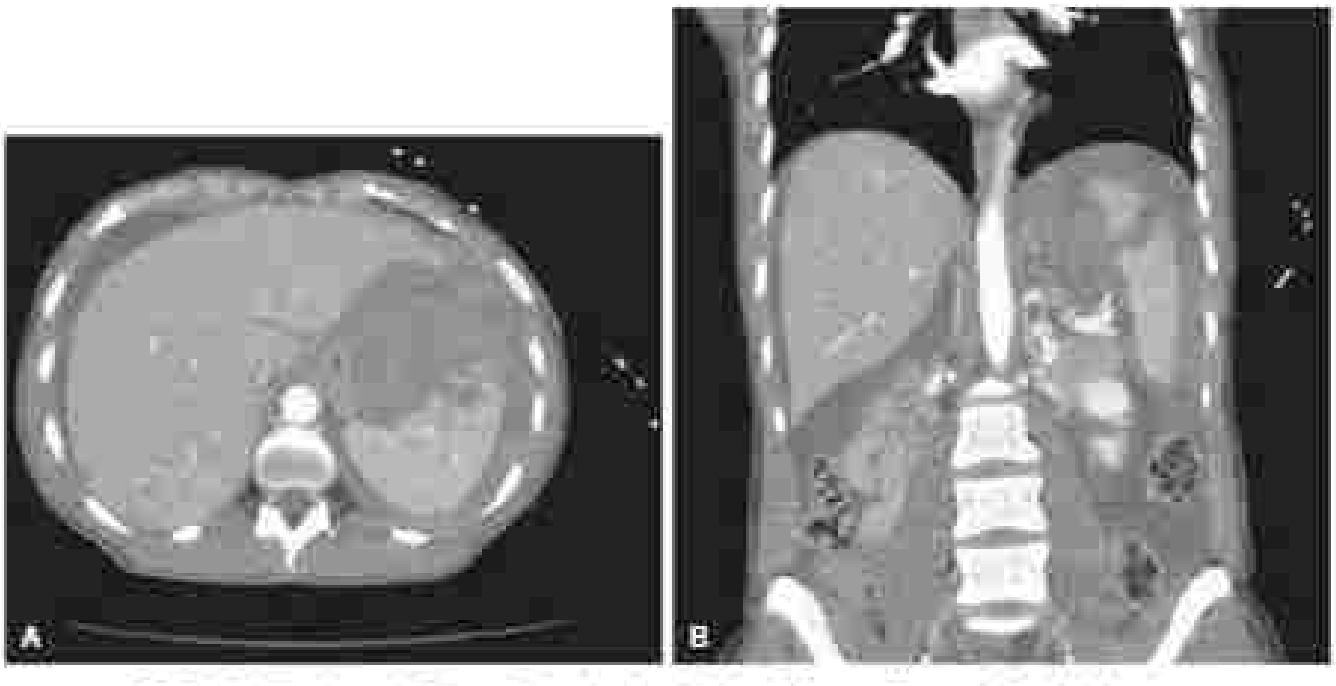

FIG. 1 Axial (A) and coronal (B) views of an American Association for the Surgery of Trauma grade 3 splenic laceration.

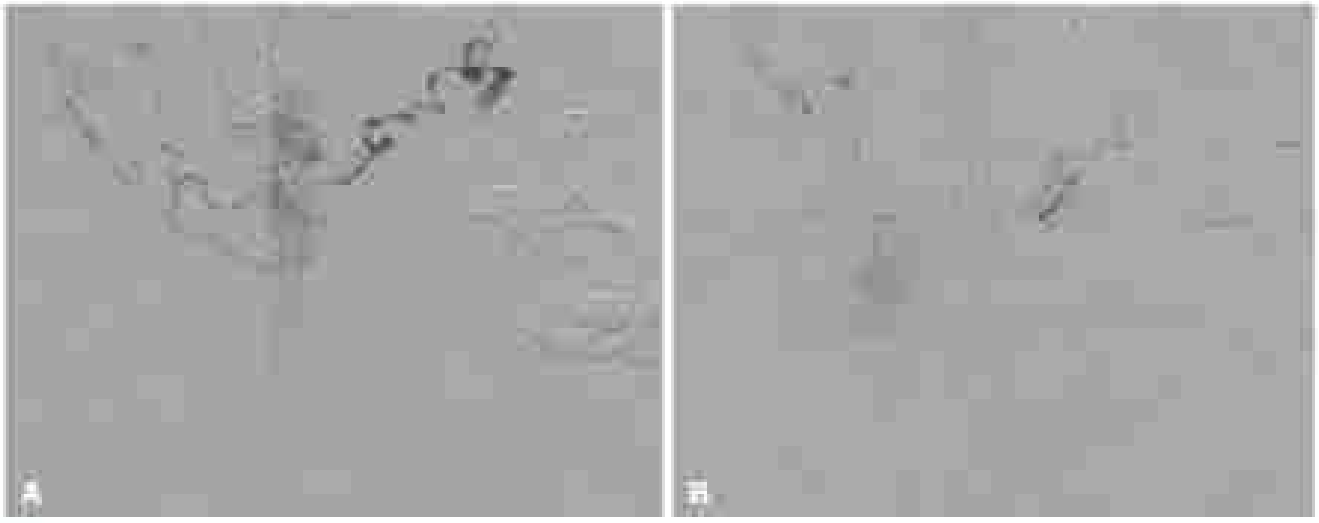

FIG. 2 (A) Angiographic demonstration of splenic artery pseudoaneurysm within splenic parenchyma following abdominal packing at laparotomy. (B) The same patient status after coil embolization.

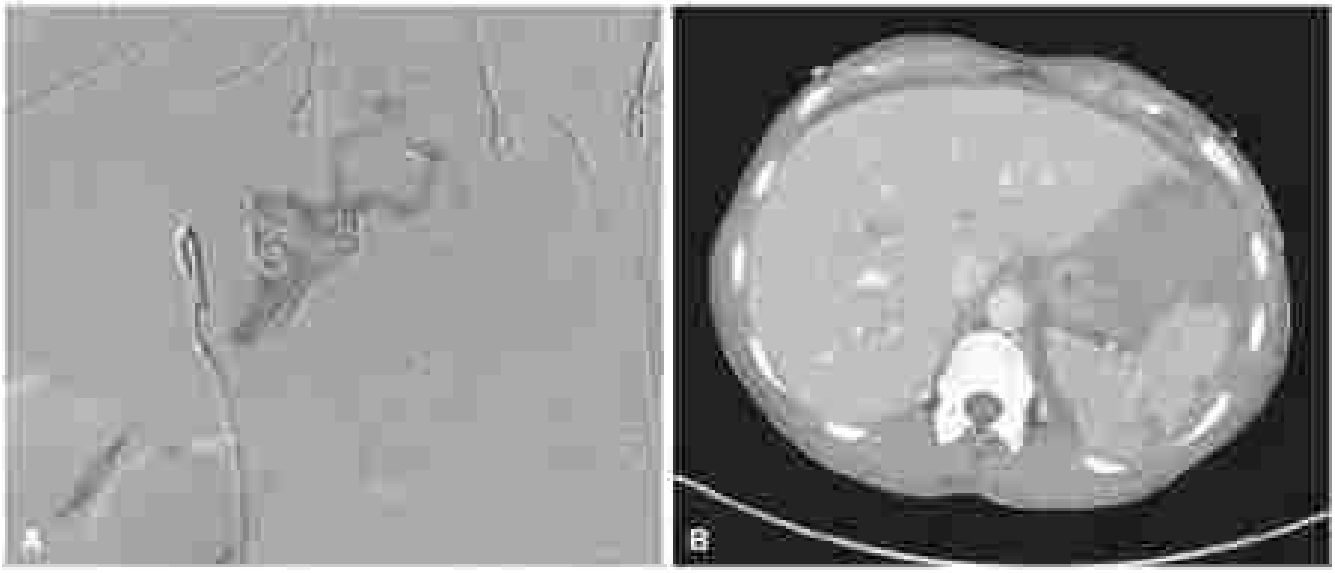

FIG. 3 (A) Combined proximal and distal coil embolization of the splenic arterial supply. (B) Axial computed tomography image of the same patient postembolization demonstrating splenic infarction.

Embolization is typically performed with either metal coils or gelatin sponge (Fig. 2). Conflicting data exist regarding the superiority of embolization material, but tend to favor coils when differences are noted with regard to both success rate and subsequent complications, both hemorrhagic and infectious.

Splenic artery angioembolization can be performed proximally at the main splenic artery or more distally or a combination of both. Proximal embolization reduces global parenchymal perfusion of the spleen (that is, theoretically decreases arterial pressure) to facilitate thrombus formation, whereas distal embolization more definitively abrogates arterial inflow to the affected region. Selection of technique is commonly driven by operator expertise and the location and extent of the injury. Failure, as defined by need for operative intervention appear to be comparable between the two strategies, rates of nonoperative splenectomy are similar as well. Distal embolization unsurprisingly incurs increased risk of infarction, and late complications thereof are uncommon but primarily consist of splenic abscesses and cysts that may necessitate subsequent operative intervention (Fig. 3).

Assessments of splenic function following proximal and distal embolization consistently demonstrate superiority over splenectomy in multiple hematologic and immunologic parameters. Disparities between the two techniques have been subtle, in part because of limited study sizes, but trend toward favoring distal embolization for greater preservation of function when any difference is detected. This finding, in the context of partial splenic infarction after distal embolization, suggests that preserved splenic after distal embolization remains functionally intact, whereas proximal embolization may compromise global function without radiographic evidence of infarction. The data remain far from definitive. Additionally, no strong recommendations can as yet be made to the need for vaccines against encapsulated bacteria following splenic embolization, so practice remains varied.

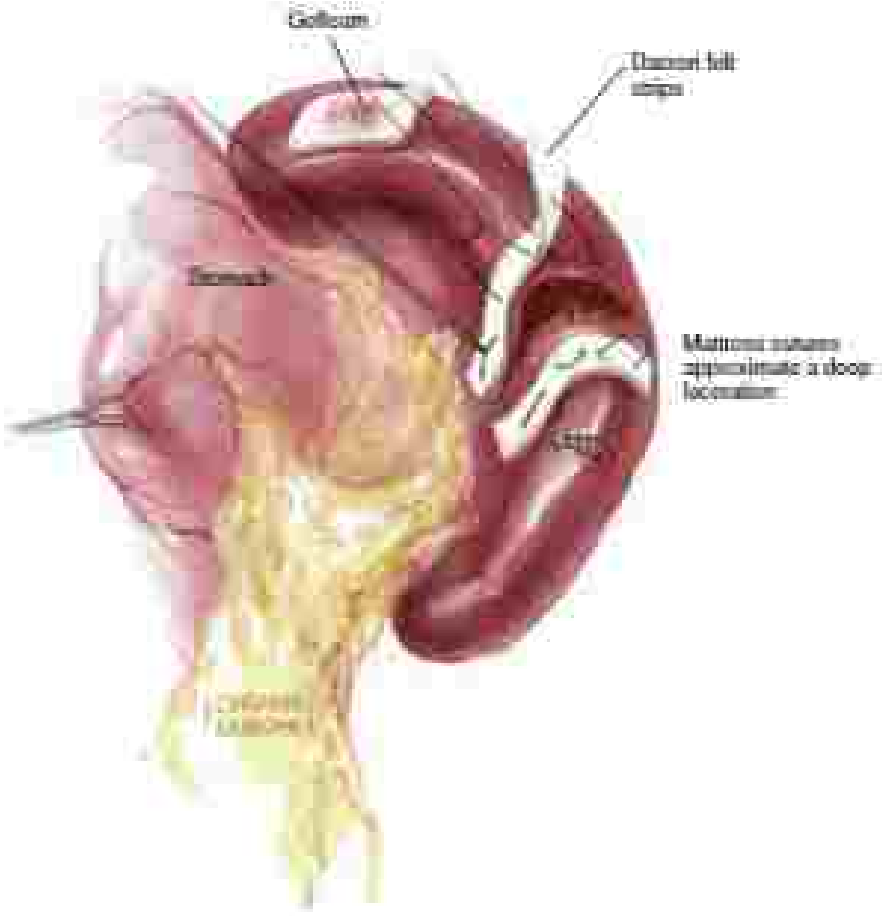

FIG. 4 Demonstration of topical hemostatic agent and technique of pledgeted repair of splenic laceration. [...]

In children, the use of angiography is held for those with evidence of ongoing bleeding but is not recommended prophylactically for patients, even those with pseudoaneurysms or bleb.

Operative Techniques

Although operative management of splenic injury incurs the morbidity of abdominal access and a potential for secondary hemorrhage, operative salvage techniques retain the benefits of preserved splenic function. Use of these techniques, however, should be considered in the context of the scenario mandating operation (e.g., primary operation vs previous failure of nonoperative management, timing, concomitant injuries). Penetrating abdominal trauma, for example, may mandate abdominal exploration that precludes imaging and nonoperative strategies. Because the decision to pursue operative intervention frequently stems from an acuity that makes operative salvage higher risk or time consuming in an often times sensitive situation, and must be weighed against the more definitive hemorrhage control of splenectomy, particularly in patients at risk for coagulopathy and those who will be intolerant of even transient hypoperfusion such as in traumatic brain injury.

After abdominal access, exposure of the spleen is performed in a manner paralleling that for splenectomy. Provided more urgent injuries have been addressed, the omentum is mobilized and the splenic hilum identified. The short gastric, splenocolic, splenophrenic, and splenorenal ligaments are divided if not already dissected by hematoma. The spleen can then be mobilized on its main vascular pedicle adjacent to the tail of the pancreas, either manually or with the assistance of packing along the posterior peritoneum to elevate the spleen into the operative field. Care should be taken to avoid injury to the pancreas during this dissection. Once the spleen is adequately in the field, salvage techniques or splenectomy may then be selected based on the nature and location of injury.

In more minor injuries, direct thermal cautery may suffice with the argon beam (the standard electrocautery device usually does not work by itself). There are a variety of topical hemostatic agents commercially available as adjuncts to direct pressure and packing. Available as powders, foams, gels, and sheets of various dimensions, these products may contain either active or passive hemostatic agents, most commonly cellulose or kaolin. Impregnated gauzes in particular offer the ability to maintain adherence to injured tissue and simultaneously allow application of direct pressure to promote hemostasis, though not all products are appropriate to leave in the abdomen outside of damage control situations.

Pledgeted suture splenorrhaphy offers more stability when anatomically practical, most commonly deeper linear lacerations (Fig. 4). As with similar repairs for hepatic injuries, pledgets are commonly fashioned from polyethylene terephthalate, fibrocellulose strips, or other hemostatic materials and secured with large mattress sutures, 0-0 or 2-0, with care taken to avoid further lacerating parenchyma while securing the suture.

If the injury extent is not amenable to topical or suture repair but is limited to one anatomic aspect of the spleen, partial splenectomy allows for splenic salvage of remaining viable tissue (Fig. 5). After embolization of the splenic, the distal branches of the splenic artery are isolated. The vessel supplying the infarcted pole can be clamped or encircled with a vessel loop to assess for adequate hemostasis on vessel occlusion; if not, an alternate technique or splenectomy should be used. The vessel is then suture ligated and sharply divided, and a demarcation of ischemic tissue identified. Depending on tissue dimensions, a linear stapler with a vascular load or cautery may be

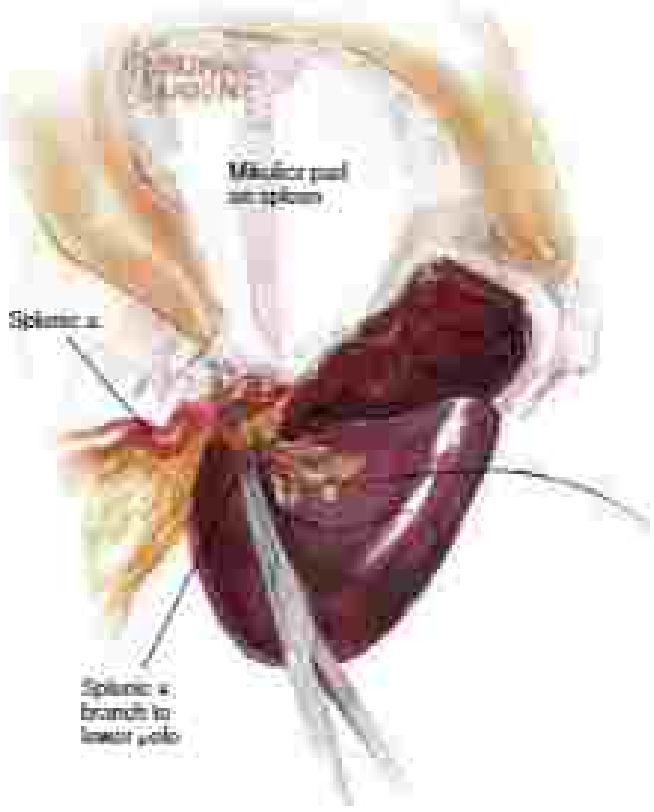

FIG. 1 Technique of partial splenectomy. (From Cameron JL, Maddern GJ, Atlas of Gastrointestinal Surgery, 2nd ed. Vol 1. Hamilton, ON: BC Decker Inc; 2007, p. 1.)

mesh for the parenchymal resection. The raw visceral surface is then oversewn with running suture or can be reinforced with reabsorbable pledgets or omentum.

When the injury pattern is not amenable to pledgeted repair or partial splenectomy, mesh splenorrhaphy remains an alternative for tamponade, but has somewhat fallen out of favor because the technique can be relatively time consuming, implants a foreign body with concomitant infectious concerns, and requires an organ sufficiently injured to preclude alternative strategies while remaining viable. A mesh of polyglactin or similar material is sized and trimmed, then a purse string suture is initiated hemitransdiaphragmatically. After fully mobilizing the spleen and achieving vascular control of the hilum, the mesh is wrapped around the lateral surface and then bunched around the hilar vessels with the sutured perimeter posterior. The purse string can then be completed along the anatomical circumference to the appropriate tension to achieve hemostasis in the parenchyma. Care should be taken to avoid strangulation of hilar vasculature when tightening the purse string so exciting excessive pressure on splenic tissue causing ischemia.

Although damage-control laparotomies have become commonplace for managing polytrauma, caution should be exercised if considering salvage in the form of abdominal packing for all but the most trivial splenic injuries. Even though prompt recuperation limits the mortality of temporary closure, splenectomy at initial operation can be performed rapidly for definitive hemorrhagic control and may facilitate correction of physiologic derangements during the resuscitative phase.

Intensive Care Unit Considerations

Patients with splenic injuries managed by salvage techniques should be serially monitored for potential rebleeding. Hemoglobin measurements are typically obtained at intervals ranging from every 2 to 4 hours during the first 12 to 24 hours, then spaced out as the patient demonstrates hematologic and hemodynamic stability. After 24 to 48 hours, and depending on injury severity and selected management strategy, level of care can then be deescalated, but clinicians should be cognizant of the possibility for delayed splenic rupture. Delayed splenic rupture typically occurs in fewer than 5% of patients and carries a higher mortality in the 10% range, likely from delayed recognition. Although case reports for delayed rupture have described events sometimes months removed from initial injury, the first week is the typical window for this complication.

Leukocytosis and thrombocytosis are commonplace following both splenectomy and splenic salvage as cells normally removed from circulation by the spleen are allowed to persist, and the relative proportions of different hematologic lineages may vary over time. Splenectomy typically produces more pronounced leukocytosis than embolization and similar degrees of thrombocytosis. However, unlike splenectomy, these alterations often normalize by between 4 and 6 weeks postintervention for angioembolization. Distinguishing expected leukocytosis from infection can be challenging, but existing literature for splenectomy suggests a white blood cell count greater than 15,000/μL and a platelet/white cell ratio less than 20 on or after postoperative day 5 are indicative of ongoing infection. Similar thresholds for angioembolization and other salvage techniques have not been established, but trends in the appropriate direction should raise the index of suspicion in these patients.

Anticoagulation, most commonly as prophylaxis against venous thromboembolism, must be weighed against hemorrhagic risk following splenic salvage. Though not studied rigorously, the available evidence suggests prophylactic low molecular weight heparin can be initiated within 24 to 48 hours with comparable outcomes and transfusion requirements. Meanwhile, delay of prophylaxis in a trauma population significantly increases risk of venous thromboembolism, with reports of a significant increase after 72 hours. Optimal timing of therapeutic anticoagulation when indicated remains unclear.

Follow-up

Late complications such as arteriovenous fistula or pseudoaneurysm formation, though rare, may occur, particularly when observation without operative or angiographic intervention is used. As the initial posttrauma thrombus resolves, pseudoaneurysms previously not appreciated may be identified. Though there are no formal recommendations regarding repeat imaging in these scenarios, a venous contrast abdominal computed tomography (CT) scan is commonly selected when any imaging modality is used. Timing of repeat examinations is also controversial, and have ranged from 48 hours to 1 week in the literature depending on the center. If any abnormalities are identified at this point, angioembolization is recommended.

The utility in the outpatient setting is even more unclear, often falling under the purview of primary care physicians, with Doppler ultrasound or CT being described. Injury grade is proportional with rate of healing. Most will studied in children and adolescents, specific time to radiographic healing has varied between reports, ranging from 1 to 6 months for grade I injuries and 5 to 11 months for grade IV. Consequently, return to physical activity is similarly contentious, but light activity at 1 month postinjury and full activity after 3 months has been suggested in the general population. Imaging as a tool to guide activity restrictions is not supported in existing data.

Though vaccination against encapsulated organisms has been used in the past with splenic salvage, immunologic data and peripheral smear findings affirm the preservation of splenic immunologic function and suggests this is likely unnecessary in most patients after splenic salvage. Volumetric assessments of residual splenic tissue have not been well correlated with immunocompetency. The decision to vaccinate therefore should reflect the clinician's assessment of anticipated splenic function given the nature of the injury and selected salvage technique.

SUMMARY

Splenic salvage offers multiple benefits over splenectomy and should be attempted in patients with sufficient stable tissue and appropriate clinical risk. With injury patterns that do not mandate primary abdominal exploration, low grade (I–II) injuries can often be observed, whereas higher grade (III–V) injuries should be offered angioembolization. The decision to pursue open intervention does not preclude salvage but is generally higher risk given the underlying process mandating exploration.

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MANAGEMENT OF INGUINAL HERNIA

Gina L. [illegible] M.D., F.A.C.S. [illegible] and Mark [illegible]

[illegible]

INDICATIONS AND TIMING OF REPAIR

[illegible]

CONSIDERATIONS IN SELECTING THE OPTIMAL APPROACH

A variety of surgical repairs has been developed. Selection of the appropriate technique is largely surgeon dependent based on experience, with the best outcomes associated with the repair most frequently performed. Patient and hernia characteristics should guide decision making in procedural selection. Although there are no absolute contraindications to laparoscopic repair, those patients who are not candidates for general anesthesia are better approached with an open technique that can be performed with spinal or local anesthesia with sedation. Although laparoscopic inguinal hernia repair can be performed under epidural anesthesia, inadequate muscular relaxation limits the working space with this approach so that the large majority of these repairs are conducted with general endotracheal anesthesia. The choice of total extraperitoneal repair (TAPP) versus transabdominal preperitoneal repair (TAPP) may also be dictated by the patient characteristics as well as surgeon experience. Patients who have previously undergone surgery may have adhesions that make laparoscopy more difficult, in particular, patients who have had a prostatectomy have usually obliterated the preperitoneal space required for minimally invasive techniques.

There is compelling evidence to support laparoscopic inguinal hernia repair for patients with bilateral inguinal hernias as well as recurrent inguinal hernias after prior open inguinal hernia repair. For the majority of inguinal hernia patients, open and minimally invasive mesh repairs are equivalent.

OPEN INGUINAL HERNIA REPAIR

Tissue Repair

Although direct comparisons are limited and available randomized controlled trials are of low quality and subject to bias, the Shouldice repair is the best-researched inguinal hernia repair technique with supporting level IA evidence. Compared with other tissue repairs, Shouldice reports lower recurrence, hematoma, and chronic pain rates. Surgeon experience and meticulous technique have significant impact on outcomes. From a 2012 Cochrane systematic review, the recurrence rate for Shouldice was tighter than mesh Lichtenstein repair. There was no significant difference in chronic pain, surgical site infection, or seroma. Because there was inclusion of heterogeneous studies with questionable external validity, the comparison was not robust. Given the risk of mesh repair in contaminated cases and strangulated hernias as well as increasing patient concerns about mesh, it is important to have a primary tissue repair in one's surgical armamentarium.

Lichtenstein Repair

The most common open mesh repair is the Lichtenstein, which was the original tension-free repair that reinforces the inguinal floor with a prosthetic mesh. Initially described in 1987, the repair involves fixation of mesh using a permanent suture to the anterior rectus sheath, internal oblique aponeurosis, the pubic tubercle, and the shelving edge of the inguinal ligament. The approach is via an incision inferior and medial to the anterior superior iliac spine which is extended medially for approximately 6 to 8 cm. The dissection is carried down to the aponeurosis of the external oblique muscle which is opened in the direction of the muscle fibers. Using Metzenbaum scissors, this incision in the aponeurosis is extended through the external inguinal

ting. Upon opening the aponeurosis, the ilioinguinal nerve will be visualized and should be preserved. The internal oblique fibers are dissected bluntly from the overlying external oblique muscle flaps that reveal the shelving edge of the inguinal ligament. In addition, the iliohypogastric and ilioinguinal nerves are identified and preserved. The spermatic cord, along with an indirect hernia sac if present, should be identified and encircled with a Penrose drain. The hernia sac will usually be seen on the anteromedial surface of the cord structures. At this point, the genital nerve is visualized along the inferolateral surface of the cord adjacent to the external spermatic vein. The floor of the inguinal canal should be carefully assessed for weakness indicating a direct hernia. The medial aspect of the mesh is secured to the aponeurotic tissue overlying the pubic tubercle with an overlap of approximately 2 cm. The mesh should be secured using a running nonabsorbable monofilament suture, which is continued laterally along the inferior edge of the mesh to the shelving edge of the inguinal ligament to just lateral to the inguinal ring. The mesh is split to encircle the spermatic cord, with two thirds of the mesh above and one third below. The two tails are secured with a single nonabsorbable suture to the shelving edge to recreate a new internal ring. Interrupted absorbable monofilament sutures firmly secure the superior edge of the mesh to the internal oblique aponeurosis and muscle with avoidance of entrapment of the iliohypogastric nerve. The layers of the abdominal wall are then closed, starting with the aponeurosis of the external oblique, Scarpa's fascia, and skin. A modification of the Lichtenstein repair uses the addition of a mesh plug that is placed through the internal ring to the case of an indirect inguinal hernia. For a direct hernia, the plug is sutured to Cooper's ligament, the inguinal ligament, and the internal oblique aponeurosis. However, the use of mesh plugs is discouraged due to the risk of migration, mesh contraction, and chronic pain.

Local Anesthetic Block

Local anesthetic block is a safe and cost-effective method of delivery of anesthesia for open inguinal repair and postoperative analgesia. Regardless of whether general anesthesia is used, preoperative local anesthetic injection before the surgical incision may decrease postoperative pain by reducing the stimulation of nociceptors. A 50:50 mixture of 1% lidocaine and 0.5% bupivacaine is used with addition of epinephrine. Subdermal infiltration under the planned incision is performed transversely with approximately 5 mL followed by intradermal injection to raise a wheal at the incision. Deeper subcutaneous vertical injection is performed. Proximal ilioinguinal nerve anesthesia is applied with injection medial to the anterior superior iliac spine though there is risk of direct nerve injury with this blind technique, injecting 10 mL of the local anesthetic directly under the exposed external oblique aponeurosis bathes the peripheral inguinal nerves with additional solution reserved for injection at the spermatic cord and pubic tubercle and final subaponeurotic and subcutaneous injection before closure.

MINIMALLY INVASIVE INGUINAL HERNIA REPAIR

Transabdominal Preperitoneal Repair

The transabdominal preperitoneal inguinal hernia repair is performed with the patient in the Trendelenburg position with tilt toward the contralateral side to allow the viscera to fall away from the operative field. The abdomen is accessed via a curvilinear incision at the inferior umbilical rim and placement of a 10-mm port. There is a less a concomitant umbilical hernia, this should be assessed by examination preoperatively and at the time of incision. The TAPP approach is well suited to the patient with an umbilical hernia because it allows use of this abdominal wall defect for midline port placement after clearance of the hernia contents, avoids the risk of leak of insufflation into the peritoneal cavity that could be seen with the total extraperitoneal approach, and provides for repair of the umbilical and inguinal hernias. Visual inspection of both inguinal regions allows

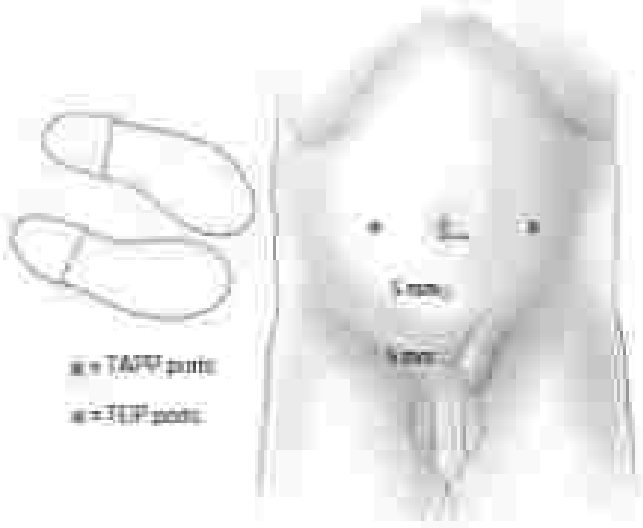

FIG. 1 Proper ports placement for one operator working for one component TAPP and one component TEP. The umbilical port is placed at the level of the umbilicus and at least 1 cm (ideally 2 cm) from the superior extent of the operative field. The 5-mm ports are placed at least 10 cm apart to allow for triangulation of instruments. TAPP, transabdominal preperitoneal; TEP, total extraperitoneal.

for port placement adjustment to triangulate the instruments to the target space. A 5-mm 30 degree laparoscope is preferred. Bilateral hernias are approached via two 5-mm working ports placed about 8 cm lateral to and slightly below the umbilical port. For the unilateral repair, the ipsilateral 5-mm trocar is placed at the level of the umbilicus, whereas the contralateral 5-mm trocar is placed several centimeters lower than the umbilicus for ergonomic optimization (Fig. 1). Robotic TAPP can also be performed, in which case the three robotic ports are placed at or above the level of the umbilicus at least 15 cm (10 cm from the superior extent of the operative field), with one midline port and two working ports 8 to 10 cm on each side of the midline.

Wide exposure of the preperitoneal surface is critical to the operation. The peritoneum is opened from just lateral to the inferior superior iliac spine to the medial umbilical ligament and dissected down to well over the pubis and iliac vessels leaving the bladder down (Fig. 2). Although the size of the opening in the peritoneum may be reduced after gaining experience with the technique to limit the time for peritoneal closure, the preperitoneal dissection should be ample to allow for identification of all hernia defects at the preperitoneal surface and for wide mesh coverage. A wider opening allows the peritoneal flap to lay down more fully and this visual advantage can be helpful early in the surgeon's experience. Lateral and the most medial dissections are performed first to allow the peritoneum to fall away and improve operative exposure prior to dissection of the indirect hernia sac. The inner edge of the peritoneum should be at minimum 1 to 2 cm away from the inferior edge of the mesh to avoid folding of the mesh when the peritoneum is closed.

The lipoma of the direct hernia defect should be fully reduced and removed. The white edge of the attenuated transversalis fascia can be seen at the intersection with the lipoma and denotes the plane of dissection (Fig. 3). Caution is exercised to identify and avoid injury to the corona mortis, the sometimes present aberrant vessels from the epigastric vessels to the obturator vessels located below the direct defect at Cooper's ligament. The external iliac vein should be visible. If there is overlying fat, this suggests a femoral hernia with lipoma that should be reduced.

The hernia sac at the indirect space is dissected from the cord structures during cephalad retraction of the hernia sac. The TAPP approach provides an advantage during complex hernia cases, such as the scrotal inguinal hernia, by allowing visualization from both the preperitoneal and peritoneal spaces of herniated viscera. The fat and tissue should be cleared between the vas deferens and Cooper's ligament, and the hernia sac and peritoneum should be separated fully

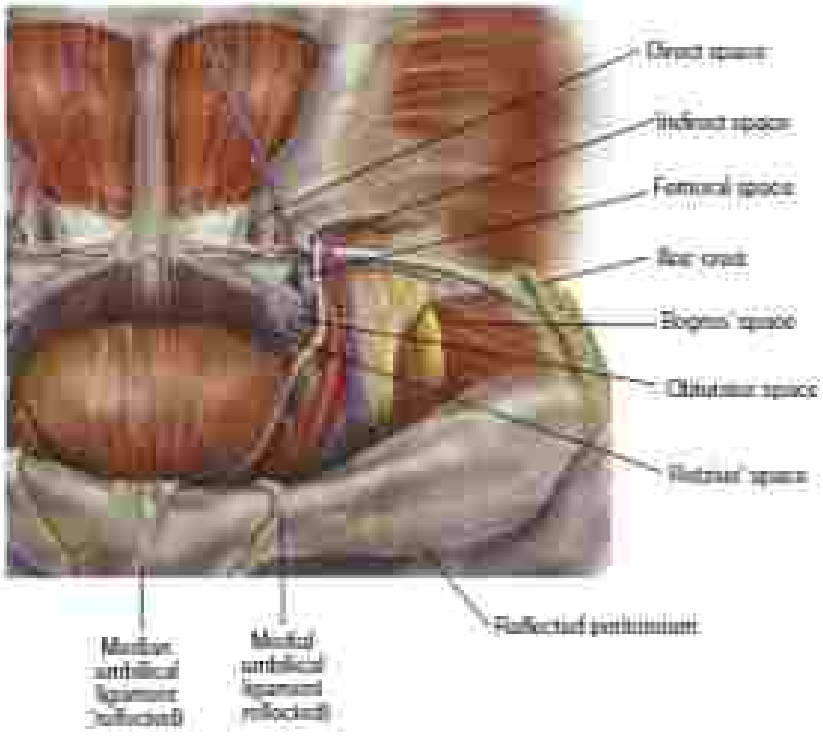

FIG. 2 Preperitoneal sagittal anatomy.

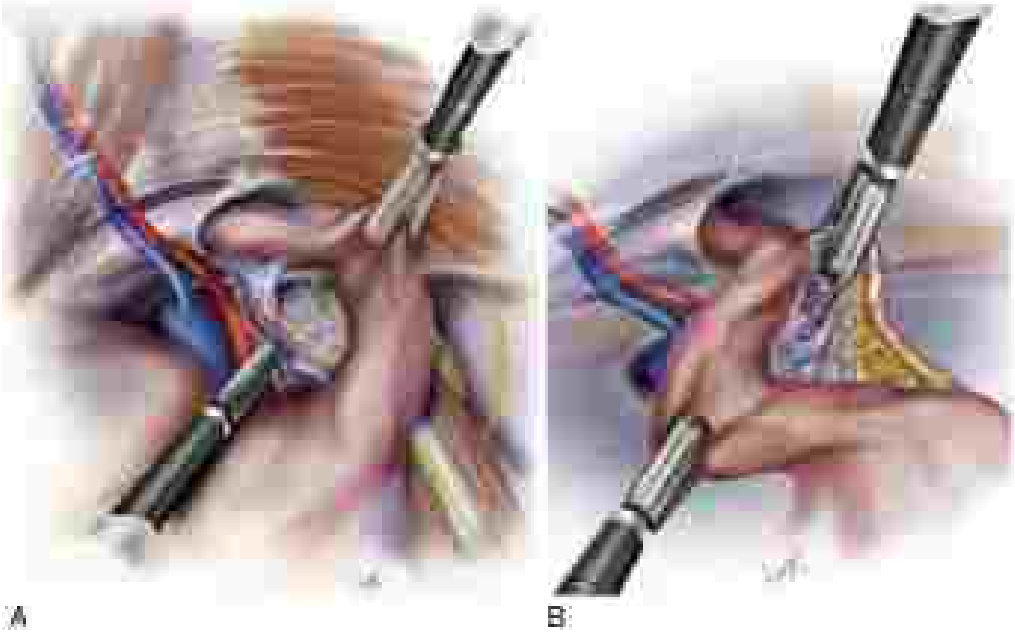

FIG. 3 (A–B) Dissection of the hernia sac. Apply gentle traction on the hernia sac and carefully dissect away from the spermatic structures.

from the cord structures well over the iliac vessels and psoas. The indirect lipoma is identified just lateral to the vas and gonadal vessels and this is retracted cephalad and fully reduced. This may appear small but can be larger beyond the inguinal ring. Leaving a retained lipoma may result in continued groin pain.

Meticulous attention should be paid to fascial closure and other aspects that can reduce the risk of hernia recurrence. The weakened transversalis fascia of the direct hernia sac should be inverted and sutured to reduce the hernia recurrence risk for larger direct hernias and likely decrease the seroma rate. A wide mesh should be used for ample coverage of the myopectineal orifice (Fig. 4). The mesh should lay smoothly against the abdominal wall extending below the pubis and Cooper's ligament and anterior to the bladder so that the mesh will not shift when the bladder fills. Fixation of the mesh may not be needed routinely; however, if there is a large hernia defect, fixation is recommended whether by sutures, a minimal number of tacks, or self-gripping mesh to avoid shifting of the mesh because of seroma or contraction of the mesh.

The mesh should be completely repetitionealized. The peritoneum closure should be complete without gaps. Sutured closure with absorbable 2-0 or 3-0 suture is preferred. A self-locking knot is placed on the suture before lowering the suture reduces operative time. Caution is urged regarding barbed suture to ensure it is well covered and exposure minimized to avoid bowel adherence to the barbs.

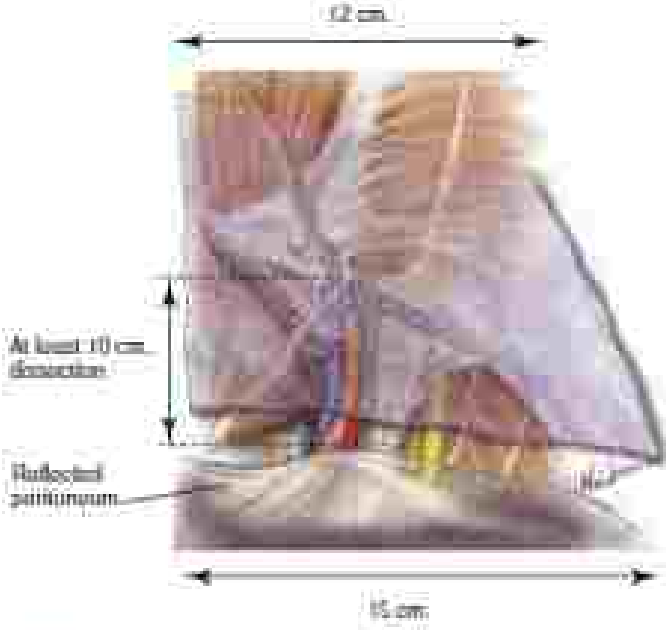

FIG. 4 Preperitoneal mesh placement with white arrows at the myopectineal orifice.

Total Extraperitoneal Repair

Patient preparation is similar for both TEP repair and TAPP: the patient is supine with arms out or tucked and the abdomen and inguinoscrotal areas are clipped if necessary. Patients are required to void before surgery; however, a urinary catheter is used by many surgeons to ensure bladder emptying. Entry is via an infraumbilical 12 mm port through which the anterior rectus sheath is incised just off the midline. After opening the sheath, the rectus muscle is split to access the posterior sheath, and a balloon trocar can facilitate the dissection of the preperitoneal space. By inflating the balloon under direct vision, the epigastric vessels can be visualized along the anterior abdominal wall, and the hernia is usually identified as well. Inadvertent entry into the peritoneal cavity will be readily apparent and may occasionally require conversion to a TAPP or open repair. Once the balloon has expanded the preperitoneal space, it is removed and the space is insufflated to a pressure of 12 to 15 mm Hg. A 10 mm camera is used, preferably a 45- or at least 30-degree angled scope. Two 5-mm ports are placed in the midline, allowing for several fingerbreadths between the lowest port and the pubic symphysis as well as between the ports themselves. The lateral abdominal wall is identified first, by bluntly dissecting the fatty areolar tissue anterior to the hernia sac but inferior to the epigastric vessels, which should be identified and protected. Medially, Cooper's ligament is identified and cleared of any overlying fat while taking care to avoid the venous circle of Taradeau as well as the femoral canal tributary. The spermatic cord and hernia sac can be grasped and retracted cephalad while taking care to reduce an adherent cord lipoma as well. If the peritoneum is inadvertently torn during dissection, which most commonly occurs in patients who have had prior surgery, the defect should be closed, if possible, with an endoscopic clip or with an EndoAcus. In addition, the resulting pneumoperitoneum may decrease the working space significantly and the pneumoperitoneum can be decompressed via a Veress needle or 5 mm port in the left upper quadrant of the abdomen.

TAPP VERSUS TEP?

The International Guidelines for Groin Hernia Management published by the HerniaSurge Group and endorsed by multiple major international hernia societies offer statements and recommendations regarding comparison of laparoscopic TAPP and TEP techniques. These are largely equivalent operations with similar operative time and cost, complication risk, pain incidence, and recurrence rates. Robotic assisted TAPP adds additional cost. TEP confers a higher conversion rate than TAPP but the incidence is low. The Guidelines note that although very rare, there is a trend for more visceral injuries in TAPP and more vascular injuries in TEP. Meticulous fascial closure at the umbilical port site in TAPP is avoided. Though the risk of port site hernia is very low with TAPP, there is a known increased incidence of port site hernia for umbilical sites. Because the surgical outcomes are similar, the choice should be based on the surgeon's skills, training, and experience.

There are certain situations that are better suited for one minimally invasive approach over another. The recurrent hernia after laparoscopic repair is better addressed by TAPP or open repair rather than TEP. TEP holds an advantage for the bilateral inguinal hernia without a large scrotal component as the midline does not require peritoneal closure. Patients with prior lower abdominal surgery, particularly by midline laparotomy incision, scrotal hernia particularly with incarceration, prior prostatectomy, prior inguinal hernia plug and patch repair, and those with uncertain diagnosis in which diagnostic laparoscopy would be beneficial, should undergo laparoscopic or robotic assisted TAPP rather than T/P. The enhanced TEP techniques with access to the preperitoneal space higher or more lateral in the abdominal wall addresses some of these shortcomings with traditional TEP, allowing an extraperitoneal approach in cases in which lower abdominal surgery would otherwise be prohibitive.

Risk Factors for Inguinal Hernia Development and Recurrence

Patients with family or personal history of inguinal hernia, older age (direct hernias), male sex, collagen disorder with decreased mature type I collagen, and history of prostatectomy are risk factors for inguinal hernia development. Interestingly, in contrast to risk factors for ventral incisional hernia, obesity is protective to inguinal hernia development, with lower body mass index associated with higher inguinal hernia incidence.

An outlined, surgical technical factors contribute to the risk of hernia recurrence, including decreased mesh overlap. Lower case volume is associated with a higher recurrence risk. Surgical outcomes are poorer for female patients. Direct and sliding hernias are associated with a higher rate of recurrence.

CHRONIC PAIN AFTER INGUINAL HERNIA REPAIR

The incidence of chronic pain after groin repair is higher than the risk of recurrence. There is a higher risk of pain associated with open repair. The ilioinguinal, iliohypogastric, and genitofemoral nerves should be identified during open repair. Retraction of the nerves and disruption of the perineurium should be avoided. The genitofemoral nerve is often the hardest to identify by the spermatic vessels. Neurectomy proximal to the site of nerve injury should be performed at the time of repair if an injury is suspected. The nerve should be allowed to retract into the muscular bed.

Chronic groin pain is a small but known risk after laparoscopic inguinal hernia repair. The lateral femoral cutaneous nerve may be seen in the fatty layer below the iliopubic tract and this should be left undisturbed with avoidance of disruption of the perineurium. The femoral branch of the genitofemoral nerve is seen more medially. The genitofemoral nerve will be found medially near the spermatic cord vessels. In the female patient, the genitofemoral nerve will join the round ligament closer to the inguinal canal. When performed, division of the round ligament should be performed close to the peritoneum to avoid nerve injury. If mesh fixation tacks are used, care is taken not to press too deeply into the abdominal wall to avoid a nerve injury superficially. The number of tacks used should be minimized because the risk of chronic pain increases resulting from potential nerve injury. Fixation should be performed medially to the epigastric vessels and anteriorly with avoidance of the lateral space, particularly below the iliopubic tract (Fig. 5).

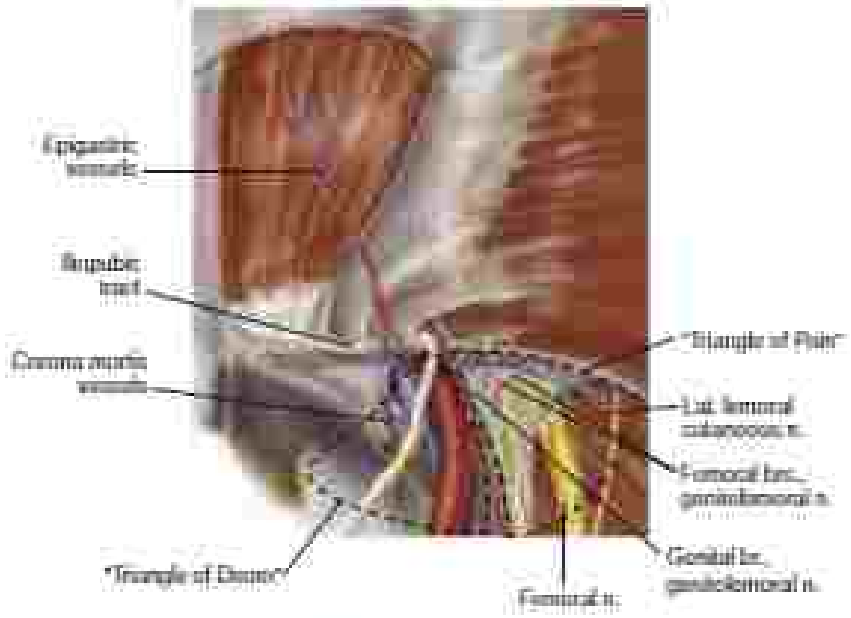

FIG. 3 Triangle of pain.

CONCLUSION

Elective repair of symptomatic inguinal hernias is recommended; however, observation is appropriate for those without symptoms or who do not wish to undergo surgery. The choice of minimally invasive or open repair is primarily surgeon preference, and the use of prosthetic mesh will significantly reduce the risk of recurrence. The major risks of operative repair are usually minimal, but some patients may develop chronic pain from nerve injury and potential mesh complications. These morbidities must be considered during the preoperative discussion regarding repair, particularly in those patients with minimal symptoms.

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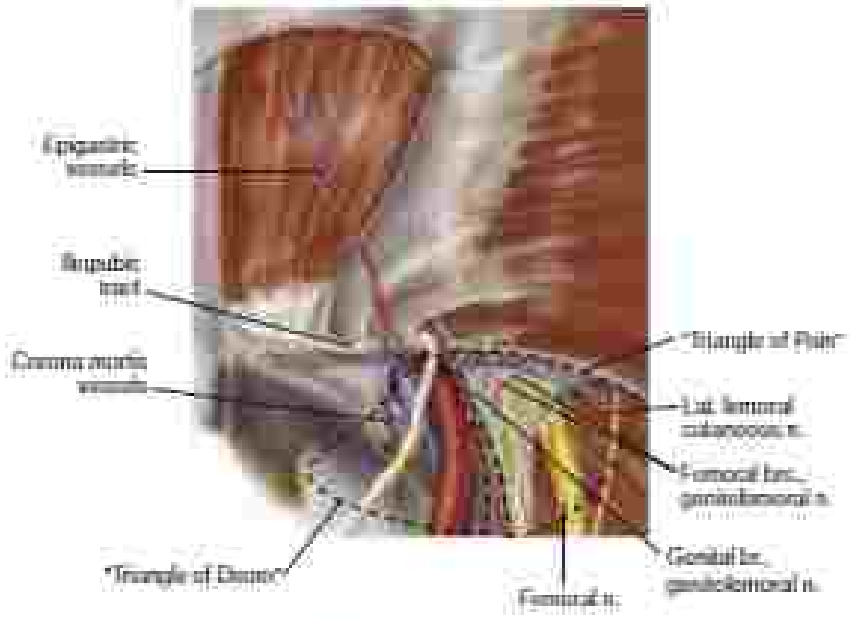
MANAGEMENT OF RECURRENT INGUINAL HERNIA

Brian Jacob, MD, and Kathryn Ely Pla ce Chaspari, MD

Inguinal hernias are common, with a lifetime risk of 2 % in men and 3% in women. More than 500,000 inguinal hernia repairs are performed each year in the United States. With many diverse ways of performing an inguinal hernia repair and no consensus proving that one method is more optimal than another, the published data often conflict regarding a recommended technique. As such, hernia surgeons and general surgeons continue to perform the technique that they are best trained to perform. Recurrences will happen regardless of whether the repair was performed via open anatomic (tissue)-based, open mesh–based, or minimally invasive technique (with or without mesh). Inguinal hernia recurrence remains frequent, with many large studies reporting a recurrence rate as high as 10%. Even the most experienced surgeon will encounter recurrences. When it comes to the topic of outcomes after inguinal hernia repair, recurrences are just one outcome metric that is important. Other important postoperative issues, such as chronic groin pain, will be discussed in other chapters.

DEFINING RECURRENT INGUINAL HERNIAS

Recurrent inguinal hernias that happen in the first 3 to 6 months after the surgery are called early recurrences and are generally considered a result of a technical error during the initial repair, although this is not always the case. Technical factors that may contribute to hernia recurrence are discussed in the following sections. Patients with a chronic cough who have a coughing attack during the first few weeks after a repair, or violent intubation immediately after a repair, are also at risk for developing a recurrence despite having a solid repair the first time.



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MANAGEMENT OF RECURRENT INGUINAL HERNIA

Brian Jacob, MD, and Kathryn Ely Pierce Chaspis, MD

Inguinal hernias are common, with a lifetime risk of 27% in men and 3% in women. More than 500,000 inguinal hernia repairs are performed each year in the United States. With many diverse ways of performing an inguinal hernia repair and no consensus proving that one method is more optimal than another, the published data often conflict regarding a recommended technique. As such, hernia surgeons and general surgeons continue to perform the technique that they are best trained to perform. Recurrences will happen regardless of whether the repair was performed via open anatomic (tissue)-based, open mesh–based, or minimally invasive technique (with or without mesh). Inguinal hernia recurrence remains frequent, with many large studies reporting a recurrence rate as high as 10%. Even the most experienced surgeon will encounter recurrences. When it comes to the topic of outcomes after inguinal hernia repair, recurrences are just one outcome metric that is important. Other important postoperative issues, such as chronic groin pain, will be discussed in other chapters.

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Recurrent inguinal hernias that happen in the first 3 to 6 months after the surgery are called *early recurrences* and are generally considered a result of a technical error during the initial repair, although this is not always the case. Technical factors that may contribute to hernia recurrence are discussed in the following sections. Patients with a chronic cough who have a coughing attack during the first few weeks after a repair, or violent extubation immediately after a repair, are also at risk for developing a recurrence despite having a solid repair the first time.

Late recurrences occurring after 6 to 12 months are generally from patient factors (discussed later); however, late recurrence can also be due to the same technical factors seen after early recurrence, as well as from mesh shrinkage or migration.

When considering repair of a recurrent inguinal hernia, it is important to know how and when the initial hernia was repaired. Because the previous repair always dictates the optimal approach to repair of a recurrent inguinal hernia, all efforts should be made to obtain the previous operative report before a repair is planned. Patients who had a previous inguinal hernia repair as a child likely had an open nonmesh repair. Patients can also be divided into having a previous open (anterior) repair with or without mesh or into having a previous laparoscopic (or robotic) repair with or without mesh. If a previous anterior repair was performed with mesh, it is important to know what type of mesh was used (e.g., Lichtenstein, plug and patch, PHS system).

RISK FACTORS FOR RECURRENT INGUINAL HERNIAS

Technical Factors

The most important technical factor contributing to hernia recurrence is failure to achieve a tension-free repair. Mesh-free repairs such as the Bassini, Halsted, and McVay techniques have been shown to have a 30% to 75% higher recurrence rate than mesh repairs from tension on the approximated tissue. The use of mesh to achieve tension-free repair is now considered the gold standard. There has been some debate over the use of heavyweight versus lightweight mesh, but meta-analyses have shown no difference in recurrence rate based on the weight of mesh used. Additionally, no difference in recurrence rates has been found when comparing self-gripping mesh to suture- or tack-secured meshes.

Other technical factors that contribute to hernia recurrence include incomplete dissection of the preperitoneal orifice from anterior superior iliac spine to symphysis, insufficient reduction of the hernia sac, insufficient reduction of hernias, inadequate mesh implant size or material, mesh migration, or mesh folding (claw-shelling). Failure to resect a cord lipoma may also result in primary recurrence, so care should be taken to reduce or excise these lipomas. Complete and masterful dissection following the steps as outlined by Daes and Felix and originally described to the International Hernia Collaboration closed Facebook group will minimize early recurrence rates. That said, a recurrence does not mean that the procedure was performed incorrectly or that a technical error was experienced during the surgery. Hernia recurrence is a known risk and should always be mentioned in the informed consent.

One source of debate is whether a laparoscopic inguinal hernia repair is associated with higher recurrence rates than open hernia repair. Studies vary significantly, with many studies pointing toward an increased recurrence rate with laparoscopic repair; however, several large meta-analyses did not find a significant long-term difference between recurrence rates in laparoscopic and open approaches. Other studies have demonstrated that surgeon experience with laparoscopic repair has a significant impact on recurrence rates, those performing a higher volume of laparoscopic repairs experience a lower recurrence rate, eventually equaling that of open repair.

Patient Factors

Any risk factor for poor wound healing contributes to the risk of hernia recurrence, including immunosuppression, smoking, diabetes, and obesity. Smoking not only contributes to tissue hypoxia, but also alters collagen synthesis and remodeling, leading to weaker tissue. Obesity puts undue strain on the initial repair and increases the risk of wound infection. Additionally, a large meta-analysis found that being female, initial operation for direct inguinal hernia, and operation for recurrent hernia were all risk factors for recurrence. Female sex risk is hypothesized to be due to the higher incidence of femoral hernias that may be missed at initial open operation. The reason for a higher recurrence after initial operation for direct inguinal hernia is unclear, but may be due to inherent tissue weakness. Although this study did not find family history of recurrent hernias to be a significant risk factor, it is well documented elsewhere that collagen synthesis disorders such as Marfan's syndrome and Ehlers-Danlos syndrome carry a higher risk of hernia and poor wound healing. The recovery from the original surgery may also play a role in recurrence rates. It is important to note any postoperative infections, hematomas or seromas, especially if the mesh implant shifts or migrates secondary to that process.

Mesh Factors

We, as authors, do not intrinsically blame the mesh for a recurrence. We believe that the products on the market have been adequately studied such that causation of recurrences cannot be attributed to the mesh alone; thus, when referring to mesh factors, we are describing what happens to the mesh after it is implanted. Shrinking of the mesh can lead to recurrence, as well as pain from the product pulling on surrounding structures. Some three-dimensional shaped mesh (plugs, PHS systems, and others) placed during open repairs can also shrink, migrate, or are designed to mesh, leading to a space for a recurrence, and often chronic pain. Mesh can also migrate or fold, which usually happens very early after it is placed. Additionally, it can conform to the space it was bridging. Imaging is indicated when a mesh issue is suspected. We usually prefer investigation with a computed tomography (CT) scan; however, a normal CT scan does not necessarily rule out a mesh factor. Mesh issues related to recurrences after a laparoscopic repair, in our opinion, can only be truly confirmed with diagnostic laparoscopy.

DIAGNOSING RECURRENT INGUINAL HERNIAS

Diagnosing a recurrent inguinal hernia involves taking a careful history, performing a focused physical examination, and contributing imaging. Most patients are asymptomatic and do not realize they are experiencing a recurrence; therefore, not all inguinal hernia recurrences will need immediate repair. When patients are symptomatic, they will sometimes state that they had a previous inguinal hernia repair with an interval without symptoms, followed by the onset of vague, temporary, discomfort located in just one spot near the inguinal canal. As the size of the hernia grows, patients will often complain of an intermittent bulge with or without localized nonradiating pain. Nevertheless, there is no single way a recurrent inguinal hernia presents. The symptoms are usually present or exacerbated when standing, exercising, or lifting. Once symptomatic, a repair is typically indicated.

When a patient with a history of inguinal hernia repair presents with groin pain, it is vital that the surgeon not assume that the pain is from a recurrent inguinal hernia until all other possible etiologies have been ruled out and documented. Other causes of groin pain are numerous (Table 1). Often, the history alone will help the most in determining the cause of the pain. In general, pain from a recurrent hernia is intermittent and elicited directly over the bulge or defect. Pain from a recurrent hernia should not generally be made worse with movement of the hip joint or leg or with palpation of the symphysis or pubic tubercle. Acute onset of pain after an event (sport or traumatic) is musculoskeletal injury until proven otherwise. Cyclic pain can be from an endometrioma or endometriosis. Constant pain can be due to old sutures, mesh, fractures, infections, or other causes, but is usually not from a recurrent inguinal hernia. If history suggests a hernia recurrence, then the workup may also include sonography, CT, or magnetic resonance imaging (MRI) with an athletic pubalgia protocol. Once other etiologies have been ruled out, an inguinal hernia repair can be safely planned.

Sometimes, recurrent inguinal hernias are not palpable and are not seen on imaging, which can be especially true for tiny femoral hernias or tiny indirect inguinal hernias (as well as for small lipomas).

TABLE 1 Causes of Groin Pain by System

System	Cause
Musculoskeletal	Avascular necrosis Avulsion fracture Osteoarthritis Sacroiliitis Muscle strain or tear Tendinitis Piriformis syndrome Athletic pubalgia Referred or radiating back pain
Genitourinary/gynecologic	Epididymitis Orchitis Retrograde ejaculation Hydrocele Varicocele Testicular cancer/tumor Endometriosis/endometriosis Kidney stone
Gastrointestinal	Inguinal hernia Colitis/diverticulitis
Neurologic	Sciatica Nerve entrapment
Infectious	Lymphadenopathy Urinary tract infection Sexually transmitted infection

These are termed hidden hernias or occult hernias. All types can be symptomatic and are best identified during a diagnostic laparoscopy.

Role of Physical Examination and Imaging With a Recurrent Inguinal Hernia

The diagnosis of a recurrent inguinal hernia is essentially the same as for a primary inguinal hernia and, again, is largely a clinical diagnosis, based on history and physical examination. Imaging is useful when the diagnosis is unclear. Nevertheless, it is important to again state that inguinal hernias may be missed on imaging; therefore, normal imaging does not exclude the presence of a recurrent inguinal hernia.

Ultrasound is an inexpensive tool with a sensitivity of greater than 90% and a specificity of approximately 85%. This method allows for the groin to be examined both at rest and under a Valsalva maneuver. CT of the abdomen and pelvis has a role in the diagnosis of recurrent inguinal hernia because it can detect mesh mass, metallic tack location, and recurrences that may not be readily palpable on examination. CT has a sensitivity less than 80%, with a specificity of only 25% to 85%. When pain is part of the complaint, we strongly recommend that a radiopaque marker be placed at the site of the pain while obtaining the CT scan because this can more precisely define the location of the structure involved. An MRI, on the other hand, though more expensive and time consuming, has a very high sensitivity, greater than 95%, and can also be performed at rest and with Valsalva. Although not essential for the workup of most inguinal hernias, MRI is recommended by Miller et al. in the workup of an occult hernia because it demonstrates the highest sensitivity, specificity, and negative predictive value compared with ultrasound and CT. The authors of that study state that MRI scans resulted in correct identification of an inguinal hernia in 91% of the cases of a false negative CT scan. Representative images of an ultrasound, CT scan, and MRI of inguinal hernia are shown in Fig. 1.

Repair of the Recurrent Inguinal Hernia

Repair of a recurrent inguinal hernia is often more difficult than the initial operation because of distorted tissue planes. Repair operations carries a higher rate of complications, including chronic pain, damage to cord structures, ischemic orchitis, and a higher risk of recurrence. Before repair of an inguinal hernia, patient controlled risk factors should be optimized, particularly smoking cessation and weight loss, and counselling regarding the previously mentioned risks.

Watchful waiting for asymptomatic inguinal hernia is a well established option to primary inguinal hernias, but has not been specifically studied for recurrent hernia. This is, however, included as an option for recurrent inguinal hernia in many of the guidelines. Surgical repair is specifically recommended for the symptomatic recurrent hernia. The only true contraindication to repair of a recurrent inguinal hernia is active infection because mesh should be used in all repairs and use of prosthetic mesh is contraindicated in infection.

To minimize risks, as discussed in The International Guidelines for Groin Hernia Management, the main tenet of recurrent inguinal hernia repair is to approach the hernia through unfamiliar tissue planes. Thus, the approach will be dictated by the prior surgery as discussed in the following section. A summary of our approach to a recurrent inguinal hernia is found in Fig. 2.

Recurrent Inguinal Hernia After a Previous Open (Anterior) Repair

Following an open inguinal hernia repair, recurrence is more likely to occur in the direct space, most often from inadequate mesh coverage at the pubic tubercle. These cases should almost always be approached by minimally invasive surgery (MIS) posterior method (laparoscopy or robotic) to avoid dissected and scarred anterior tissue planes. Dissecting through previously dissected tissue planes increases the risk of nerve entrapment, chronic pain, and testicular atrophy. In addition, the MIS approach has been associated with earlier return to work and lower incidence of chronic groin pain. Either transabdominal preperitoneal repair (TAPP) or total extraperitoneal repair (TEP) is reasonable. The choice of approach depends on surgeon preference and whether the surgery will be done laparoscopically or robotically. Although a minimally invasive approach is recommended, if expertise in MIS technique is not available, an open posterior approach is acceptable as well.

Recurrence After a Previous Laparoscopic or Robotic (Posterior) Repair

Following a minimally invasive hernia repair, recurrence is more likely to occur in the indirect space or inferiorly near the femoral canal, possibly resulting from incomplete reduction of the hernia sac or herniation of the sac around the mesh. Also, retained spermatic cord lipomas are not uncommon. Guidelines still recommend an anterior open repair of a recurrent inguinal hernia initially repaired using an MIS technique to avoid the dissected posterior tissue planes and mesh. With growing experience and comfort, however, laparoscopists are increasingly able to identify and repair a recurrence via MIS approach, even after a previous TEP or TAPP technique. The major advantage to MIS repair is that the surgeon possesses a view of all potential sites of recurrences, which is especially helpful when the location of the recurrence (direct, indirect, or femoral) is unclear. Because the dissection of the preperitoneal tissue plane is more difficult after a prior posterior repair, an attempt at TEP often results in tearing of the peritoneum, thus forcing conversion to TAPP. Any surgeon who is attempting a MIS revision of a recurrent hernia after a prior MIS repair must be comfortable with both TEP and TAPP techniques.

Recurrence After a Previous Anterior and Posterior Repair

For complex cases in which a patient is presenting with more than one recurrence, in which case both the anterior and posterior planes have

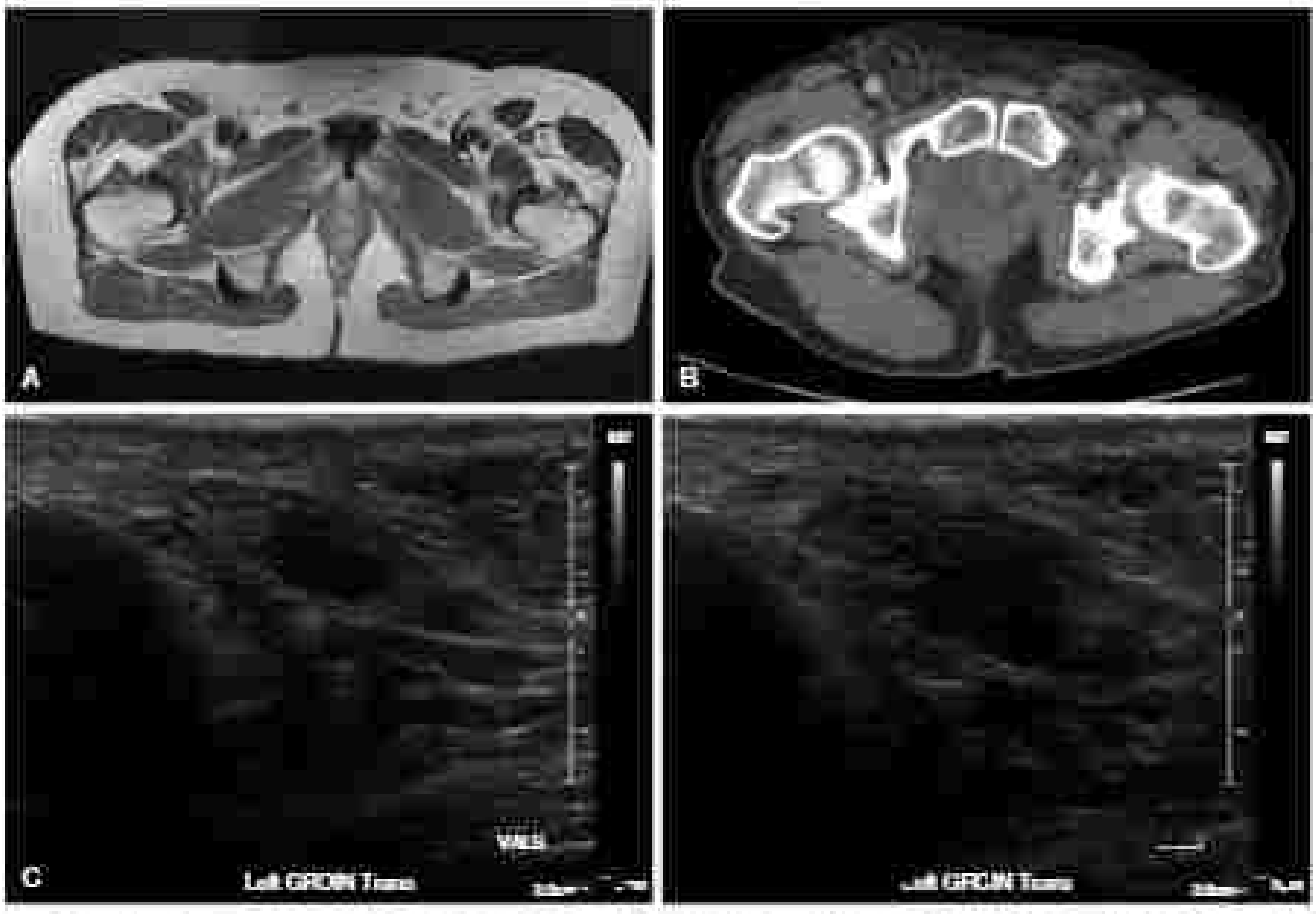

FIG. 1 (A) Coronal reconstructed image of an inguinal hernia. (B) Computed tomography image of an inguinal hernia. (C) Ultrasound of a left inguinal hernia at rest and with valsalva maneuver.

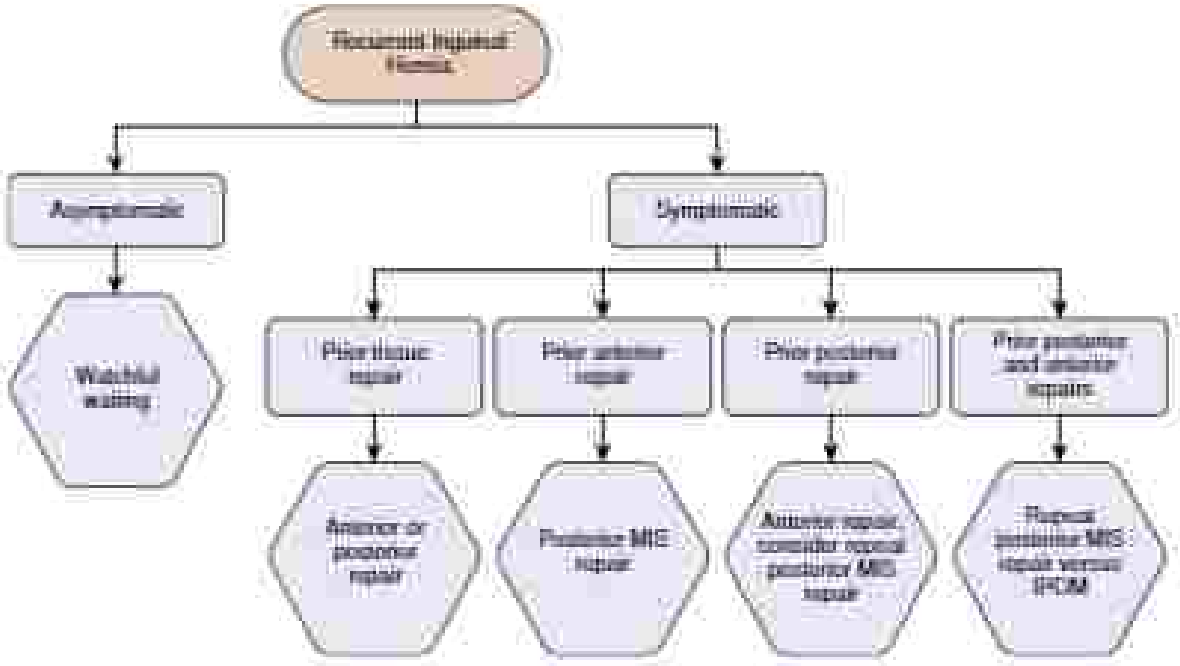

FIG. 2 Algorithm for management of recurrent inguinal hernia. IPOM, intraperitoneal onlay mesh; MIS, minimally invasive surgery.

been violated and mesh exists in the anterior and/or posterior space, the procedure of choice will depend on the surgeon experience. In our group, we prefer laparoscopy (or a robotic approach) in most of these cases initially as a diagnostic tool, to identify precisely the location and etiology of the recurrence. Often the prior MIS placed mesh can be taken down to identify the femoral space, the direct space, and the indirect space sufficiently to make a diagnosis and perform an MIS repair. In cases in which the peritoneum is damaged during the dissection, an intraperitoneal onlay mesh repair can be safely performed. The mesh can be sutured to the anterior abdominal wall or to the old mesh, as well sutured to the retroperitoneum. No tacks should be deployed in the region of the nerves below the inguinal ligament.

CONCLUSIONS

Recurrent inguinal hernias should not be taken lightly. Careful review of the history, a focused physical examination, selective imaging, and using a standard technique will help optimize the outcomes. Having a detailed history, including the previous operative reports, not only dictates the approach for the recurrent hernia, but gives the surgeon an idea of what to expect at reoperation.

Some operations for recurrent inguinal hernias will be straightforward, but some of them will be quite difficult. As with the index operation, the approach will ultimately depend on surgeon skill, comfort, and preference. It is unreasonable to expect a surgeon who is uncomfortable with laparoscopy to use an MIS approach to address a recurrent hernia solely because it was repaired using an open technique previously. Conversely, it is acceptable for a surgeon who is comfortable and proficient with MIS hernia repair to approach a recurrence using MIS techniques even if the initial hernia was repaired laparoscopically or robotically.

For any inguinal hernia, including the recurrent hernia, the surgeon should be sure to look for and expect any cord lipoma because a cord lipoma alone can present as an inguinal bulge that creates the same symptoms as a true hernia. Even if a hernia itself is repaired or recurrent, if a cord lipoma is left behind, the patient may still be symptomatic.

Finally, the steps for MIS inguinal hernia repair, as outlined by Bates and Felix in their paper "Critical View of the Myopectineal Orifice" (2017), applies to recurrent hernias and should be thought of as the "nine commandments" of inguinal hernia repair. These rules describe wide and safe dissection of the myopectineal orifice, adequate visualization of all potential hernia defects (direct, indirect, femoral), sufficient reduction of hernias and cord lipomas, and secure placement of the mesh. If these rules are followed by the surgeon during MIS inguinal hernia repair, fewer recurrences can be expected.

Inguinal hernia is a prevalent surgical problem, and with recurrence rates of approximately 15%, every general surgeon will encounter recurrences in their career. Defining and diagnosing the recurrent inguinal hernia, as well as ruling out other causes of inguinal pain, are of paramount importance before reoperation. Surgical approach to repair is dictated by the method of the index surgery as well as the surgeon's comfort with minimally invasive surgical techniques. In all, general surgeons should have a thorough understanding of inguinal anatomy from both anterior and posterior approaches and be comfortable with both minimally invasive and open repair of the inguinal hernia.

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Burcharth J, Pommergaard HC, Bisgaard T, Rosenberg J. Patient-related risk factors for recurrence after inguinal hernia repair. Surg Innov 2014;21(6):562–572.

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Incisional, Epigastric, and Umbilical Hernias

Jason A. H. Ilham, MD, MS, and Mike K. Liang, MD*

Ventral hernias are a common clinical problem with nearly 350,000 ventral hernia repairs performed each year in the United States. Despite this, ventral hernia repair is associated with a high rate of surgical complications, such as infection and hernia recurrence. To obtain optimal outcomes, there are a number of important clinical decisions that should be considered when approaching a patient with a ventral hernia. This chapter discusses patient selection and optimization, surgical techniques, and complex settings (including emergent repairs and cases with contamination). Primary (e.g., umbilical or epigastric hernias) and incisional ventral hernias have considerable differences in anatomy, pathophysiology, and outcome; therefore, they are discussed separately.

PATIENT SELECTION

For elective cases, careful patient selection is critical. Nonoperative management of ventral hernias is safe and feasible and should be the strategy of choice in certain patients. Significant comorbidities, including metastatic cancer, advanced arthritis, severe cardiopulmonary disease, and other conditions causing a life expectancy less than 2 years are relative contraindications to elective surgery.

Patients with certain modifiable risk factors should also be initially managed nonoperatively. These patients can benefit from medical optimization before elective surgery. If and when they are able to meet the goals set out for them, then can be offered elective repair. For example, patients who smoke should not be offered elective surgery because of an increased risk of wound complications and hernia recurrence. Rather, they should be educated on smoking cessation and offered resources to aid with successful smoking cessation. In addition, obese patients should be counselled on weight loss before elective surgery. Elective surgery is considered for patients with a body mass index (BMI) less than 30. For patients with a BMI greater than 40, we opt for nonoperative management until the patient is able to lose weight. For patients with a BMI between 30 and 40, we recommend preoperative weight loss with individualized patient goals. Referrals to a physical therapist and a dietician can be offered to help patients with weight loss. Patients with poorly controlled diabetes should be referred to their primary care physician to better control diabetes before scheduling elective surgery. At our institution, a hemoglobin A1c less than 8.0% is recommended. Finally, asymptomatic or oligosymptomatic patients should be considered for nonoperative management because these patients are unlikely to see any improvement in quality of life following repair.

All patients managed nonoperatively should be counseled on signs and symptoms that should prompt a visit to the emergency department. Symptoms may include increased pain at the hernia site, obstructive symptoms such as nausea, vomiting, distension, or obstipation. Signs may include changes in hernia characteristics such as increased firmness, new inability to reduce the hernia, and changes to surrounding skin color.

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Incisional, Epigastric, and Umbilical Hernias

Julie L. Heiffan, MD, MS, and Mike K. Liang, MD

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TREATMENT OF PRIMARY VENTRAL HERNIAS

Umbilical and Epigastric Hernias

Umbilical hernias are a defect through the umbilical ring not associated with a prior incision, whereas epigastric hernias are primary ventral hernias located along the linea alba and superior to the umbilical ring. Primary ventral hernias are an extremely common problem, present in nearly one half of the population on radiologic imaging or physical examination. In low risk patients with a BMI less than 30 and small defects (<2 cm), we use an open approach. For an umbilical hernia, a supraumbilical incision is made for a bulge superior to the umbilicus, and an infraumbilical incision is made for a bulge inferior to the umbilicus. The tissue is dissected down to fascia, and the umbilical stalk is freed circumferentially. The hernia sac is then dissected off the umbilical stalk down to the fascia. The layers of the abdominal wall are freed around the umbilicus, so the fascia is incised circumferentially 2 mm from the umbilical ring to enter the preperitoneal space without entering the retromuscular space. The preperitoneal space is bluntly dissected in a radial fashion developing a space 3 to 5 cm in radius circumferentially. A large piece, mid-density polypropylene mesh is placed in this preperitoneal space. The fascial defect is closed with transverse interrupted 2-0 polydioxanone sutures. Small epigastric hernias (<2 cm) are repaired similarly. An incision is made directly over the hernia defect. The hernia sac is freed circumferentially and dissected down to fascia. It is reduced. With epigastric hernias, the fascia does not need to be incised because the planes are not fused. Simple blunt dissection to free the preperitoneal space is adequate. Mesh is placed in the preperitoneal plane, and the defect is closed transversely with interrupted 2-0 polydioxanone sutures.

A laparoscopic approach is preferred for larger umbilical or epigastric hernias (>2 cm). This is because, for a larger hernia, an open approach would require a much larger incision to achieve adequate mesh overlap. We also use laparoscopy for patients at increased risk for wound complications, such as patients with a BMI greater than 30. The use of laparoscopy has been shown to decrease surgical site infections compared with open repair. For laparoscopic repair, the abdomen is entered with a 5-mm optical port in the left upper quadrant. A second 5-mm port is placed along the left flank (Fig. 1). The peritoneum and preperitoneal fat are incised circumferentially around the hernia defect. It is best to perform this dissection at least 2–3 cm from the hernia edge. The hernia sac and preperitoneal fat are gently reduced en bloc. We place a 10- to 12-mm port through the defect to minimize port site hernias and use this larger port to introduce an antiadhesion barrier coated mid-density polyester or polypropylene mesh into the abdomen. We aim for at least 5 cm of mesh overlap on each side of the hernia but typically use a 12- or 15-cm rounded mesh. For smaller defects (<3 cm), the mesh is small enough to be held in place by a central stay suture while it is secured circumferentially using permanent tacks placed in a double crown. For a larger defect, transfascial stay sutures (0 polydioxanone sutures) are placed in each side of the mesh, and the mesh is then secured circumferentially with a double crown of permanent tacks (Fig. 2). After the abdomen is desufflated, the fascia is closed through the 10- to 12-mm trans-hernia port site with 0 polyglactin suture. For umbilical hernias, the umbilicus can also be tacked or secured to the fascia with a 2-0 polyglactin suture.

The role of robotics in primary ventral hernia repair remains to be established. There are multiple approaches that can be used for robotic primary ventral hernia repair, including standard laparoscopic intraperitoneal onlay mesh, retromuscular, or preperitoneal techniques. Preperitoneal placement of the mesh is attractive because it allows for mesh placement outside of the peritoneal cavity without violating the retromuscular space and for the use of uncoated mesh. When possible, we prefer a preperitoneal technique. The abdomen is typically entered with a 5-mm optical port in the left upper quadrant. Two 8-mm ports are placed along the left flank and just medial and superior to the ipsilateral anterior superior iliac spine (Fig. 3). The

FIG. 1 Laparoscopic port placement.

FIG. 2 (A) Securing mesh with double crown of permanent tacks. (B) Completed double crown of permanent tac s.

FIG. 3 Robotic port placement.

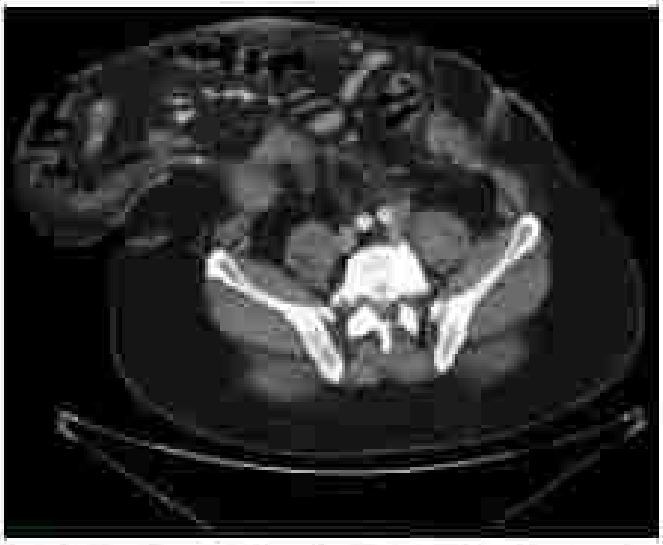

FIG. 4 Hernia demonstrating loss of domain, where most of the visceral contents are outside the abdomen.

original 5-mm port is exchanged for a third 8-mm port. The bed can be flexed to increase space between the costal margin and anterior superior iliac spine in smaller patients. A bump placed under the patient on the side with the ports can also facilitate more lateral port placement. Ports placed too close to the costal margin or anterior superior iliac spine may interfere with movement of the robotic arms.

Before docking the robot, we insert a 2-0 barbed suture, an appropriately sized uncoated mid-density polypropylene mesh (typically 10 × 15 cm), and a 0 barbed suture (inserted in this order). The robotic platform is docked. To optimize the proportional dimension, we typically use saline into the preperitoneal space to dissect the space 3–6 cm lateral to the hernia on the right and left sides. The preperitoneal space is inflated and dissected to allow for at least 3 cm of mesh overlap but preferably 5 cm of overlap. The proportional fan is reduced and defect is closed with 0 barbed suture. The uncoated polypropylene mesh is inserted into the preperitoneal space, and the flap is closed with a 2-0 barbed suture.

Treatment of Incisional Ventral Hernias

An incisional ventral hernia is a ventral hernia associated with any prior incision. Incisional hernias are associated with a substantially higher risk of complications than primary ventral hernias (with mesh, 24% vs 5% recurrence at 2–3 years postoperatively). We prefer a laparoscopic approach for incisional hernias whenever feasible because laparoscopy has been shown to have fewer surgical site infections and a shorter hospital length of stay with no difference in hernia recurrences compared with open repair. Open repair is reserved for large incisional hernias in which defect closure is not feasible laparoscopically. Large incisional hernias are typically greater than 10 cm in width. Hernias with loss of domain, where the majority of visceral contents lies outside of the abdomen, also fall into this category (Fig. 4).

For laparoscopic incisional hernia repair, the abdomen is typically entered with a 5-mm optical port in the left upper quadrant. A right-sided approach can be used for patients more likely to have left-sided adhesions (e.g., prior left colon resection, splenectomy, gastric surgery). A second 5-mm port is placed along the left flank (Fig. 1). The hernia is reduced using gentle traction and dissection. Unlike in primary hernia repair, the hernia sac is not excised for incisional hernias because it is often too scarred to excise and can be used to assist with defect closure. For hernias larger than 3 cm, we close the hernia defect using transfascial sutures. For hernias smaller than 3 cm, we do not typically close the defect. Before defect closure (when applicable), the hernia is measured to determine appropriate mesh size. The edges of the hernia are marked on the skin. The abdomen is desufflated, a mesh is chosen that will allow for coverage of the hernia with at least a 5 cm overlap on each side. The mesh is prepared by placing 0 polydioxanone stay sutures on the four sides of the mesh. A 10- to 12-mm port is placed through the hernia defect, the mesh is introduced into the abdomen through this port. When closing the hernia defect, 0 polydioxanone sutures are placed 1 to 2 cm apart for the length of the defect. Occasionally, we will lower the abdominal pressures from 15 down to 8 to 12 mm Hg to assist with suture passage. A stab incision is made in the skin in the midline of the hernia defect. A suture passer is used to tunnel through the subcutaneous tissue, along the hernia sac, to the edge of hernia defect, and 1 cm lateral to the fascial edge. The suture passer is then placed through the same stab incision and tunneled to the opposite side of the defect to grasp the suture. The most cranial and most caudal sutures are placed first, and the abdomen is desufflated as these are tied down. We include the hernia sac in the closure to reduce the risk of seromas. The abdomen is reinsufflated and the remainder of the fascial closure sutures are then placed (Fig. 5). All fascial closure sutures are tied with the abdomen completely desufflated. The four transfascial sutures on the mesh are then positioned and tied down. The mesh is secured circumferentially using a double crown of permanent tacks (Fig. 2).

Open incisional hernia repair is reserved for large hernias. Often, these large hernias can still be closed primarily; however, we will discuss options for closure when primary closure is not possible. A laparotomy incision is made along the midline. Adhesiolysis is performed to clear the abdominal wall. The hernia sac is excised. Our preferred mesh location is in the sublay or retromuscular position because this is associated with the fewest surgical site occurrences and hernia recurrences. If the fascia is able to be primarily closed, the retromuscular space is entered taking care not to damage the underlying peritoneum. Before closing the peritoneal cavity, we placed antiadhesion barrier sheets throughout the abdomen. The posterior rectus fascia is closed with running 0 polydioxanone suture. The retrorectus space is developed to accommodate the mesh with additional lateral, superior, and inferior dissection. A mid-density polypropylene mesh is used in most cases; however, in contaminated settings, a biologic mesh such as porcine acellular dermal matrix can be considered. We fixate the mesh with a limited number of 0 polydioxanone sutures. After placing the mesh, the anterior rectus fascia is closed

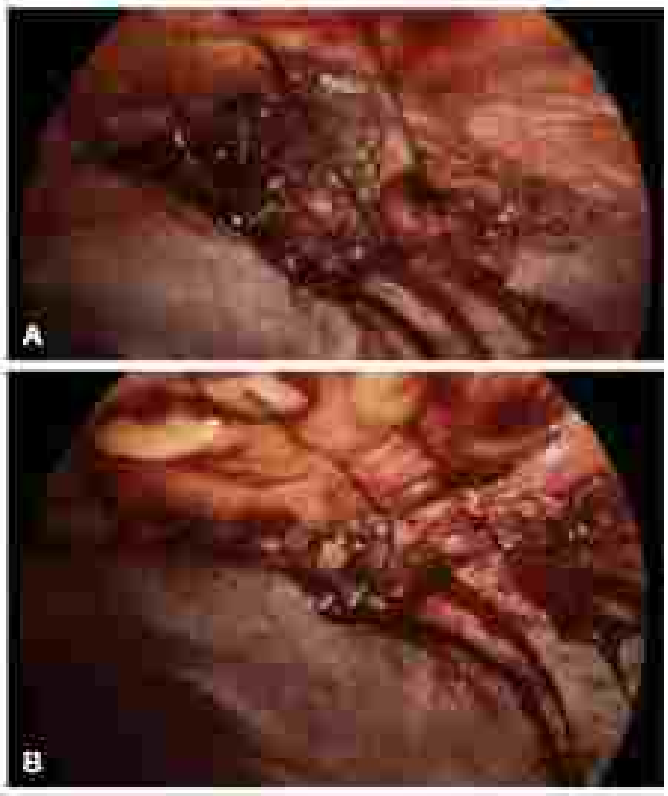

FIG. 1 (A) Transfacial sutures spanning hernia defect used to close the defect laparoscopically. (B) Closed hernia defect.

using running 0 polydioxanone sutures. In some cases, there can be significant excess skin that is excised to minimize seroma formation.

When the fascia is unable to be closed, there are a number of options, the simplest of which is a bridged repair. This is where the fascia is left open, and a mesh is used to span the hernia defect. This type of repair has a high rate of surgical site occurrence and hernia recurrence and should be avoided when other options are available. However, a bridged repair may be considered in the setting of an emergent repair, a contaminated case, or in an unstable patient where the goal is to temporize the patient rather than create a durable repair.

In stable patients with defects too large to close primarily, a myofascial advancement flap, or component separation, may be necessary. An anterior component separation can provide the most release, up to 7 to 10 cm per side. Anterior component separations can have significant wound complications because of undermining and creation of large skin flaps. A perforator sparing anterior component separation preserves the blood supply to the abdominal wall near the umbilicus, which can alleviate some of these complications but can be technically challenging for surgeons who do not routinely perform these procedures. For an anterior component separation, skin flaps and subcutaneous fat are dissected free from the anterior rectus sheath leaving a few millimeters of fat on top of the fascia. The external oblique aponeurosis is identified and incised 2 cm lateral to the semilunar line, separating the internal from the external oblique muscles. We prefer to err farther lateral to the semilunar line compared with what others report. Care must be taken to avoid accidentally incising the semilunar line or damaging the internal oblique. After completing the external oblique incision, the external oblique and internal oblique muscles must be gently separated through a combination of blunt and electrocautery dissection carried to the spinal muscles. This dissection is needed to "separate the components" and allow medial retraction. The anterior rectus fascia is then approximated. If large flaps are created, we consider placement of drains in the lateral space to minimize formation of fluid collections.

Posterior component separations are preferred for lateral hernias or hernias associated with ostomy. In addition, a posterior component separation avoids the large skin flaps and wound complications associated with anterior component separation. In a posterior component separation, the retrorectus space is entered and dissected out to the semilunar line. The transversus abdominis is divided, preserving the transversalis fascia if possible, allowing the posterior rectus fascia to be pulled medially. Thus, the components must be "separated": the posterior layers (peritoneum, transversalis fascia, and divided portion of transversus abdominis) must be gently dissected free and away from the anterior layers. This allows wide release of the posterior layer and space for a large piece of mesh to be placed in the sublay position as described previously. Posterior component separation can be more technically challenging than anterior component separation and risks damaging the posterior sheath/peritoneum, destabilizing the semilunar line, or denervating the rectus muscle. When done properly, it can provide wide posterior space with lower wound complication rates compared to traditional anterior component separation.

There is increasing interest in the role of robotic ventral incisional hernia repair. Port placement is similar to what is described previously for primary ventral hernias, with few exceptions (Fig. 3). For lower abdominal incisional hernias (especially infraumbilical and suprapubic hernias), ports placement across the upper abdomen (right and left upper quadrant and off midline in the epigastric region) is preferred. For high incisional hernia defects, such as in the subxiphoid position, ports placed across the lower abdomen allow for easier suturing. The robotic platform is docked, and adhesiolysis is performed.

There are two possible methods for robotic ventral hernia repair: first, is replicating a laparoscopic repair. A 12 mm port is placed through the defect, a mesh is unable to be placed through an 8 mm robotic trocar, and two or three 2-0 barbed sutures, an appropriately sized coated synthetic mesh, and one to three 0 barbed sutures are inserted. The defect is closed with 0 barbed suture subcutis. The 0 barbed suture(s) are also used to position the mesh. The mesh is sutured circumferentially with 2-0 barbed sutures.

The second method is replicating an open repair. Ports are typically placed along the right and left lateral positions. Right and left rectus completes are incised to enter the retrorectus space. For larger defects, a robotic, posterior component separation can be performed. A 12 mm port is placed through the defect and an appropriately sized uncoated synthetic mesh and four to six 0 barbed sutures are inserted. The anterior fascia is closed with running 0 barbed sutures. The mesh is placed in the retrorectus space and can be centered and fixated with the 0 barbed sutures. The posterior sheath is closed with running 0 barbed sutures. If robotic posterior component separation is performed, the posterior sheath is typically closed first, followed by introduction and positioning of mesh and closure of the anterior fascia.

EMERGENT AND CONTAMINATED CASES

With each hernia repair, there is a risk of complications and hernia recurrence. As a result, cases with a high risk of surgical complication require special surgical planning. In some cases, it may be best to do as little as possible. Examples of this include emergent cases and cases with contamination. Emergent hernia repairs are associated with higher risk of complication and hernia recurrence than elective repairs. This may be due to lack of patient selection because patients with comorbidities are prohibited from undergoing elective surgery and can present to an emergent fashion and require surgery. It may also be due to the presence of contamination. Examples of contamination in ventral hernia repair include a strangulated hernia with necrotic bowel, a hernia repair in the setting of an ostomy, or a hernia encountered during an operation for another indication such as diverticulitis.

In these high risk settings, the surgeon may consider a staged repair. This means leaving a planned ventral hernia (closing skin and

leaving fascia open or placing an inlay with an absorbable mesh with plans to perform a definitive repair at a later time. This allows for a better repair to be done in an elective setting, but it subjects the patient to additional surgery.

If the surgeon decides to repair the hernia at the initial operation, he or she must decide whether to perform a suture or mesh repair. A suture repair eliminates the possibility of mesh-related complications; however, in this setting, the risk of hernia recurrence may be extremely high. The recurrence rate is likely extremely high even with mesh repair.

If mesh is used, mesh type must be considered. Synthetic mesh is often avoided in contaminated settings because of the increased risk of infection and fear of future need for mesh explantation. Furthermore, intraperitoneal synthetic mesh is contraindicated in contaminated cases. However, a low- or mid-density synthetic mesh in a sublay position can be considered. Another option is to use biologic or bioabsorbable mesh. Biologic and bioabsorbable mesh may be more resilient to infection than synthetic mesh, but they are generally considerably more expensive than synthetic mesh. Our typical practice is to place a biologic mesh in the sublay position when an experienced hernia surgeon is performing the case and there is limited contamination. When the situation is suboptimal (e.g., substantial contamination, patient or technique issues), we follow the practice that "less is more" and perform suture repair, bridge repair, or leave the abdomen open depending on the individual setting. When surgeons who do not have hernia expertise are performing emergency or are working with contaminated cases, we recommend the same "less is more" practice and advise either suture repair or underlay (intraperitoneal) repair with biologic mesh.

POSTOPERATIVE CARE

Postoperative care can vary significantly depending on the size of hernia repaired and the approach taken. Most of our small- and medium-sized hernia repairs go home on the day of surgery. We do not typically place strict restrictions on these patients with regard to activity but caution them against doing anything that is painful. Patients are managed with perioperative blocks (transversus abdominus plane and rectus sheath blocks) along with multimodal pain regimen (acetaminophen, ibuprofen, gabapentin, ± tramadol), and a bowel regimen (docusate, polyethylene glycol). For larger hernias or open retromuscular repairs, patients are typically kept in the hospital for pain control. We follow an enhanced recovery after surgery style approach to which diet is started immediately after surgery, early mobilization is encouraged, and narcotics are minimized. For very large hernias (>10 cm), we consider placement of an epidural to aid in pain control. In cases where drains are placed, they are removed after 2 consecutive days with less than 30 mL output per day.

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MANAGEMENT OF SPIGELIAN, LUMBAR, AND OBTURATOR HERNIATION

Robert J. Fitzgibbons, Jr, MD, ACS, Gary Anthone, MD, ACS, and Myles L. Jones, MD, FACS

The anatomy, clinical presentation, and treatment of these unusual hernias are the subject of this chapter. Most of the literature devoted to Spigelian, lumbar, and obturator hernias consists of case reports with associated reviews of the literature. Because of the relative rarity of these hernias, high-quality, level 1 data from randomized controlled trials are not practical or possible. Nevertheless, the available literature provides some consistent themes, and they will be presented here.

SPIGELIAN HERNIA

Anatomy

The key to understanding a Spigelian hernia is a working knowledge of the location of two anatomic structures. A discussion of these anatomic structures can be confusing because of the numerous synonyms with similar names (Box 1). The first is the arcuate line, which is a transverse line that marks the point where the posterior surface of the rectus abdominus muscle is only covered by the transversalis fascia and peritoneum and is the site of entry of the inferior epigastric vessels into the rectus muscle. Above the arcuate line, the rectus abdominus is surrounded by an anterior layer of the rectus sheath and a posterior layer. The anterior layer is derived from the external oblique aponeurosis and the anterior lamina of the internal oblique aponeurosis. The posterior layer is made up of the posterior lamina of the internal oblique aponeurosis and the transversus abdominus aponeurosis. Inferior to the arcuate line, all three muscle aponeuroses contribute only to the anterior rectus sheath (the rectus sheath). The other important anatomic structure is the semilunar line, which can also be confusing because of varying definitions in the literature, such as a line marking the transition from transverse abdominis muscle to its aponeurosis; from the costal margin to pubis; tubercle versus the site of splitting of the internal oblique aponeurosis at the lateral edge of rectus abdominis muscle. From a surgical standpoint, the Spigelian

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Semilunar Line

Linea semilunaris
Spigelian line
Semilunar line of Douglas

Arcuate Line

Linea semicircularis
Douglas' line
Arcuate line of Douglas
Arcuate line of the abdomen
Linea arcuata vaginae musculi recti abdominis
Semicircular line

Spigelian Hernia

Hernias of the semilunar line
Hernias through the conjoint tendon
Spontaneous lateral ventral hernias

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MANAGEMENT OF SPIGELIAN, LUMBAR, AND OBTURATOR HERNIATION

Robert J. Fitzgibbons Jr, MD, FACS, Gary Anthone, MD, FACS, and Myles Tiernan, MD, FACS

The anatomy, clinical presentation, and treatment of these unusual hernias are the subject of this chapter. Most of the literature devoted to Spigelian, lumbar, and obturator hernias consists of case reports with anecdotal reviews of the literature. Because of the relative rarity of these hernias, high-quality, level 1 data from randomized controlled trials are not practical or possible. Nevertheless, the available literature provides some consistent themes, and they will be presented here.

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Spontaneous lateral ventral hernias

fascia, which is a small strip of aponeurosis of the transversus abdominis muscle bounded laterally by the linea semilunaris and medially by the lateral margin of the rectus abdominis muscle; it is most important (Fig. 1). This fascia was described by Adriaan van den Spiegel (1578–1625), a Flemish anatomist. The first description of a hernia through this area was by Klinkosch in 1764. Spigelian hernias usually are located at the junction of the arcuate line and the semilunar line in the Spigelian fascia. However, the exact location of the arcuate line is variable, which gave rise to the concept of the "Spigelian hernia belt," which is located between horizontal lines drawn just below the umbilicus cranially and at the anterior superior iliac spines caudally and is usually about 6 cm in length. Spigelian hernias can occur anywhere along the Semilunar line, but 90% occur in the Spigelian hernia belt.

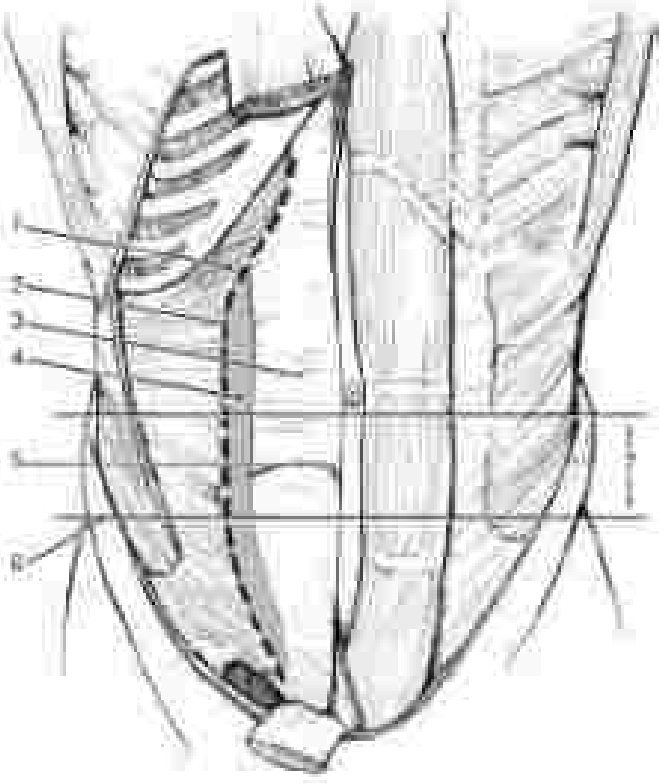

FIG. 1 View of the anterior abdominal wall with the external oblique, internal oblique, and rectus abdominis muscles pulled away on the left. (1) Transversus muscle, (2) semilunar line, (3) posterior rectus sheath, (4) Spigelian aponeurosis, (5) arcuate line, (6) anterior superior iliac spine, (7) Spigelian hernia belt. [illegible]

Clinical Presentation

The hernia, which is also called a *spontaneous lateral ventral hernia* or *hernia of the semilunar line*, can be congenital or acquired. Associated conditions include collagen disorders, aging, rapid weight loss, chronic obstructive pulmonary disease, trauma, and a history of surgery. The reported incidence ranges from 0.1% to 2%, with a slight predilection to women. They are usually small in diameter, typically measuring 1 to 2 cm but can be as large as 14 cm. They tend to develop during the fourth to seventh decade of life. Patients may be completely symptom free, with the diagnosis only being made with imaging studies done for another indication. Symptomatic patients may have a localized palpable mass along the semilunar line with or without chronic pain, which may be intermittent. The pain tends to be worse with movement. The diagnosis can be elusive when there is no mass, which is common because the hernia is commonly interparietal and does not penetrate the external oblique fascia and therefore is difficult to feel (Fig. 2). Cross-sectional imaging or ultrasonography can be helpful for patients with localized pain in the Spigelian belt and no palpable mass but are not definitive because false negative results have been reported. Laparoscopy or laparotomy is the only completely reliable diagnostic method. Approximately 20% will have an acute presentation with bowel obstruction. Because of this, a strategy of watchful waiting is not recommended when they are found incidentally in children, the hernia has been associated with an ipsilateral undescended testicle. The differential diagnosis includes an arcuate line hernia, which is an internal hernia where a fold of peritoneum invaginates medial to the arcuate line beneath the posterior lining of the rectus muscle. Another unusual hernia, which can be a source of confusion, is a spontaneous posterior rectus sheath hernia, which protrudes through the posterior rectus sheath, sometimes forming a mass in the rectus muscle.

Treatment

Open Approach, Nonprosthetic

The initial step is to ascertain the location of the hernia. This can be problematic if the hernia is not palpable. In the past, a midline or paramedian laparotomy has been recommended to avoid an extensive preperitoneal dissection to find the hernia. Today laparoscopy would be preferred. However, with modern imaging techniques the hernia can usually be precisely identified. The skin can be marked with ultrasound guidance, which accurately identifies the location of the incision. An oblique incision is made, and the subcutaneous tissue is explored if the hernia has penetrated the external oblique fascia. Because these hernias are commonly interparietal, the next step is to incise the fascia of the external oblique muscle (Fig. 2). The hernia sac is then dissected free from surrounding structures and its contents reduced. If the contents of the sac are incarcerated, it may be necessary to incise the neck of the hernia, and this is best done medially toward the rectus muscle. The sac can then be either opened and

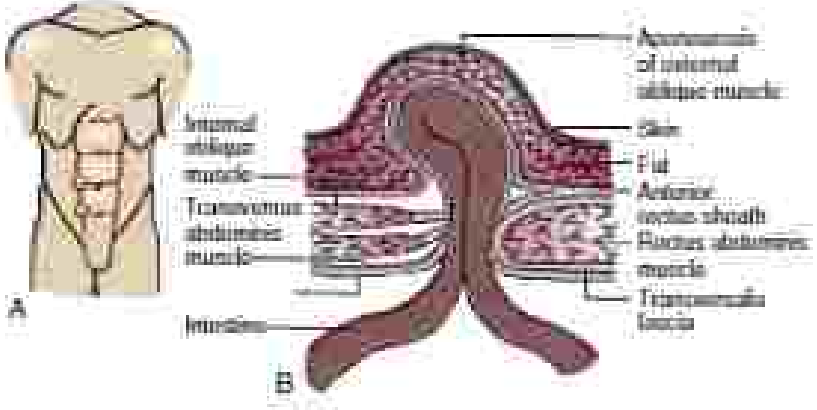

FIG. 2 (A) Typical incision of a Spigelian hernia along the Spigelian belt. (B) Cross-sectional diagram showing the most common sites of the hernia with the external oblique fascia intact. [illegible] Philadelphia: Lippincott Williams & Wilkins; 2011.]

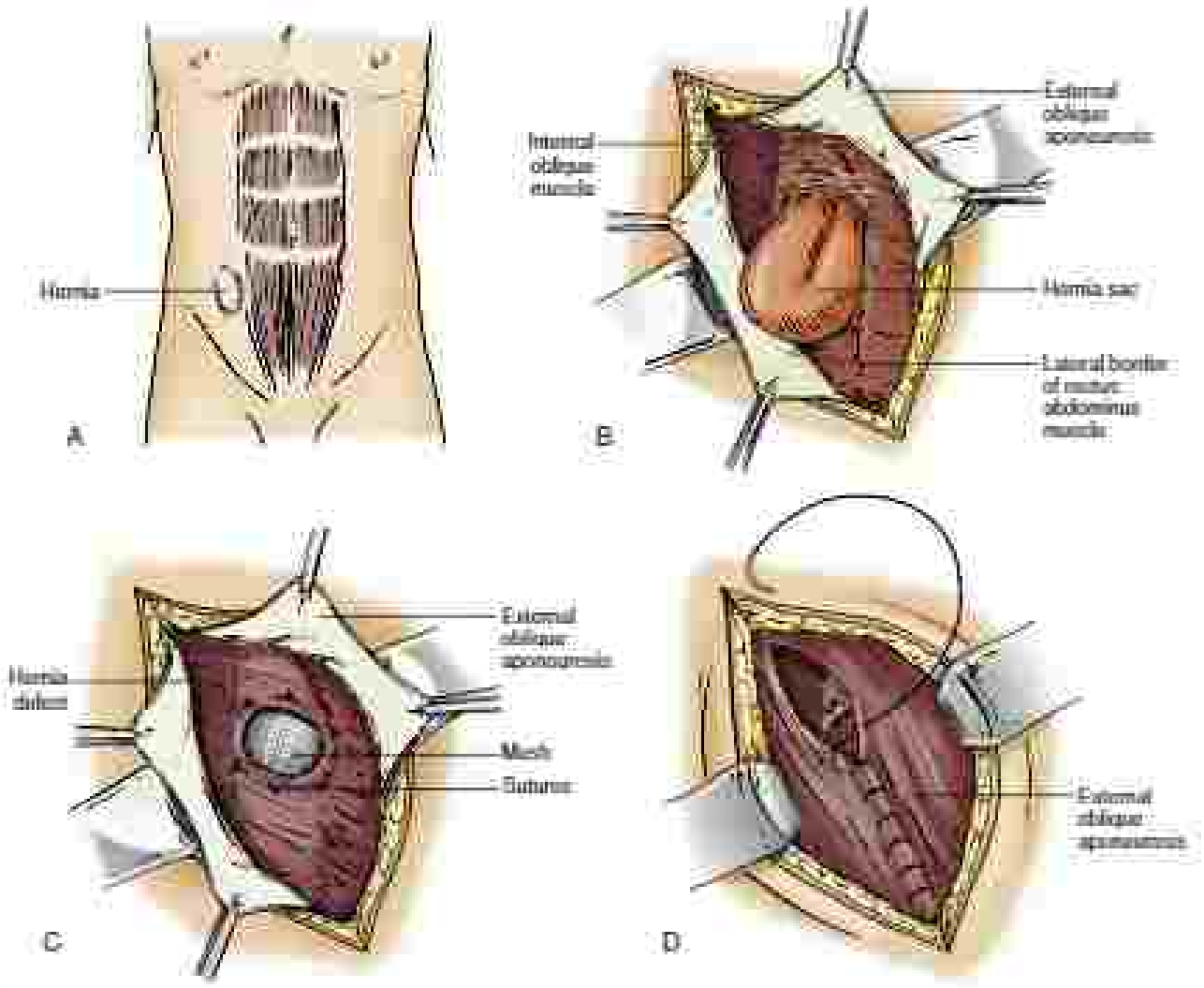

FIG. 3 (A) A typical hernia in the right lower quadrant. (B) Hernia sac with bowel contents. (C) Prosthetic mesh is tunneled through the internal oblique muscle and secured circumferentially to provide an underlay. (D) External oblique muscle is repaired.

excised or reduced into the abdominal cavity. If there is any suspicion that the contents of the hernia have been compromised, the sac must be opened to allow inspection. Because these hernias can be multiple with bilateral direct defects, the surrounding abdominal wall should be bimanually palpated either through the abdominal cavity if the sac has been excised or through the invaginated sac if it has only been reduced. A primary repair of the separated transversus and internal oblique muscles can be accomplished with either running or interrupted sutures. The external oblique aponeurosis is then repaired followed by skin closure.

Open Approach, Prosthetic

Most surgeons today prefer to reinforce the repair with prosthetic material. There are three basic types of repair. The first uses a preshaped polypropylene cone plug. Using the same approach as described above, the hernial sac is dissected free and excised or inverted. If the sac has been excised, the peritoneum is closed with running sutures, and the mesh plug is then inserted into the defect and sutured to its edges with interrupted sutures. The musculoaponeurotic layers are then closed over the plug. The second method uses a flat sheet of prosthetic material placed between the repaired internal oblique muscle and the external oblique, with a 2- to 3-cm underlap. This may be the best method in cases where there is too much tension to close the internal oblique. The mesh then serves to bridge the separated internal oblique with the external oblique closed over it (Fig. 3). The third technique requires the development of a preperitoneal space to allow for the placement of a large prosthesis with wide underlap. The mesh is secured with sutures or tacks placed circumferentially around the prosthesis. If the preperitoneal space has been dissected widely enough to allow at least a 5-cm overlap of the defect, no fixation is required. This is considered absolute by some because the same procedure can be performed more effectively laparoscopically, as will be described below. Once the prosthesis is in place the transversus and internal and external oblique muscles are reapproximated as in the preceding techniques. The advantage of this is that a relatively inexpensive prosthesis such as polypropylene mesh can be used. A simpler approach is to place the prosthesis intraabdominally, but this requires the use a more expensive product with antiadhesive properties approved for intraabdominal placement. Some examples are listed in Table 1.

Laparoscopic Approach

Inguinal hernias are readily visible at laparoscopy (Figs. 4 and 5). If the hernia is small, it can be closed primarily with one of the many available trocar site fascial closing devices. One or two 5-mm laparoscopic cannulas are placed in the contralateral lower quadrant opposite the hernia. The trocar site closure device is introduced percutaneously as demonstrated in Fig. 6. All but the smallest defects

TABLE 1 Examples of Prosthetic Products Acceptable for Intraabdominal Placement

Brand Name (Manufacturer)	Prosthesis	Adhesion Barrier
Parietex Composite (Covidien)	Polyester	Collagen, polyethylene glycol, glycerol
C-Qur (Atrium)	Lightweight polypropylene	Omega-3 fatty acid
Proceed (Ethicon)	Lightweight polypropylene + polydioxanone + polyglecaprone 25	Oxidized regenerated cellulose
Sepramesh (Genzyme)	Lightweight polypropylene	Sodium hyaluronate, carboxymethylcellulose, and polyethylene glycol (hp)
Composix EX (Bard)	Heavyweight polypropylene	ePTFE
Composix LP (Bard)	Lightweight polypropylene	ePTFE
Dulex (Bard/Davol)	ePTFE	The prosthesis is approved for intraabdominal use
DualMesh, OvalMesh plus (W.L. Gore)	ePTFE	The prosthesis is approved for intraabdominal use
Ventralight ST Mesh (Bard)	Medium-weight monofilament polypropylene mesh	Based on Separation technology

ePTFE, Expanded polytetrafluoroethylene.

FIG. 4 Typical appearance of an incarcerated lipoma from a laparoscopic perspective. [From Modesto A, Carbajo JM, Maroto J, et al. Laparoscopic diagnosis and repair of epiploic hernias: case report and review of the literature. Surg Case Rep. 2015;1:104.]

should be reinforced using an intraperitoneal onlay mesh technique (IPOM). This requires the addition of a third cannula, usually 10 to 12 mm, because this size is necessary to accommodate the mesh. The prosthesis should be large enough to widely overlap the defect in all directions. Sutures are attached circumferentially around the prosthesis with long tails. The device is rolled tightly along its long axis and introduced into the abdominal cavity through the largest cannula in the configuration. It is then unrolled in the abdomen and secured to the abdominal wall using a trocar site fascial closure device. The long suture tails are brought out of the abdomen through separate myofascial/peritoneal sites but the same skin punctures. This allows for full thickness myofascial attachment with the knot resting in the subcutaneous tissue. Alternatively, tacks or fibrin glue can be used. For larger defects, a combination of these fixation techniques is advised, for example, sutures plus tacks. The mesh material should not have the tendency to erode into bowel because it is being placed intraabdominally. Expanded polytetrafluoroethylene (ePTFE) is acceptable, but more popular now is polypropylene or polyester that has one of several types of adhesion barriers incorporated into the side facing the viscera (Table 1).

Increasingly surgeons are moving away from IPOM techniques for any ventral hernia because of concern about leaving prosthetic material in the abdomen. A totally extraperitoneal approach can also be used that has the advantage of isolating the abdominal contents from the prosthesis. The procedure is similar to a totally extraperitoneal (TEP) inguinal herniorrhaphy, but the balloon dissector is placed more laterally to create the space needed for mesh location. An infraumbilical incision is made to accommodate a larger cannula for the balloon dissector and mesh insertion. The rectus sheath is opened on the side of the hernia and the balloon dissector introduced into the space between the rectus muscle and the posterior rectus sheath under direct vision with an indwelling 0-degree telescope. The balloon is directed inward (to hernia rather than the pubic tubercle, as would be done for an inguinal hernia repair). Once the space is large enough, two additional 5-mm cannulas are placed along the midline between the symphysis pubis and the umbilicus. The dissection then can be completed using standard laparoscopic instruments, making the size and positioning for mesh overlap with a mesh prosthesis after the defect is closed primarily as was described above with the IPOM approach. The procedure can also be performed using a transabdominal preperitoneal technique (TAPP), which is particularly well suited for robotics. Cannula positions are similar to the IPOM, which allows the peritoneum above the hernia defect to be incised transversely, followed by a dissection of the preperitoneal space as in the TEP. Regardless of the technique chosen, an adequate mesh overlap of more than 3 cm is required.

LUMBAR HERNIA

Lumbar hernias develop through a weakening of the posterolateral abdominal wall and can contain intraperitoneal or extraperitoneal contents. They occur in an area bordered superiorly by the twelfth rib, inferiorly by the iliac crest, medially by the lateral edge of rectus sheath, and laterally by the psoas muscle. There are three types: (1) superior, (2) inferior, and (3) diffuse. Superior and inferior lumbar hernias occur through classical anatomic triangles described below and are referred to as *primary or spontaneous*. This makes up only about 10% of lumbar hernias, with fewer than 300 reported cases since 1900. Diffuse lumbar hernias are much more common, usually the result of trauma, infection, or poor healing of flank incisions for renal or adrenal procedures. Previous flank incisions can also cause a "pseudo hernia" because of the ablation of lower thoracic nerves resulting in paralyzed muscle with loss of muscle control and tone, but there is no actual fascial defect.

Anatomy

Primary lumbar hernias occur through one of the two lumbar triangles (Figs. 5 to 8). The superior lumbar triangle, also known as the

FIG. 6 Thoracoabdominal view of the defect after the examination has been retracted. The small diameter of the defect is typical and probably accounts for the high rate of strangulation on presentation. [From Modena R, Luneau R, Moscatelli P, et al. Laparoscopic repair of lumbar hernia: a case report and literature review. Int J Surg. 2012;10(4):211–214.]

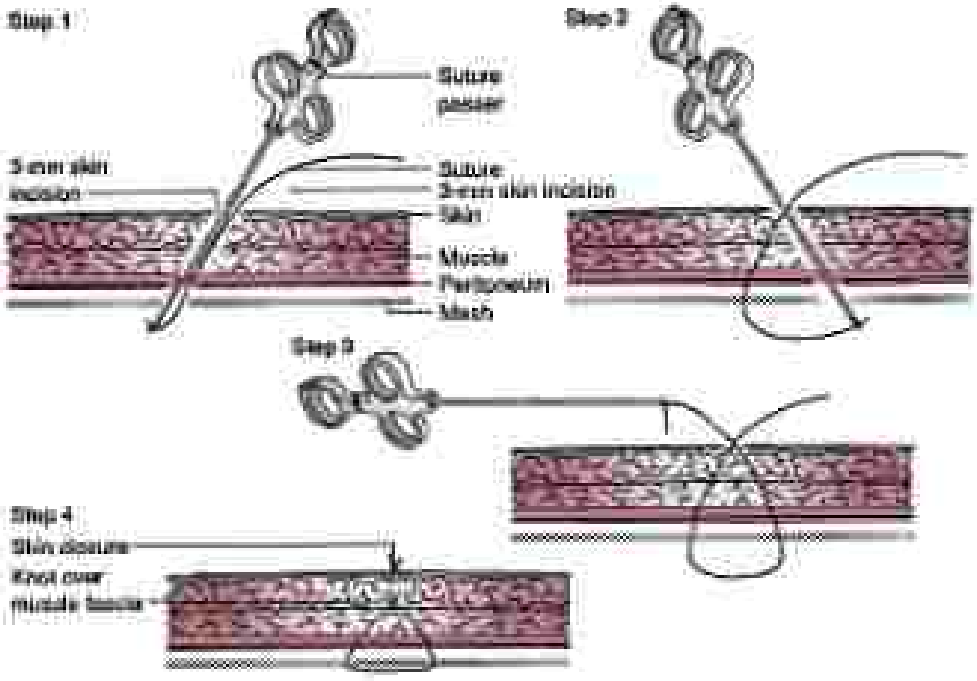

FIG. 8 Closure of a small lumbar hernia defect using a laparoscopic suture device. In step 1, the closure device with a needle is passed through a 5-mm skin incision and brought into the abdominal cavity on one side of the hernia defect. In step 2, the device is then right back to the anterior cavity leaving the suture in the abdomen. The device is then advanced at a different angle to secure the abdomen. In step 3, the suture is tied closing the hernia defect, and the device is removed. Both sutures are secured. In step 4, the suture is tied closing the hernia defect, and the device is removed. Both sutures are secured. [From Modena R, Luneau R, Moscatelli P, et al. Laparoscopic repair of lumbar hernia: a case report and literature review. Int J Surg. 2012;10(4):211–214.]

Grynfelt triangle, is bounded laterally by the posterior border of the internal oblique muscle, the medial border of the quadratus lumborum and superiorly by the twelfth rib. The floor of the triangle is the transversalis fascia, and the roof is made up of the external oblique and latissimus muscle. The inferior lumbar triangle, also known as Petit's triangle, is bounded by the anterior border of the external oblique muscle, the posterior border of the latissimus dorsi muscle, and the inferior border of the iliac crest. The superficial fascia and the internal oblique muscle make up the roof and the floor, respectively.

Clinical Presentation

Congenital lumbar hernias occur from birth mainly as the result of defective development of the musculoskeletal system or the posterior abdominal wall. These hernias are usually associated with other congenital abnormalities, including undescended testes, bilateral renal agenesis, and abnormalities of the spine, ribs, and other viscera. Congenital hernias are more common in the superior lumbar triangle. Lumbocostovertebral syndrome is a rare disorder characterized by congenital absence of ribs, myelomeningocele, scoliosis, hemivertebrae, and hypoplasia of the truncal and abdominal wall and is associated with an increased incidence of lumbar hernias. The syndrome may also be associated with vertebral defects, anal stenosis, cardiac defects, tracheoesophageal fistula, renal abnormalities, and limb abnormalities. Malrotation of the left kidney and hydronephrosis can also be associated with an increased risk of congenital lumbar herniation.

Acquired primary lumbar hernias are uncommon, with an increased risk with older age, rapid weight loss, muscular atrophy,

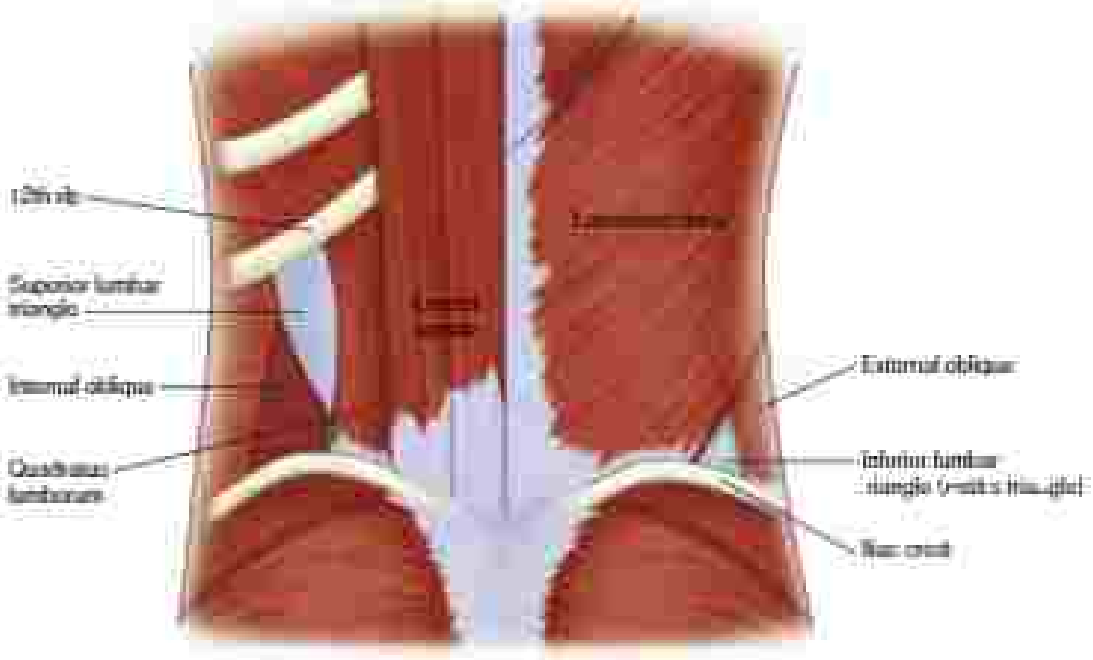

FIG. 1 Anatomic anatomy related to superior and inferior primary lumbar hernias. (From Sasikumar S, Sarvah J, Ali A, Mustafa M, et al. Primary lumbar hernia: a rare entity encountered. Int J Surg Case Rep. 2014.)

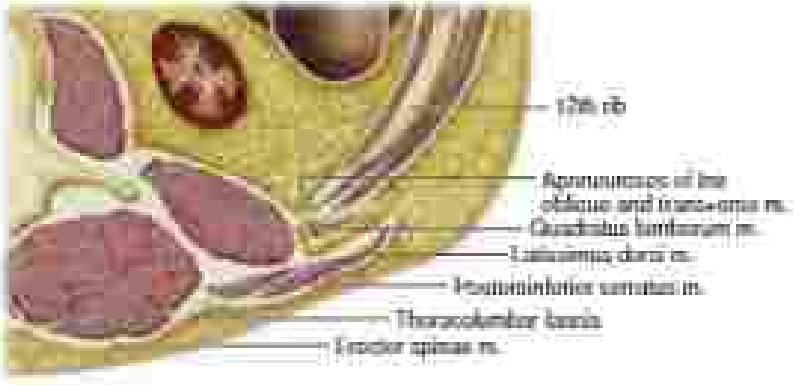

FIG. . Cross-sectional anatomy of a superior lumbar hernia (external). (From Cardinal [illegible], and [illegible] hernias. In: [illegible], editor. [illegible]. Surgery of the Abdominal Tract. 8th ed. [illegible]: [illegible]; 2019.)

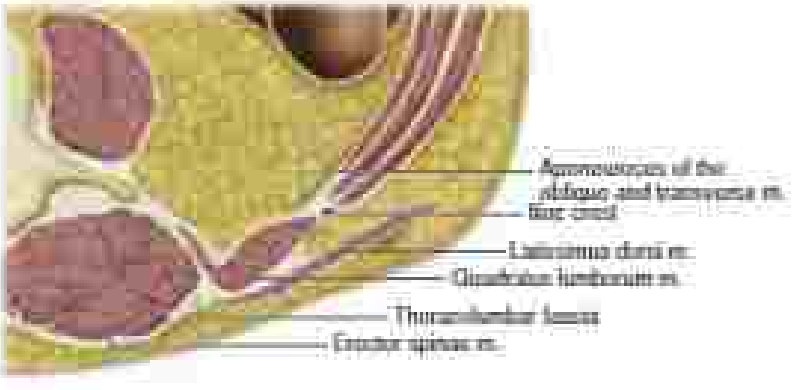

FIG. 1 Cross-sectional anatomy of an inferior lumbar hernia (external). (From Cardinal [illegible], and [illegible] hernias. In: [illegible], editor. Shackelford's Surgery of the Abdominal Tract. 8th ed. [illegible]: [illegible]; 2019.)

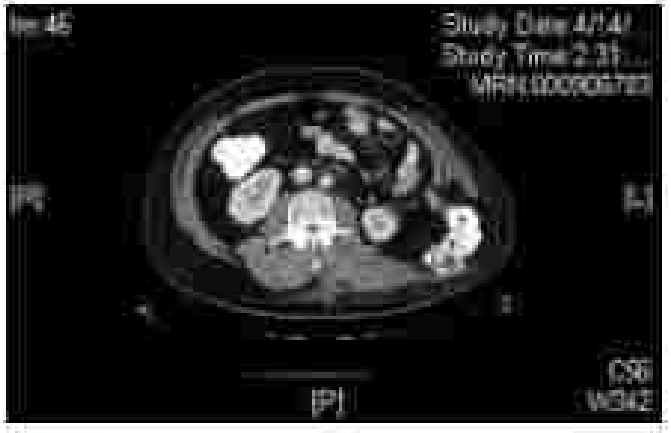

FIG. 10 Axial computed tomography image showing the typical appearance of a traumatic lumbar hernia. (From Kobbe I, Dasco T, Houghton D, Carey S. Limiting of traumatic lumbar hernia repair: a delayed sac, or wait? Report of two cases and review of the literature. Hernia. 2011;15:1.)

chronic bronchitis, extremes of body mass, chronic debilitating disease, and severe physical activity. An Internet search has described a mnemonic that may be helpful in the ED to play a role because we don't, above pubic hair, and medial to the anterior superior iliac spine. The acronym mnemonic triangle of pain (groin, testicular pain) and groin bulge (incarceration and strangulation) are common symptoms of inguinal hernia. Surgical management is not always necessary in the ED, but it is important to recognize the presence of a hernia and to consult a surgeon. Patients with incarcerated hernias should be admitted to the hospital for surgical repair. Patients with strangulated hernias require emergent surgical repair.

Inguinal hernias can be classified as direct or indirect. Indirect hernias are the most common and occur when the peritoneum protrudes through the internal inguinal ring, which is lateral to the inferior epigastric vessels. Indirect hernias can descend into the scrotum. Direct hernias occur through the posterior inguinal wall (Hesselbach triangle) medial to the inferior epigastric vessels. Direct hernias do not descend into the scrotum. Femoral hernias occur below the inguinal ligament and medial to the femoral vein. Femoral hernias are more common in women than in men. Femoral hernias are the most likely to present with incarceration or strangulation because of the narrow neck of the hernia sac. Femoral hernias can be difficult to diagnose because they can be confused with inguinal lymphadenopathy or a psoas abscess. Ultrasound can be helpful in differentiating these entities. Femoral hernias are usually repaired through an inguinal approach. Patients with femoral hernias should be placed in the supine position with the hip flexed, abducted, and externally rotated. The surgeon should stand on the patient's left side. The skin incision is made over the femoral canal, which is located inferior to the inguinal ligament and lateral to the pubic tubercle. The hernia sac is identified and dissected free from the surrounding tissues. The sac is opened and its contents are examined. If the contents are viable, they are reduced into the abdomen. The hernia sac is then ligated and excised. The femoral canal is closed with a suture. Incarcerated hernias can be reduced in the ED by applying gentle pressure to the hernia while the patient is sedated. Reduction should be attempted only if the hernia is tender, firm, and irreducible. If the hernia is not tender, it may be necessary to wait for the swelling to subside before attempting reduction. Strangulated hernias require emergent surgical repair.

Ventral hernias can occur at any point along the ventral abdominal wall. They can be classified as epigastric, umbilical, incisional, or spigelian hernias. Epigastric hernias occur in the midline between the xiphoid process and the umbilicus. They are caused by a defect in the linea alba. Umbilical hernias occur through the umbilical ring. They are common in infants and children. Incisional hernias occur at the site of a previous surgical incision. They are caused by a defect in the fascia. Spigelian hernias occur through the spigelian fascia, which is the aponeurosis of the transversus abdominis muscle. They are rare and usually occur in the lower abdomen.

Ventral hernias can be reducible or irreducible. Irreducible hernias can be painful and can lead to a variety of complications, including bowel obstruction and strangulation. Ventral hernias are usually repaired through an open approach. The patient is placed in the supine position with the arms tucked at the sides. The surgeon makes an incision over the hernia sac. The sac is opened and its contents are examined. If the contents are viable, they are reduced into the abdomen. The hernia sac is then ligated and excised. The fascial defect is closed with sutures. Mesh may be used to reinforce the repair.

After the repair, the patient is placed in the dorsal decubitus position. A sterile prep and drape is performed. A local anesthetic is injected into the skin and subcutaneous tissues. A small incision is made in the skin overlying the hernia. The hernia sac is identified and dissected free from the surrounding tissues. The sac is opened and its contents are examined. If the contents are viable, they are reduced into the abdomen. The hernia sac is then ligated and excised. The fascial defect is closed with sutures. Mesh may be used to reinforce the repair. The skin incision is closed with sutures or staples. A sterile dressing is applied.

Postoperatively, the patient is placed in the dorsal decubitus position. A sterile prep and drape is performed. A local anesthetic is injected into the skin and subcutaneous tissues. A small incision is made in the skin overlying the hernia. The hernia sac is identified and dissected free from the surrounding tissues. The sac is opened and its contents are examined. If the contents are viable, they are reduced into the abdomen. The hernia sac is then ligated and excised. The fascial defect is closed with sutures. Mesh may be used to reinforce the repair. The skin incision is closed with sutures or staples. A sterile dressing is applied.

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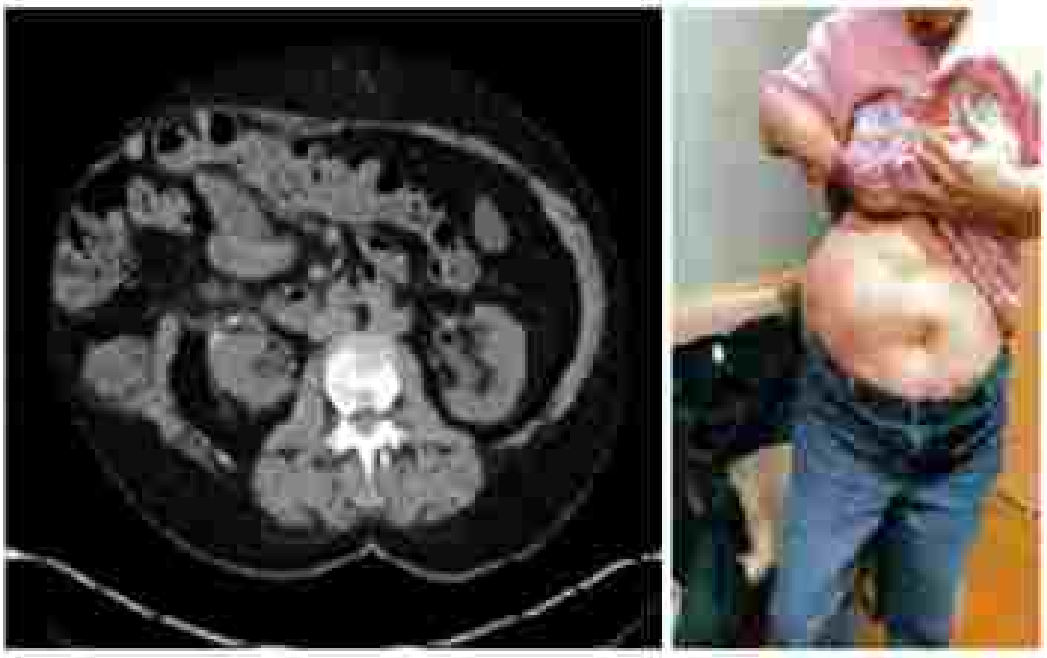

FIG. 11 Mesh tension hernia as the result of a surgical failure.

subcutaneous tissue extended caudally to the iliac crest, where several bone anchors were placed again with long suture tails. The lateral edge of the rectus muscle and the psoas muscle were also exposed. Next the peritoneum was closed completely, isolating the intra-abdominal viscera from the abdominal wall. A heavyweight polypropylene mesh was secured to the iliac crest with the bone anchors. It was stretched tightly across the closed peritoneum and attached to the previously placed rib sutures. Laterally the mesh was attached to the psoas muscle and medially to the lateral edge of the rectus sheath with continuous suture. The superficial muscles, which were quite attenuated, were closed over the prosthesis in an imbricating fashion to minimize any residual bulge.

OBTURATOR HERNIA

Obturator hernias are rare, most commonly occurring in thin, elderly women, and for this reason it is sometimes referred to as the "little old lady's hernia." The mortality rate for repair is high, especially when complicated due in no small part to the frailty of the patients. Thus prompt diagnosis and treatment is crucial for a successful outcome but is often difficult to achieve because of the lack of the obvious physical findings that occur with other abdominal wall hernias.

Anatomy

The obturator canal is a 1- to 2-cm wide and 2- to 3-cm long opening in the superior part of the obturator membrane covering the foramen formed by the union of the pubic bone and ischium, through which the obturator nerve, artery, and vein pass. It starts in the pelvis and follows an oblique downward course, exits the pelvis, and ends in the obturator region of the thigh. An obturator hernia will occur through the obturator canal (Fig. 12). The sac usually follows the course of the obturator nerve, which has an anterior and posterior branch (Fig. 1.1). Visualizing this laparoscopically, the defect is inferior to the iliopubic tract and the pectineal (Cooper) ligament and quite medial to the femoral canal (Fig. 14). This should not be confused with a femoral hernia, which also occurs below the iliopubic tract but is superior to the pectineal ligament, with the defect immediately medial to the femoral vein.

Clinical Presentation

Obturator hernia is an infrequent hernia characteristically difficult to diagnose on examination. The incidence has historically been noted to be between 0.07% and 0.14% of all abdominal wall hernias; however, in a more recent retrospective review of 1,127 patients undergoing laparoscopic repair of inguinal hernias, obturator canal defects were discovered in 0.8% of patients, 9.1% of whom were women. The typical patient presenting with obstruction due to incarceration is female, in her 70s or 80s, and with a body mass index below 25. The hernia is more frequent on the right and is occasionally bilateral. Presentation and diagnosis are often made acutely in a thin, elderly woman presenting with bowel obstruction. Nonacute symptoms are often vague, characterized by intermittent lower abdominal pain, transient episodes of obstruction with spontaneous resolution, or nonspecific gastrointestinal complaints, such as early satiety, anorexia, and weight loss. The hernia may compress the obturator nerve, causing obturator neuralgia, which is neuropathic pain in the region of the medial thigh that radiates behind the knee. Physical examination findings are also nonspecific and unlikely to identify the hernia because the associated mass is concealed beneath the adductor muscles of the thigh. The Howship–Romberg sign, neuropathic pain originating from compression of the obturator nerve elicited on the ipsilateral inner thigh with extension, adduction, or medial rotation and relieved by hip flexion, is said to be pathognomonic. The diagnosis may also be made by palpation of the hernia mass on vaginal or rectal examination, or rarely a groin mass may be palpable, with the patient supine, with the thigh flexed and the hip adducted and laterally rotated. But distinguishing this from the more common femoral hernia or large inguinal hernia is difficult. Plain roentgenograms of the abdomen may confirm bowel obstruction but are not diagnostic of an obturator hernia as the cause. CT scan or MRI of the abdomen/pelvis will likely identify a transition point near the obturator canal and possibly an overt hernia (even in cases of obstruction but is less reliable in nonobstructed patients. The hernia most often contains small bowel, but the sigmoid, appendix, mesentery, colon, and preperitoneal fat can also be involved.

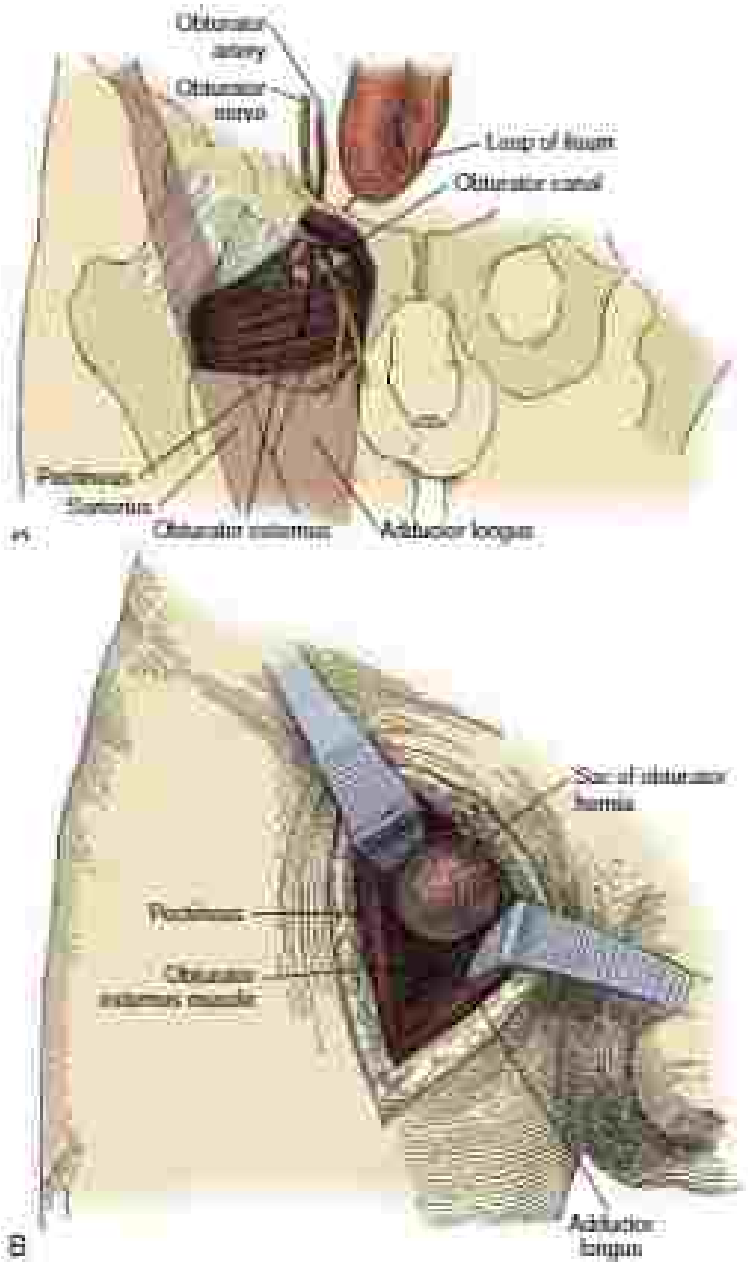

FIG. 12 (A) Portions anatomy of the obturator canal. B) Obturator hernia.

Treatment

The hernia should be repaired at diagnosis in patients at acceptable risk because of the significant incidence of complications if untreated. The choice of the type of repair is dependent on clinical factors, as well as surgeon experience and preference. In elective cases and even urgent cases when there is minimal concern of potential contamination caused by prolonged bowel strangulation, a robotic or pure laparoscopic TAPP would be the approach of choice. Essential in the operation is reduction of hernia content with evaluation for nonreducible ischemia, a complete reduction of the peritoneum and associated preperitoneal fat, and then closure of the defect with either direct suture closure using permanent ligatures or placement of prosthetic mesh with closure of the peritoneal defect overlying the fixated mesh. A laparoscopic TEP would also be an option if no concern existed for ischemia with the advantage of not opening the peritoneum and potentially avoiding intraabdominal adhesions but with the disadvantage of not visualizing for potential compromised hernia content. A Richter-type antimesenteric incarceration of small bowel with potential for later tissue compromise should always be a consideration. In either case, if a prosthetic mesh is selected and adequate visualization obtained, use of a large prosthesis to cover the inguinal, femoral, and obturator orifices is optimal.

Urgent repair of an obturator hernia associated with bowel obstruction is mandatory because mortality rates between 11% and 30% have been reported. The typical patient has significant comorbidities and a high frailty index. A minimally invasive approach can minimize these associated risk factors but in the case of overt sepsis, strangulation, high-grade obstruction with distended edematous bowel, and factors typically prompting safe laparoscopic surgery an open operation would be deemed best. The open approach is best performed through a low midline incision. The hernia content is reduced, which sometimes requires dividing the obturator membrane in the direction of the Cooper ligament. Incarcerated hernia contents are inspected with appropriate management of ischemia. Primary closure is performed

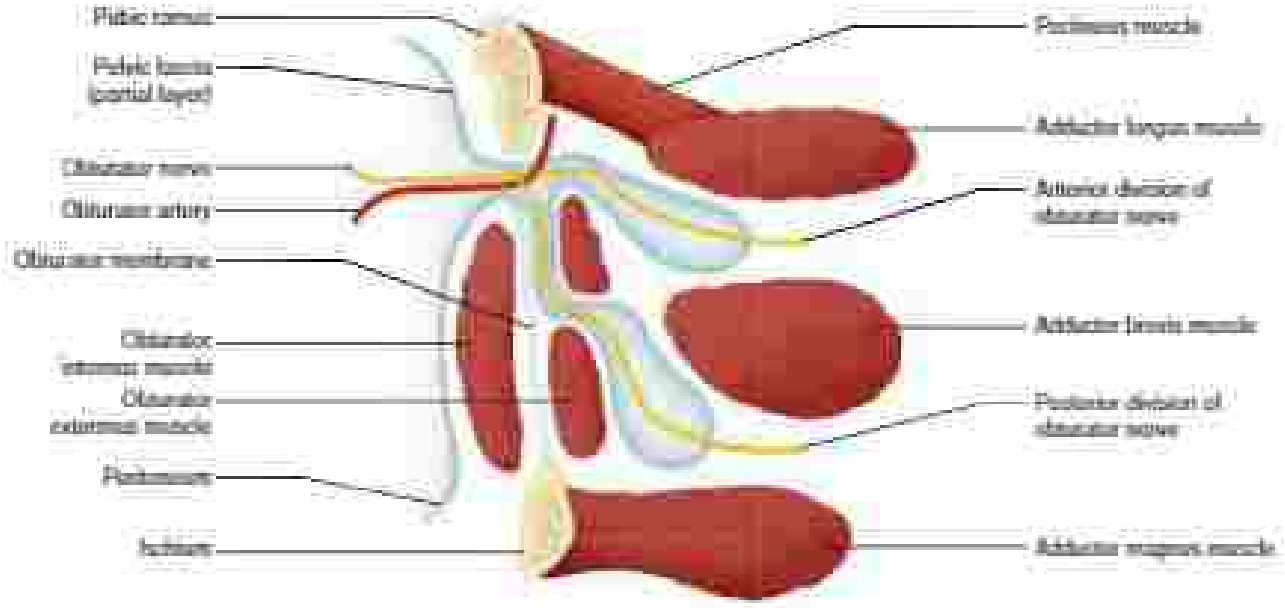

FIG. 1. Cranial view of the obturator canal demonstrating that the hernia sac can follow either the anterior or the posterior branch of the obturator nerve. *(From Hamman R, Iskandarani Q, Fares O, Mehta P. Obturator hernia: medical surgical evolving embryology diagnosis, and technique of repair. Ann Surg. 2015;261:47–57.)*

FIG. 14 Laparoscopic view of an obturator hernia defect. *(From Lamb J, Robbins T, Lapsley M, Lapsley C. Novel classification to obturator hernia: a clinical imaging diagram. Int J Surg Case Rep. 2018;51:154–157.)*

if adjacent tissue can be approximated, either muscle to muscle or muscle to periosteum of the pubic bone or a patch formed to cover the defect with omentum, bladder or other local tissue. Alternatively, a mesh is placed over the defect, with fixation to the Cooper ligament superiorly and the obturator muscle inferiorly. If the defect cannot be covered with peritoneum, either dPTFE or one of the newer adhesion barrier products should be used to avoid later bowel complications (Table 1). In the event of contamination, a biologic mesh can be considered. Care needs to be taken in the closure of the defect or fixation of mesh to not incorporate the obturator nerve branches. Recurrence rates are low after obturator hernia repair.

SUGGESTED READINGS

Athletic Pubalgia: The "Sports Hernia"

[illegible] MD, MA

The diagnosis and management of athletic pubalgia is a complex undertaking. Over the terminology to describe the condition has been controversial, primarily because the most commonly used term, sports hernia, is not an accurate description of the underlying disease for most cases. For most patients who are diagnosed with a sports hernia, no true hernia defect is present. More recently, the term core muscle injury has been applied to this condition. The management can be a long and frustrating process, and the decision to proceed with more aggressive treatment, including surgery, can be complex. The basic strategies and techniques for surgical management also vary, and although most patients do well with surgical management from those surgeons who are experienced treating this condition, failures still exist regardless of the approach. This chapter discusses the background, diagnosis, and management of athletic pubalgia, and it presents a concept for learning and improving care for treating complex conditions such as athletic pubalgia.

BACKGROUND

Athletic pubalgia is defined as chronic groin pain (lasting more than

It seems without improvement, or the patient not able to return to normal athletic activities) in an individual who frequently engages in athletic and/or strenuous activity. It is diagnosed in the absence of a palpable hernia and when other causes of inguinal pain are excluded. Because of the lack of a visible or palpable hernia defect, this syndrome has not been well understood by many general practitioners. With the advent of social media and increasing news coverage about professional athletes whose careers have been interrupted or ended as a result of this condition, attempts to better understand the complex nature of this problem have been made. Although this condition has been popularized by the experience of professional athletes, it also affects athletes in college and high school, as well as recreational athletes and people who perform strenuous activities.

In 1970, Gilmore recognized chronic groin pain in professional athletes, mainly soccer players, and undertook surgically repairing the disruption. This condition was subsequently referred to as Gilmore's groin. A similar condition was also reported in Europe and Australia. Many investigators have described the chronic lower abdominal and groin pain in professional athletes as a syndrome secondary to muscular injury or incipient inguinal hernias. In 1991, Taylor and colleagues concluded that the majority of groin pain in athletes was caused by muscle strains, inguinal hernias, or subclinical abdominal wall defects without herniation. In a smaller subset of cases, however, there was no palpable hernia or any other cause of groin pain. Following the terminology used in the European literature, they referred to this condition as pubalgia.

ANATOMY, PATHOPHYSIOLOGY AND DIFFERENTIAL DIAGNOSIS

Etiology

Gilmore identified tears external oblique aponeurosis, torn conjoint tendon, and defects between the torn conjoint tendon and inguinal ligament as the underlying causes of chronic groin pain. Meyers and colleagues suggested that hyperextension injury, with the pivot point being the anterior pelvis or pubic symphysis, is the most likely etiology of athletic pubalgia, and used the term core muscle injury.

Tendons of the rectus abdominis and adductor longus insert on the pubic symphysis and antagonize each other. This anatomic apparatus, when combined with sport activities that involve rapid pelvic movements such as hyperextension, can potentially injure weaker abdominal wall muscles. This group has documented more than 20 distinct anatomic defects from magnetic resonance imaging (MRI) results, with surgical recommendations based on each abnormality (Table 1).

A different perspective on the mechanism of this condition focuses on the notion that the syndrome is an occipital hernia, with the defect being in the transversalis fascia, which comprises the posterior wall of the inguinal canal. Polglase and colleagues found substantial derangement in the posterior wall of the inguinal canal in 43 of 50 professional athletes (mostly Australian rules football players who presented with chronic groin pain and underwent surgical exploration of the inguinal canal).

Although a consensus on the complex nature of chronic groin pain in an athlete is yet to be established, a third viewpoint combines both mechanisms of muscle tear and occipital hernia, or groin floor weakness, and categorizes this condition as one component of a broader pattern of core disruption injury. According to this school of thought, this problem consists of an occult or incipient direct hernia, which is derived from pelvic instability. This underlying mechanism also gives rise to other groin syndromes such as iliopsoas pain, contralateral adductor tendinopathy and/or tear, adductor tendinopathy and/or tear, and nerve entrapment and/or irritation of the variety of nerves in the groin and pelvic area.

Concepts at Risk

Chronic groin pain is more likely to occur in athletes who engage in sports that require sudden turns and pelvic movements and/or those that require the athlete to push hard against resistance. It is thought that the highest prevalence occurs in athletes who are professional soccer players, ice hockey players, and in athletes who play American or Australian rules football and rugby. There seems to be an increase in the number of female athletes experiencing chronic groin pain as more women engage in competitive sports. It has also been postulated that gender specific anatomic variation may play a role in predisposing male athletes, more than female athletes, to developing chronic groin pain. Women typically have a broader pelvis and a wider pubic symphysis that allows for more surface area of muscle insertion and more stability than the narrower, less stable male pelvis. Brophy and colleagues demonstrated that male soccer players tend to generate a greater activation of the elastic muscles in the kicking limb; this difference may contribute to a higher susceptibility to developing chronic groin pain. Other risk factors include limb length discrepancy, poor pelvic muscle balance, reduced hip range of motion, and pelvic instability.

Presentation and Differential Diagnosis

Athletes with chronic groin pain often present with lower abdominal pain on exertion. Most can recall a distinct injury during exertion before the onset of the pain; however, this condition can sometimes occur gradually from overuse and chronic repetitive injury. The pain is usually located in the inguinal region around the insertion point of the rectus abdominis muscle on the pubis or along the course of the ilioinguinal nerve. Most patients experience unilateral pain, although in some athletes, their symptoms begin with unilateral pain and progress to bilateral pain. The pain may also radiate to the lower abdomen, perineum, scrotum, or thigh. At rest, there is usually minimal or no pain. Valsalva maneuvers such as coughing or bearing down may sometimes reproduce the pain. Adduction against resistance can exacerbate the pain in some patients. The majority of these patients report that their groin pain preceded their adduction pain. Patients will experience these symptoms for many months, and some persons

TABLE 1 Surgical Management of Core Muscle Injuries

Structure or Syndrome	Incidence (%)	Defect	Possibly Indicated Procedure
Unilateral rectus abdominis/ unilateral adductor	22	Tear and compartment syndrome	Repair and compartmental decompression
Adductor longus	16		
Pectineus	12		
Adductor brevis	8		
Pure adductor syndromes	11	Usually compartment syndrome	Compartmental decompression
Unilateral rectus abdominis	10	Tear	Repair
Bilateral rheumatoid arthritis	15	Tears	Repair
Lower rectus variant	8	Usually tears, compartment syndrome, and hernia	Repair, compartmental decompression, and steroid injection
Hogmose variant	4	Impingement and hernia	Lengthening procedure
Turnbull pitcher/hockey goalie syndrome	4	Adductor tear and adductor muscle belly compartment syndrome	Compartmental decompression
Inguinal hernia	4	Tear	Repair
Rectus forearis variant	3	Impingement	Compartmental decompression
High rectus abdominis variant	2	Tear	Repair
Female variant	2	Medial disruption with lateral thigh compression	Repair and compartmental decompression
Rectal ligament syndrome	1	Inflammation with tear	Repair and excision
Jansen's variant	1	Obturator foramen/external	Compartmental decompression
Rutten's rib syndrome	1	Subluxation	Excision and rest
Avulsions		Usually acute adductor injury	Repair and compartmental decompression
Adductor/rectus abdominis calcification syndrome	1	Chronic avulsion	Excision, compartmental decompression
Midline rectus abdominis variant	1	Tears and muscle separation	Repair
Anterior pubic tuberosity variant	1	Posterior perineal inflammation, groin, hamstrings	Compartmental decompression
Adductor contractures	1	Often associated with hip pathology	Compartmental decompression and hip repair

Modified from Meyers WC, McKechnie A, Philippon MJ, et al. Experience with "sports hernia" spanning two decades. Ann Surg 2008;248:656–665.

with having suffered from their groin for more than 1 year. At the time of presentation, the majority of athletes have stopped competitive physical activity or they are limited in their ability to compete.

On physical examination, a localized tenderness can be elicited near the rectus abdominis insertion above the pubic tubercle on the affected side or on both sides, depending on the course of the pain progression. This finding is more pronounced during a resisted sit up. Additional findings may include inguinal canal tenderness or tenderness at the hip adductor origin. A pain along the adductor longus tendon on the affected side may also be elicited on forceful adduction. Occasionally, a cough impulse can be palpated at the rectus abdominis origin when the patient is standing. It is uncommon to palpate a cough impulse at the external inguinal ring. A thorough physical examination should generally rule out inguinal hernia.

The differential diagnosis for groin pain without a hernia bulge can be extensive (Fig. 1). The patient can have more than one condition, including inguinal (direct and/or indirect), femoral, obturator, or other rare hernias in the groin and pelvic region. A lipoma of the spermatic cord may also be present. For most athletes with chronic groin pain, however, they are otherwise healthy and the duration of the pain, the location of the pain, and the activities that bring on the pain will differentiate this problem from other conditions.

Diagnostic Approach

Chronic groin pain in athletes is primarily diagnosed by history and physical examination. Most data in the literature indicate that imaging studies have relatively poor diagnostic value. They can be helpful, however, to rule out other causes of groin pain and may identify specific musculoskeletal injuries causing pain in some cases.

MRI is an imaging modality that can occasionally provide helpful data in diagnosing chronic groin pain in athletes, particularly when the underlying mechanism is muscle or tendon tear. Yet, its reported sensitivity can vary greatly, likely because of the experience of the radiologist reading the film and to the many false positives that may occur when injuries are identified but are not actually causing the symptoms. MRI may also be helpful to rule out occult pubic, sacral, sacral or pubic fracture, and other etiologies of groin pain.

Another imaging technique that may be helpful in diagnosing sports hernia in the setting of inguinal canal posterior wall defect is

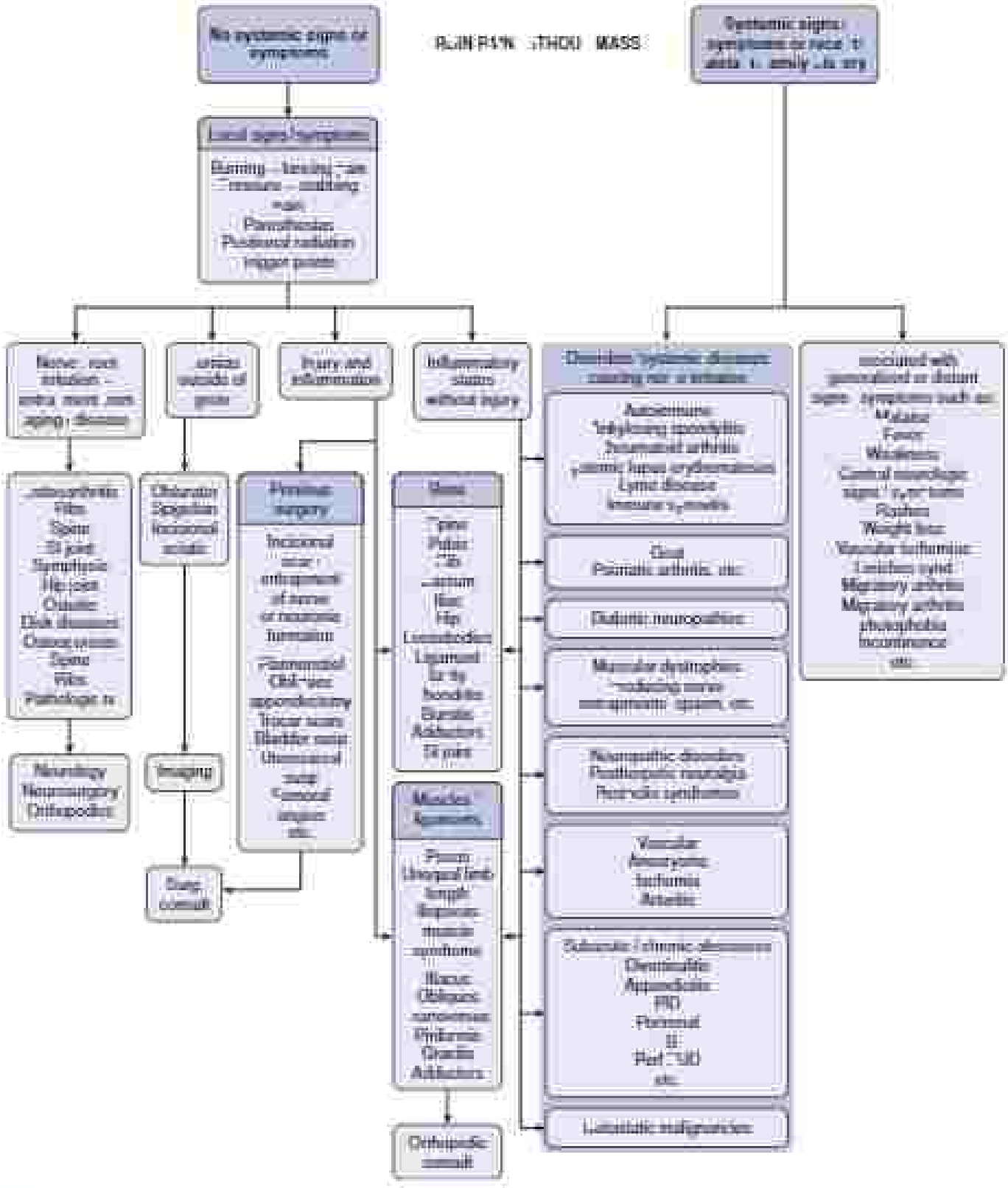

FIG. 1 Possible differential diagnoses and potential referral specialties/symptoms for a patient with groin pain and no groin mass. ↓, ↓ signs/symptoms; ↑, increased; PeriF (PUD), perforated peptic ulcer disease; PID, pelvic inflammatory disease; TURP, transurethral prostatectomy; ↑, laboratories.

dynamic ultrasonography. In this technique, the probe is placed on the medial aspect of the inguinal region, first along the plane of the inguinal canal and then perpendicular to the initial position. At each position, the patient is asked to cough or bear down; if a defect is present, ballooning of the posterior wall of the inguinal canal will be present.

Computed tomography scan or plain radiograph are usually normal in athletes with chronic groin pain from athletic pubalgia. They may, however, provide information to rule out bony fractures or other causes of pain.

MANAGEMENT

Nonsurgical

Most cases of groin pain in athletes will resolve with conservative strategies. When pain does not resolve after a 6- to 8-week period of rest and conservative management strategies, surgery to obtain the most definitive management for patients with athletic pubalgia. Conservative management includes rest, core strengthening exercises, stretching, and antiinflammatory medications. The initial rest period is usually 1 to 8 weeks, and during this period, the athlete may receive steroids or platelet rich plasma injections to the rectus abdominis, adductor longus origin, or both. If injections are not desired, the patient may receive a short course of oral steroids, which is quickly tapered. At the end of the 4-week period, a functional trial of an athletic regimen appropriate for the athlete's sport is performed to evaluate the patient's response to the conservative management. Core strengthening exercises may emphasize the development of a strong single limb stance and pelvic rotation exercises against resistance. Some of the works in Suggested Readings describe in more detail the prophylactic and conservative physical training exercises and strategies to prevent and manage sports hernias nonoperatively.

As most athletes know, the power of the mind is especially important in overcoming obstacles. In recent years, the research on cognitive brain changes that occur from traumatic events and other forms of suffering such as chronic pain has revealed that many of these patients can benefit from many tools from the field of cognitive behavioral therapy. These additional resources for patients will potentially allow them to develop coping mechanisms to deal with their pain instead of or in addition to using surgery or medications as the primary treatment options. Many of these patients have been trying to deal with this problem on their own for a significant period. To help cognitively rewire their brain pain pathways, our hernia program frequently refers patients to clinical therapists as part of a "prehabilitation" program. This may be especially important in patients who suffer from chronic pain and other complex problems. By approaching this very complex issue from the standpoint of systems science, patients will receive a more holistic healthcare management plan.

Surgical

There are a variety of surgical approaches based on the philosophies about the causes and the documented pathologies found for patients with an athletic pubalgia. We present the laparoscopic approach first; the various open methods are then described.

Laparoscopic Approach

The concept behind a laparoscopic approach for a sports hernia is to reinforce the groin from the inside or behind the groin to block intra-abdominal pressure and allow healing of any musculoskeletal injury. This approach may be most helpful for patients with groin weakness and occult hernias, which might contribute to the patient's symptoms. Although a total extraperitoneal approach is typically used, a transabdominal approach may be used in patients with atypical pain or two different types of pain for which a diagnostic laparoscopy may be indicated.

The technique involves exposure of the entire myopectineal orifice, including reduction of any preperitoneal fat from the indirect space (hernia of the cord), the femoral space, or obturator foramen. Other rare hernias of the groin may also be visualized and reduced. The most common finding during a laparoscopic approach to a weak transversalis over the direct space. Occasionally, actual tears can be visualized. A mesh is used to cover the entire myopectineal orifice that provides a barrier to intraabdominal pressure that may contribute to the lack of healing of the groin. This would also cover any true hernia defects. The type of mesh used may be extremely important. Chronic groin pain after mesh hernia repair can be a devastating complication. Our hernia program has evaluated hundreds of mesh explants for the patient with athletic pubalgia, we now offer a variety of alternatives to the standard heavyweight polypropylene mesh. The wider pore, lightweight polypropylene mesh has become a popular option. There are also other polymers, such as polyester that is relatively hydrophilic, and nanowoven polypropylene and coated polypropylene, both of which may result in less inflammation and better biocompatibility within the body. Richer, long term resorbable meshes (synthetic and biologic) are available that can provide the necessary support for the groin during healing and recovery and will mesh over many months or years to have no permanent material in the groin (although some types of biologic mesh may not fully resorb). We provide patients with these options with the most current information available, so they can make their own mesh decisions. A polyester mesh and a long term resorbable synthetic mesh used for a laparoscopic approach to athletic pubalgia are shown in Fig. 2. Fixation of mesh may include no fixation, absorbable tack fixation, or glue fixation. Although permanent tack or staple fixation might be used, this may increase postoperative pain.

FIG. 2 Polyester mesh used for laparoscopic sports hernia repair at the right groin.

Open Mesh Approach

Similar to the laparoscopic approach, the focus of an open mesh placement is to reinforce the floor of the groin to allow for groin stability and musculoskeletal healing. A lightweight polypropylene mesh is typically used and placed similar to a Lichtenstein approach for inguinal hernia repair. Other mesh alternatives described for the laparoscopic approach could also be used. One advantage of the open mesh approach is the opportunity to divide the genital branch of the genitofemoral, the ilioinguinal, and/or the iliohypogastric nerves if they are entrapped in scar tissue or in the tissue disruption caused by musculoskeletal injury. Alternatively, a neurolysis may be performed if a scar tissue release appears appropriate.

Combined Laparoscopic and Open Approach

Although this technique has been described in the literature for patients with previous hernia repair who developed chronic groin

FIG. 2 Long-term mechanistic mesh used for laparoscopic sports hernia repair of the left groin.

pain, a combined laparoscopic and open approach could be used in patients with athletic pubalgia. As stated, patients with athletic pubalgia typically have been dealing with chronic pain for many months before seeking treatment. In a study by Lindsay and colleagues, when comparing strictly laparoscopic versus strictly open repair versus a combined open and laparoscopic technique, patients who underwent a combined laparoscopic and open surgery had better resolution of their pain postoperatively.

Open Nonmesh Approaches

A variety of open nonmesh approaches have been described. One approach popularized by Muschaweck is presented as an open minimal repair technique. The procedure involved a repair of the posterior inguinal floor with two running sutures, including imbrication of the rectus muscle with the second suture. Selectively, the genital branch may be divided if it is impinged by the scar or damaged in use. The internal ring is reinforced with a buttress of internal oblique muscle to protect the pampiniform plexus.

Meyer has promoted a more targeted approach to repair of the groin with a variety of techniques used, depending on the findings on the MRI and at surgery. General descriptions of these approaches include a variety of repair, release, and excision procedures that may include the reconstruction of the rectus abdominis to the pubis and a selective adductor tenotomy as indicated by the radiographic, clinical, and surgical findings. An adductor tenotomy may include partial release of the fibers approximately 1 to 2 cm from its attachment to the pubis. Transection with or without reattachment of the adductor longus has also been described.

Postoperative Course

In general, the postoperative recovery is quicker with the less invasive approaches. The laparoscopic approach is the least invasive and has the quickest recovery, with the open reconstructive approaches often requiring the longest recovery. Many factors, however, can affect recovery. The degree of preoperative pain, the nature of the athletic activity, and the dictates of the athlete's trainer, athlete, team owner, coach, and so on all play a role in the timing of return to full activity. In general, athletes may return to light activity in the first 1 to 2 weeks and may try their regular training regimen within 3 to 4 weeks. After appropriate strength, endurance, and flexibility are attained, return to full competition is appropriate. For very high level athletes, appropriate game conditions may be simulated to test the appropriateness of a return to full competition.

As mentioned, when performed by surgeons with experience treating sports hernias, all the procedures described achieve a relatively high rate of success in returning an athlete to his or her sport, but all of these techniques have failures as well. This demonstrates the reality that an athlete with chronic groin pain, as with most problems in health care, is a complex medical problem. For complex problems, a one size fits all solution will not work for every patient. In addition, the most aggressive, costly treatment cannot be used for every patient because of wasteful use of limited resources. The ideal situation would be to learn which patient subpopulations would be best treated with nonsurgical approaches, which would be best treated with minimally invasive approaches, and which would require the most aggressive or costly approaches requiring the longest recovery.

A relatively new science is now being applied to health care that can begin to determine the appropriate indications for the various presentations of complex medical problems such as chronic groin pain in athletes. Complex systems science tools such as continuous learning and clinical quality improvement can potentially lead to lower costs and better outcomes when the value of care is measured for the whole cycle of care for each definable problem such as chronic groin pain in an athlete. The first step in applying clinical quality improvement is to define the dynamic processes for the entire cycle of care in the context of a specific medical problem. In this case, the processes of care would be defined for an athlete from the time of the initial symptoms of groin pain until the ability to return to full competitive activity with no future incidence of groin pain. All appropriate treatment options would be included in the dynamic care processes, and the outcome measures that determine the value of care would be determined and documented. These outcome measures would include the cost for the entire cycle of care, quality measures, such as the relief of pain and the ability to return to full activities, and the patient's experience with his or her care process. By defining and documenting the care process and measuring the outcomes that determine the value of care, we can then use these results to provide feedback to improve the processes of care relentlessly over time. With more and more data and experience, this will allow for a better understanding of what the best value of care will be for each patient subpopulation.

Another element of complex systems science applied to health care is the emergence of care communities on the Internet for guidance in caring for complex medical problems, such as chronic groin pain in an athlete. Through websites, blogs, chat rooms, and other communication methods, more and more athletes experiencing the symptoms of chronic groin pain substituting the ability to play their sport are sharing their stories and experiences with symptoms and treatments. For complex medical problems, these groups and this body of information have been a relatively untapped resource as we strive to improve the value of care for athletes with chronic groin pain and other complex medical problems.

SUMMARY

Athletic pubalgia or core muscle injury is a problem that can be very frustrating for athletes suffering from pain and the inability to return to an activity they enjoy. This is usually a quality of life issue, but for high-level athletes, this can also be a serious economic problem as well. As with any complex medical problem, we will need models for continual learning and the application of complex systems science to better understand which patients will receive the most value from the variety of surgical and nonsurgical treatment options available based on their respective subpopulation. Ultimately, the goal of improving the value of care will lead to the development of innovative strategies to prevent this condition and to continuously improve outcomes for this group of patients.

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Abdominal Wall Reconstruction

Adam Fra[illegible], MD, and Ale[illegible]y P. Tu[illegible], DO, MA, FACS

Abdominal wall hernia repairs are among the most common operations performed by general and plastic surgeons worldwide, and it is estimated that over 350,000 ventral hernia repairs are performed annually in the United States. Generally speaking, abdominal wall hernias are classified as incisional, epigastric, or umbilical depending on the hernia's location and underlying etiology but can be classified as "complex" with the addition of certain attributes such as loss of abdominal domain, associated enterocutaneous fistulas, parastomal location, mesh/graft location, bony abutment, and recurrence. The surgical management of simple abdominal hernia repair has been discussed elsewhere in this text and is not discussed in this chapter. In cases requiring advanced techniques for complex hernia repair, the term abdominal wall reconstruction (AWR) is a vastly more accurate appropriation and will be the focus of this chapter.

Complex abdominal wall hernias develop from multiple factors and scenarios. Whether a patient's hernia is simply a large defect associated with a stoma or enterocutaneous fistula, or the result of an abdominal catastrophe from trauma with a prolonged open abdomen has little impact on the goals of the reconstructive surgeon. These goals are the restoration of the integrity of the abdominal wall and its function to eliminate or prevent symptoms and/or complications. The etiology and presentation do, however, delineate the available options for reconstruction. In this chapter, following review of the relevant anatomy and preoperative evaluation, we will discuss the acute management of abdominal defects resulting from abdominal catastrophe, a frequent precursor to the development of complex abdominal wall hernias, and then review multiple surgical technical options for AWR.

ANATOMY

Successful reconstruction of the abdominal wall is based on a sound comprehension of the involved anatomy, especially the details regarding abdominal wall innervation and correct surgical dissection planes. It is also important to delineate the precise anatomy of the semilunar line, as its role in the correct execution of the traditional component separation, along with its many modifications cannot be overstated. Component separation techniques will be discussed further in the operative techniques section of this chapter.

The neurovascular supply of the anterior abdominal wall is important to understand in complex AWR. The motor and sensory innervation stems from T7–11, the fibers of which course in a plane between the internal oblique (IO) and the transversus abdominis (TA). They then penetrate the posterior rectus sheath roughly 3 cm medial to the semilunar line (Fig. 1). These structures are important to identify and protect during reconstruction to preserve the innervation and function of the abdominal wall. The primary blood supply is derived from the deep inferior epigastric artery, which is a branch of the external iliac artery prior to its travel beneath the inguinal ligament and its transition into the common femoral artery. The deep inferior epigastric artery travels cephalad within the lateral umbilical fold until passing anterior to the arcuate line and the posterior rectus sheath, and then provides a medial and lateral row of musculocutaneous perforators. The highest density of these perforators lies in the periumbilical region. Preservation of this blood supply during reconstruction will help to optimize the resulting skin perfusion and lessen chance of wound breakdown from flap ischemia.

The semilunar line is a composition of the aponeuroses of the external oblique (EO), IO, and the TA. Rises dissection the abdominal wall and the anatomy of the semilunar by separating it into thirds. In the upper third of the abdominal wall, the posterior lamellae of the IO aponeurosis and the muscle belly of the TA extend medial to the semilunar line (Fig. 1). In the middle third, the muscle belly of the TA ends laterally to the semilunar line, but its aponeurosis joins with the posterior lamellae of the IO aponeurosis as they form the posterior rectus sheath. This configuration continues in the lower third until the arcuate line, where both structures join the remaining lateral abdominal wall aponeuroses as part of the anterior rectus sheath, leaving only the transversalis fascia and peritoneum deep to the rectus below this level. The knowledge of the relationship of the TA muscle belly and the IO aponeurosis is key when performing the release of the TA in posterior component separation (PCS). The details of this technique will be discussed later in this chapter.

PREOPERATIVE OPTIMIZATION

When not in the setting of acute abdominal wall management, preoperative optimization is necessary to mitigate modifiable risk factors known to negatively impact AWR. These modifiable factors include smoking, obesity, diabetes, and malnutrition. The influence of smoking on postoperative complications is well known and includes decreased blood and tissue oxygen tension levels, impaired oxygen metabolism, increased platelet adhesiveness, and vasoconstriction. Patients undergoing AWR should quit smoking at least 4 weeks prior to surgery, as this amount of time has been shown to be the minimal effective time for reducing 30-day complications in surgical patients. Nicotine replacement therapy can be allowed as this seems to provide

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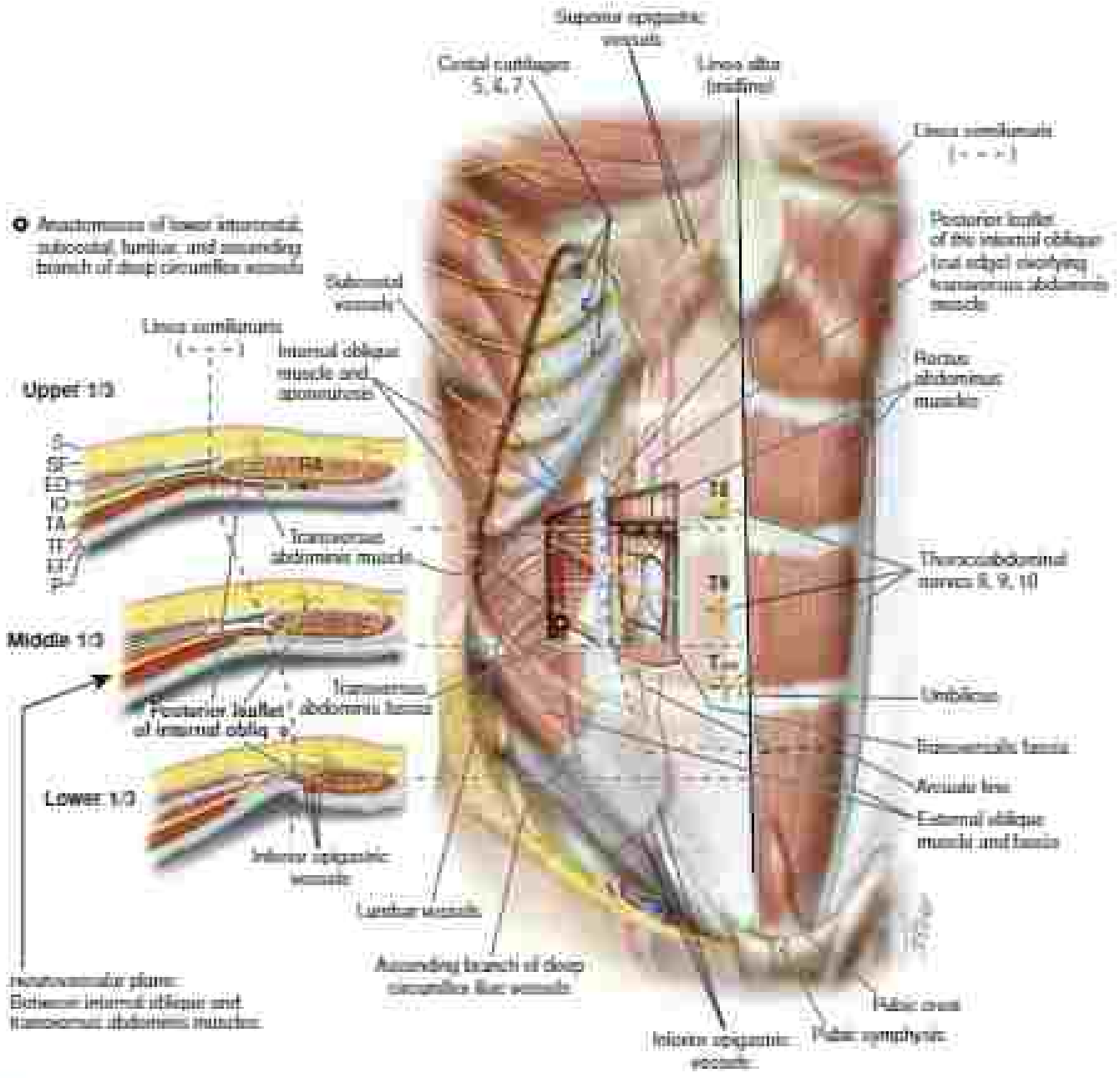

FIG. 1 Myofascial relationships and neurovascular anatomy of the upper, middle, and lower thirds of the abdominal wall. EF, transversus fascia; EO, external oblique muscle; F, peritoneum; IO, internal oblique muscle; R, rectus abdominis; S, skin; SF, subcutaneous fat; TF, transversalis fascia; TO, transversus abdominis. (From Rosen J, Ahn J, Salibian AA, Butler CE. Surgical Anatomy of the Abdominal Wall. Semin Plast Surg. 2014;28(3):101–109.)

no negative effect on surgical outcomes, and in all patients undergoing smoking cessation, blood or urine testing should be used for confirmation before surgery. Obesity is a significant risk factor for surgical site occurrence (SSO) including seroma, hematoma, dehiscence, abscess, and fistula. Multiple articles have displayed the association between increased body mass index (BMI), postoperative complications, and hernia recurrence. Most surgeons would delay elective AWR in patients with BMI greater than 40 without the presence of acute surgical indications. Weight loss counseling and bariatric surgery referrals are necessary in these patients. Perioperative glycemic control is extremely important in reducing infection risk and other postoperative complications. A hemoglobin A1C level of 7.5% is a common cut off for elective AWR, and those patients with difficulty in achieving this level should be referred for endocrine evaluation and management. Postoperative glucose levels should never exceed 200 mg/dL with a target range of 110 to 180 mg/dL. Next, poor nutritional status has also been closely associated with higher rates of postoperative complications and worse outcomes. Patients with albumin levels less than 3.0 g/dL and prealbumin levels less than 15 mg/dL should undergo a complete nutritional assessment, including vitamin deficiencies with counseling and supplementation as needed before elective AWR. All patients should be administered a first generation cephalosporin within 1 hour of incision to decrease surgical site infection risk. Bowel preparation before AWR has been shown to be associated with an increased risk for SSO and should be avoided.

ACUTE MANAGEMENT

In cases in which definitive AWR cannot be performed, the management of the acute abdominal wall defect and control of abdominal

viscera are the primary objectives. These cases include those with hemodynamic instability, gross contamination, an elevated risk of complications, the need for reoperation, and surgeon inexperience and are usually associated with trauma and damage control laparotomy in which patients are left with an open abdomen. There are numerous available options for temporary abdominal closure in these situations including skin only closure, interposition intravenous fluid bag (Bogota bag), bridging permanent or absorbable mesh, biologic mesh, artificial liner or Wittman Patch, and vacuum assisted closure systems. Each of these temporary closure methods is employed to accomplish the same goals of preventing evisceration and contamination, evacuating abdominal fluid and decreasing bowel edema, avoiding damage to bowels, fascia, or skin, preventing fistula formation, allowing easy access to the abdominal cavity, and preventing the loss of abdominal domain while preventing abdominal compartment syndrome. The ideal situation will result in delayed primary closure of the fascia by 8 days, as closure achieved beyond 8 days is associated with increased complications. At our institution, we commonly use the ABThera (KCI) negative pressure system. If delayed primary fascial closure remains impossible, several options exist for managing these defects and transitioning to the accepted ventral hernia with plans for future AWR. First and foremost is simple closure of the skin and subcutaneous tissues. We believe that this is not a viable option in current therapy because of the larger risk for evisceration. Next, the fascia can be bridged with absorbable synthetic or biologic mesh covered by closure of the skin and subcutaneous tissues. Either mesh type can be used with an expected hernia occurrence of 50% to 100%. Because of the greater expense of biologic matrices, the majority of surgeons at our institution will use absorbable synthetic mesh in these cases (Vicryl, polyglactin 910, Ethicon Inc.). A valid concern for the use of synthetic mesh in bridging cases is the risk for fistula formation. It seems that literature discussing this topic acknowledges fistula formation being because of either the lack of underlying omentum, the presence of an enteral feeding tube, or the breakdown of intestinal sutures and anastomoses. Reported fistula occurrence rate in these situations is 0% to 11%, similar to or better than those reported with prolonged use of abdominal vacuum assisted closure systems. Further investigation regarding complication occurrence with the use of bridging biologic and synthetic mesh in these types of cases is needed.

In the remainder of patients in which there is not sufficient overlying skin or soft tissue to cover the bridged repair, options include the continuing of local wound management (vacuum systems or traditional dressings) with or without placement of a bridging synthetic absorbable mesh. Both options can be expected to lead to eventual granulation across the exposed viscera and the option for split thickness skin grafting. In our experience, the time for formation of an appropriate bed of granulation tissue after Vicryl mesh placement is 2 to 3 weeks. Again, fistula rates are 0% to 11% or higher, but definitive data are lacking. An additional option is the use of a bridging biologic matrix with the hope for full thickness integration and eventual skin grafting, but this technique is unfounded and expensive. Integration of a biologic matrix without complete soft tissue coverage has not been studied, and unless a significant improvement in complication rates, such as fistula formation, compared with traditional techniques can be displayed, the expense of this option cannot be justified. Some may consider the use of fascial advancement in these settings, but we would argue against the use of component separation techniques simply to achieve fascial edge approximation as potential future options for AWR may be lost. Following skin graft coverage or skin closure, a delay of 6 to 12 months before AWR is typical, during which time comorbidities can be optimized. Prior to AWR, the skin graft should be able to be pinched away from the underlying viscera on examination, indicating reasonable safety for intra-abdominal dissection.

OPERATIVE TECHNIQUES

Component Separation

Component separation techniques are commonly employed to repair complex abdominal wall hernias and are generally described according to the anatomic location of the myofascial release that is performed (anterior vs posterior). Anterior component separation (ACS) and PCS techniques have similar rates of hernia recurrence (~10%), but comparative studies between these techniques are challenging. Some authors suggest that there are fewer wound complications associated with the posterior technique, but definitive results are lacking, and there are no comparative studies regarding quality of life or function.

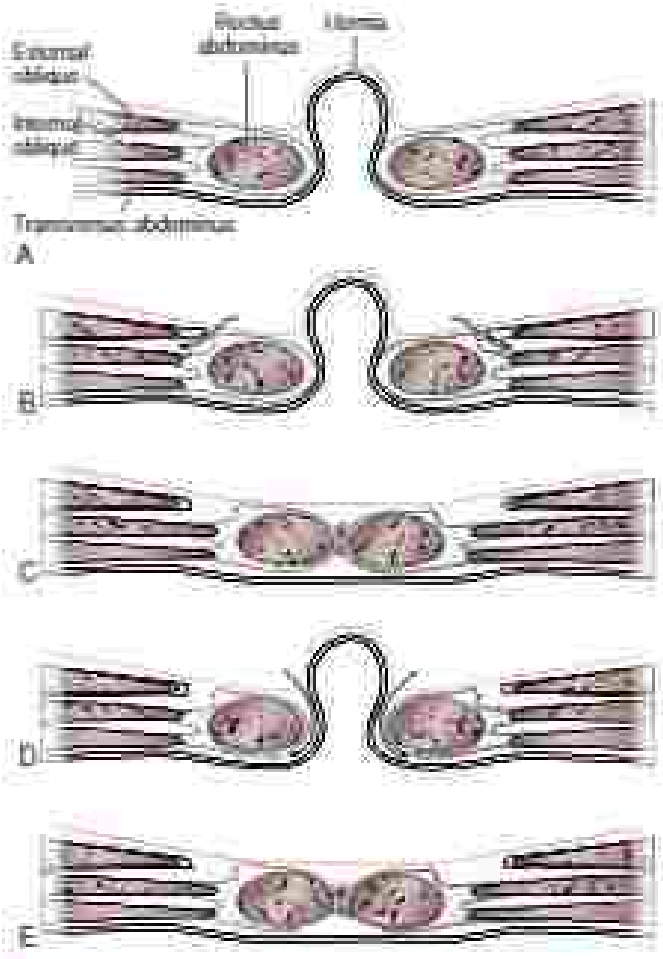

FIG. 2 (A) External oblique (EO), internal oblique (IO), transversus abdominis (TA), rectus abdominis (RA), EO aponeurosis. (B) EO aponeurosis is incised and a plane is developed between the EO and IO muscles (arrow). (C) Lateral edge of rectus sheath is incised, revealing the EO aponeurosis. (D) Medial edge of rectus sheath is incised, revealing the [illegible] plane between the EO and IO muscles. (E) Midline closure of the EO aponeurosis, and closure of the skin and subcutaneous tissues.

Anterior Component Separation

The ACS (Fig. 2) was first described in 1990 by Oscar Ramirez. Following mobilization and reduction of the abdominal viscera, large bilateral myofascial flaps of skin and subcutaneous tissue are elevated to expose the EO aponeurosis and its junction with the semilunar line. The aponeurosis is then opened longitudinally 1 to 2 cm lateral to the semilunar line from the costal margin superiorly to the external inguinal ring inferiorly. A plane can be bluntly developed between the EO muscle belly and the underlying IO to facilitate fascial mobilization. Next, the medial aspect of the rectus sheath is incised longitudinally from the sternum to the arcuate line, and a plane is bluntly

developed separating the rectus muscle belly from the posterior sheath [illegible] to the midline [illegible] posterior to the [illegible] [illegible] commonly [illegible] [illegible] with [illegible] looped or unlooped [illegible] suture. [illegible] closed suction drains are placed [illegible] [illegible] [illegible] [illegible] [illegible] to some studies [illegible] [illegible] [illegible] [illegible] [illegible] separation and [illegible] separation [illegible] [illegible] of the [illegible] repair of [illegible]

Posterior Component Separation and Transversus Abdominis Release

The PCS has evolved from the classic [illegible] retromuscular hernia repair and was first described in [illegible] and [illegible] before later modification with the addition of the transversus abdominis release (TAR) in 2012. This technique allows for advancement of the [illegible] midline closure with the placement of prosthetic mesh in an underlay fashion beneath the abdominal wall muscles but on top of the peritoneum. The technique also does not require creation of large abdominal wall lipocutaneous flaps. The initial PCS technique [illegible] [illegible] from the [illegible] retromuscular dissection beyond the semilunar line to open the plane between the [illegible] and the [illegible]. This allowed for myofascial advancement of the [illegible] and posterior rectus sheath to the midline over which a large prosthetic mesh could be placed. Similarly, the [illegible] and [illegible] sheath could be advanced to the midline. [illegible] this dissection involves the division of the neurovascular bundles passing through the semilunar line, and thus the TAR technique is now commonly employed during PCS.

The TAR dissection first begins with meticulous intra-abdominal dissection, minimizing enteral contamination and damage to the peritoneal lining as damage to these structures can lead to difficulty in the later dissection. Next, the medial aspect of the rectus sheath is opened from the xiphoid to the arcuate line to gain access to the retrorectus plane (Fig. 3). This plane is easily bluntly dissected until reaching the semilunar line where the neurovascular bundles can be seen perforating the posterior lamellae of the [illegible] aponeurosis (Fig. 4). These bundles are preserved and the posterior lamellae are incised just medial to them exposing the underlying TA muscle (Fig. 5). The TA muscle only extends behind the [illegible] in the upper abdomen, so this portion of the dissection should be performed there [illegible] [illegible] muscle fibers are divided with electrocautery to expose the underlying transversalis fascia and peritoneum (Fig. [illegible]). This plane between the [illegible] and the peritoneum can be developed all the way to the psoas muscle laterally (Fig. [illegible]). The dissection plane can extend to the central tendon of the diaphragm superiorly and Cooper's ligament inferiorly. Any perforations in the peritoneal

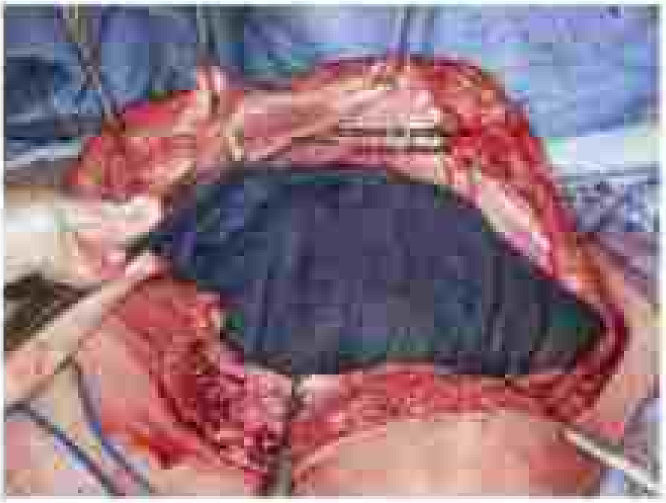

FIG. 3 Posterior rectus sheath incised just medial to the linea alba.

FIG. 4 Neurovascular bundles 1 to 2 cm medial to the linea semilunaris.

FIG. 5 In a posterior component separation, the transversus abdominis is exposed after the posterior lamellae of the internal oblique is incised. *Neurovasc*, Neurovascular.

FIG. 6 The transversus abdominis is noted after the posterior lamellae of the internal oblique is cut.

FIG. 7 Permacol is separated from the transversus abdominis creating the posterior rectus sheath for closure and creating a sublay pocket for mesh placement.

lining should be repaired with absorbable suture if possible. If large holes are present, grafts from the resected hernia sac or synthetic plugs can be used for interposition. The posterior sheath is then closed in the midline with absorbable suture, and a large prosthetic mesh is placed in the dissection plane and fixated at its boundaries using a transfascial suture passer to the anterior abdominal wall using multiple stab incisions in the skin along the periphery of the mesh. Similarly, a nonirritating, self gripping mesh can be used. Surgical drains are placed overlying the mesh and the linea alba is closed in the midline with large caliber absorbable suture followed by the skin and subcutaneous tissue in layers.

Staged Reconstruction

When there is concern for prosthetic contamination at the time of AWR, a staged procedure may be the most appropriate course. Difficult stoma reversal procedures and those involving complex adhesiolysis or with bowel injury should warrant concern for breaches in sterility and prosthetic contamination. In these cases, we will place an ADM in underlay fashion to temporize the abdominal wall closure with plans for prosthetic reinforcement in the future. First, a limited suprafascial

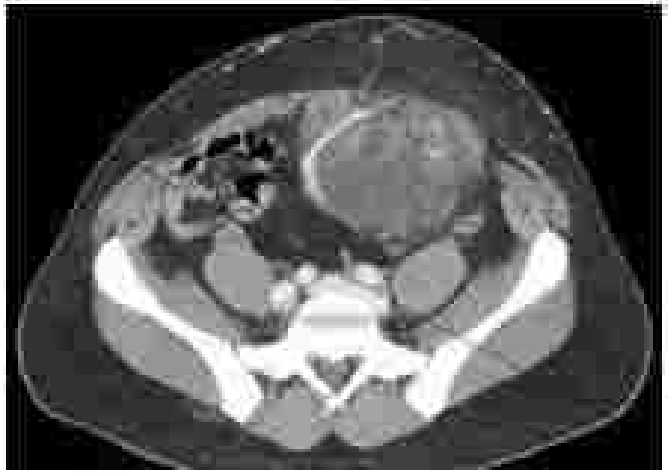

FIG. 8 Large angiolipoma of the left rectus abdominis muscle.

dissection is performed to facilitate placement of transfascial delayed absorptive sutures, providing 5 cm of ADM extension beyond fascial edges. This fixation could also be performed using a suture passer, but we feel a limited suprafascial dissection does not lead to the increased morbidity associated with large flaps developed in traditional AWR. If fascial edges are not able to be approximated in this setting, we refrain from performing myofascial advancement and instead let the ADM underlay act as a fascial bridge as well and accept the definitive hernia until delayed repair or reinforcement. It is important to have soft tissue coverage when using this bridge to promote integration of the ADM. Two drains are placed, one on top of the ADM and one above the fascial closure, and the skin and subcutaneous tissues are closed in layers. The second stage is performed after a 6 month recovery period and begins with excision of the laparotomy scar. Next, bilateral suprafascial dissection is performed for 10 cm bilaterally, and a large piece of permanent prosthetic mesh is sutured in an onlay fashion, taking care to ensure complete apposition between the mesh and the underlying fascia using numerous quilting sutures between the mesh and the underlying soft tissue. Surgical drains are left in place for 3 to 5 days, and the patient is allowed to go home from the recovery room. We have achieved hernia recurrence rates of less than 5% with this staged method along with minimal wound complications.

COMPOSITE ABDOMINAL WALL RESECTION AND RECONSTRUCTION

Composite defects of the abdominal wall can be considered to fall into two categories, acute and chronic. Acute defects are often the consequence of resection of a tumor, such as a sarcoma or desmoid, resulting in a defect of skin and subcutaneous tissues, fascia, muscle, and peritoneum (Figs. ...). The main goal of the reconstructive exam would be to obtain a closed abdominal cavity, protection for the visceral organs, control of wound loss, and some plan for stable soft coverage. The advantage of reconstruction of these defects is that there is often an opportunity for the surgeon to fully assess the patient and the planned defect prior to reconstruction. Also, often this will be managed by two teams, the ablative team and the reconstruction team. One of the most important aspects of successful management of these complicated problems is coordination of the two teams so that realistic expectations are discussed prior to the surgery. The size of the anticipated defect, the tissues involved, and the use of available local regional tissues for reconstruction should be understood by the members of the teams. The use of the standard techniques of lateral release of the ED muscles and component separation can assist in reducing the size of the acute defect. However, it may be better to carry out a complex reconstruction as described later in conjunction with a components separation rather than depend on a reconstruction under undue tension that will fail.

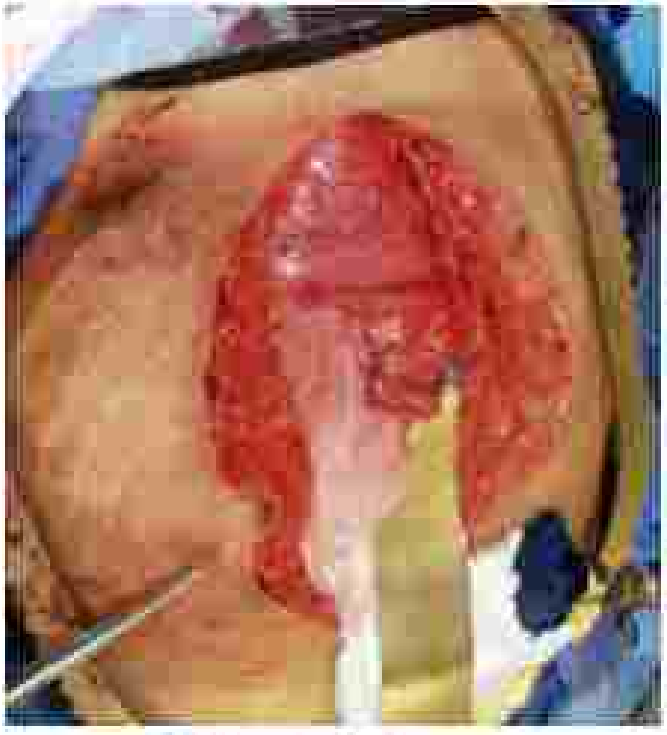

FIG. 9 Composite defect after resection.

FIG. 10 Permacol mesh strip sutured to native fascia and the dermal matrix that has been used as a bridge between the fascial edges with 3 cm of excursion beyond these edges.

The reconstruction of a peritoneal layer is the first step in reconstruction. Our choice is to use an underlay of ADM. First, we make a paper template of the defect. This template is transferred to a sheet of ADM. About 2 to 3 cm of extension is planned around the template for suturing of the material. A 2-0 monofilament absorbable suture in an interrupted horizontal mattress fashion is used to anchor the ADM. Particular care is taken to lay out our sutures in an organized fashion so that there is even spacing and the bowel cannot become trapped between the interrupted sutures and the margin of the defect. The sutures are placed through-and-through the abdominal wall and the ADM is anchored to the peritoneal surface. The sutures are positioned so that the ADM is taut without ridges or excess material. The ADM must be covered with a more permanent material to ensure that the abdominal wall will remain in integrity when faced with constant load bearing. We have used a wide pore polypropylene mesh. The mesh is sutured across the abdominal wall and anchored to stable structures such as the inguinal ligament, costal margin, and anterior superior iliac spine. The mesh is pulled tautly across the abdominal wall and fixed to the surrounding normal fascia with interrupted 2-0 monofilament absorbable sutures. The mesh is then quilted to the fascia and ADM with interrupted sutures (Fig. 10). This will create a single construct with the two materials fixed to each other, further stabilizing the abdominal wall. By fixing the mesh to the ADM, we eliminate fluid collection between the two layers and avoid seroma and potential infection. Over time, the mesh will be anchored to the native tissues by soft tissue ingrowth through the wide pores. The use of a wide pore size will decrease the stiffness and chronic fibrosis encompass tissue associated with the inflammatory reaction to the polypropylene. If the skin was spared in the resection it can be closed as normal over closed suction drains. The skin and subcutaneous soft tissue flaps are anchored to the mesh and fascia to reduce dead space and seroma formation.

If the skin is resected, a negative pressure wound dressing can be placed over the mesh to generate granulation tissue that can be skin grafted. Smaller skin defects can be addressed with local tissue rearrangement and flaps. Tissue expansion can be used in these situations. It is important to remember to place the expander over a bony base, ribs, pelvis, or sternum if employed. This avoids the problem of expanding the soft tissue beneath the expander that cannot be mobilized into the defect. The local flap donor site can then be closed with a split thickness skin graft. Larger soft tissue defects can be addressed with free tissue transfers such as an anterior lateral thigh flap or a latissimus dorsi flap. The standard ADM and polypropylene construct will need to be used prior to placing the free flap. Thin soft tissue flaps will not be able to stand up to the forces placed on it by the underlying viscera and the forces of normal function.

POSTOPERATIVE CARE

Following AWR, oral intake should be advanced depending on the nature of any coincident visceral procedures, otherwise early enteral feeding should be initiated. Nasogastric tubes are not routinely used. Pain control consists of multimodal therapy with use of acetaminophen, gabapentin, nonsteroidal anti-inflammatory drugs, and antagonists to limit the use of narcotics. Additionally, the use of local and regional anesthesia before and during surgery including transversus abdominis plane blocks have shown a reduction in postoperative pain, narcotic usage, and length of inpatient stay. Some institutions will employ the use of epidural anesthesia before AWR, and it has been demonstrated to decrease systemic narcotic usage, improve postoperative nausea and vomiting, and improve postoperative pulmonary function. We believe that routine epidural use in AWRs is not necessary with the use of adequate local and regional blocks and multimodal therapy. Serum glucose is closely controlled not to exceed 200 mg/dL to reduce wound complications. After skin closure in clean cases, there is no benefit to the use of prolonged antibiotics, and these should be avoided. There are no clear data to support or deny the use of prophylactic antibiotics in the setting of surgical drains, but the use of prolonged antibiotics is associated with adverse consequences such as *Clostridium difficile* diarrhea and bacterial antibiotic resistance. We advocate *not* to use postoperative antibiotics for prophylactic drain coverage. Drains are removed once

the output is less than 30 mL over a 24-hour period, which is typically 3 to 5 days in cases with synthetic mesh, and 7 to 10 days with AWM. Patients are discharged to home with strict activity restrictions against strenuous activity, straining, and heavy lifting that will continue for 8 weeks. First clinic follow up visit is generally within 1 week from hospital discharge.

Suggested Readings

Novitsky YW, Elliott HL, Orenstein SB, et al. Transversus abdominis muscle [illegible]

[illegible] Rosen MJ. Primary fascial closure with staged skin grafting versus [illegible]

[illegible] Ramshaw BJ, Esartia P, Schwab CM, et al. Long-term assessment of [illegible]

[illegible] Novitsky YW, Elliott HL, Orenstein SB, et al. Transversus abdominis muscle [illegible]

[illegible] Rosen MJ, Jones M, Phillips S, et al. Preoperative skin tissue expansion [illegible]

[illegible] Ramshaw BJ, Esartia P, Schwab CM, et al. Long-term assessment of [illegible]

[illegible] Novitsky YW, Elliott HL, Orenstein SB, et al. Transversus abdominis muscle [illegible]

[illegible] Rosen MJ, Jones M, Phillips S, et al. Preoperative skin tissue expansion [illegible]

BREAST

BENIGN BREAST DISEASE

Richard C. Gilmore, MD, and Julie R. Lange, MD, ScM

S[illegible]

EVALUATION OF COMMON BREAST COMPLAINTS

[illegible]

[illegible] complaint begins with a focused history and clinical breast examination. [illegible] should involve a complete assessment of the patient's symptoms including duration, severity, and the presence of aggravating/alleviating factors in addition to pertinent obstetric, gynecologic [illegible] personal or family history of cancer.

Physical examination should begin with visual inspection for asymmetry and skin lesions [illegible]. [illegible] palpation should be systematically cover all areas of both breasts including the axillary tail and should include examination of the axillary and supraclavicular nodal basins. If nipple discharge is present, it should be characterized [illegible] and location as well as whether it comes from a single duct or multiple ducts [illegible].

Although many breast complaints [illegible] imaging [illegible] it is important to [illegible] imaging evaluation. For most [illegible] younger than age 30 [illegible] ultrasound [illegible] mammography is not usually [illegible] in this patient group. For patients age [illegible] mammography is indicated [illegible] because they [illegible] breast tissue [illegible]. At age [illegible] should include bilateral mammography with diagnostic views of the area [illegible] and targeted ultrasound as needed. In general, mammography and ultrasound are [illegible] imaging for evaluation of [illegible]. [illegible] imaging such as magnetic resonance imaging should be reserved for [illegible] clinical or imaging findings that remain indeterminate despite complete mammographic and sonographic evaluation [illegible] an image-guided [illegible] needle biopsy is generally preferred [illegible].

Breast Mass

A breast mass [illegible]. The most common breast complaint [illegible] is accompanied by substantial anxiety [illegible] because women [illegible] that breast cancer [illegible] with a palpable mass [illegible] women, most [illegible] found to [illegible] be cysts, fibrocystic change, or fibroadenomas [illegible] minority are [illegible] cancer [illegible]. [illegible] is an essential part of the evaluation [illegible] postmenopausal women [illegible] should be assumed to be cancer until proven otherwise. [illegible] findings [illegible] smooth [illegible] well circumscribed [illegible] round, well-marginated firm rubbery mass in a premenopausal woman [illegible] can be distinguished from a cancer [illegible] density. Today, most solid masses are evaluated [illegible] image-guided core needle biopsy [illegible] well visualized on ultrasound, ultrasound-guided core needle biopsy is usually the preferred technique.

Nipple Discharge

Nipple discharge is common and usually of benign cause. Most women who have lactated can induce a small amount of discharge, usually from both nipples and multiple ducts; this type of induced discharge requires no further evaluation other than age-appropriate screening imaging. True galactorrhea is uncommon and characterized by larger volume, bilateral, spontaneous, milky nipple discharge arising from multiple ducts in a nonlactating woman. Diagnostic evaluation includes obtaining a serum prolactin level and age-appropriate breast imaging. Patients with an elevated prolactin level should be referred to an endocrinologist for further management.

Nipple discharge that is spontaneous, persistent, unilateral, and involving a single duct requires further diagnostic evaluation and occasionally surgical intervention. It may be sanguinous or serous. Evaluation begins with physical examination as well as mammogram and ultrasound. If a specific, targetable suspicious lesion such as abnormal microcalcifications or a solid mass is found, the lesion can be targeted for core needle biopsy. If no suspicious lesion is found, an excisional biopsy of the discharging duct is necessary to make a specific diagnosis and rule out a cancer. A ductogram (galactogram) is sometimes useful in preoperative planning to identify ductal filling defects. The fluid-producing duct is cannulated and contrast material is injected, followed by a mammogram to identify the location of filling defects within the duct. Cytology and hemoccult testing are seldom of significant value in the evaluation of patients with nipple discharge.

Surgical duct excision is sometimes needed for diagnosis and to remove the source of the discharge. The duct producing the discharge can be marked by placing a structure such as a stiff large monofilament suture or a small lacrimal duct probe into the duct in question. Then the duct can be approached from a periareolar incision and the offending duct excised. Younger patients should be aware of the potential for difficulty in future breastfeeding after this procedure.

Most causes of nipple discharge are benign, especially in younger women. Benign causes include intraductal papilloma, mammary duct ectasia, and fibrocystic change. The risk of cancer in patients presenting with nipple discharge is between 5% and 15% overall and increases with age.

Breast Pain

Breast pain (mastalgia) is common throughout life, especially during the reproductive years. It is most often related to fibrocystic and hormonal changes, cyclic in nature, and is uncommonly associated with cancer. In premenopausal women, a history of breast pain that is cyclic and improves significantly after the onset of menses is reassuring. If there are no other findings on physical examination or age-appropriate imaging, no further evaluation is required. Ultrasound may be reassuring, or may detect problems such as a breast cyst as the cause of pain. Breast pain may resolve on its own without intervention. Conservative measures are often helpful and can include well-fitting support bras and dietary modifications to reduce fat and caffeine intake. Nonsteroidal antiinflammatory agents can provide relief for persistent pain. Additional agents reported to sometimes help alleviate breast pain include vitamin E, fish oil, and evening primrose oil, but they are not routinely effective.

Pain that is unrelated to menses, is new onset in a postmenopausal age, or is associated with a mass or other physical examination or radiologic abnormality requires further diagnostic evaluation. Common benign causes of noncyclic breast pain include cysts, fibrocystic changes, abscess, and mastitis.

Skin Changes

Benign skin changes may include erythema as a sign of infection or a rash resulting dermatitis. Most breast infections are exquisitely painful and present with significant erythema and warmth. If infection is clinically suspected, ultrasound is a simple way to clarify whether an abscess is present.

Worrisome skin changes of the breast include skin dimpling, nipple retraction, nipple excoriation or scaling, and skin thickening with erythema. These findings should prompt further mammographic and sonographic evaluation to rule out a cancer, with biopsy as indicated by imaging evaluation. If the radiologic evaluation is negative, a skin punch biopsy may be indicated for diagnosis.

Abnormal Screening Mammogram

With increased use of routine screening mammography and improvement in mammographic technology, many women may have abnormalities reported without associated physical examination changes, most of which are of benign origin. These can include developing masses or densities, new microcalcifications, or architectural distortions. The most important issue to be addressed is whether the finding represents a cancer.

A screening mammogram with a new abnormal finding requires evaluation by a radiologist specializing in breast imaging and usually an initial diagnostic mammographic views, including spot compression or magnification views, and often diagnostic ultrasound. If the lesion is concerning, an image-guided core biopsy is often indicated. Correlation of the mammographic finding with the physical examination is important because it is sometimes possible to detect subtle physical changes if attention is directed to the vicinity of the mammographic finding. In patients with abnormal mammographic findings that do not meet criteria for biopsy, follow-up mammography in 6 months can be indicated.

MANAGEMENT OF BENIGN BREAST LESIONS

Fibroadenoma

Fibroadenoma is the most common benign solid mass of the breast. They are often mobile, well circumscribed with smooth edges and have a rubbery consistency. They are most commonly seen in the reproductive years, may increase in size during pregnancy, and often involute after menopause. Their identity can be confirmed with ultrasound-guided core needle biopsy. Most can be left in place and observed over time with serial ultrasound. A fibroadenoma should be excised if it is large (>3 cm at diagnosis), symptomatic, if it increases in size, or if it significantly contributes to patient anxiety. If the pathology of the core biopsy does not clearly confirm the clinical impression of fibroadenoma the lesion may need to be excised to rule out more serious findings.

Benign Phyllodes Tumor

A benign phyllodes tumor is a fibroepithelial tumor with a variable range of behavior. Most benign phyllodes tumors present similarly to a fibroadenoma but can grow more rapidly and become locally aggressive. Ultrasound alone cannot distinguish a fibroadenoma from a phyllodes tumor so core needle biopsy is required. A core biopsy reported as cellular fibroepithelial lesion could represent either a fibroadenoma or a phyllodes tumor and should be excised for diagnosis and local control. All benign phyllodes tumors should be excised in a clear margin to reduce the chance of local recurrence.

Cysts

Cysts are a common cause of breast pain or a focal mass; they are usually seen in the reproductive years but can occasionally occur in postmenopausal women as well. By ultrasound, cysts that are well circumscribed, thin walled, and without septations or an associated solid component are referred to as simple cysts and are unlikely to be associated with a cancer. Ultrasound- or palpation-guided aspiration is appropriate for simple cysts that are large or symptomatic. Routine aspiration of small, asymptomatic simple cysts is not needed. Cyst fluid that is bloody should be sent for cytopathology, additionally cyst fluid is usually discarded. Cysts that by ultrasound have septations, debris, or an associated solid component are known as complex cysts and should be biopsied. Ultrasound-guided core needle biopsy should be performed with a clip left in place to mark the location in the event that excisional biopsy is subsequently required.

Fibrocystic Changes

Fibrocystic change is the most common benign breast entity and occurs commonly in women of reproductive age. Women often present with a history of bilateral, menstrual-related cyclic pain, with tender, nodular breasts often most prominent in the upper outer quadrants. If the diagnostic evaluation is complete with no suspicious lesion found, then symptom control and reassurance is the most appropriate management strategy.

Diabetic Mastopathy

This uncommon, dense, fibrous lesion usually occurs between ages 30 and 50 in patients with a long history of type 1 diabetes, particularly those with microvascular complications, although it has been described in type 2 diabetics as well. Patients present with a dense,

hard mass, both the physical examination and radiologic studies may appear suspicious for carcinoma. In the correct clinical setting, a core needle biopsy may be diagnostic, with excisional biopsy occasionally needed for confirmation. No active intervention is required beyond confirmation of the diagnosis.

Infection

Breast infections are common and can be painful and difficult to clear. Mastitis can be divided into lactational and nonlactational. Lactational mastitis is common in the postpartum period in lactating women. The most common causative agents are *Staphylococcus* and *Streptococcus*. Breast ultrasound should be used to evaluate for abscess. Antibiotic choice empirically should have good gram positive coverage, such as dicloxacillin, cephalexin, or other broad spectrum antibiotics. In settings where there is suspicion for methicillin resistant *Staphylococcus aureus*, antibiotics such as clindamycin or trimethoprim/sulfamethoxazole may be preferred. In addition to antibiotics, other conservative measures such as warm compresses and nonsteroidal antiinflammatory agents are helpful to reduce local pain and swelling in mastitis without abscess. Continuation of breastfeeding or pumping should be encouraged because this may significantly reduce symptoms. Complete resolution of uncomplicated mastitis may take a few weeks; however, mastitis that fails to resolve on antibiotics or worsens could be secondary to an undrained abscess. Follow-up ultrasound may be diagnostic.

Nonlactational mastitis can be divided into periductal mastitis and idiopathic granulomatous mastitis (IGM). Periductal mastitis is more common in women who are smokers, have large breasts, are overweight, or have had previous surgery or radiation to the breast. As with lactational mastitis, *Staphylococcus* and *Streptococcus* are the most common pathogens and treatment should involve symptom relief, antibiotics, ultrasound to rule out an abscess.

IGM is a rare benign inflammatory breast disease of unclear etiology. Patients may present with a painful mass sometimes in association with fistulas, abscesses, and inflammatory changes. Its presentation is sometimes similar to inflammatory breast cancer and appropriate diagnostic workup with biopsy may be required. IGM usually behaves as an inflammatory mastitis that generally resolves within 9 to 24 months, although recurrences are common. There are reports of medical management with steroids, methotrexate, or antibiotics, and yet it is unclear whether the underlying course of the disease can be improved with medical management. Management should be pursued for treatment of any associated infections.

Abscess

If a discrete abscess is present in association with either lactation or nonlactational mastitis, drainage is indicated. Ultrasound can be used to further characterize the abscess and facilitate adequate drainage. Limited simple abscesses can usually be adequately managed by serial needle aspiration, antibiotics, and close follow up. It is important to document sonographic resolution of the abscess after aspiration because unilocular collections can lead to recurrent infection. Recurrent or deep seated loculated collections may require open incision and drainage, often with general anesthesia or deep sedation because this is often a very painful procedure. Mastitis and breast abscesses can usually be managed on an outpatient basis. One occasional exception is in patients with diabetes in whom severe breast infection can be accompanied by systemic sepsis requiring hospitalization and intravenous antibiotics.

Lipoma

Lipomata can be found in the breast as elsewhere. If large or symptomatic, they can be managed with simple excision.

Fat Necrosis

Fat necrosis in the breast can result from injury to the soft tissues. Typical radiologic characteristics include a rounded density with or without calcifications. Fat necrosis sometimes cannot be distinguished from cancer radiographically and core needle biopsy can be necessary. A large area of fat necrosis can form a focal hard mass that can cause anxiety and some patients prefer to have it excised.

Proliferative Lesions without Atypia Requiring Excision

Today, most core needle breast biopsies of benign lesions are definitive and no excision is required; however, some lesions found on core breast biopsy should be excised to rule out a coexisting malignancy. Some proliferative lesions without atypia usually recommended for excisional biopsy include complex sclerosing lesion, radial scar, and intraductal papilloma. The chance of finding a malignancy on excision of these lesions is generally about 5%. In the future, it may be possible to define some such lesions with core biopsy results that may safely be managed by observation and repeat imaging rather than excision at original presentation.

Proliferative Lesions with Atypia

Atypical hyperplasia includes both atypical ductal hyperplasia and atypical lobular hyperplasia (ALH). Its both identify a patient as being at increased risk of breast cancer diagnosis, especially if the patient also has a first degree relative with breast cancer. Atypical ductal hyperplasia found on core needle biopsy requires excisional biopsy because between 3% and 10% are found to have ductal carcinoma in situ or invasive cancer on excisional pathology. On the other hand, the chance of finding cancer on excision following a core biopsy diagnosis of ALH is lower. Patients with ALH, diagnosed on core biopsy may not require excision if the imaging and pathology are concordant. If a decision is made to forego excision, the patient should return for short term diagnostic imaging follow up to assess for stability.

Patients with Benign Findings Who are at Increased Cancer Risk

Patients with benign findings that indicate increased risk of breast cancer should be offered enrollment in high risk screening program with the goal of early detection of subsequent cancers. There are many different statistical models that can estimate an individual patient's relative risk of breast cancer. Women with increased risk of breast cancer can be encouraged to make lifestyle modifications that include dietary fat and alcohol reduction, attention to maintaining a normal body weight, smoking cessation, and exercise. Drugs such as tamoxifen and raloxifene are approved for use in chemoprevention in high-risk women. They can be considered in the context of a high risk screening program and with careful consideration of risks and calculation of the chance that an individual patient might benefit.

SPECIAL CIRCUMSTANCES

Male Breast Complaint

Male breast cancer is rare, but gynecomastia is common. Changes suggestive of cancer in the male breast include skin or nipple changes, particularly nipple retraction or nipple discharge, and a firm, painless mass. Gynecomastia usually presents with a firm, sometimes painful thickening of the subareolar tissues and may be bilateral or unilateral, core if caused by systemic factors. Gynecomastia has been associated with estrogen excess or testosterone deficiency. It may be associated with cirrhosis of the liver, primary hypogonadism, testicular tumors, obesity, and numerous drugs including steroids, estrogens, flutamide, ketoconazole, digoxin, spironolactone, phenothiazines, and marijuana use. Radiologic evaluation includes diagnostic mammography and ultrasound. Mammography may be helpful to rule out

findings such as abnormal microcalcifications that may suggest cancer. If a discrete mass can be seen by ultrasound, it can be targeted for a core biopsy. If evaluation is consistent with benign gynecomastia and the medical history implicates a specific drug, discontinuation of that drug (if medically acceptable) with reevaluation in 3 to 6 months may be reasonable. Gynecomastia can also sometimes regress spontaneously. A persistent mass, particularly if painful, may be most appropriately managed by excisional biopsy for definitive diagnosis and symptom relief.

Pregnancy and Lactation

Most pregnancies occur in healthy young women, and any physical changes are likely to be benign. Common benign breast changes include fibroadenomata, which may enlarge in response to the stimulation of pregnancy-related hormones, and lactating adenoma, a benign, well-circumscribed mass. Either may be diagnosed with ultrasound and core biopsy during pregnancy. If an excisional biopsy is necessary during pregnancy, local anesthetics can be used in most cases. If a biopsy must be performed during the months a woman is lactating, a milk fistula may occur regardless of whether the biopsy is an excisional biopsy or a core needle biopsy, particularly if the biopsied area is central within the breast. Some women choose to continue to lactate and manage the fistula locally during that time, knowing that it will close after lactation ceases. Galactoceles are caused by an obstructed milk duct leading to cyst formation. Diagnosis is based on clinical history and ultrasound; they can be managed conservatively with warm compresses and continued lactation.

With increased use of reproductive technologies, more women are pregnant in their late 30s and 40s, when the incidence of breast cancer begins to rise. Attention to abnormal physical breast changes is particularly important because such women will not be receiving screening mammography during that time, and the changes of pregnancy may mask the early physical signs of cancer.

Surgical Planning

Women often view their breasts as part of their identity and any procedure, no matter how minor, represents a change to physical appearance and identity. Thus, surgical planning for benign breast disease should be considered carefully to minimize cosmetic defect. A well-placed surgical incision allows the woman an aesthetically pleasing result. If, on the other hand, further surgical procedures are required,

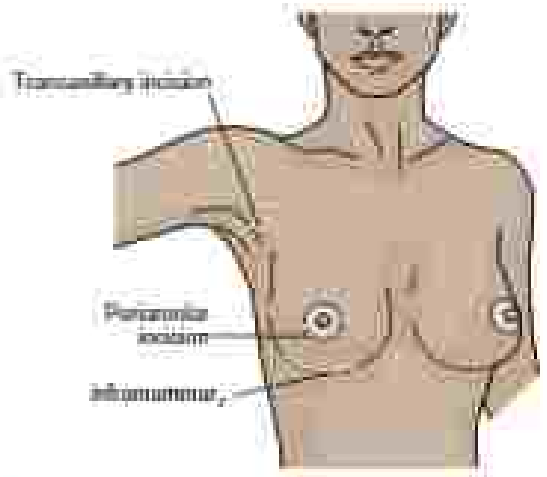

FIG [illegible]

the same incision can be used or extended as appropriate to complete a formal surgical resection. Some cosmetically favorable incisions are illustrated in Fig. 1. With few exceptions, it should possible to avoid making an unfavorably placed incision given careful preoperative consideration of the options. The transaxillary incision can be used to access lesions in the upper outer quadrant of the breast or axilla. The circumareolar or periareolar incision is made at the edge of the areola, allowing the scar to blend in with the darker skin of the areola. It can be used to access lesions circumferentially around and deep to the nipple areolar complex. The inframammary incision can be used to access lesions in the lower quadrants of the breast. These incisions can be technically more challenging, but they award the patient a worthwhile, durable, and cosmetically favorable result.

Suggested Reading*

[illegible]

Screening for Breast Cancer

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Breast cancer is the most common noncutaneous malignancy diagnosed in women with more than 230,000 new cases reported in 2015. The disease is responsible for more than 41,000 deaths yearly and continues to be the second leading cause of cancer mortality in women. Cases between the ages of 55 and 64 years are most frequently diagnosed, with a median age of death at 68. In 1–39, the American Cancer Society (ACS), the National Cancer Institute, and nine other organizations joined to issue a uniform set of guidelines for breast cancer screening. Since, these organizations would add guidelines for screening of women at high to moderate risk. More recently, based on accumulated evidence from long-term follow-up of randomized controlled trials and observational studies of population-based screening, several organizations have published revisions, in some cases diverging significantly from prior recommendations and contemporary guidelines from other societies. This has been driven by a trend of placing a greater emphasis on estimating harms from screening and recognizing the interplay between published recommendations and an individual woman's values, preferences, and informed decision making.

This chapter reviews the advantages and limitations of screening modalities used to identify early breast cancer in asymptomatic women. This includes women without a personal history of breast cancer, a confirmed or suspected genetic mutation known to increase risk of breast cancer, or a history of previous radiotherapy to the chest at a young age. We then review the recommendations for screening generated by government-sponsored groups, medical societies, and institutions in the United States.

findings such as abnormal microcalcifications that may suggest cancer. If a discrete mass can be seen by ultrasound, it can be targeted for a core biopsy. If evaluation is consistent with benign gynecomastia and the medical history implicates a specific drug, discontinuation of that drug (if medically acceptable) with reevaluation in 3 to 6 months may be reasonable. Gynecomastia can also sometimes regress spontaneously. A persistent mass, particularly if painful, may be most appropriately managed by excisional biopsy for definitive diagnosis and symptom relief.

Pregnancy and Lactation

Most pregnancies occur in healthy young women, and any physical changes are likely to be benign. Common benign breast changes include fibroadenomata, which may enlarge in response to the stimulation of pregnancy-related hormones, and lactating adenoma, a benign, well-circumscribed mass. Either may be diagnosed with ultrasound and core biopsy during pregnancy. If an excisional biopsy is necessary during pregnancy, local anesthetics can be used in most cases. If a biopsy must be performed during the months a woman is lactating, a milk fistula may occur regardless of whether the biopsy is an excisional biopsy or a core needle biopsy, particularly if the biopsied area is central within the breast. Some women choose to continue to lactate and manage the fistula locally during that time, knowing that it will close after lactation ceases. Galactoceles are caused by an obstructed milk duct leading to cyst formation. Diagnosis is based on clinical history and ultrasound; they can be managed conservatively with warm compresses and continued lactation.

With increased use of reproductive technologies, more women are pregnant in their late 30s and 40s, when the incidence of breast cancer begins to rise. Attention to abnormal physical breast changes is particularly important because such women will not be receiving screening mammography during that time, and the changes of pregnancy may mask the early physical signs of cancer.

Surgical Planning

Women often view their breasts as part of their identity and in particular, we realize how much, represents a change to physical appearance and identity. Thus, surgical planning for benign breast disease should be considered carefully to minimize cosmetic defect. A well-placed surgical incision allows the woman an aesthetically pleasing result. If, on the other hand, further surgical procedures are required, the same incision can be used or extended as appropriate to complete a formal surgical resection. Some cosmetically favorable incisions are illustrated in Fig. 1. With few exceptions, it should possible to avoid making an unfavorably placed incision given careful preoperative consideration of the options. The transaxillary incision can be used to access lesions in the upper outer quadrant of the breast or axilla. The circumareolar or periareolar incision is made at the edge of the areola, allowing the scar to blend in with the darker skin of the areola. It can be used to access lesions circumferentially around and deep to the nipple areolar complex. The inframammary incision can be used to access lesions in the lower quadrants of the breast. These incisions can be technically more challenging, but they afford the patient a worthwhile, durable, and cosmetically favorable result.

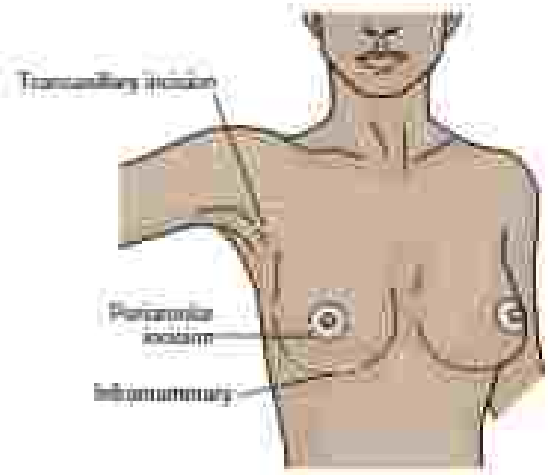

FIG. 1 Cosmetically favorable breast incisions. (From Phillips N, Berry A, Kuhn J. Operative Breast Techniques. 2 DVDs set. St Louis: Elsevier; 2014.)

Suggested Readings

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This chapter reviews the advantages and limitations of screening modalities used to identify early breast cancer in asymptomatic women. This includes women without a personal history of breast cancer, a confirmed or suspected genetic mutation known to increase risk of breast cancer, or a history of previous radiotherapy to the chest at a young age. We then review the recommendations for screening generated by government-sponsored groups, medical societies, and institutions in the United States.

SCREENING MODALITIES

There is more scientific evidence regarding screening for breast cancer than for any other cancer. As with all cancers, screening practices for breast cancer should be based on evidence regarding the prevalence of disease in the screened population, the effectiveness of the screening procedure, and any attendant harms, including the risks and costs associated with the screening test, and any additional tests and procedures that follow a positive screen. In breast cancer, this translates into debates about who should be screened, at what age, and with what method. As more data have emerged regarding the frequency and consequences of false positive test results (leading to unnecessary biopsy procedures) and overdiagnosis (i.e., the diagnosis of low grade, nonaggressive tumors that likely would not affect a person's life), and as breast cancer treatments become more effective, the tradeoff between benefits and harms of screening has shifted.

Breast Palpation

Breast Self-Examination

Although monthly breast self-examination (BSE) was recommended for many years, it recently has been recognized to have limited value in detecting early cancer. Large randomized clinical trials have failed to demonstrate reduction in breast cancer–specific or all-cause mortality from BSE in populations at average risk. Organizations such as the ACS, American College of Obstetrics and Gynecology, and US Preventative Service Task Force (USPSTF) have found insufficient evidence to recommend for or against performance of BSE. The emphasis on monthly BSE has been replaced by the concept of "breast self-awareness" in which women become knowledgeable about the normal appearance and feel of their breasts but without a specific schedule or examination technique. We share the opinion still held by many, however, that BSE has value. Physicians should educate women to enhance their awareness to report any skin changes, dimpling, nipple discharge, or presence of new lumps or bumps. The limitation of using BSE as a screening tool is related to the increased number of biopsies performed for benign breast disease, which comes at a financial and emotional cost.

Women who choose to perform BSE should do so when their breasts are least likely to be tender or swollen, often a few days immediately after a menstrual period. The examination is best done in both supine and upright positions using the finger pads of the three middle fingers. Different pressure levels (light, medium, firm) are used to examine the breast. Although various techniques can be used, women should be consistent in their technique used. One of the easier techniques involves palpating the breasts in a circumscribed clockwise fashion and working from the nipple outward, alternatively, a vertical (up down) pattern can also be used.

Clinical Breast Examination

Because recent randomized trials have included both clinical breast examination (CBE) and mammography, the utility of CBE on early detection of breast cancer remains unclear. However, 10% to 20% of breast cancers are not visible on screening mammography and CBE performed by trained personnel has been shown to increase breast cancer detection over mammography alone. Factors associated with greater accuracy of CBE include longer durations and a higher number of specific techniques used for the examination. Guidelines vary with regard to CBE in breast cancer screening. The ACS does not recommend CBE for screening at any age among average risk women. The American College of Obstetrics and Gynecology recommends CBE every 3 years for patients age 20 to 39 years and annually thereafter. The USPSTF states that current evidence is insufficient to assess the contribution of CBE beyond screening mammography in patients age 40 and older. We believe it provides an important clinical opportunity to discuss breast health, to instruct patients on BSE technique, and to review findings with them that should prompt a clinical visit and CBE.

Mammography

Mammography is the primary imaging modality for the early detection of breast cancer among asymptomatic women because it is the only method of breast imaging that consistently has been found to decrease breast cancer–related mortality. Screening mammograms provide two views of each breast: the mediolateral oblique projection images the breast from an oblique medial to lateral approach, and the craniocaudal projection images the breast from a superior to inferior view. The use of two views allows physicians to localize an abnormality to a particular quadrant within the breast and increases the sensitivity of mammography. The mammography interpretation always is appended by an American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) classification (Table 1). In 2014, the fifth edition of the BI-RADS lexicon was released to further

TABLE 1 Breast Imaging Reporting and Data System Classification

Category		Management	Likelihood of Cancer in the Mammographic Finding
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	
1	Negative	Routine screening	
2	Benign	Routine screening	Essentially 0
3	Probably benign	Short interval follow-up (6 months)	0 but >2%
4	Suspicious	Tissue diagnosis	4a: Low suspicion for malignancy (>2% to <10%)
			4b: Moderate suspicion for malignancy (>10% to <50%)
			4c: High suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	>95%
6	Known, biopsy proven malignancy	Surgical excision when clinically appropriate	

standardize the classification of mammographic findings and to provide a level of suspicion for clinicians. Each category is associated with specific guidelines for patient management to assess the need for subsequent biopsy and follow up recommendations. The use of this lexicon has also aided the field in quality assurance, communication, research, and improved patient care.

Screening mammograms are performed without a radiologist present, and suspicious findings are never classified as representing malignancy but prompt a call back for a diagnostic mammogram, which is performed with a radiologist present, who decides whether additional spot or magnification views are necessary to interpret the positive finding on screening mammography. Diagnostic mammography (which is more expensive than screening mammography) should be the first test ordered in the case of a palpable abnormality.

Nine randomized controlled trials, including more than 650,000 asymptomatic, average risk women have been conducted on screening mammography and have reported data on mortality. With long term follow up, pooled results from these studies found a 20% relative risk reduction for breast cancer mortality in women invited to screening compared with controls, with the benefit most pronounced in older age groups (all >50 years). Pooled estimates from observational studies have demonstrated an even greater effect. The magnitude of these estimates is influenced by a number of factors, including whether they are based on invitation or exposure to screening and on the heterogeneity of the studied populations. Estimates of the number needed to invite or number needed to screen to prevent a breast cancer death—increasingly cited as meaningful measures of benefit by organizations drafting guidelines—depends heavily on the relative risk reduction applied in the modeling, the underlying risk of mortality in the modeled population, and the duration of projected follow up. As a result, they can be disparate (more information about number needed to invite and number needed to screen calculations can be found in the ACS and the USPSTF guidelines). Further complicating interpretation of existing evidence is that most of the trials and observational studies were performed in the 1990s, before significant advances in the adjuvant treatment of breast cancer, and with the use of film mammography. Although the majority of breast cancers in the United States are diagnosed as a result of an abnormal screening study, and death rates from breast cancer in the United States have decreased by 30% since the 1990s, it is estimated that approximately one third of that effect is due to screening, with the rest attributable to treatment advances.

There are several limitations specific to mammography as a screening tool. First is that mammography uses radiation, which is itself carcinogenic, although models suggest that the radiation risk from mammography is low enough to result in a net benefit from screening with respect to lives saved. Another limitation is that of overdiagnosis: the detection of disease by screening that would not have become clinically important in a woman's lifetime, including ductal carcinoma in situ (DCIS; which may not progress to invasive cancer), a slow growing cancer, or one that regresses. Results from randomized trials and cohort studies consistently demonstrate a higher rate of cancer diagnosed in a population screened by mammography versus an unscreened population, despite a long follow up. Depending on method of estimation and definition (e.g., whether DCIS is included as an event), estimates for overdiagnosis and thus overtreatment of breast cancer resulting from mammography range from less than 10% to more than 30%. Not unique to mammography but central to the controversy surrounding screening recommendations is the risk of false positive screening tests, which result in additional imaging and procedures, potentially even surgical excision, all for a benign condition. False positive screening tests are more common in younger women because mammography is less specific in this population and because cancer is less common.

Breast Density

The density of breast tissue reflects the estimated amount of fibrous and glandular tissue relative to fat and is important because mammographic sensitivity is lower in dense breasts. In addition, there is suggestion that breast density is an independent risk factor for breast cancer. This importance tends to be overestimated in studies that compare women with the highest density to those with the lowest density, resulting in an estimated fourfold to sixfold increase in risk. With use of average breast density as a reference point, the risk among women with heterogeneously dense breasts is 1.2 times as great as the average, and with extremely dense breasts, 2.1 times as great. This is equivalent to the elevated risk of breast cancer associated with having a first degree relative with unilateral, postmenopausal breast cancer. Breast density does not appear to be associated with increased mortality from breast cancer. It is not clear at this time whether breast density represents a modifiable risk factor for cancer, whether screening recommendations should be altered for women with dense breasts, or how women who have dense breasts should be counselled. Because breast density influences cancer risk and the performance of mammography as a screening tool, the American College of Radiology includes classification of breast density as a mandatory component of mammographic interpretation. The fifth edition of the BI-RADS lexicon states that breast density characterization is entirely subjective and can be described as four categories: almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense. In a development that some feel to be premature, there also have been laws passed in 22 states mandating that women found to have dense breasts on mammography be notified in writing of the finding and be encouraged to consider additional testing. These policies have attracted criticism because there are no data that additional testing in women with dense breasts is effective in preventing breast cancer death and because they do not address insurance coverage for and reimbursement issues surrounding additional screening tests.

Digital Mammography

All of the randomized controlled trials addressing the effectiveness of screening used film mammography, and there is no direct evidence that digital mammography reduces breast cancer–related deaths. Nonetheless, digital mammography has replaced film as the primary screening modality in the United States. In addition to facilitating remote reading and more efficient storage, the real advantage of digital image collection over film systems is higher contrast resolution and the ability to postprocess the image to enlarge it or change contrast and brightness, helping radiologists more easily detect subtle abnormalities, particularly in a background of dense breast tissue. Most studies that have compared the performance of digital and film mammography have found little difference in cancer detection rates. With digital mammography, there is a suggestion of an increase in detection of invasive cancer in premenopausal and perimenopausal women and in women with dense breasts, but also an increase in false-positive findings.

Tomosynthesis

Tomosynthesis (or three dimensional [3D] digital mammography) is a rapidly emerging technology that involves the acquisition of multiple images of the breast recorded at different angles while the detector is held stationary, providing the radiologist with a series of thin slice (1 mm) images through the breast. Recent data have shown an improvement in cancer detection rate up to 6.5 per 1000 with 3D versus 5 per 1000 with two dimensional (2D) imaging; additionally, the recall rate may decrease as much as 20% to 40% with 3D compared with 2D imaging, particularly for baseline examinations. Although this modality has been found to decrease false-positive and false-negative rates, before performing reconstructed synthesized 2D as part of the 3D mammogram, there was

an increase in the radiation dose compared to a traditional 2D digital mammogram. Several manufacturers now offer the capability to reconstruct synthesized 2D (s2D) mammograms from digital breast tomosynthesis datasets as a replacement for digital mammography. In this way, patients only receive radiation from the tomosynthesis components with elimination of the digital mammographic component, decreasing the overall radiation exposure by up to 45%. Early studies have shown that screening with s2D mammography and digital breast tomosynthesis is not inferior to screening with digital mammography and tomosynthesis. Additionally, s2D imaging has been associated with decreased recall rates and multicenter cancer detection rates. Because this is a relatively new imaging modality, further study is needed to confirm these early results.

Magnetic Resonance Imaging

Nearly all invasive breast cancers are visible on gadolinium contrast–enhanced magnetic resonance imaging (MRI), and the reported sensitivity of MRI is between 88% and 100%. Unfortunately, benign lesions can also enhance on MRI, and low specificity currently limits MRI as a screening tool. The positive predictive value of any test is enhanced as the prevalence of disease rises, and it follows that MRI would have higher utility in patients at higher relative risk for breast cancer. Indeed, the efficacy of MRI as a screening tool in patients at high risk has been validated in multiple studies. In 2007, the ACS recommended annual screening MRI as a supplement to screening mammography for women with high risk for breast cancer, based either on a known *BRCA* mutation, a first-degree relative of a known *BRCA* mutation carrier, or a predicted lifetime risk of 20%–25% or greater according to risk modeling. On the basis of expert consensus opinion, the National Comprehensive Cancer Network (NCCN) also recommended annual MRI screening for those individuals who received radiation to the chest between the ages of 10 and 30 years, those with Li-Fraumeni, Cowden's, or Bannayan-Riley-Ruvalcaba syndromes, and their first-degree relatives. Data are still insufficient for recommendation for or against MRI screening for individuals with a lifetime risk of 15% to 20%, those with lobular carcinoma in situ, atypical ductal or lobular hyperplasia and dense breast on mammography, and those with a personal diagnosis of breast cancer, including DCIS. The downsides to MRI include the significant cost of the test, as well as discomfort on the part of the patient, which may be a limiting factor in a non-insignificant subpopulation.

Other Technologies and Adjuncts to Screening

Whole-Breast Ultrasound

Although ultrasound does not yet have a proven primary role in breast cancer screening, it is often used as a supplemental screening modality after mammography, CBE, or MRI. Focused breast ultrasound characterizes palpable or image-detected lesions on screening studies and can be used to perform image-guided biopsies of mammographically visible lesions. Additionally, multiple studies have demonstrated the effectiveness of sonography as an adjunct to mammography for screening women with dense breast tissue; these lesions were often small (<1 cm) and node negative. Supplemental screening with whole-breast ultrasound has been shown to increase mammographic sensitivity by about 20%–30%. The American College of Radiology Imaging Network whole-breast ultrasound screening trial (ACRIN 6666) assessed the role of whole-breast ultrasound for screening of high-risk women with dense breasts and found only 4 cancers/1000 women were detected with ultrasound alone; additionally, there were a high number of false-positive findings. Considering the increased number of false-positive findings, the length of time it takes to perform, and its operator dependent variability, it remains useful as a supplemental and not a primary screening modality.

Molecular Breast Imaging

Molecular breast imaging (MBI) is a technology used most commonly in women with dense breasts, in whom screening mammography has decreased sensitivity. MBI is based on the observed preferential uptake of a radiotracer (such as ^{99m}Tc sestamibi) in tumors relative to normal tissue, independent of breast density. This modality offers the advantage of detecting the physiologic changes that manifest in early breast cancer as the radiotracers can diffuse into interstitial space and be taken up by the abnormal cells before the presence of a distinct mass or neovascularity. The major disadvantages of MBI include the high radiation dose associated with the injection of radiotracer as well as the long imaging time (6 × 10 minute images). Early results indicate that MBI has comparable sensitivity to breast MRI, but at a fraction of the cost while maintaining an acceptably low false-positive rate. In a screening study of high-risk women with dense breast tissue, MBI detected three times as many tumors as mammography while maintaining a lower false-positive rate. Currently, there is not enough evidence to support MBI as a breast screening tool, but it remains under investigation as a modality that may be useful, especially in patients with dense breasts.

SCREENING GUIDELINES

The recommendations from the ACS, USPSTF, and the NCCN for asymptomatic women who do not have a preexisting breast cancer or a previously diagnosed high-risk breast lesion and who are not high risk for breast cancer because of a known underlying genetic mutation or a history of chest radiation at a young age are summarized in Table 2.

Past screening recommendations from the USPSTF (http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-screening1) included annual mammography starting at the age of 40, however, recent analyses of data pooled from screening trials have suggested that there is an elevated number of false-positive results and unnecessary biopsies for women aged 40 to 49 years. These trends have led to an increased risk of overdiagnosis and overtreatment. Specifically, in their recommendations, the USPSTF estimates that 1904 women ages 50 to 69 would need to be screened to prevent one death from breast cancer after at least 11 years of observation, compared with 1339 women in their 50s and 377 women in their 40s. Additional analyses suggested that annual versus biennial mammography also did not carry a survival advantage. Thus, in their 2009 revision, the USPSTF raised the age at which they recommended initiating mammographic screening from 40 to 50 and revised their recommendations to include screening mammograms only every 2 years for women between the ages of 50 and 74 years of age. Critics of this decision pointed out that the false-positive rate and number needed to prevent a breast cancer death were substantially different between women in their 40s and women in their 50s and that the decision to alter screening recommendations at this age cutoff was somewhat arbitrary. Moreover, it did not provide patients with the knowledge necessary to contribute to the decision. The most recent USPSTF guidelines were released in 2016 (https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1). The statement maintains the recommendation for biennial screening for women age 50 to 74. It softens the language of the recommendations surrounding screening among women age 40 to 49, stating that the decision to perform mammography in this group should be an individual one based on considerations of the risks and benefits of screening in this population, and notes that women age 40 to 49 with a first-degree relative with breast cancer may benefit potentially more than average-risk women in this age group.

The USPSTF also concluded that current evidence is insufficient to assess the balance of benefits and harms for women age 75 years and older. The USPSTF maintains its 2009 recommendation against routine screening MRI and finds insufficient evidence to make recommendations

TABLE 2 Screening Guidelines for Asymptomatic Women of Average Risk for Invasive Breast Cancer From the ACS, the Current USPSTF, and the NCCN

Age	ACS	USPSTF	NCCN
25 but <40			CBE every 1–3 years (25 but <40) Breast awareness
40–44	Women should have the opportunity to begin annual screening between the ages of 40 and 44 years[a]	Through age 50: The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefit and harm.	Through age 50: Annual CBE Annual screening mammogram Breast awareness
45–50	Women should undergo regular screening mammography beginning at age 45 years[b] Screening should be annual[b]		
51–54	Women should undergo regular screening mammography[b] Screening should be annual.	Through age 74: Biennial screening mammography Current evidence is insufficient to assess the additional benefit and harm of CBE beyond screening mammography	Through age 74: Annual CBE Annual screening mammogram Breast awareness
55–74	Women age 55 and older should transition to biennial screening or have the opportunity to continue screening annually[a] Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer	Current evidence is insufficient to assess the benefit and harm of screening in this age group	
75+	Anatomy	Current evidence is insufficient to assess the benefit and harm of screening in this age group	Annual CBE Annual screening mammogram Breast awareness The upper age limit for screening is not yet established; consider life expectancy and whether therapeutic interventions are planned
All women	CBE is not recommended for breast cancer screening among average risk women at any age.[c] All women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.	The USPSTF recommends against teaching BSE.	Women should be counselled regarding potential benefits, risks, and limitations of breast screening. Women should be familiar with their breasts and promptly report changes to their healthcare provider.

The USPSTF recommendations are currently under review for revision.

[a]Qualified recommendations; qualified recommendations indicate that there is clear evidence to favor it in screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions.

[b]Strong recommendations; a strong recommendation conveys the consensus that the benefit of adherence to that intervention outweighs the undesirable effects that may result from screening.

[c]ACS, American Cancer Society; BSE, breast self-examination; CBE, clinical breast examination; NCCN, National Cancer Comprehensive Network; USPSTF, United States Preventive Services Task Force.

regarding CBE, although it does support all patients being aware of changes in their bodies.

The ACS recommendations for breast cancer screening are maintained on the ACS website (http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/index). The recommendations were updated in October 2015 from earlier guidelines published in 2003. The major departure is that BSE and CBE, previously suggested for all women starting at the age of 20, were eliminated from the recommendations entirely. The recommended age to start mammography also was raised, reflecting changes to the USPSTF recommendations published in 2009. The reasoning for this change was the same, based on an analysis of the risks of false positives and overdiagnosis versus the small incremental benefits with respect to preventing breast cancer deaths in a relatively low prevalence age group. Whereas previous recommendations suggested annual mammography start at the age of 40, the current expression qualifies this recommendation as a choice, and one that should be made with consideration of risks and benefits of screening. Strong recommendation for annual mammography starts at the age of 45 years. This decision was based on (1) clear data regarding the benefits of screening mammography to women between the ages of 50 and 75 and (2) the observation that the incidence of breast cancer and proportion of incident breast cancers in women 45 to 49 more closely resembled the 50 to 54 group than did the 40 to 44 group. Annual screening mammography should continue while a woman's life expectancy is at least 10 years, with the option to transition to biennial screening at the age of 55. There is no age after which the ACS recommends halting screening for breast cancer.

Concerns surrounding these new guidelines echoed some of the criticisms of the USPSTF guidelines, including that the recommendations of the USPSTF and ACS focus primarily on the outcome of breast cancer lives saved. Other outcomes that may be important to patients were sparsely (if at all) addressed, and some may be undervalued. These include quality of life, although the ACS found the quality of evidence regarding the effect of screening on quality adjusted life years to be too low to incorporate this outcome into their screening recommendations, and the stage at which a breast cancer is diagnosed, which may influence a woman's options for breast conserving therapy. These issues and questions as to the magnitude of overdiagnosis that results from screening continue to pose a challenge in providing complete and accurate information to women about what to expect from breast cancer screening.

As of July 2015, the screening guidelines of the NCCN still recommends CBE every 1 to 3 years and states that women of all ages should be familiar with their breasts and promptly report changes to their healthcare provider. Annual screening mammogram begins at the age of 40 and is accompanied by annual CBE. The NCCN does not support an upper age limit for screening but does note that comorbidity, life expectancy, and the expectation that a positive examination finding would be followed by invasive treatment be incorporated into decision making in this age group. These recommendations are classified as evidence level 2A, "based on lower level evidence, [and] there is uniform NCCN consensus that the intervention is appropriate."

Many other organizations have issued recommendations about mammography screening of asymptomatic women not known to be at increased risk for breast cancer. The American College of Physicians recommends that clinicians should inform women ages 40 to 49 years about the potential benefits and harms of screening mammography and that screening decisions should be based on individualized assessment of risk for breast cancer and the benefits and harms of screening in this age group. They also should incorporate the woman's preferences and breast cancer risk profile. The American Congress of Obstetricians and Gynecologists recommends that mammography screening be offered annually to women beginning at age 40 years. The American College of Radiology and the Society for Breast Imaging, in a 2018 joint recommendation, also advise screening begin annually at 40 and continue until life expectancy is less than 5 to 7 years or when abnormal results of screening would not be acted on because of age or comorbid conditions. In addition, the statement is the first to recognize that African American women are at high risk and as such should begin risk assessment at age 30. The Canadian Task Force on Preventive Health Care recommends routine screening mammography every 2 to 3 years in women ages 5 to 74 years and recommends against screening women ages 40 to 49 years.

Screening in High-Risk Individuals

Several national medical organizations have developed guidelines and recommendations for screening women at high risk. The greatest evidence-based risk is in those women with *BRCA1* and *BRCA2* mutations. *BRCA1* or *BRCA2* mutation carriers are at the highest risk: 57% to 87% will be diagnosed with an invasive breast cancer by the age of 70. In 2017, a prospective cohort of 9676 women revealed the estimated cumulative risk for developing breast cancer by age 80 with *BRCA1* and *BRCA2* mutations was 72% and 69%, respectively. Women who have had a prior diagnosis of breast cancer, atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ are also considered higher than average risk, as are women with a family history suggestive of familial breast and/or ovarian cancer, or a first degree relative who has tested positive for a breast cancer–associated genetic mutation are also at high risk. Additionally, women who received mantle-cell irradiation between the ages of 10 and 30 years of age qualify them for the high risk screening approach. Finally, special screening schedules apply to those women who are calculated to have an elevated lifetime risk of being diagnosed with invasive cancer according to the predictive model. A variety of models are available to predict risk, of which the most widely used is the Gail model. This prediction algorithm assesses breast cancer risk based on age, number of first-degree relatives with breast cancer, age of menarche, age of first live birth, number of previous biopsies (including presence of atypia), and race or ethnicity. The Claus model includes a more comprehensive family history. The BRCAPRO model is a statistical model for assessing the probability that an individual carries a germline deleterious mutation of the *BRCA1* and *BRCA2* genes based on personal history and family history data, including a history of breast and ovarian cancer, male breast cancer, and Jewish ancestry. The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model includes family history of prostate and pancreatic cancer in addition to breast and ovarian cancer family history. Finally, the Tyrer-Cuzick model incorporates family history and gynecologic history.

Table 3 contains a summary of screening recommendations based on high risk category. Whereas NCCN guidelines are specific with respect to the age and modality of screening recommended, the ACS has only published guidelines for screening with MRI as an adjunct to mammography (see Table 3). In general, annual screening mammography is recommended for women of appropriately high risk beginning at 30 years, supplemental screening with breast MRI is recommended for a cohort with very high risk, and screening ultrasound scan is recommended for women in whom MRI is unavailable. The results of a recent study with computer simulated modeling concluded that annual MRI at age 25 years, alternating every 6 months with digital mammography beginning at age 30 years, may be the most effective screening strategy for mutation carriers.

TABLE 3 NCCN and ACS Guidelines for Women With Elevated Risk for Breast Cancer

NCCN	Prior history of breast cancer	History and physical examination 1–4 times per year as clinically appropriate for 5 years after diagnosis, then annually Annual screening mammography starting at diagnosis
	5-year risk[a] ≥1.7% in women ≥35 years of age according to the Gail model	Annual screening mammogram and CBE every 6–12 months
	History of LCIS or ADH/ALH	Annual screening mammogram and CBE every 6–12 months, consider annual MRI Beginning at diagnosis but no earlier than age 30
	Lifetime risk[a] ≥20% according to models largely dependent on family history (e.g., Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick)	Annual screening mammogram and CBE every 6–12 months, recommend annual MRI Beginning 10 years before youngest family member but not earlier than age 20 Referral to genetic counseling
	Prior thoracic RT (e.g., mantle irradiation) between ages 10 and 30 years old	Age ≤25: annual CBE to start 8–10 years after RT Age >25: Annual screening mammogram and CBE every 6–12 months, recommend annual MRI Begin 8–10 years after RT
	Pedigree suggestive of or known genetic predisposition	Refer for genetic counseling, genetic testing as appropriate Screening recommendations depend on the cancer syndrome identified[b]
ACS[c]	*BRCA* mutation First-degree relative of BRCA carrier but untested Lifetime risk ~20% or 25% or greater, as defined by BRCAPRO or other models that largely depend on family history Radiation to chest between ages 10 and 30 years	Annual MRI screening (based on evidence from nonrandomized screening trials and observational studies)
	(1) Treatment syndromic and first-degree relatives: Cowden's and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives	Annual MRI (based on expert consensus opinion)

[a]If invasive breast cancer.

[b]See National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian (Version 2.2010). http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed August 20, 2010.

[c]The ACS states that women at increased risk of breast cancer may benefit from additional screening strategies beyond those offered to women of average risk, such as earlier initiation of screening, shorter screening intervals, or the addition of screening modalities other than mammography and clinical examination, such as ultrasound or magnetic resonance imaging, but that the evidence currently available is insufficient to yield recommendations for any of these screening approaches.

ADH, Atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CBE, clinical breast examination; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging; RT, radiation therapy.

Suggested Readings

Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA*. 2014;311(24):2499–2507.

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Role of Stereotactic Breast Biopsy in the Management of Breast Disease

Ronald F. Jones, MD, and Michael D. Grant, MD

It is estimated that there will have been 240,120 cases of new breast cancer diagnosed in 2010 in the United States. This is in addition to 63,960 cases of ductal carcinoma in situ (DCIS) and lobular carcinoma in situ, representing 30% of all new breast cancers, and more than 2,000 cases of male breast cancer. Screening has improved early breast cancer detection in early stage cancer that is often nonpalpable. The preferred initial biopsy is percutaneous. There are now four percutaneous methods: ultrasound, stereotactic, magnetic resonance imaging, and (unsynthesized) biopsies. Surgical biopsies should generally be used only if percutaneous image guided biopsy is not feasible. Approximately 80% of breast biopsies are now performed percutaneously. Of these, 25% will reveal breast carcinoma; thus, three fourths of patients will have benign disease, avoiding an open surgical biopsy. There is a significant reduction in cost using percutaneous biopsy over open surgical biopsy. The procedure can be performed in approximately 30 minutes and the patient does not require a general anesthetic or going into the operating room. It is an outpatient procedure and the patient can return to work the following day. There are no stitches required, and there is less scarring and less deformity of the breast than with surgical biopsy. Future mammograms will not look significantly different following needle biopsy; however, the radiologist should be informed that the patient has had a breast biopsy. There is almost no confusion diagnosing possible breast cancer as a result of scarring from a previous percutaneous biopsy.

Women with multiple lesions within a breast may benefit from stereotactic biopsy because multiple areas can be biopsied as part of a single biopsy procedure. Different clips can be placed in the different biopsy sites in the event that one is carcinoma. If the mass biopsied with a needle turns out to be a cancer, the breast surgeon can plan the surgical treatment and biopsy of lymph nodes in a single trip to the operating room.

In 1977, stereotactic fine needle aspiration was first reported in Sweden and in 1987 ultrasound guided fine needle aspiration was first described by Burrage. In the late 1980s, Dowlat introduced stereotactic breast biopsy technology in the United States. As breast biopsy tools became more advanced and spring loaded and later vacuum assisted core devices were developed, the image-guided biopsy approach has become predominant for initial tissue diagnosis. More than one half of all breast biopsies are performed stereotactically. It is endorsed by the American Society of Breast Surgeons and a quality measure for National Accreditation Program for Breast Centers.

The sensitivity of core needle biopsies performed stereotactically or with ultrasound guidance is 87% to 99%. The accuracy of stereotactic biopsy can be increased with a larger needle size (i.e., 9 to 11 gauge) and with the use of vacuum assisted devices.

INDICATIONS

There are six Breast Imaging Reporting and Data System (BI-RADS) categories: (1) negative, (2) benign finding, (3) probably benign finding, (4) suspicious, (5) highly suggestive of malignancy, and (6) known biopsy proven malignancy. Depending on the clinical suspicion, patient anxiety, or physician preference, BI-RADS 3 group lesions may be referred for biopsy. BI-RADS 4 and 5 lesions require histologic sampling to rule out malignancy. Lesions visible by ultrasound typically are biopsied with ultrasound guidance because it is less expensive, more easily tolerated by the patient, and does not require exposure to additional radiation. Mammographic lesions (such as ultrasound most commonly are calcifications, but also may include masses, developing asymmetries, and architectural distortions) that may require stereotactic biopsy (Box 1).

CONTRAINDICATIONS

A cooperative patient is imperative to performing a successful stereotactic biopsy. It requires the patient to lie immobile as the breast remains in compression for approximately 30 minutes; therefore, any physical limitations of the patient, such as movement disorders, limited range of motion, kyphosis, or weight, must be considered. A patient who weighs more than 300 pounds is not a candidate for stereotactic breast biopsy if a prone table is used. If a patient has thin or small breasts, adequate breast tissue thickness may not be available while in compression to allow access for the computerized biopsy equipment. There may not be enough breast tissue to compress to safely biopsy without the needle penetrating through to the other side of the breast. If the breast is too large and the lesion is deep, stereotactic biopsy may not be technically feasible. If the lesion is too close to the nipple, superficial in the skin, or posterior and near the chest wall, or if patient has a breast implant, stereotactic biopsy may be contraindicated (Box 2). Stereotactic core biopsy is also not indicated in pregnant women.

In the relatively small number of patients not suitable for stereotactic biopsy, the patients should be referred for surgical biopsy. Surgical biopsy may also be recommended for those patients who had core needle biopsy showing high risk abnormalities such as atypical hyperplasia, radial scar, papilloma, or lobular carcinoma in situ.

It is important to ensure adequate pain control with local anesthetic for patient comfort and technical success. Anxiety and vasovagal reactions are symptoms commonly reported. Occasionally antianxiety medication given before the procedure may assist with patient cooperation.

EQUIPMENT

Stereotactic biopsy can be performed with a traditional prone stereotactic biopsy table or upright with an add-on stereotactic biopsy unit that attaches to the standard mammography equipment. There are advantages and disadvantages to both systems. If a patient is wheelchair bound or obese, the traditional prone table may not be ideal; however, wheelchair bound patients may be elevated on a stretcher and rolled onto the table, if this can be safely performed. Otherwise, the biopsy must be performed with the add-on unit. Advantages of the prone position are less patient anxiety and there is more room for the physician and technologist to maneuver because they can work under the table. When an add-on unit is used, the patient can visualize the needle, which can result in more anxiety and motion. However, the advantage of the add-on unit is that the resolution and quality of the images acquired are similar to diagnostic mammography. At most facilities, a special examination table will allow the patient to lie face down with the breast hanging freely through an opening in the table.

Biopsy Needles

The standard for stereotactic biopsy is now the vacuum assisted biopsy needle devices. They offer a number of advantages over spring loaded biopsy devices. The vacuum-assisted devices can obtain multiple specimens in a 360 degree fashion, require only one needle insertion, and provide larger specimens. The needles are

BOX 1 Indications for Stereotactic Core Biopsy

- Certain probably benign lesions, BI-RADS 3, depending on clinical suspicion, patient or physician preference, or when short-term follow-up is not practical
- BI-RADS 4, suspicious lesions
- BI-RADS 5, highly suspicious lesions
- BI-RADS 6, known biopsy-proven malignancy
- New suspicious mass- or calcification-type abnormalities, or architectural distortions
- Nonpalpable asymmetry, focal asymmetry, or density on mammogram not seen on ultrasound
- Magnetic resonance imaging–only lesions, corresponding to suspicious areas of enhancement on magnetic resonance imaging
- New mass or area of previous surgery site
- Area of abnormal tissue change

BI-RADS, Breast Imaging Reporting and Data System.

BOX 2 Contraindications for Stereotactic Core Biopsy

- Patient unable to lie prone or cooperate
- Patient's excess weight
- Lesion location near chest wall, axilla, or inframammary fold position to chest wall, or too close to implant
- Lesion too small or not well seen
- Patient unable to move table or move from one machine to another
- Lack of adequate skin-to-lesion distance (e.g., lesion too superficial)
- Pregnancy

powered by a suction device and have a rotating cutter. The automated biopsy guns usually have 14- to 18-gauge needles, whereas the vacuum-assisted biopsy guns have 7- to 11-gauge needles allowing for up to 12 biopsies. A 9-gauge needle is very popular and allows almost 1 cm of tissue removed. Regardless of the number or size of core biopsy samples obtained, most important is ensuring adequate sampling of the intended target. The biopsy should demonstrate presence of targeted calcifications on specimen radiography with radiologic-pathologic correlation to ensure the pathologic diagnosis are concordant and explain the imaging findings. For patients with microcalcifications, stereotactic vacuum-assisted biopsy is the standard approach; however, if calcifications are associated with a solid mass, then ultrasound-guided biopsy may be used.

Technique and Lesion Targeting

In the late 1990s, vacuum-assisted core biopsy devices became available, allowing larger specimen samples to be obtained. The patient is positioned, the skin is cleansed, and local anesthetic is administered. A small nick is made in the skin and the vacuum-assisted device is inserted into the breast under image guidance placed either in the suspicious lesion or adjacent to it. The device is typically rotated and multiple biopsies are taken from the suspicious lesion. The ideal approach is the shortest distance from skin to a targeted lesion. A scout view is obtained and after the target is identified, two additional images are obtained 30 degrees apart, at +15 degrees and −15 degrees. The basis of stereotactic localization is the principle of parallax, which is used to locate the lesion in the three-dimensional breast from a pair of two-dimensional images. Scout view provides the *x* (horizontal) and *y* (vertical) coordinates of the lesion to be targeted in the breast. Two additional images are then used to determine depth (*z* coordinate). The distance from needle tip to image receptor plate should be 5 mm or more to avoid penetration of the opposite side of the patient's skin and penetration of the image receptor plate. Once the needle device is introduced into the breast, and preimages are obtained to confirm the position, the needle is fired and then postfire images are obtained to confirm position (Fig. 1).

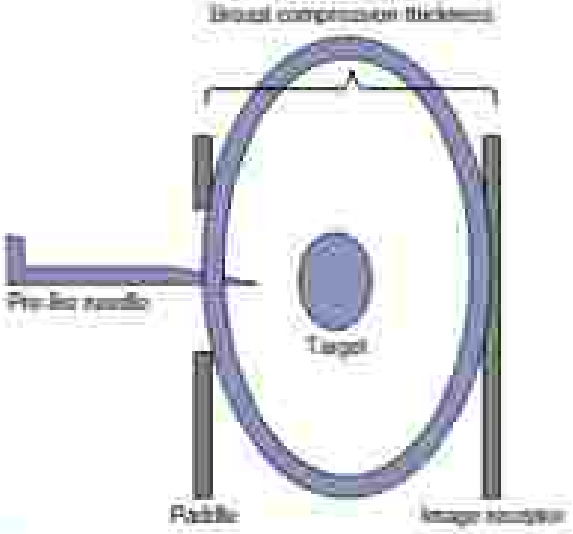

FIG. 1 This image demonstrates scenario of pre-fire positioning to target. (*See bottom, left.*) *x*, *y*, and *z* axes. (*See bottom, right.*)

When the vacuum-assisted biopsy device is used, tissue sampling is performed in a 360-degree fashion. Typically, 6 to 12 samples are obtained. The breast is compressed and held in position throughout the procedure.

Core Specimen Handling

To ensure adequate sampling, a specimen radiograph is obtained of the histologic samples collected during core biopsy to document targeted lesion retrieval (Fig. 2). After the specimen cores have been retrieved, a postbiopsy marker (clip) should be placed at the biopsy site. This marker facilitates mammographic surveillance and serves as a guide if surgical excision is required. If more than one lesion is biopsied, different types of clips are placed in the respective biopsy sites that will be visible on future mammograms and will show the physician which area has been biopsied. If the biopsy is being performed to evaluate calcifications, the specimens will be x-rayed to ensure that they do contain calcifications (Fig. 3). To ensure that the clip is deployed at the biopsy site, a postprocedure mammogram should be obtained. Clip migration can occur in up to 20% of cases.

Image-guided percutaneous biopsy is minimally invasive, causes minimal breast deformity and scarring, is faster than open surgical biopsy, and is well tolerated by the patient. The advantage of the vacuum-assisted biopsy device is that only one tube is inserted and the biopsies can be performed in a full degree fashion, with removal of the biopsy needle leaving the tube in place. Although overall accuracy is higher and false negative rates are low, these findings are heavily influenced by technique and experience of the physician performing the procedure.

Pathologic Correlation

Pathologic findings should correlate with imaging findings; however, when pathologic findings do not correlate with imaging, there is discordance, and excision is recommended. If the imaging has numerous calcifications, but the pathologic report lacks calcifications and indicates only benign breast tissue, the accuracy of the biopsy is suspect. If the calcifications were noted in the specimen radiograph, the pathologic blocks should be imaged to determine if calcifications remain unsampled in the block prompting additional levels being cut for pathology review.

Certain lesions require surgical excision to exclude a high-grade lesion malignancy (Box 3).

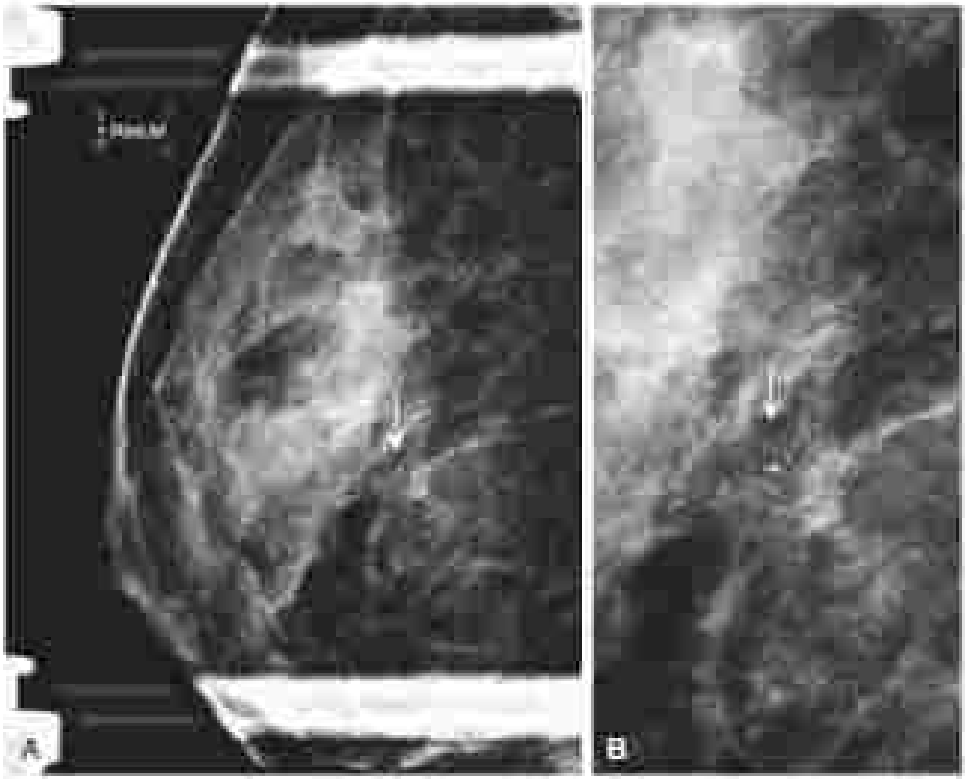

FIG. 2 (A) Mammographic images showing targeted stereotactic vacuum-assisted core biopsy of a pleomorphic microcalcification cluster (lateral view, (B) magnification mediolateral oblique view) in a patient undergoing stereotactic breast biopsy. (Courtesy of Carlos D'Alessio, MD.)

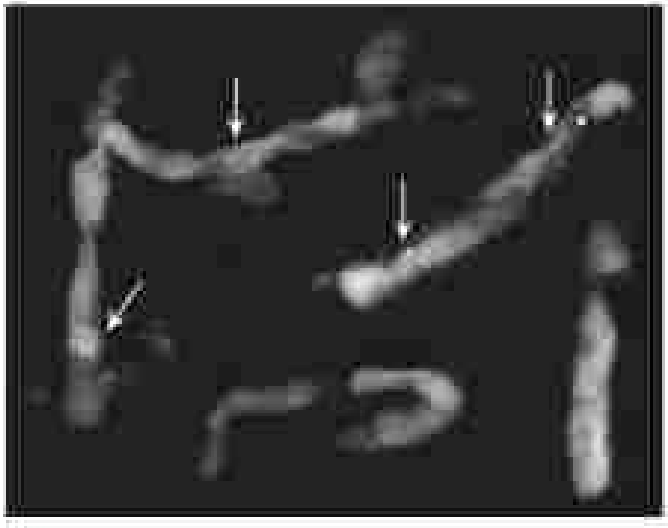

FIG. 3 Specimen radiograph demonstrating target microcalcifications contained within the tissue core. (Courtesy Carlos D'Alessio, MD.)

COMPLICATIONS

The incidence of severe complications is less than 1%. These include bleeding resulting in hematoma, infection, pneumothorax from biopsying lesions near to the chest wall, and vasovagal reactions. Core needle biopsies may obviate the need for open surgical procedures in about 72% of women.

The referring physician should stop anticoagulant therapy a few days before core biopsy. Core needle biopsy may still be performed safely in patients receiving anticoagulant therapy or aspirin, but the patient should be informed of increased risk of bleeding and hematoma formation.

BOX 3 Indications for Surgical Excision After Stereotactic Core Biopsy

- Imaging findings and pathologic findings do not correlate (discordance)
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia
- Radial scar, complex sclerosing lesion
- Papillary lesions
- Cellular fibroepithelial lesions and Phyllodes tumors
- Lobular carcinoma in situ
- Mucocele-like lesions

For most patients with concordant radiologic pathologic findings after biopsy, a follow-up mammogram is suggested at approximately 6–12 months. Following excision of DCIS associated with larger areas of malignant calcifications, a postoperative mammogram is suggested to ensure completeness of resection beyond specimen radiography and pathologic margin assessment. A shorter imaging period may be indicated in certain situations. If the patient is older than 35 years, a unilateral diagnostic mammogram is generally obtained as a new baseline study within 6 to 6 months of the procedure.

WHAT'S NEW

Tomosynthesis

Digital breast tomosynthesis is rapidly replacing two-dimensional full field digital mammography as the preferred method of breast cancer screening. This technique acquires a series of 1-mm sections throughout the breast that can be viewed as a three-dimensional image set or individual slices. Although detection of microcalcifications is not improved, the ability to remove superposition artifacts allows the reviewer to better discern areas of architectural distortion, especially within dense breasts (Fig. 4A–C). These clinical utilities

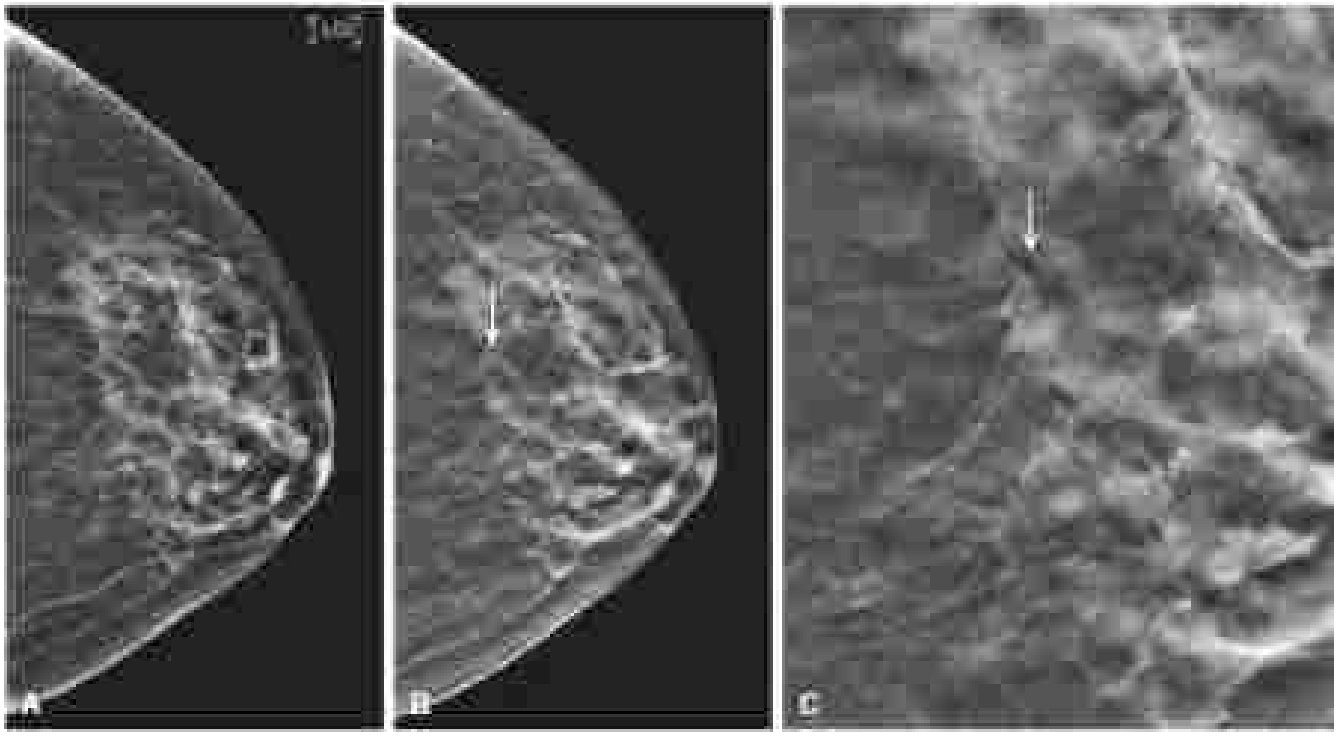

FIG. 4 (A) Two-dimensional digital craniocaudal mammogram and (B) tomographic image of the same view revealing suspicious area of architectural distortion (*arrow*) in a dense breast. (C) Magnification of the region depicts abnormal features. This lesion could not be localized sonographically and proved to be a low-grade invasive ductal and cribriform carcinoma on tomosynthesis-guided needle biopsy. (*Courtesy Northern Westchester Hospital, Mount Kisco, NY.*)

frequently require tissue sampling, but may not be able to be localized by additional sonographic or conventional two-dimensional radiographic techniques for percutaneous needle biopsy. Fortunately, an upright, add-on biopsy system is available that is attached directly to the three-dimensional mammography unit. This stereotactic tool can accurately localize these lesions for vacuum biopsy that may only be seen on one of the tomosynthesis sections.

SUMMARY

Stereotactic core needle biopsy is indicated in approximately 10% of biopsies and is safe with high specificity. It is the preferred method of diagnosis for nonpalpable lesions and microcalcifications. It is much more cost effective than surgical biopsy and results in shorter procedure time and return to normal activity. Newer technology is tomosynthesis screening and biopsy of architectural distortion.

SUGGESTED READINGS

Elmore JG, Longton GM, Carney PA, et al. Diagnostic concordance among pathologists interpreting breast biopsy specimens. JAMA. 2015;313:1122–1132.

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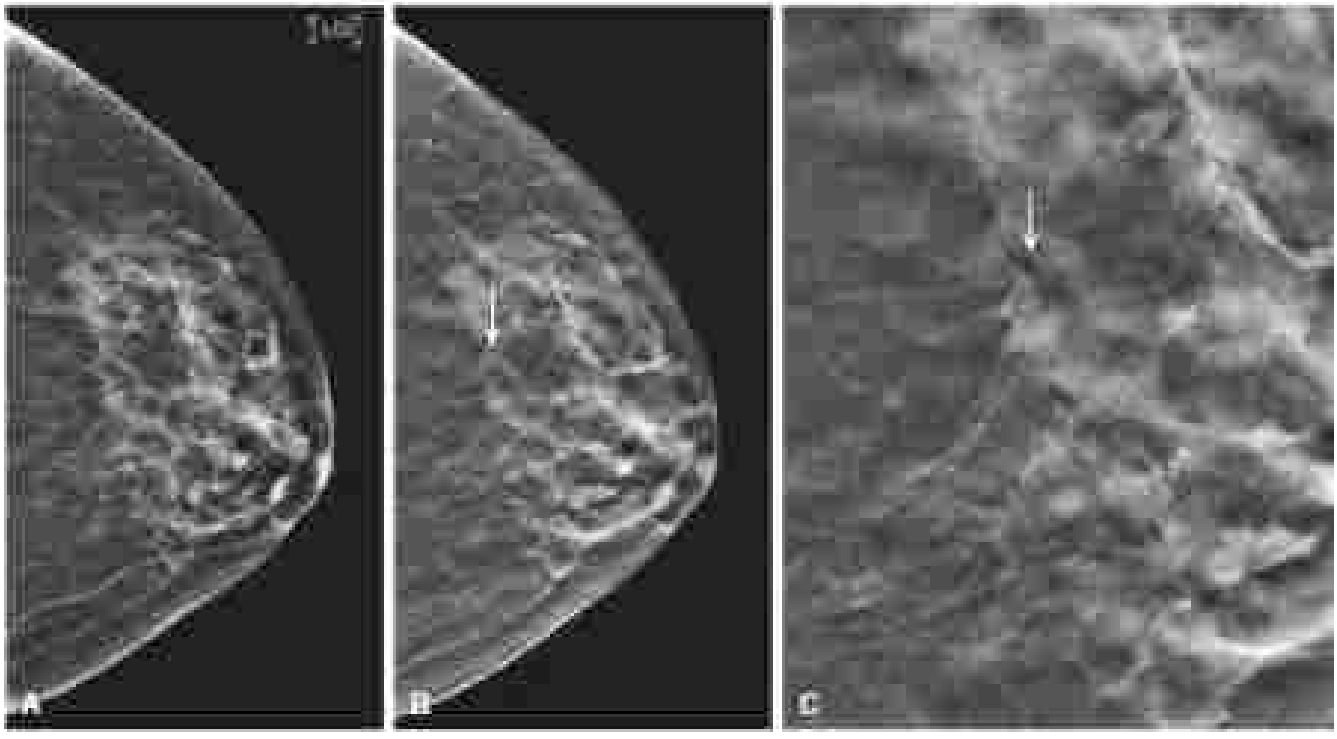
MOLECULAR TARGETS IN BREAST CANCER

Meredith O. Wittke, MD, Helen Kourlaba, MD, Kirby L. Bland, MD, FACS, and Rachael B. Jacobstein, MD

Breast cancer, the most frequently diagnosed non-skin cancer in women is named based on a single tissue of origin, however, breast cancer is a heterogeneous disease with a multitude of presentations, prognoses, and treatments. Although most women with breast cancer have an excellent prognosis, many women will die from this disease. Breast cancer remains the second leading cause of death among women in the United States, reflecting the systemic aggressiveness of many of these tumors. Understanding tumor biology is critical to providing appropriate, personalized, and comprehensive cancer care. A thorough understanding of molecular profiling, breast cancer subtypes, and targeted drug therapies is both key to providing complete breast cancer care and clinically relevant to surgeons.

MOLECULAR PROFILING

Previously, breast cancer heterogeneity was defined in terms of anatomic staging (American Joint Committee on Cancer tumor node metastasis) and histologic appearance (ductal vs lobular, grade, lymphovascular invasion, etc.). These characteristics provided prognostic information on treatment response, risk of recurrence, and survival. However, molecular characteristics of tumors provide further and more specific characterization offering additional information regarding prognosis and tailored treatment options.



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Schrading S, Distelmaier M, Dirrichs T, et al. Digital breast tomosynthesis-guided vacuum assisted breast biopsy: initial experiences and comparison with prone stereotactic vacuum assisted biopsy. Radiology. 2015;276(3):644–652.

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Meredith O. Wittke, MD, Helen Krontiras, MD, Kirby I. Bland, MD, FACS, and Rachael R. Lancaster, MD

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TABLE 1 Breast Cancer Intrinsic Subtypes

Subtype	Characteristics	Markers
Luminal A	Low grade High ER ~80% of all breast cancer Good prognosis	ER+, PR+, HER2- Low Ki-67 (<14%)
Luminal B	Higher grade Lower ER ~20% of all breast cancer Poorer prognosis than luminal A	ER+, PR+/-, HER2 +/- High Ki-67 (>14%)
HER2 enriched	High grade Often node positive *TP53* mutations ~10%–15% of all breast cancer	ER-, PR-, HER2+
Basal like	High proliferation *BRCA* dysfunction ~15%–20% of all breast cancer Poor prognosis	ER-, PR-, HER2- CK5/6+ Or EGFR+

CK, Cytokeratin; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.

In 2000, Perou and colleagues first described intrinsic breast cancer portraits, or molecular classifications based on microarrays and hierarchal cluster analysis. These subtypes are essential to determining the surgeon's management and timing of surgical intervention of breast cancer. The four major molecular portraits are (1) estrogen receptor (ER)–positive, (2) basal like, (3) human epidermal growth factor receptor 2 (HER2) enriched, and (4) normal like. ER positive tumors are further divided into luminal A and luminal B subtypes. Complete molecular profiling is not feasible on individual patients; therefore, immunohistochemically defined surrogates were developed, and are generally comparable with the genomic profile (Table 1).

LUMINAL SUBTYPES

The majority of breast cancers are classified within the luminal subtypes are generally low grade with a favorable prognosis. The term *luminal* indicates a similar molecular expression of these tumors when compared with the epithelium of normal breast tissue. The two main ER positive subtypes are divided into luminal A and luminal B, which have different gene expressions, prognosis, and treatment responses.

Luminal A breast cancers express high levels of ER and demonstrate the best response rate to endocrine therapy. They represent the most common subtype (80%) and have the best prognosis compared with other breast cancer subtypes. Luminal B breast cancers are less common (20%) and, although they still have a good overall prognosis, they demonstrate more aggressiveness and a worse prognosis compared with luminal A tumors. Luminal B tumors display a higher grade, lower levels of ER positivity, and higher expression of the proliferation cluster (Ki-67) compared with luminal A tumors. In accordance with the lower ER expression, their response to endocrine therapy is lower than luminal A tumors; however, their response to traditional chemotherapy is superior to luminal A tumors. When compared with basal like and HER2 enriched tumors, luminal B tumors have a superior prognosis.

TABLE 2 Treatment According to Breast Cancer Subtype

Subtype	Treatment Response and Prognosis
Luminal A	Responds to endocrine therapy • Premenopausal: ER—Mx (amenorrhea) • Postmenopausal: AIs (exemestane, anastrozole, letrozole)
Luminal B	Response to endocrine therapy lower Response to chemotherapy greater than luminal A
HER2 enriched	Responds to anti-HER2 agents (trastuzumab, pertuzumab, lapatinib)
Basal like	No response to endocrine therapy or anti-HER2 agents Chemotherapy only treatment outside of a clinical trial

AI, Aromatase inhibitors; HER2, human epidermal growth factor receptor-2; SERMs, selective estrogen receptor modulators.

ER SIGNALING PATHWAYS

In 1896, Beatson first reported the regression of advanced breast cancer by removing the ovaries in premenopausal patients with this disease. Currently, it was noted, that oophorectomy only benefited approximately one third of women with breast cancer; for other women with breast tumors, there seemed to be no benefit to oophorectomy. In the 1970s, Jensen and colleagues described determining the presence of the ER within breast tumors and furthermore demonstrated that ER rich tumors were more likely to respond to endocrine modification than those with ER poor breast tumors.

The ER, a member of the steroid hormone receptor superfamily, is a ligand dependent transcription factor. The transcription factor is composed of two receptors, the ER alpha receptor and the estrogen beta receptor, both binding with high affinity to the ligand estrogen. When estrogen binds to the receptor, dimerization occurs and facilitates interaction of the receptor with promoter regions in the DNA.

In clinical practice, the assays used to define ER expression measure ER alpha levels, referred to as the classic ER. ER positivity is traditionally quantitatively with immunohistochemistry (IHC). Almost 65% of ER positive tumors are also progesterone receptor (PR) positive. The level of expression of ER is used to predict response to endocrine therapy. Approximately 70% of ER/PR positive breast cancers respond to endocrine therapy. A small percentage of breast cancers are ER negative/PR positive, and some of these tumors have shown a response with endocrine therapy, suggesting downstream endocrine pathway activation.

Endocrine therapy is administered with either selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) (Table 2). SERMs are competitive ER antagonists in breast tissue but act as partial agonists in other tissues. The most common and widely used SERM for breast cancer treatment, tamoxifen, was introduced in 1977. Tamoxifen competitively inhibits the binding of estradiol to estrogen receptors in the breast but has agonist activity in endometrial tissue.

Tamoxifen reduces the risk of breast cancer recurrence and death in premenopausal and postmenopausal women with ER positive tumors. A number of landmark trials have investigated the safety and efficacy of tamoxifen in the adjuvant setting. The Early Breast Cancer Trialists' Collaborative Group meta analysis included 18,445 patients from randomized trials and found that tamoxifen

reduced the 15-year probability of breast cancer recurrence and breast cancer mortality. These results led to establishing 5 years of adjuvant tamoxifen in premenopausal women with ER-positive breast cancers.

In 1982, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 performed a randomized, double-blind, placebo-controlled trial in 2800 patients with primary operable, ER-positive, and lymph node–negative breast cancer to determine the effectiveness of adjuvant tamoxifen therapy. Disease-free survival was prolonged significantly through 10 years of follow-up in women treated with tamoxifen (69%) versus placebo (57%). There was also a 37% relative reduction in the cumulative incidence of a second primary breast cancer in the contralateral breast at 10 years of follow-up, 3.8% for tamoxifen-treated patients versus 6.1% for those on placebo ($P = .007$).

Tamoxifen is an oral drug taken daily (20 mg) with side effects commonly including hot flashes and vaginal dryness or discharge. The more severe side effects are rare and include thromboembolic events and development of endometrial cancer. The majority of the risk related to development of endometrial cancer is carried by postmenopausal women taking tamoxifen. With a risk of less than 1% per year, postmenopausal women taking tamoxifen should be monitored for symptoms of endometrial hyperplasia or cancer such as vaginal bleeding or spotting.

With a different mechanism of action than SERMs, AIs are the endocrine therapy of choice for postmenopausal patients with ER-positive tumors. The AIs currently approved in the clinical setting include exemestane, anastrozole, and letrozole. AIs block the conversion of adrenally synthesized androgens to estrogens, the final step in steroid conversion to the active form of the hormone. AIs do not alter the estrogen production from the ovary and are therefore contraindicated as single agent endocrine therapy in premenopausal women, but AIs can be administered to premenopausal women with ovarian function suppression (OFS) therapy. Reported in 2014, the combined results from the Tamoxifen and Exemestane Trial and the Suppression of Ovarian Function Trial demonstrated an improved disease-free survival in premenopausal women with ER-positive breast cancer who were treated with exemestane and OFS compared with tamoxifen and OFS. AIs are superior to tamoxifen for postmenopausal women displaying improved effectiveness and lower toxicity. Prospective randomized trials show the risk of local recurrence is reduced and disease-free survival is improved with AIs compared with tamoxifen. The Arimidex, Tamoxifen, Alone or in Combination trial studied ER-positive breast cancers in postmenopausal women by comparing anastrozole with tamoxifen, alone or in combination. The trial evaluated 9366 postmenopausal women with localized breast cancer. Anastrozole significantly prolonged disease-free survival and time to recurrence, in addition to reduced distant metastases and contralateral breast cancers. Almost all patients completed their scheduled treatment, with fewer withdrawals from anastrozole than tamoxifen. Anastrozole had fewer gynecologic and vascular events, but myalgia, arthralgia, and fractures were more common.

Extended Adjuvant Hormone Therapy

The typical ER-positive breast cancer recurrence occurs in a delayed fashion (15–20 years or more after diagnosis). Several studies investigated and showed value in extending endocrine therapy from 5 to 10 years. Ongoing trials are analyzing the impact of an initial 5 years of tamoxifen or an AI followed by another 5 years of an AI, as well as the concept of continuous versus intermittent extended AI therapy. In the Adjuvant Tamoxifen Longer Against Shorter trial, 6846 women with ER-positive breast cancer who had completed 5 years of tamoxifen were randomly assigned to either stop tamoxifen or continue tamoxifen for another 5 years. A reduction in breast cancer recurrence and mortality was observed in the group that took tamoxifen for an additional 5 years suggesting that 10 years of tamoxifen can reduce breast cancer mortality by one half in the second decade after diagnosis. The 20-year outcomes from the Adjuvant Tamoxifen Longer Against Shorter trial will be reported in 2018.

Endocrine Resistance

Although endocrine therapy is the most effective treatment for ER-positive breast cancers, the outcomes are limited by significant rates of both de novo resistance and resistance acquired during treatment. Methods of overcoming endocrine resistance include optimizing the schedule and dose of endocrine therapies, in addition to combining different agents. For example, the Southwestern Oncology Group (SWOG) S0226 trial showed anastrozole plus fulvestrant to be superior to anastrozole alone in terms of progression-free survival and overall survival. Endocrine resistance can also be addressed by understanding, identifying, and targeting crosstalk between ER and other signaling pathways, such as HER2, cyclin-dependent kinase, and phosphatidylinositol 3-kinase/mammalian target of rapamycin. This strategy becomes particularly important in the setting of stage IV disease. Largely because of results from the Evaluation in Combination With Exemestane in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole II phase III clinical trial, the US Food and Drug Administration (FDA) has approved everolimus (mammalian target of rapamycin inhibitor) in combination with exemestane for the treatment of ER-positive/HER2-negative women who have recurrence or progression after anastrozole or letrozole therapy.

Targeted Treatment Through Gene Expression

With a greater understanding of tumor biology and molecular signatures, breast cancer treatments focus on characteristics of the individual tumor leading to appropriately administered chemotherapy in the high-risk ER-positive patient and avoidance of overtreatment in the low-risk ER-positive patient. Prognostic breast cancer tests based on gene expression profiling have been developed and are used in today's clinical setting to select patients that will obtain benefit from chemotherapy. Genetic expression profile analysis is covered by most insurance carriers. These assays are typically used in ER-positive/HER2-negative, node-negative breast cancers as an adjunct to other prognostic markers. Current National Comprehensive Cancer Network breast cancer guidelines recommend the use of gene expression profiles in patients with ER-positive, node-negative breast cancers to assess the benefits of additional therapy.

First described in 2004, Oncotype Dx (Genomic Health) is a multigene assay to predict recurrence of ER-positive breast cancers. Using reverse transcriptase polymerase chain reaction assay of 21 genes (5 reference genes and 16 cancer-related genes) in formalin-fixed, paraffin-embedded tumor tissue, Paik and colleagues used tissue samples collected from patients with node-negative, tamoxifen-treated breast cancer enrolled in NSABP B-14 to generate individual risk of recurrence. An individualized risk estimate or recurrence score (RS) of 0 to 100 is provided for each tumor sample: low risk, less than 18; intermediate risk, 18 to 30; and high risk, 31 or greater (Fig. 1). A low RS indicates that hormone therapy alone is adequate treatment. A high RS shows a high-risk patient who would benefit from chemotherapy followed by hormonal therapy. Studies have shown that associations of RS with survival are independent from standard clinicopathologic factors. Published in 2018, the Trial Assigning Individualized Options for Treatment (Rx) randomized 6711 patients with node-negative, ER-positive breast cancer with an RS of 11 to 25 randomly assigned to chemotherapy followed by endocrine therapy

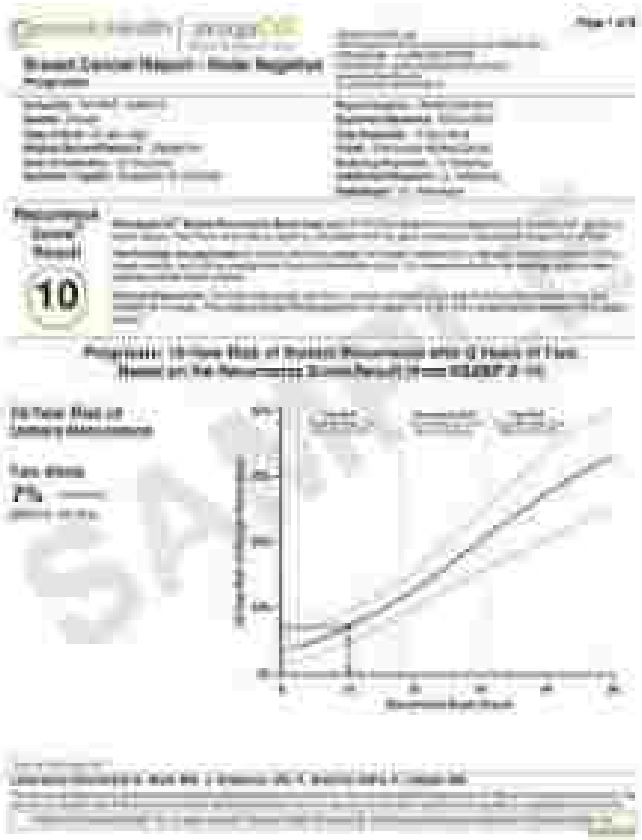

FIG. 1. Sample oncotype DX individual recurrence score (RS). The report shows an RS score on a scale of 1 to 100, which corresponds with a likelihood of distant recurrence at 10 years based on the average 10-year distant recurrence rate for that RS in the clinical trial population. Note that the clinical trial population was created with ... *(Oncotype DX and the genomic Score are in various trademarks of Genomic Health, Inc. Reproduced with permission.)*

versus endocrine therapy alone. Results showed that in women older than 50 years of age with RS 11 to 25 endocrine therapy alone was noninferior to combination of chemotherapy and endocrine therapy. Disease-free survival was similar between the two groups, and the overall survival was approximately 93% for both groups. Disease-free survival was affected with the combination of RS and age, however, with women younger than 50 years and an RS of 11 to 25 showing some benefit from chemotherapy. Investigators are also testing the value of the 21-gene assay in ER-positive, node-positive breast cancers. Retrospective studies such as the SWOG 8814 trial have investigated the prognostic utility of the 21-gene recurrence score in ER-positive, node-positive breast cancer. In this retrospective analysis, a low RS predicted little benefit from chemotherapy despite positive lymph nodes; high RS predicted significant benefit from chemotherapy. Studies have also shown this information has already changed clinical practice, with clinicians being influenced by the RS in node-positive patients before prospective data have been reported. Currently, the ongoing prospective SWOG RS for Positive Node, Endocrine Responsive Breast Cancer trial aims to answer the question regarding utility of RS in the setting of positive lymph nodes. Women with ER-positive/HER2-negative breast cancer with one to three positive nodes and an RS of 25 or lower are currently being enrolled and randomly assigned to chemotherapy followed by hormonal therapy versus hormonal therapy alone.

Other commercially available genomic assays include MammaPrint (Agendia) and PAM50 (Prosigna). MammaPrint is a 70-gene microarray assay performed originally only on freshly collected tissue, now also FDA-approved with formalin-fixed, paraffin-embedded tissue. Analysis of tumor generates a low-risk or high-risk result (without an intermediate group) to provide assistance with determining the benefit of adjuvant chemotherapy in selected patients with ER-positive or ER-negative disease. The Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy trial evaluated women with T1 to T2 operable disease and up to three positive lymph nodes. Total accrual of 6693 patients and patients with high clinical risk and high genomic risk went on to receive chemotherapy. Women with low clinical risk and low genomic risk received endocrine therapy alone; however, 1550 were deemed high clinical risk and low genetic risk. At 5 years, the rate of survival without metastatic disease in those who did not receive chemotherapy was 94.7%. The absolute difference between the two groups was 1.5 percentage points and was lower than the group receiving chemotherapy, indicating that 6% of women with breast cancer at high clinical risk may not require chemotherapy. PAM50 provides a Prosigna Score (0–100) with formalin-fixed, paraffin-embedded tissue. Prosigna is indicated for use in postmenopausal women with ER-positive, node-negative breast cancers.

HER2-Enriched

HER2-enriched tumors account for only 10% to 15% of all breast cancers. This subtype is characterized by high expression of HER2

TABLE 3 HER2 Immunohistochemistry (IHC) Result Interpretation

Staining Pattern	Score	Assessment
No observable staining, or membrane staining that is incomplete and is faint/barely perceptible in <10% of invasive tumor cells	0	Negative
Incomplete membrane staining that is faint/barely perceptible in >10% of invasive tumor cells	1+	Negative
Circumferential membrane staining that is incomplete and/or weak/ moderate in >10% of invasive tumor cells, or complete and circumferential intense membrane staining in <10% of invasive tumor cells	2+	Weakly positive (equivocal)
Homogeneous, dark, circumferential (chicken wire) pattern in >10% of invasive tumor cells	3+	Positive

HER2, Human epidermal growth factor receptor 2; IHC, immunohistochemistry.

TABLE 4 HER2 FISH Result Interpretation

	Copy Number	Ratio
Positive	>4.0	≥2.0
	<2.0	≥2.0
	≥6.0	<2.0
Negative	<4.0	<2.0
Equivocal	≥4.0 or <6.0	<2.0

HER2, Human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization.

and proliferation gene clusters but low expression of the luminal cluster; these tumors are typically HER2 positive and ER/PR negative. However some are also ER positive and included in the luminal B subtype. Before HER2 targeted therapy this subtype was associated with a short time to relapse, decreased overall survival, and carried a poor prognosis. HER2 overexpression is an independent poor prognostic indicator. HER2 should be tested on all invasive breast cancers because of its significant implications for prognosis and treatment. HER2 status can be determined through IHC testing or fluorescence in situ hybridization (FISH). In the United States, 80% to 90% of testing is done with IHC with confirmatory FISH testing for equivocal results (Tables 3 and 4).

HER2-Targeted Therapy

Four receptors make up the epidermal growth factor receptor (EGFR) family: HER1 (ERBB1/EGFR), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). These receptors are transmembrane proteins, and the best characterized of the EGFR family is HER2. The HER2 gene, also known as *HER2/neu* or *ERBB2*, is a proto-oncogene located on chromosome 17q21 and encodes a transmembrane protein composed of a ligand-binding extracellular domain and an intracellular tyrosine kinase domain. Normally, HER2 is expressed at a low level on the surface of epithelial cells and is necessary for the development of many tissues; however, the subset of breast cancer is characterized by an amplification or overexpression of the HER2 receptor on tumor cells.

Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody directed against the extracellular domain of the HER2 protein. Approved in 1998 for the treatment of metastatic breast cancer, trastuzumab significantly improved patients' outcomes and paved the way for developing targeted approaches in adjuvant breast cancer treatment. Several randomized controlled trials (NSABP B-31, North Central Cancer Treatment Group N9831, BCIRG 006, Finland Herceptin) using trastuzumab as adjuvant therapy have shown significantly improved disease-free and overall survival. As a result, current guidelines for patients with HER2 positive tumors include giving adjuvant trastuzumab with chemotherapy for tumors larger than 1 cm in diameter and node positive disease. In addition, trastuzumab should be considered for patients with tumors between 5 and 10 mm and micrometastatic nodal disease. The optimal duration of trastuzumab was determined through clinical trials to be 1 year of therapy.

Pertuzumab (monoclonal antibody directed at a different site of the HER2 extracellular domain) was approved in 2012 for use in metastatic HER2 positive breast cancers in combination with docetaxel and trastuzumab, based on results from the Neo*Sphere phase II study demonstrating that pertuzumab increased pathologic complete response rate; however, the FDA subsequently approved the use of pertuzumab in combination with trastuzumab and chemotherapy for early stage HER2 positive breast cancers in the neoadjuvant setting.

Overcoming HER2 Resistance

Primary or acquired resistance to trastuzumab is a major obstacle to the clinical management of HER2 positive breast cancers. Approximately 15% of patients relapse after therapy with trastuzumab. In understanding the mechanisms of trastuzumab resistance, new anti-HER2 agents are emerging as treatment alternatives. Antibody drug conjugates (T-DM1) consisting of the monoclonal antibody trastuzumab linked to the cytotoxic agent emtansine (DM1) are another emerging type of anti-HER2 targeted therapies. Lapatinib (oral, reversible, small molecule dual inhibitor of both HER1 [EGFR] and HER2 tyrosine kinases) for use in combination with capecitabine in trastuzumab refractory, HER2 positive, metastatic breast cancers was approved in 2007. However, thus far, randomized controlled trials have not shown any benefit in comparing trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2 positive metastatic breast cancer previously treated with trastuzumab and taxanes. Current trials are investigating dual blockade and the potential synergistic effect of different combinations of both new and approved targeted HER pathway blockers to determine if chemotherapy may be avoided.

BASAL-LIKE

The basal-like subtype has a gene cluster profile similar to basal epithelial cells and is characterized by low expression of the luminal and HER2 gene clusters. Basal-like breast cancers have a high expression of EGFR and basal epithelial cytokeratins (CK) CK5/6, CK14, and CK17. Typically these tumors are ER, PR, and HER2 negative and are termed triple negative breast cancer (TNBC). The American Society of Clinical Oncology/College of American Pathologists guidelines used to define TNBC include lack of ER/PR (<1%) and HER2 expression (0 or 1+) by IHC and confirmation of HER2 status by FISH if indeterminate (2+) by IHC. The terms basal-like subtype and TNBC often are used interchangeably but they are not completely synonymous. For example, 20% of basal-like tumors

are not triple negative, and 23% of TNBCs are composed of other messenger RNA subtypes. TNBC is the clinical surrogate for the basal-like subtype.

TNBC accounts for about 10% to 20% of all breast cancers and is biologically the most aggressive. TNBC frequently affects younger patients (<40 years) and is more prevalent in African American women than in other demographic groups. These tumors tend to be larger, palpable, higher grade, and more often seen as interval cancers occurring between mammogram screenings; therefore, TNBC is associated with a higher relapse rate and a poorer survival rate than non-TNBC. Distant metastases typically occur at visceral sites rather than bone and often present within the first 3 years after diagnosis.

Triple-Negative Paradox

Triple-negative tumors lack estrogen and HER2 expression without current available targeted therapies. The standard of care for TNBC is anthracycline- and taxane-based combination chemotherapy (Table 2). Although patients with TNBC have a poor overall prognosis, their primary tumors are more sensitive to chemotherapy (higher pathologic complete response [pCR]) than luminal subtype breast cancers. This is termed the "triple-negative paradox." Although there is no overall survival advantage to receiving neoadjuvant versus adjuvant chemotherapy, it provides a surrogate marker for patients with TNBC who achieve pCR. Approximately 20% to 45% of TNBCs achieve pCR after anthracycline- or anthracycline/taxane-based treatments. Studies investigating the impact of pCR on overall survival in TNBC versus non-TNBC found that if pCR is achieved, patients with TNBC and non-TNBC have similar survival rates. However, TNBC patients with residual disease have a poor outcome, with a higher risk of relapse.

Triple-Negative Subtypes

Investigators recently have identified six different TNBC subtypes each displaying unique biology, and these subtypes have been found to be an independent predictor of pCR status. There are actually few overlapping gene mutations within the subtypes of TNBC with the exception of germline *BRCA1* mutations. The subtype genetic mutations differences are thought to drive the strikingly different responses to chemotherapy and progression of disease seen among these types of tumors. There are two basal-like subtypes, a mesenchymal subtype, a mesenchymal stem-like, an immunomodulatory type, and a luminal subtype driven by androgen signaling (luminal androgen receptor). Different cell types have different sensitivities to targeted therapeutic agents. Analysis of distinct gene expression signatures and the results of current clinical trials will assist in the selection of initial neoadjuvant chemotherapy regimens and ongoing treatment for those patients who do not achieve pCR.

Potential Targets for TNBC

There is ongoing research to identify potential targets within the subtypes of TNBC to deliver more targeted therapy. The Cancer Genome Atlas network discovered that basal-like breast cancers are more similar to high-grade serous ovarian cancer on the genomic level than to other subtypes of breast cancer. Approximately 20% of basal-like tumors had germline or somatic *BRCA1/BRCA2* mutations, suggesting shared driving events of basal-like breast cancer and serous ovarian cancer; therefore, TNBC lacking functional *BRCA1/BRCA2* might benefit from poly(ADP-ribose) polymerase inhibitors (olaparib, niraparib, rucaparib). Given the clinical similarities between sporadic TNBC and *BRCA1* mutation–associated breast cancer, it has been suggested that sporadic TNBC also may possess underlying DNA repair defects and demonstrate similar chemosensitivity, resulting in renewed interest in platinum agents. A subset of triple-negative breast cancers express androgen receptors. Enzalutamide, an androgen receptor inhibitor, has been studied and shown clinical activity and tolerability among patients with metastatic disease. Research and treatment recommendations regarding the androgen receptor and its role in triple-negative breast cancer is ongoing. Immune checkpoint inhibition is another potential future therapy for triple-negative breast cancer. The Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors, a multicenter nonrandomized phase Ib trial of single-agent pembrolizumab given to patients with TNBC as well as gastric, urothelial, and head and neck cancers. Subsequent analysis of the TNBC subset showed that there was clinical activity with an acceptable safety profile.

FUTURE DIRECTION AND CONCLUSIONS

Through the discovery of cell receptors and molecular subtypes, there is a better understanding of tumor biology. Breast cancer subtypes provide prognostic information and direct therapeutic treatments. Gene expression profiling assays in the clinical setting provide personalized breast cancer care. Current investigations regarding immunotherapy in breast cancer are ongoing and will be an area of interest in the future. New therapies are needed to address resistance to current targeted drugs and lack of tailored therapy for TNBC. Surgeons caring for breast cancer patients should be well versed in the importance of tumor subtypes and their effect on treatment.

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Breast Cancer: Surgical Therapy

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Surgery is a crucial element in the multidisciplinary treatment of breast cancer. The main benefits of surgery are to achieve locoregional control of the existing disease and to reduce the risk of locoregional recurrence. Surgery is most effective in achieving these goals when used in conjunction with systemic therapy and radiation. Since the era of the Halsted radical mastectomy, first performed in 1882 and the standard of care until the 1970s, the surgical management of breast cancer has changed dramatically. Over time, there has been a trend toward minimizing surgery in both the breast and axilla, with no detrimental effect on survival. This is due in large part to the significant advances in systemic therapy and radiation, both of which contribute to decreased rates of locoregional recurrence. Moreover, improvements in systemic therapy have led to enhanced long-term prognosis and survival. Thus, in the contemporary era, patients with breast cancer will often have an array of surgical options to choose from.

DIAGNOSIS OF BREAST CANCER

With screening mammography, many breast cancers are detected before they are palpable by the patient or by a physician on clinical examination. Imaging abnormalities, such as suspicious calcifications or a speculated mass, should undergo core needle biopsy for tissue diagnosis. If malignancy is identified, pathology from the core needle biopsy will provide information regarding in situ versus invasive cancer, the type of cancer such as ductal versus lobular, the grade of the cancer, and the receptor status (estrogen, progesterone, and human epidermal growth factor receptor 2 [HER2]). This information helps to guide decisions regarding surgery as well as other therapies.

Once a diagnosis of cancer is obtained, further imaging workup may be necessary to evaluate the extent of disease. In addition to mammography, other imaging modalities that could be used include ultrasound (US) of the breast, axillary US if there is a concern on clinical examination for axillary nodal involvement, and breast magnetic resonance imaging (MRI) if the extent of disease is difficult to define by mammography and US.

A clinical stage is assigned based on the size of the largest tumor in the breast and the clinical axillary nodal status. For patients with clinical stage III breast cancer and any patients with signs/symptoms of possible metastatic disease, a computed tomography (CT) scan of the chest/abdomen/pelvis plus a bone scan or a positron emission tomography (PET) should be performed to evaluate for distant metastatic disease.

DISCUSSION OF SURGICAL OPTIONS

For patients with early stage breast cancer (clinical stage I or II), surgery is typically the first step in treatment. The pathology results from surgery are then used to inform decisions regarding adjuvant systemic and/or radiation therapy. With respect to surgical management of the cancer in the breast, the two main options are breast conservation (lumpectomy plus radiation) versus mastectomy. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 was a large, prospective randomized trial that demonstrated no difference in overall survival when comparing lumpectomy plus radiation versus mastectomy. The risk of local recurrence after lumpectomy plus radiation is a little higher than after mastectomy, but the risk of local recurrence after mastectomy is not zero. With modern systemic therapies and delivery of adjuvant radiation, the risk of local recurrence after lumpectomy and radiation is approximately 5% to 8%. The risk of local recurrence after mastectomy is approximately 2%.

Deciding between lumpectomy plus radiation versus mastectomy is often a very difficult choice for many patients. In some cases, mastectomy is necessary because of the presence of multicentric disease or due to prior radiation to the ipsilateral breast or chest wall. In other cases, the size of the tumor in relation to the size of the breast makes lumpectomy a less cosmetically desirable choice. But for many women with early stage breast cancer, they will have the option for either lumpectomy or mastectomy. It is the role of the surgeon to discuss both options in detail, with the associated pros and cons. It is important to emphasize that the long-term prognosis and overall survival are equivalent with lumpectomy plus radiation versus mastectomy, and that decisions about systemic therapy are completely independent of the type of surgery performed. Recommendations regarding chemotherapy, HER2 targeted therapy, and hormone blocking therapy are based on the characteristics of the tumor itself, and the type of surgery performed has no bearing on these recommendations. Adjuvant radiation therapy is recommended following lumpectomy but is sometimes omitted in women older than 70 with hormone sensitive tumors <2 cm in size. As demonstrated in the Cancer and Leukemia Group B (CALGB) 9343 trial, receiving radiation in addition to hormone blocking therapy does not improve overall survival, but adding radiation does contribute to a lower risk of local recurrence in this subset of patients (2% vs 9% at 10 years). Following mastectomy, radiation is indicated for women with tumors larger than 5 cm, positive margins, or evidence of axillary lymph node involvement.

Other factors that may affect surgical decision-making include a strong family history of breast cancer, a genetic predisposition to breast cancer (such as BRCA, p53, PTEN, or PALB2 mutation carrier), a personal history of prior chest wall radiation, or a history of lobular carcinoma in situ or atypia. A thorough family history should be obtained from the patient to determine eligibility for genetic testing. In general, any woman diagnosed with breast cancer before age of 50 (or with triple negative breast cancer before age of 60), woman diagnosed with breast cancer at any age who have a strong family history of breast and/or ovarian cancer, woman diagnosed with breast cancer who are of Ashkenazi Jewish descent, and any male diagnosed with breast cancer should be referred for genetic counseling and testing. Appropriate surgical management of the current breast cancer should be paramount, but it is also important to take into consideration the risk of development of a new primary breast cancer (either in the ipsilateral or contralateral breast). Women with a substantially elevated risk of developing another breast cancer in the future may opt for a more aggressive risk reducing surgical approach, such as bilateral mastectomy.

LUMPECTOMY

The goal with lumpectomy is to remove the area of malignancy with clear or negative margins. For nonpalpable lesions, preoperative localization is performed with a wire (Fig. 1), radioactive seed, or other device. Incision placement can vary according to the location of the lesion. If feasible, a periareolar incision may allow for a less noticeable scar and be more cosmetically appealing. If the location of the lesion dictates placement of the incision elsewhere on the breast, following the skin tension lines can guide the location and shape of the incision. This may result in a curvilinear incision in the upper outer and lower outer quadrants, horizontal incisions in the upper inner and lower inner quadrants, and radial incisions at the 3 and 9 o'clock positions. Confirmation of successful retrieval of the lesion is generally assessed with intraoperative specimen radiograph of the lumpectomy specimen. Recent American Society for Radiation Oncology (ASTRO) consensus guidelines for appropriate margins in the setting of lumpectomy are an inked surface of the lumpectomy specimen

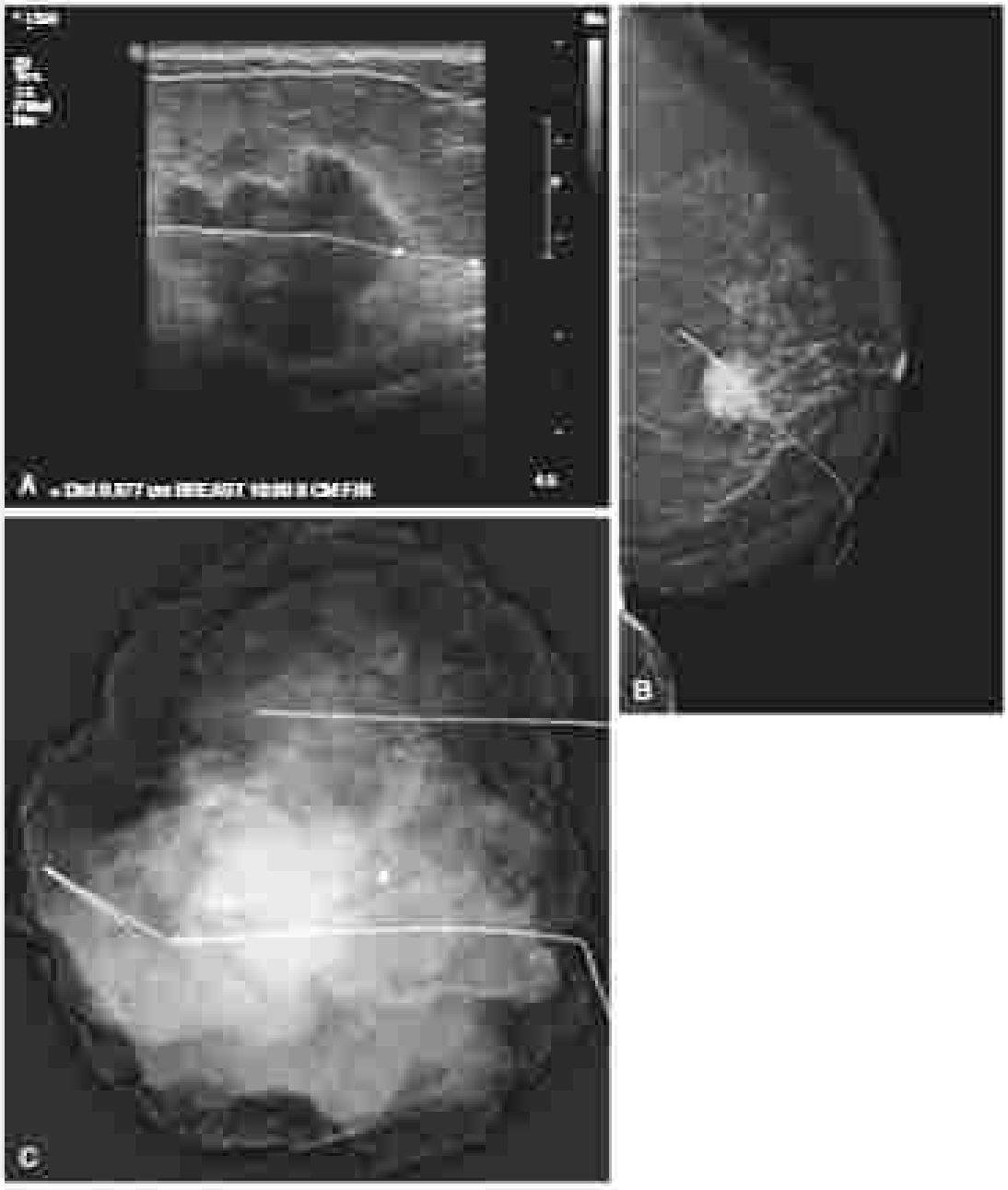

FIG. 1 W [illegible] Lumpectomy (A) A [illegible] with a guidewire [illegible] (B) [illegible] (C) [illegible]

for invasive cancer and a 2 mm margin for ductal carcinoma in situ. Wider margins have not been shown to reduce the risk of local recurrence, assuming appropriate adjuvant radiation and systemic therapies are delivered. If margins are positive following lumpectomy, then reexcision to achieve negative margins is indicated. The number of reexcisions that can be attempted if margins are persistently positive will depend on the volume of tissue already resected in relation to the breast size, as well as the number of positive margins requiring reexcision. If margins are persistently positive despite attempts at reexcision, then completion mastectomy is indicated.

Some surgeons will perform shave margins of the lumpectomy cavity after the lumpectomy specimen has been resected. Shave margins sample the six faces of the lumpectomy cavity and are considered to represent the final margins. Shave margins have been shown to reduce the risk of positive margins and need for reexcision by approximately 50%. Additional separate microscopic foci of disease are found in the shave margins about 12% of the time and may be indicative of a multifocal disease process that was not previously identified by imaging.

Oncoplastic techniques can be used in the setting of lumpectomy for rearrangement of the remaining tissue into the resultant defect, allowing for an improved cosmetic result. For women requiring a very large lumpectomy, or for women with large breasts who desire breast reduction, oncoplastic rearrangement of the affected breast can be performed in conjunction with reduction of the contralateral breast for symmetry.

MASTECTOMY

Mastectomy entails removal of all the breast tissue, which extends to the clavicle superiorly, to the sternum medially, to the inframammary fold inferiorly, and to the latissimus dorsi muscle laterally. Mastectomy can be performed either with or without reconstruction. For a simple mastectomy performed without reconstruction, a large elliptical incision is made encompassing the nipple areolar complex. Enough skin should be resected such that the remaining skin lies flat against the chest wall and the lateral portion of the incision may need to be tailored to resect any redundant skin. A flat chest wall surface following mastectomy without reconstruction aids in the fitting of a breast prosthesis postoperatively.

Mastectomy performed with reconstruction can be done in a skin sparing or nipple sparing fashion. A skin sparing mastectomy includes resection of the nipple and areola but preserves the majority of the skin overlying the breast to allow for reconstruction. A skin-sparing incision commonly consists of a small ellipse including the nipple areolar complex, but can be oriented obliquely or vertically (such as an inverted teardrop). Incision planning should take into account the location of the tumor if it is in close proximity to the skin, and the orientation of the incision should also be planned in concert with the plastic surgeon who will be performing the reconstruction.

Nipple sparing mastectomy is appropriate in some patients and preserves the entire skin envelope of the breast including the nipple and areola. The preferred options for incision placement are typically in the inframammary fold or along the mid-lateral border of the breast. A bi-lateral incision allows for access to the axillary lymph nodes to perform a sentinel lymph node biopsy or an axillary lymph node dissection. Other incisions, such as a lateral horizontal incision, can also be used for a nipple sparing approach. Eligibility for nipple-sparing mastectomy depends on the proximity of the cancer to the nipple, as well as risk factors for poor blood supply to the nipple such as large breast size, significant breast ptosis, current smoking status, and longstanding diabetes. Additional risks inherent to nipple sparing mastectomy include a positive subareolar margin and nipple necrosis, both of which could necessitate removal of the nipple areolar complex at a later date. The subareolar margin is the ductal tissue removed from directly underneath the nipple and sent to pathology for examination separately from the main mastectomy specimen. If there is evidence of malignancy in the subareolar margin, then the nipple should be resected to ensure no disease is left behind.

A modified radical mastectomy includes the removal of the level 1 and 2 axillary lymph nodes in addition to the breast and is indicated for clinically and biopsy proven positive lymph node involvement. A modified radical mastectomy can be performed with or without reconstruction. If immediate reconstruction is performed, a skin sparing or nipple sparing approach can be used. For patients undergoing modified radical mastectomy for inflammatory breast cancer, reconstruction should be performed in a delayed fashion. Radical mastectomies with resection of the entire pectoralis major and minor muscles are rarely performed in the current era, but limited resection of the pectoralis muscle is recommended if there is any evidence of pectoralis muscle invasion identified on preoperative imaging or the operative intraoperatively.

AXILLARY STAGING

The axillary nodal status is important in patients with breast cancer for staging and for decision making regarding adjuvant therapy. Moreover, it carries prognostic implications. For patients with clinically node negative disease, a sentinel lymph node biopsy is the standard of care. A sentinel lymph node biopsy can be performed in conjunction with a lumpectomy or a mastectomy, and sentinel node mapping can be accomplished using blue dye, radioactive tracer colloid radiotracer, or both. Patients who are found to have positive sentinel lymph nodes may or may not need to undergo a completion axillary lymph node dissection. According to the Z0011 trial, patients with T1 to T2 tumors who are clinically node negative and undergoing lumpectomy with sentinel lymph node biopsy do not require a completion axillary lymph node dissection if they are found to have one or two positive sentinel lymph nodes. There is no difference in overall survival or locoregional recurrence in this subset of patients if they undergo a completion axillary dissection versus no further axillary surgery. This suggests that adjuvant radiation and systemic therapies have a significant effect on any potential remaining positive nodes and contribute to effective local control without a completion axillary lymph node dissection.

Z0011 does not apply to patients with three or more positive sentinel lymph nodes, patients undergoing mastectomy, or patients who received neoadjuvant therapy. The After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial included patients undergoing lumpectomy or mastectomy with positive sentinel lymph nodes, and randomized patients to completion axillary dissection versus axillary radiation. There was no statistically significant difference in overall survival or axillary recurrence, but the patients who underwent completion axillary dissection had a twofold increased risk of lymphedema compared with the patients who underwent axillary radiation (10% vs 22% at 1 year and 20% vs 14% at 5 years). The majority of patients in the AMAROS trial (82%) underwent lumpectomy, but 18% of patients did undergo mastectomy; therefore, postmastectomy radiation can be considered in place of completion axillary dissection for patients undergoing mastectomy with a limited number of positive sentinel lymph nodes.

For patients who present with clinically positive axillary lymph nodes, axillary US should be performed. US guided core needle biopsy or fine needle aspiration (FNA) should be performed of any lymph nodes with abnormal features. If malignancy is confirmed on pathology or cytology of needle biopsy of the lymph node, then a level 1 and 2 axillary lymph node dissection is indicated for patients undergoing surgery first. Biopsy proven lymph node involvement, however, warrants consideration of neoadjuvant therapy. Subsequent surgical management of the axilla will then depend on the response to neoadjuvant therapy.

LOCALLY ADVANCED BREAST CANCER

For patients who present with larger tumors and/or lymph node involvement at diagnosis, surgery may not be the first step in treatment. Systemic staging (with either a positron emission tomography CT or CT scan of the chest/abdomen/pelvis plus bone scan) should be performed to rule out the presence of distant metastatic disease. If disease is confirmed to be confined to a locoregional distribution, then neoadjuvant therapy should be considered to downstage the breast as well as the axilla. Repeating imaging with mammography, US and breast MRI following neoadjuvant therapy can assess response to treatment and determine eligibility for certain surgical options. MRI is typically the most sensitive imaging modality for evaluating response to neoadjuvant therapy. If breast conservation is planned, repeat mammography and US are very useful in preparation for localization of any residual imaging abnormality.

Management of the axilla following neoadjuvant therapy is dependent on the nodal status at diagnosis and the response to treatment in the axilla (Fig. 2). For patients eligible for neoadjuvant therapy who are clinically node negative at presentation, axillary US can be performed to confirm normal appearing axillary lymph nodes. In this subset of patients, a sentinel lymph node biopsy should be performed at the conclusion of neoadjuvant therapy. If any indeterminate or suspicious axillary lymph nodes are identified on axillary US, a US-guided FNA or core needle biopsy should be performed for tissue diagnosis. A biopsy clip, preferably a clip that is visible mammographically, should be placed into the lymph node at the time of biopsy. If needle biopsy is negative for malignancy, then a sentinel lymph node biopsy would be recommended at the conclusion of neoadjuvant therapy. As demonstrated in the Sentinel Neoadjuvant (SENTINA)

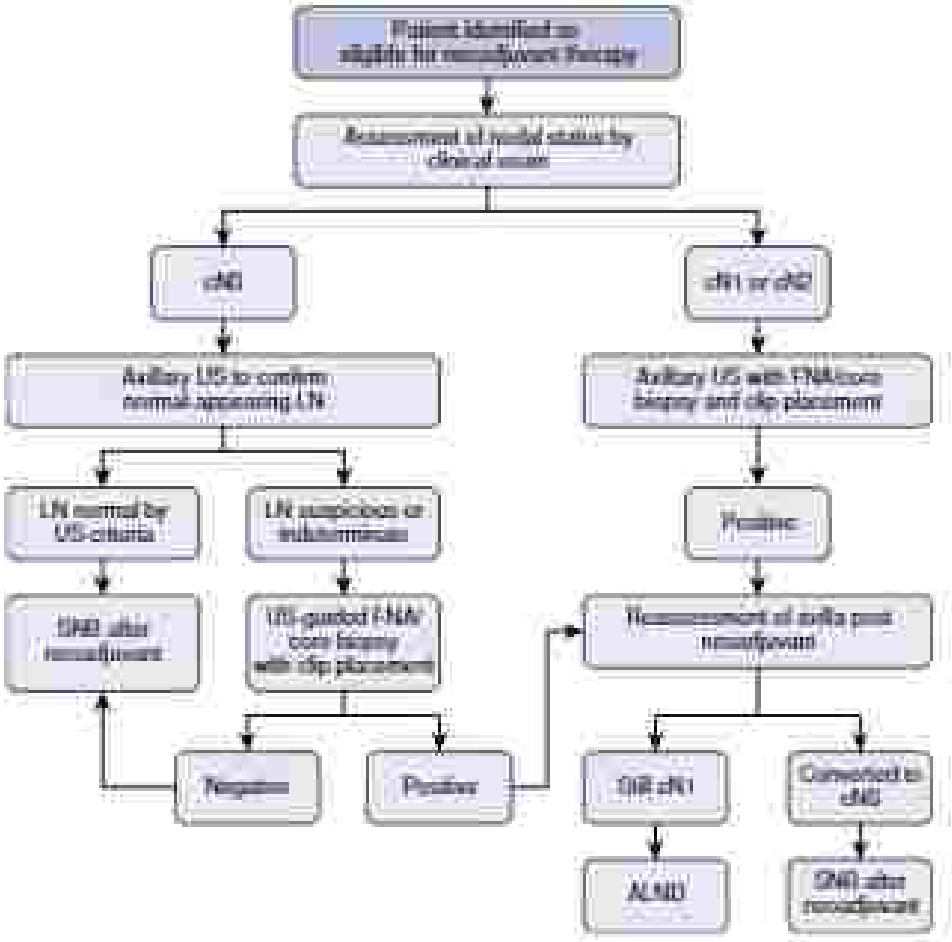

FIG. 2 Schematic diagram depicting management of the axilla for patients receiving neoadjuvant therapy. ALND, Axillary lymph node dissection; LN, lymph node; SNB, sentinel node biopsy.

trial, the false negative rate of a repeat sentinel lymph node biopsy (e.g., a sentinel lymph node biopsy performed before neoadjuvant therapy and then repeated again after neoadjuvant therapy) is unacceptably high. Thus, the preferred approach is to perform a sentinel lymph node biopsy following neoadjuvant therapy in patients who are clinically node negative at diagnosis. If a patient is clinically node negative on examination but needle biopsy of an indeterminate or suspicious axillary lymph node were on US to positive for malignancy, then the axilla should be reevaluated following neoadjuvant therapy to assess response to treatment.

For patients who present with clinically positive axillary lymph nodes at diagnosis, an axillary US followed by an US-guided FNA or core needle biopsy is indicated for tissue diagnosis. A xenographically visible clip should be placed into the lymph node at the time of biopsy. If pathology confirms evidence of lymph node involvement, then the axilla should be reassessed following neoadjuvant therapy. In the setting of persistently clinically positive nodes, an axillary lymph node dissection is recommended. If the axilla has converted to clinically node negative, then a sentinel lymph node biopsy may be appropriate to select patients. Important surgical considerations include the extent of nodal involvement at diagnosis (minimal vs extensive lymphadenopathy), the tumor biology (with respect to the likelihood of achieving a pathologic complete response in the axilla), as well as the clinical and imaging response following neoadjuvant therapy. The surgical technique used during the sentinel lymph node biopsy procedure is also critical to minimize the false negative rate to an acceptable level. As demonstrated by the ACOSOG Z0011 and SENTINA trials, the use of dual tracer (methylene blue dye and technetium sulfur colloid radiotracer), attempting to remove at least 3 sentinel lymph nodes, and successfully retrieving the previously biopsied clipped lymph node all contribute to a lower false negative rate. Approximately 25% of the time, the clipped lymph node is not one of the sentinel lymph nodes. The term "targeted axillary dissection" has been coined to refer to retrieval of the clipped lymph node in addition to the sentinel lymph nodes. Localization options to aid in successful retrieval of the clipped lymph node include use of intraoperative US to identify a sonographically visible biopsy clip, preoperative wire or radioactive seed localization of the clipped lymph node, and injection of tattoo ink into the clipped lymph node to assist in intraoperative visualization.

BREAST CANCER STAGING: AJCC 8TH EDITION

Breast cancer staging, according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging guidelines released in late 2017, is now based on anatomic as well as biomarker information. The standard anatomic TNM criteria apply (T representing the size of the tumor, N representing the number of lymph nodes involved, and M representing the presence or absence of distant metastatic disease), but the new staging guidelines also incorporate biomarkers including the grade of the tumor and the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) receptor status. Oncotype Dx score, if applicable, is also included. If Oncotype Dx has been performed on a T1 or T2 N0, ER+, any PR status, HER2-negative tumor, and the score is less than 11, then the tumor is classified as Stage IA regardless of tumor size. If the Oncotype Dx score is 11 or greater, then the pathologic staging is based on TNM grade, ER, PR, and HER2 criteria. Oncotype Dx is currently the only multigene panel included in the staging system, but others may be added in the future.

TABLE 1 Anatomic Staging Groups, AJCC, 8th Edition, Staging

When T is...	And N is...	And M is...	Then Stage Group is:
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

From Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017. Used with the permission of the American College of Surgeons.

The staging groups in the AJCC staging system are divided into anatomic and prognostic staging groups. The anatomic staging groups are based purely on TNM criteria and should only be used if biomarker information is unavailable (Table 1). The prognostic staging groups are based on TNM criteria and biomarker information, and are further subdivided into clinical prognostic and pathologic prognostic staging groups. Clinical prognostic staging can be used for all patients, regardless of neoadjuvant therapy, and is based on history, physical examination findings, biopsy results, and biomarker information (see example in Table 2). Pathologic prognostic staging is only applicable to patients who undergo definitive surgical resection as their initial treatment (see example in Table 3).

As depicted in Tables 2 and 3, the anatomic and clinical pathologic prognostic stages for a given tumor may differ because of the incorporation of biomarker information. The assigned stage based on clinical/pathologic prognostic staging groups reflects the biology of the tumor and expected prognosis based on treatment with appropriate therapies. Clinical/pathologic staging is therefore preferred, but anatomic staging can be performed in places where biomarker information is not readily available.

SURGERY IN PATIENTS WITH STAGE IV BREAST CANCER

For patients who present with distant metastatic disease at diagnosis, a prompt referral to medical oncology to discuss systemic therapy is indicated. Surgery may or may not be performed, depending on the extent of metastatic disease and the response to systemic therapy. In the setting of oligometastatic disease with an excellent response to systemic therapy, surgery to address the breast primary and locoregional lymph nodes may be contemplated. This approach should involve a multidisciplinary discussion with input from surgery, medical oncology, and radiation oncology. For patients with widespread metastatic disease and/or a poor response to systemic therapy, surgery is sometimes considered for palliation of locoregional progression.

TABLE 2 Clinical Prognostic Stage Groups, AJCC, 8th Edition, Staging

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	...Then Clinical Prognostic Stage Group is:
T0N1M0 T1N1M0 T2N0M0	1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB

TABLE 2 Clinical Prognostic Stage Groups, AJCC, 8th Edition, Staging—cont'd

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	The Clinical Prognostic Stage Group is
T0N1M0	3	Positive	Positive	Positive	IB
T1N0M0			Positive	Negative	IIA
T2N0M0			Negative	Positive	IIA
			Negative	Negative	IIA
		Negative	Positive	Positive	IIA
			Positive	Negative	IIB
			Negative	Positive	IIB
			Negative	Negative	IIB

From Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. Used with the permission of the American College of Surgeons.

By anatomic staging, all of these TNM groups would be classified as stage IIA. With the addition of biomarker information, the Clinical Prognostic Stage ranges from IB to IIB.

TABLE 3 Pathologic Prognostic Stage Groups, AJCC 8th, Edition Staging

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	The Pathologic Prognostic Stage Group is...
T0N1M0	1	Positive	Positive	Positive	IB
T1N1M0				Negative	IIIA
T2N1M0			Negative	Positive	IIIA
T3N1M0				Negative	IIIA
T3N2M0		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

From Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. Used with the permission of the American College of Surgeons.

By anatomic staging, all of these TNM categories would be classified as stage IIIA. With the addition of biomarker information, the Pathologic Prognostic Stage ranges from IB to IIIC.

CONCLUSIONS

Surgery is a key facet in the multidisciplinary treatment of patients diagnosed with breast cancer. Over time, the integration of surgical techniques with advances in radiation and systemic therapies has allowed for less invasive surgical procedures. This has resulted in decreased surgical morbidity for patients, yet overall improved outcomes and survival.

SUGGESTED READINGS

Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

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Giuliano et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA. 2011;305(6):569–575.

Kuehn et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (AM188/B-27): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609–618.

Ablative Techniques in the Treatment of Benign and Malignant Breast Disease

Mariusa Yasa, MD, MSc, and Fernando E. Gaviria, MD, FACS, FRCSEd

Extending the trend toward less invasive treatment, ablative techniques for benign tumors and small breast cancers have continued to progress. Ablative treatments are all image guided percutaneous techniques (using ultrasonography, mammography, magnetic resonance imaging [MRI], or computed tomography [CT]). Complete tumor ablation can be achieved using different types of energy instead of or in addition to immediate or delayed surgical excision. The goal of these ablative techniques is to reduce the complications, decrease morbidity, shorten hospitalization, and improve the cosmetic outcome and quality of life while not increasing recurrence rates. Ablation techniques include radiofrequency ablation (RFA), microwave, laser ablation, electromagnetic waves, cryoablation, and high intensity focused ultrasound.

RFA

RFA is a widely used ablative technique for various solid tumors at different sites, including liver, lung, kidney, and bone. RFA uses low-frequency electromagnetic waves to generate heat and ablate these tumors. To perform RFA, a needle is inserted percutaneously within the tumor, usually with ultrasound guidance, but CT or MRI guidance may be used. A generator creates a high-frequency alternating current, in response, ions attempt to follow the changing direction, causing agitation and frictional heating. This results in destruction of the tumor tissue through thermal coagulation and protein denaturation (Fig. 1).

In most studies, RFA is followed by immediate or delayed surgical excision of the tumor. Izzo et al. performed one of the first feasibility studies that included 26 breast cancer patients with a mean tumor size of 1.8 cm (range, 0.7–3.0 cm). Complete tumor ablation was obtained in 96% (25 of 26) of the patients. Since then, multiple RFA studies have been performed with success rates varying from 77% to 100%. Only a few studies performed RFA without surgical excision. Ohara et al. included 52 patients with a tumor size of 2 cm or less who underwent RFA alone. MRI after 1 to 3 months showed no evidence of residual disease. After a follow up of 71 months, none of the patients developed locoregional or distant recurrences. Cosmetic outcome was reported excellent in 83%, good in 11%, and fair in 6% of the patients.

Excision RFA (eRFA) consists of surgical excision of the tumor followed by RFA. The aim is to decrease the rate of reexcisions after breast-conserving surgery, to improve locoregional recurrence rates by extending the margins, and ablating possible residual disease. Klimberg et al. performed a study in 100 patients undergoing breast-conserving surgery followed by eRFA in which biopsy showed at least 1 cm circumferential ablation around the resection cavity. Of these 100 patients, 78 had negative margins (>2 mm) and 22 had margins 2 mm or less, of which 3 were locally positive. Recurrence after 5 years of follow up was seen in 3% of the patients treated with systemic hormonal therapy and in 10% without systemic hormonal therapy. Recently, results of the multicenter Radiofrequency Ablation After Breast Lumpectomy study were presented. A total of 267 T0 to T2 breast cancer patients treated with breast-conserving surgery followed by eRFA were included. Results showed a reexcision rate for positive margins of <5%. The rate of breast recurrence was 2.5% after 3 years of follow-up.

RFA appears to be limited to tumors with a maximum size of 2 cm. RFA treatment is not suitable for infiltrating lobular breast tumors, tumors with an extensive in situ component, and in patients treated with neoadjuvant systemic therapy. Complications from RFA are rare and generally mild, including skin or muscle burns and seromas.

MICROWAVE ABLATION

Thermal ablation can also be performed with the use of microwaves. Microwave ablation (MWA) uses electromagnetic waves at frequencies of at least 900 mHz. Localized heat caused by water molecules moving within tissue results in tissue destruction. Tissues with high water content, such as breast tumors, are heated and damaged more rapidly compared with tissues with lower water content, such as normal breast tissue with surrounding fat, which may remain unharmed. To perform MWA, the breast must be compressed between two plates. The electric field probe is inserted into the central portion of the tumor under ultrasound or CT guidance. A fiber optic temperature probe is placed in the tumor to guide and adjust the temperature. Skin temperature probes are applied to the skin to monitor the temperature to avoid skin burns. A cooling system can be used to provide air cooling, decreasing the risk of thermal injury to the skin.

The first pilot study of MWA was performed by Carbone et al. to assess the feasibility and safety of this technique. MWA was performed in 10 breast cancer patients with a mean tumor size of 4.3 cm (range, 1.0–8.0 cm). A reduction in tumor size was seen in 60% (6 of 10) of the patients. Dooley et al. performed a small trial that

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ABLATIVE TECHNIQUES IN THE TREATMENT OF BENIGN AND MALIGNANT BREAST DISEASE

Marissa Yassa, MD, MSc, and Armando E. Giuliano, MD, FACS, FRCSEd

Extending the trend toward less invasive treatment, ablative techniques for benign tumors and small breast cancers have continued to progress. Ablative treatments are all image guided percutaneous techniques (using ultrasonography, mammography, magnetic resonance imaging [MRI], or computed tomography [CT]). Complete tumor ablation can be achieved using different types of energy instead of or in addition to immediate or delayed surgical excision. The goal of these ablative techniques is to reduce the complications, decrease morbidity, shorten hospitalization, and improve the cosmetic outcome and quality of life while not increasing recurrence rates. Ablation techniques include radiofrequency ablation (RFA), microwave, laser ablation, electromagnetic waves, cryoablation, and high intensity focused ultrasound.

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The first pilot study of MWA was performed by Carrafiello et al. to assess the feasibility and safety of this technique. MWA was performed in 10 breast cancer patients with a mean tumor size of 4.3 cm (range, 1.0–8.0 cm). A reduction in tumor size was seen in 60% (6 of 10) of the patients. Dooley et al. performed a small trial that

randomized patients to breast-conserving surgery followed by MWA versus breast-conserving surgery alone. This study found that patients with early breast cancer treated with breast-conserving surgery and MWA had 0% (0 of 34) positive tumor margins compared with 9.8% (4 of 41) for those with breast-conserving surgery only. More recently, Zhou et al. showed that complete tumor ablation using contrast-enhanced ultrasound was seen in 90% (37 of 41) of patients treated with MWA.

CRYOABLATION

Cryoablation is the only ablative technique using cold instead of heat to create tissue necrosis. It is accomplished percutaneously guided by ultrasound, MRI, or CT. Cryoablation involves two phases: freezing and thawing. Liquid nitrogen is inserted into the probe and results in a local freezing reaction; thereafter, a second gas (i.e., helium) is released through the probe to arrest the freezing process, allowing thawing to occur (Fig. 2A). Tumor cells are destroyed through direct intracellular and indirect vasculature injury. Intracellular ice formation results in shearing and irreversible rupture of cell membranes. Extracellular formation occurs, creating a hypertonic environment. Water flows out of the cells, resulting from osmosis, causing cellular dehydration and damage. When thawing occurs, water flows back into the cell, increasing intracellular volume and lysis occurs. Freezing and thawing is repeated. After at least two freeze–thaw cycles, an ice ball is created, which can be visualized with imaging. The tumor is left to remain in situ and is reabsorbed by the body (Fig. 2B).

Several studies have investigated the efficacy of cryotherapy in the treatment of fibroadenomas. The prospective Fibroadenoma Cryoablation Treatment Registry included 441 patients with fibroadenomas treated with cryotherapy. Two freeze–thaw cycles were used with a temperature of −160°C for the treatment of lesions with a median size of 1.8 cm. A reduction in size of 51% was seen after a follow-up of 6 months. Furthermore, palpability of the fibroadenomas reduced from 75% at pretreatment to 36% after 6 months and 15% after 12 months of follow-up. Recently, the role of cryoablation in the treatment for malignant breast tumors has been evaluated. The systematic review of Littrup et al. showed complete tumor ablation in 73% of included patients after a mean follow-up of 8 months. Cosmetic satisfaction was reached in 99% of the patients. In 2016, the American College of Surgeons Oncology Group undertook Z1072, a phase II trial exploring the effectiveness of cryoablation in the treatment of breast cancers, published their results. Patients with a malignant tumor size less than 2 cm with less than 5% intraductal component were included. There was a complete tumor ablation in 26% (26/87) of patients. If multifocal tumors were excluded, the success rate increased up to 92% (80/87). The Breast Journal of Resection of Small Breast Tumors trial is currently recruiting women with early stage invasive breast cancer to investigate whether cryoablation can achieve complete tumor ablation and adequate local control without surgical excision.

Criteria for cryoablation include tumor size smaller than 2 cm, location at least 1 cm from the skin surface, and lack of an extensive in situ component (<25% of carcinoma in situ). Advantages of cryoablation are patients' comfort and treatment of larger lesions with sparing of normal breast tissue. Disadvantages are potential risk of thermal

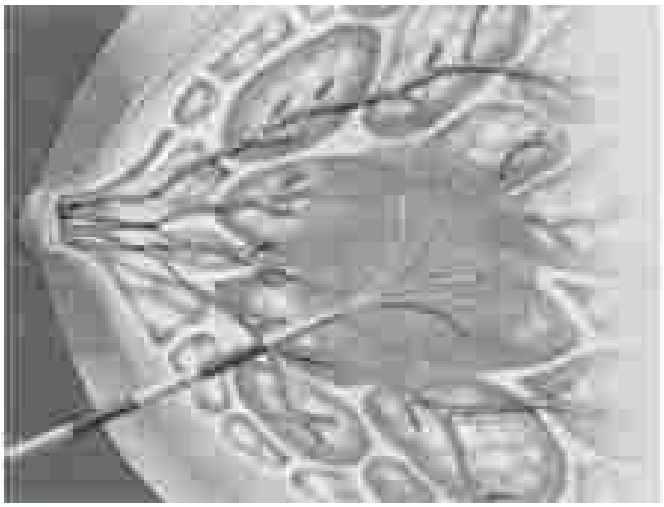

FIG. 1—Representation of radiofrequency ablation showing star array probe with breast and surrounding breast ablation zone. (Courtesy [STAR Medical Systems, Inc., Systems & Ablation techniques in the treatment of benign & and malignant breast tumors. [Am Coll Surg ... 2008;1:e1–12])

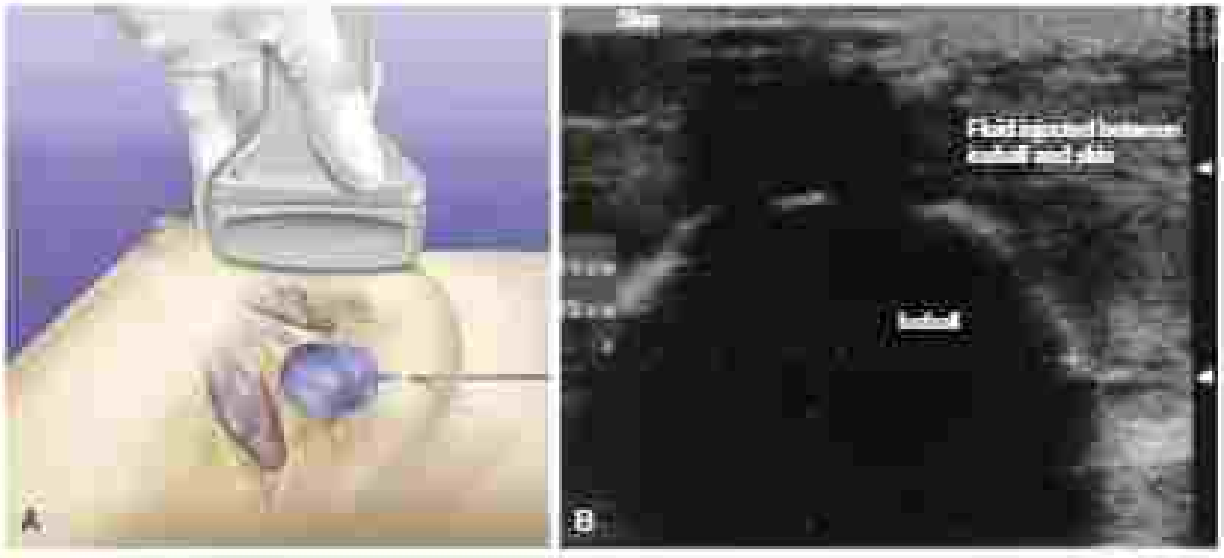

FIG. 2—(A) Sonography is used to monitor the developing cryogenic zone created by the cryoprobe. (...) Ultrasound image of hypoechoic ice ball and protective saline injection. [A from Kaufman C, Jacobs L, Lovern J, et al. [Re-] cryoablation of breast cancer: initial 3-year experience. 12 month follow up. [Am J Surg. 2014;199:97–103] B from Kaufman C, Bachman B, Young E, et al. [Re-] breast ultrasound guided cryoablation of breast fibroadenomas. [Am J Surg. 2007;194:e1–e4.])

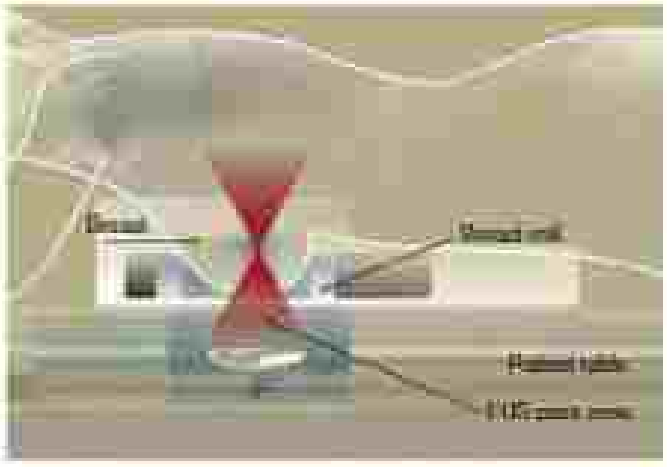

FIG. 3 Schematic diagram of magnetic resonance imaging-guided high-intensity focused ultrasound (HIFU) therapy for a breast cancer patient in prone position. *(From Zhou Y. Noninvasive treatment of breast cancer using high-intensity focused ultrasound. J Oncol Invest Ann Surg Arch Oncol. 2010;2010:617.)*

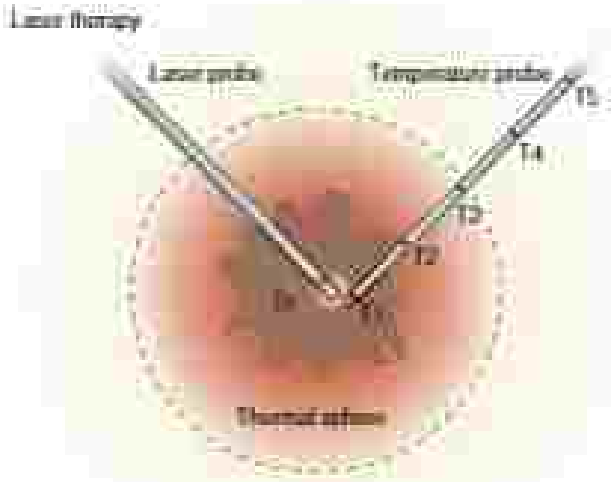

FIG. 4 Schema of laser and temperature probes in and adjacent to a breast cancer. *(From Dowlatshahi K, Francescatti D, Bhatnagar A. Preoperative doxorubicin chemotherapy: IMPACT trial update. Am J Surg. 1998;176:481.)*

injury to the skin, biopsy staging information (e.g., tumor size and margin status), and timing of the sentinel lymph node biopsy.

HIGH-INTENSITY FOCUSED ULTRASOUND

High intensity focused ultrasound (HIFU) is a completely noninvasive thermal-based ablative technique using transcutaneously focused ultrasonic waves (Fig. 3). The focused ultrasound waves cause rapid (1–2 seconds) temperature elevation within the targeted tissue up to 50°C to 95°C. This causes melting of the lipid bilayer of the cellular membrane and protein denaturation, leading to tissue necrosis, whereas tissues outside the targeted area are spared. Because of the small (1.8 × 0.2 × 0.2 mm³) ablation zone, multiple overlapping applications are required to treat an entire lesion. Complete ablation can take up to 2 to 3 hours.

Peek et al. published a systematic review, including 9 HIFU studies and 367 breast cancer patients. No residual tumor after HIFU treatment was found in 86.2% (95 of 110) of the patients. The most reported complication was pain (81.5%), followed by edema (16.8%), skin burn (4.2%) and pectoralis major injury (3.6%). Symptomatic palpable fibroadenoma patients were included in a separate HIFU fibroadenoma trial. Twenty of the included patients were treated with HIFU, whereas the other 20 underwent an ultrasound after a months. Control group). Primary outcome was reduction in treatment time; secondary outcomes were reduction in volume on ultrasound after 12 months and the complication rate. Treatment time was reduced with 20.4% to circumferential ablation compared with whole lesion ablation. Reduction in volume was reported in 45.2% of the patients after 12 months of follow up.

HIFU is a completely noninvasive ablative technique. Cosmetic outcome is very good because there is no scarring at skin entry site. Disadvantages are patient discomfort, general or spinal anesthesia, and prolonged treatment times.

INTERSTITIAL LASER

Laser interstitial thermotherapy (LITT) is a hyperthermic ablative technique. Laser fibers are percutaneously inserted into the tumor, whereas a second probe is placed to measure the temperature (Fig. 4). A refraction of laser light is produced at the tumor, producing heat and causing coagulation necrosis and protein denaturation, resulting in irreversible tissue destruction. The level of necrosis depends on the temperature and ablation time. Three types of lasers are available: carbon dioxide, argon, and neodymium-doped yttrium aluminum garnet laser. The two latter lasers have the benefit of being able to treat larger volumes. Only a few studies have evaluated LITT followed by surgical excision. Dowlatshahi et al. performed a study in 64 breast cancer patients and showed complete tumor ablation of 70% in tumors with a mean diameter of 12 mm (range, 5–25 mm). Incomplete tumor ablation was attributed to technical issues, such as inadequate laser energy, patient motion, malfunctioning thermal probes and fluid pump, and suboptimal target visualization. LITT under MRI guidance showed a complete ablation in 76% of the tumors ranging from 1.8 to 8.0 cm. LITT performed in patients with fibroadenomas (n = 24) showed a reduction of 60% after 6 months of follow up.

The advantage of LITT is that it has a photocoagulative effect that reduces bleeding during the procedure. Disadvantage is that tumors larger than 2 cm or tumor with extension in skin component are not good candidates for laser therapy.

IRREVERSIBLE ELECTROPORATION

Irreversible electroporation is a nonthermal ablative technique that uses electrical fields to create permeable cell membranes and cause cell death. Electroporation occurs when short electric pulses (1000 V/cm field) are passed across the cell membranes, resulting in membrane permeabilization. This ablative technique only affects the cell membrane while sparing the extracellular matrix and other tissues (i.e., blood vessels). Permeabilization can be reversible or irreversible, depending on the number, duration, and time between electric pulses and electric field strength. Irreversible electroporation has been investigated for a short period and much of in vivo research involves animal models only. Disadvantages of this technique are the potential occurrence of cardiac arrhythmias and general anesthesia because the electric pulses cause muscle contractions.

SUMMARY

A meta-analysis showed that complete ablation rates of ablative techniques such as RFA, MWA, cryoablation, LITT, and HIFU vary and

have been highest in patients undergoing RSA (87.1%), followed by [illegible]

[illegible]

Suggested Readings

[illegible]

[illegible] Mutually exclusive ... in the treatment of breast ... [illegible]

[illegible] ... ultrasound in the treatment of breast fibroadenomas ... [illegible]

[illegible] A phase II trial exploring the success of ... therapy in the treatment of ... breast ... [illegible]

[illegible] Ultrasound-guided ... therapy for small palpable ... breast carcinoma: a feasibility study. Ann Surg Oncol [illegible]

[illegible] Ultrasound-guided ... a promising tool ... management of ... [illegible]

Lymphatic Mapping and Sentinel Lymphadenectomy

David L. [illegible], MD

The importance of the axilla in breast cancer management has been recognized for centuries. The German surgeon, Wilhelm Fabry (1560–1634), wrote, "I found in the right breast a hidden cancer, far larger than a [illegible], hard and pale. In the axilla there was also hidden three hard swellings, one of which was as big as an egg...I cut out all of these hard swellings and she became well again." By the late nineteenth century, William Halsted had published data suggesting that axillary dissection at the time of mastectomy may be associated with reduced breast cancer mortality. This approach was predicated on the belief that breast cancer cells initially spread through lymphatic channels to the axillary nodes and from there into the blood stream where they gained access to distant organs. The Halsted radical mastectomy remained the standard of care for more than 7[illegible] years. By the 19[illegible]s, however, available data suggested that axillary dissection did not improve survival. This was confirmed by the randomized, prospective National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial conducted by the American surgeon, Bernard Fisher. Breast cancer came to be viewed as metastatic, or not, at inception. Lymph node metastases became a marker of metastatic potential, not a step in the metastatic process.

Although spread to lymph nodes is not required for systemic dissemination, identification of lymph node metastases remains one of the strongest predictors of eventual distant metastases and death. Afferent lymphatic channels maintain connections with venules to ensure unrestricted lymphatic flow. Metastatic disease in an axillary node is strong evidence that the cancer cells have already gained access to the circulation and are capable of surviving outside of the breast. Survival is strongly inversely related to the number of positive lymph nodes, especially for estrogen receptor–negative breast cancer. Lymph node metastases provide prognostic information for estrogen receptor–positive disease as well, but genomic assays performed on the primary tumor can identify the subgroup of node-positive tumors with a good prognosis.

By 1977, it was known that, for clinically node-negative women, axillary dissection does not improve survival. Nevertheless, axillary dissection remained the standard of care for all breast cancer patients, largely because nodal stage strongly influenced adjuvant therapy decisions. Axillary dissection is a morbid procedure that can cause lifelong upper extremity symptoms including lymphedema. Sentinel node biopsy provides nearly as much staging information as axillary dissection with a fraction of the morbidity.

Development of Lymphatic Mapping and Sentinel Node Biopsy

The lymphatic drainage of the breast was well described by the 1930s. In 1953, Gray described the four levels of axillary lymphatic drainage of the breast, recognizing that blue dye injection in any part of the breast stained the same few axillary nodes and that accessory

have been highest in patients undergoing RFA (87.1%), followed by microwave ablation (83.2%), cryoablation (74.1%), laser ablation (62.2%), and HIFU (47.4%). Other important, but less investigated outcomes are recurrence and complication rates. No local recurrences have been reported using microwave ablation (0%). Other ablative techniques have small but measurable recurrence rates: cryoablation (1.4%), HIFU (2.9%), RFA (3.1%), and laser ablation (10.2%). Complications occur in about 10% of patients. Most commonly seen were skin burns followed by pectoralis major muscle damage. MWA is associated with the highest postoperative complication rate of 14.8%, followed by cryoablation (10.9%), RFA (10.3%), HIFU (6.9%), and laser ablation (6.3%). Excellent cosmetic outcome has been reported in patients treated with ablation. Cryoablation results in greater than 90% excellent cosmesis compared with 85.3% in patients treated with RFA and 66.3% in patients treated with HIFU. HIFU may ultimately have the best cosmetic outcome because this technique is completely noninvasive.

All ablative techniques show several benefits compared with breast conserving surgery; however, larger multicenter randomized controlled trials are required to confirm the efficacy of ablation compared with resection. Current problems are the lack of a predictive tool for assessing complete tumor ablation, determination of accurate tumor size, information on the timing of axillary surgery, and adequate patient and tumor inclusion criteria. Ablative treatment techniques may be most suitable for patients with contraindications to operation or patients with a preference to avoid breast conserving therapy. Furthermore, ablative treatment can only be used for small (T1) breast tumors (<2 cm), T can from the skin and pectoralis major, less than 25% carcinoma in situ component and, most important, tumors must be visible using imaging modalities. In addition, many techniques result in a palpable mass, disturbing to patient and surgeon. Intraoperative RFA after surgical excision may become a means to avoid radiation after breast conserving surgery for patients with favorable tumors.

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Lymphatic Mapping and Sentinel Lymphadenectomy

David Euhus, MD

The importance of the axilla in breast cancer management has been recognized for centuries. The German surgeon, Wilhelm Fabry (1560–1634), wrote, "I found in the right breast a hidden cancer, far larger than a fist, hard and pale. In the axilla there was also hidden three hard swellings, one of which was as big as an egg...I cut out all of these hard swellings and the breast well again." By the late nineteenth century, William Halsted had published data suggesting that axillary dissection at the time of mastectomy may be associated with reduced breast cancer mortality. This approach was predicated on the belief that breast cancer cells initially spread through lymphatic channels to the axillary nodes and from there into the blood stream where they gained access to distant organs. The Halsted radical mastectomy remained the standard of care for more than 70 years. By the 1960s, however, available data suggested that axillary dissection did not improve survival. This was confirmed by the randomized, prospective National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial conducted by the American surgeon, Bernard Fisher. Breast cancer came to be viewed as metastatic, or not, at inception. Lymph node metastases became a marker of metastatic potential, not a step in the metastatic process.

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DEVELOPMENT OF LYMPHATIC MAPPING AND SENTINEL NODE BIOPSY

The lymphatic drainage of the breast was well described by the 1930s. In 1953, Crane described the four levels of efferent lymphatic drainage of the breast, recognizing that blue dye injection to any part of the breast stained the same few axillary nodes and that accessory

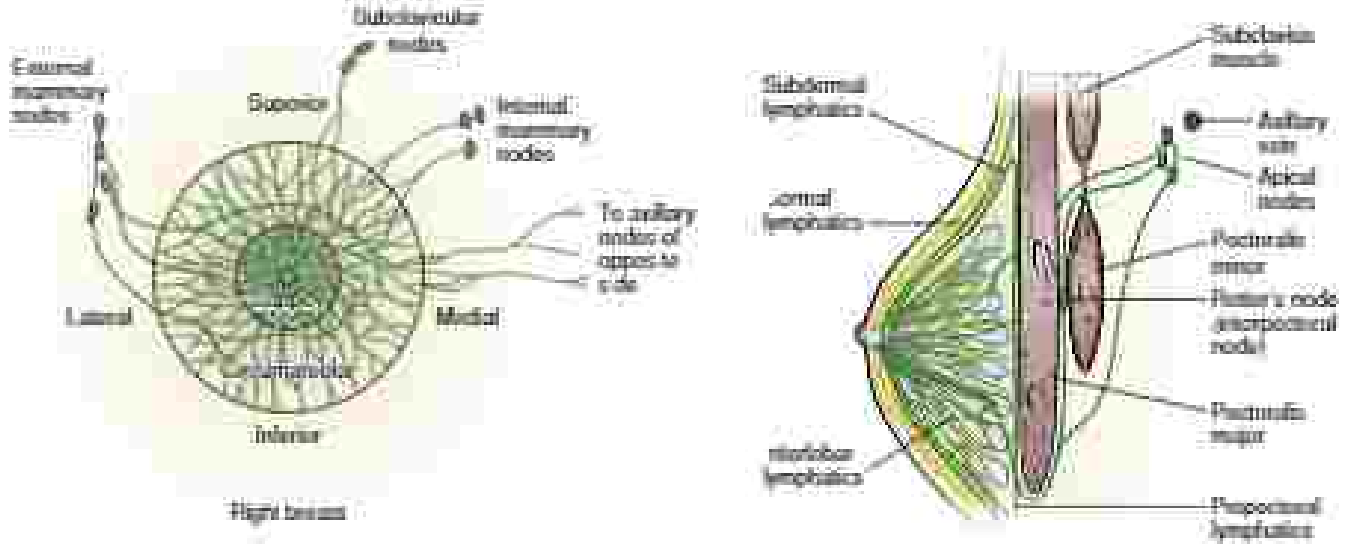

FIG. 118.1 Lymphatic drainage of the breast. There are four main [illegible] groups: one is to the breast itself, one [illegible] and three [illegible]. Each of these networks is [illegible] with the others, so that a [illegible] in the breast, they tend to [illegible] the [illegible] nodes. It is also [illegible] that [illegible] always be [illegible] that do not [illegible] with the classic pathway. These [illegible] to those [illegible] any [illegible] and other [illegible]

[illegible] mammary nodes, the contralateral axilla, or other sites [illegible]. Cabanas first coined the term [illegible] penile cancer and the [illegible] was [illegible] accepted [illegible] and [illegible] studied the concept [illegible] demonstrate [illegible] a [illegible] and [illegible] accurate [illegible] clinical ability [illegible] necessary in a series [illegible] in lymph [illegible] a case later [illegible] Gadian [illegible] this [illegible] breast cancer.

EVALUATION OF [illegible] MATTER MAPPING AND SENTINEL NODE BIOPSY IN CLINICALLY NODE-NEGATIVE WOMEN

[illegible] and [illegible] were [illegible] an accuracy [illegible] biopsy to [illegible] axillary dissection and a subsequent meta-analysis reported that SLNs reflect the status of the axilla in 97% of clinically node-negative patients. Three randomized prospective trials comparing SLN biopsy alone to axillary dissection in clinically and pathologically node-negative patients all reported a low risk of axillary recurrence in the sentinel node only arm (<10%), similar disease-free and overall survival, and significantly lower morbidity (Table 118.1). On the strength of these trials, sentinel node biopsy became accepted as a safe and accurate procedure for nodal staging in clinically node-negative women.

The next question to answer was whether axillary dissection is required in clinically node-negative women with a positive sentinel node. The International Breast Cancer Study Group (IBCSG) 23-01 trial, the Aflac Mapping of the Axilla: Radiotherapy or Surgery trial (AMAROS) and the American College of Surgeons Oncology Group Z11 trial each took on this question in slightly different ways. The IBCSG trial showed that disease-free survival is the same with or without axillary dissection in patients with one or more micrometastases (<2 mm) in SLNs. The AMAROS trial found that survival and axillary recurrence rates were similar for SLN-positive patients who were treated with axillary dissection or comprehensive regional nodal radiation, whereas lymphedema rates were reduced by one-half in the radiation arm (14% vs. 28%). Z11 was designed to exclude any axillary treatment in women with one or two positive SLNs undergoing breast-conserving surgery, though ultimately 19% of patients in each arm received nodal treatment. Although 27% of patients in the axillary dissection group had additional positive, nonsentinel nodes, the axillary recurrence rate was only about 1% in the SLN-only group. It is important to recognize that 97% of the women in the SLN group received adjuvant systemic therapy. There is now little opposition to the notion that axillary dissection can be avoided in women with clinically negative lymph nodes, T1 to T2 tumors, and one or two positive SLNs as long as these women are treated with breast-conserving surgery followed by adjuvant systemic therapy and whole-breast radiation therapy.

As neoadjuvant chemotherapy gained in popularity, there were concerns that chemotherapy itself could affect lymphatic drainage, rendering SLN biopsy inaccurate. Numerous institutional studies existed and two meta-analyses reported that SLNs can be identified in 80% of patients after neoadjuvant chemotherapy with a false-negative rate of 8% to 12%. Data from the NSABP B-27 trial confirmed a similar 80% SLN identification rate, an 11% false-negative rate, and an accuracy of 89%. These performance metrics are similar to those reported from large multiinstitutional trials in women undergoing surgery before chemotherapy. Sentinel node biopsy is the preferred approach to axillary staging in clinically node-negative women after neoadjuvant chemotherapy.

OMITTING AXILLARY DISSECTION IN CLINICALLY NODE-NEGATIVE PATIENTS

Clinically node negative is defined as no suspicious adenopathy on clinical examination. Suspicious palpable nodes should undergo needle biopsy (Box 1). If metastatic breast cancer is detected, then the patient is classified as clinically node positive. Many patients are having axillary sonography as part of their initial imaging evaluation. This may be useful before neoadjuvant chemotherapy so that nodal response can be assessed. Patients with small metastases discovered through sonography are not clinically node positive and can undergo SLN biopsy as part of their primary surgical procedure. The biopsied node can be marked with a localizing device or India ink to ensure it is excised. Patients with negative SLNs do not require axillary dissection. Most patients with one or two positive sentinel nodes do not require axillary dissection if they have T1 to T2 tumors treated by breast-conserving surgery and will undergo whole-breast radiation and adjuvant systemic therapy. Patients with one or two positive sentinel nodes undergoing mastectomy do not require axillary dissection.

TABLE 1 Pivotal Sentinel Node Trials

Name	Citation	Clinical Practice Relevance
CLINICALLY NODE-NEGATIVE PATIENTS		
NSABP B-32	[illegible], 2010	SLN biopsy alone is safe if the SLN is negative
Milan	Zurrida, 2009	
Sentinella/ INOM	Zavagno, 2008	
IBCSG 23-01	[illegible], 2013	ALND is not required for micrometastatic positive SLNs
ACOSOG Z11	[illegible], 2017	ALND is not required for macrometastatic SLNs in selected patients
AMAROS	Donker, 2014	Axillary radiation provides similar axillary control as ALND in selected SLNB patients with half the lymphedema risk
NSABP B-27	Mamounas, 2005	SLN biopsy is accurate after neoadjuvant chemotherapy
CLINICALLY NODE-POSITIVE PATIENTS		
SENTINA	Kuehn, 2013	The false negative rate of SLN biopsy after neoadjuvant chemotherapy in initial clinically node positive patients is 13%–14% but can be reduced by using dual tracer and finding ≥3 SLNs
ACOSOG Z1071	Boughey, 2013	
Alliance A011202	Accruing	Will determine if ALND adds anything to nodal RT when SLNs are still positive after neoadjuvant chemotherapy
NSABP B-51	Accruing	Will determine if nodal RT is required when the nodes convert to negative after neoadjuvant chemotherapy

[illegible] Statistics are for node-positive [illegible]

ALND, American College of [illegible] Group; ALND, [illegible]; RT, [illegible]; SLN, sentinel lymph node; SLNB, [illegible]

BOX 1 Omitting Axillary Dissection in Clinically Node-Negative Patients

Strong Clinical Trial Evidence

- T1–T2 patients with negative SLNs
  - Under [illegible] patients undergoing mastectomy
  - Some T3–T4 patients [illegible]
- Some [illegible]
  - Under [illegible] patients undergoing mastectomy
  - [illegible]
  - [illegible]
  - [illegible]

Clinical [illegible]

- [illegible]

Not [illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]

SLN, Sentinel lymph node.

if they receive regional nodal irradiation. Axillary dissection is still recommended for patients with positive SLNs after neoadjuvant chemotherapy, inflammatory cancer, or gross extracapsular extension. There is little experience with SLN biopsy in patients with T3 to T4 tumors. For these women, decisions about axillary staging should be individualized.

SENTINEL NODE BIOPSY IN CLINICALLY NODE-POSITIVE PATIENTS WHO CONVERT TO NODE NEGATIVE

Neoadjuvant chemotherapy, especially in hormone receptor–negative tumors, can eradicate all tumor cells in the breast and axillary lymph nodes (pathologic complete response). Current guidelines recommend axillary dissection for patients who were clinically node positive at diagnosis, regardless of the response to neoadjuvant chemotherapy. There is a trend, however, toward performing SLN biopsy in patients experiencing a complete clinical response to neoadjuvant chemotherapy and then foregoing axillary dissection if the SLNs are negative. The NSABP B-51/Radiation Therapy Oncology Group 1304 trial randomizes patients who have converted to SLN negative to regional nodal radiation or no axillary treatment at all. The Alliance A011202 trial is for patients who remain node positive after neoadjuvant chemotherapy. They are randomized to axillary dissection plus nodal radiation versus nodal radiation alone. Clinical trial participation is the best way to generate the data required to safely modify the guidelines, but a negative axillary dissection incurs morbidity without providing benefit. Most relevant are ~40% of breast cancer patients who are also estrogen receptor negative. Modern chemotherapy, combined with dual anti-HER2 targeting, induces pathological complete responses in as many as 72%. Many would forego axillary dissection in a patient like this with normalized posttreatment imaging and negative SLNs.

The American College of Surgeons Oncology Group (ACOSOG) Z1071 and Sentinel Neoadjuvant studies both reported that the false negative rate of SLN biopsy after neoadjuvant chemotherapy in initially clinical node positive patients is about 12%. The false negative rate can be reduced to about 9% if the following practices are observed: (1) dual tracer mapping with radiocolloid and blue dye, (2) resection of at least three lymph nodes, and (3) x-ray the nodes to verify that the previously clipped node has been removed. Because the previously biopsied and clipped lymph node is not recognized

as a SLN in about 25% of patients, it may be helpful to localize the node preoperatively using a localizing device (wire, radioactive seed, electronic tag…) or radiocolloid injection.

TECHNICAL CONSIDERATIONS

Sentinel lymph nodes are identified by injecting technetium 99m colloid (sulfur or albumin), visual dyes, or both into the breast where they are transported by afferent lymphatic channels to the first echelon lymph nodes responsible for the breast. As well illustrated by Grant in 1957 (Fig. 1), injections performed anywhere in the breast and at any depth will accumulate in the same axillary lymph nodes. Sappey's subareolar plexus is a particularly rich network and the preferred injection site for many. This is a subdermal lymphatic plexus that is not really subareolar at all. It is located in a ring just deep to the edge of the areola. If there is interest in identifying accessory drainage pathways (internal mammary or contralateral axilla, for instance) then the radiocolloid should be injected peritumoral (interlobar afferent lymphatics) and the patient imaged with a gamma camera. This is rarely done anymore because it has been recognized that it is very rare to find internal mammary metastases in patients with negative axillary sentinel nodes.

Using both technetium 99m colloid and a visual dye may increase SLN identification rate and reduce the false negative rate, but many surgeons are achieving adequate results using technetium 99m only. Technetium 99m is often filtered to achieve consistent particle sizes less than 50 nm and a dose of 0.1 to 1 mCi is used for injections on the same day as the surgery, whereas up to 3 mCi is used for the day before injections. A recent improvement to the radiocolloid is the addition of monose groups that bind to macrophages and dendritic cells in the lymph nodes targeting retention. The most common visual dyes are isosulfan blue, methylene blue, and indocyanine green. The latter is a fluorescent dye and requires specialized equipment for visualization. When methylene blue is used, it should be diluted 1:3 with injectable saline to reduce the risk of skin necrosis. One reason some surgeons have stopped using isosulfan blue routinely is the 1% incidence of anaphylaxis. A reasonable compromise is to interrogate the axilla with a gamma counter before prepping and then injecting blue dye only when there is no definite signal from the technetium. Anaphylaxis rates may be increased in patients who have previously been exposed to isosulfan blue. If isosulfan blue must be used again, the patient can be premedicated with antihistamines (H1 and H2) and steroids.

Sentinel nodes are defined as any lymph nodes that have accumulated the radiocolloid or visual dye and any lymph nodes that are suspicious by palpation. The primary SLN is usually located just deep to the midportion of the belly of the pectoralis muscle. Intercostal brachial cutaneous nerve symptoms often run just superior to the SLN. Bipolar cautery or sharp dissection may help to minimize intercostal brachial cutaneous symptoms that are common in the early postoperative period. There are at least two SLNs in most patients. The second SLN is often in close proximity to the first but is occasionally found in level 2. It is common to remove any lymph nodes with radioactive counts that are 10% or more of the most radioactive node.

Rarely (about 5%), the SLNs cannot be identified. This can happen if lymphatic channels are occluded with tumor cells but is also more common in obese patients. Practice guidelines recommend level 1 and 2 axillary dissection if an SLN cannot be identified. An alternative may be very careful axillary inspection and palpation followed by excision of a few lymph nodes from the vicinity of the underbelly of the pectoralis major muscle where the SLN usually resides. This decision can be individualized based on patient and tumor characteristics as they relate to the importance of pathologic axillary staging compared to the morbidity of axillary dissection.

HISTOLOGIC ASSESSMENT OF SENTINEL NODES

In the early days of axillary SLN biopsy for breast cancer, SLNs were serially sectioned and stained with cytokeratin immunohistochemical (IHC) stain. This significantly increased node-positive rates, but largely through the identification of very small tumor deposits. The ACOSOG Z10 and NSABP B-32 trials convincingly showed that detection of occult metastases using IHC contributed very little prognostic information. Routine IHC is no longer recommended for SLNs, but some pathologists use it in cases of invasive lobular carcinoma, where the metastatic cells can be diffuse and difficult to detect.

Historically, SLNs were assessed intraoperatively by frozen section so that node-positive patients could undergo axillary dissection under the same anesthetic. As clinical trial data have accumulated, decisions about axillary treatment have become more complex. Some patients with positive SLNs do not require any additional axillary treatment. For these who do require treatment, nodal radiation is finding broader use. It is a small minority of SLN-positive patients who will benefit from axillary dissection with or without adjuvant nodal radiation. Frozen section assessment of axillary SLNs is rarely useful in modern practice and many surgeons have abandoned it completely in favor of carefully considered multidisciplinary decisions about axillary dissection after all the information is available.

MORBIDITY OF AXILLARY SENTINEL NODE BIOPSY

The morbidity of SLN biopsy is a fraction of that incurred by axillary dissection but it is not negligible. The NSABP B-32 trial recorded a 10% or greater difference in arm volume for 7.5% at 36 months, shoulder abduction deficits of 10% or greater in 5.7% at 6 months, and arm numbness or tingling in about 8% at 36 months. The procedure should only be done when there is a reasonable probability that the results will influence treatment decisions.

A recent meta analysis that included 632 breast cancer patients who had undergone axillary surgery found that cellulitis, body mass index greater than 25, regional nodal radiation, and axillary dissection were all associated with increased lymphedema risk. Lymphedema risk was not increased by ipsilateral blood draws, blood pressure measurements, injections, or airline travel. Other than avoiding injury and infection, no special precautions are required after SLN biopsy.

LYMPHATIC MAPPING AND SLN BIOPSY IN SPECIAL SITUATIONS

Pregnancy

Lymphatic mapping using technetium 99m colloid can be performed in pregnant patients when the results will influence treatment decisions. Blue dyes should be avoided.

Male Breast Cancer

Lymphatic mapping is just as accurate in men with breast cancer as it is in women. Radiocolloid or visual dyes can be injected into Sappey's subareolar plexus.

Ductal Carcinoma in situ

About 15% of ductal carcinoma in situ (DCIS) lesions diagnosed on core needle biopsy will be upstaged to invasive cancer on excision. It seems reasonable to do SLN biopsy when mastectomy is being done for DCIS diagnosed on core needle biopsy. Sentinel node biopsy can also be considered in patients undergoing completion mastectomy after multiple failed attempts to achieve clear margins especially in cases of microinvasive DCIS. Some have advocated SLN biopsy for high grade, large (>2.5 cm), or palpable DCIS treated by breast conserving surgery because these features are associated with an even higher upstage rate. Lymphatic mapping is still possible after partial mastectomy as an alternative to re-do the SLN biopsy as a second procedure only in those who are found to have invasive cancer.

RISK-REDUCING MASTECTOMY

Occult invasive cancer is found in 2% to 4% of risk reducing mastectomies in high risk women. This poses a problem for axillary staging after the fact. Some have advocated routine SLN biopsy for all risk reducing mastectomies, but it has been estimated that more than 200 mastectomy procedures would need to be done to identify one patient with a positive SLN. It is reasonable to perform breast magnetic resonance imaging preoperatively and forego SLN biopsy in women with Breast Imaging Reporting and Data System 1 or 2 imaging. If an occult invasive cancer is identified on pathology, options would include axillary dissection, attempted lymphatic mapping and SLN biopsy postmastectomy, or ultrasound staging. Patient and tumor characteristics should guide this clinical decision.

AXILLARY RESTAGING FOR LOCAL RECURRENCE

Axillary assessment and management at the time of surgery for isolated local recurrence reduces axillary recurrence risk. Patients with local recurrence are likely to have already had SLN biopsy or axillary dissection as part of their initial treatment. This significantly reduces the SLN identification rate and increases the false negative rate. Nevertheless, lymphatic mapping can be attempted, even in patients who have had mastectomy, although this has not been systematically validated. Radiocolloid and blue dye can be injected subdermal. Imaging with a gamma camera is helpful in this setting as drainage may not be to the axilla. In any case, the axilla is opened and explored for radioactive, blue or suspicious palpable nodes.

AXILLARY REVERSE MAPPING

Axillary reverse mapping involves injection of blue dye into the upper arm and radiocolloid into the breast. Ideally, blue lymphatics and lymph nodes are preserved during sentinel node biopsy or axillary dissection. One institutional study that included 614 patients reported that arm nodes are also SLNs in 4% to 5%. The study found that 4.5% of axillary reverse mapping nodes harbored metastases. The data suggest that preservation of the arm nodes and lymphatics is associated with significantly reduced lymphedema risk (4.5% after axillary dissection) and a low rate of axillary recurrence (1%–2%).

AXILLARY STAGING IN THE ELDERLY

In general, breast cancer is treated less aggressively in elderly patients. Omission of radiation after breast conserving surgery in women over the age of 70 with small, node negative, estrogen receptor–positive tumors is common. Many surgeons are also beginning to omit SLN biopsy in patients older than age 70. There is no arbitrary age above which treatment guidelines can be modified. General health and anticipating remaining life should guide decisions. Sentinel node biopsy should be done if the results would influence decisions about adjuvant radiation or systemic therapies.

SUGGESTED READING

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MANAGEMENT OF THE AXILLA IN BREAST CANCER

Tawakalitu O. Ozanne, MD, and Barbara L. Smith, MD, MPH

AXILLARY DISSECTION

Modern axillary dissection includes clearance of level I to II nodes with sparing of important vessels and nerves. Axillary dissection remains the treatment of choice for patients with locally advanced breast cancers including those with inflammatory carcinoma or palpable nodes at the time of surgery. Such patients often require regional nodal radiation to reduce the risk of recurrence in level III and supraclavicular nodes.

Sentinel Node Biopsy

In the 1990s, improved understanding of breast anatomy revealed that breast lymphatic drainage is to a specific sentinel node. The sentinel nodes are identified by injection of radioactive and/or blue dye particles in subareolar or peritumoral tissue and excision of nodes that accumulate dye particles. In contrast to axillary dissection, lymphedema, chronic pain, or shoulder dysfunction are rare after sentinel node biopsy (SNB).

Patients with clinically negative axillary exams and no signs of inflammatory cancer are eligible for SNB for axillary staging. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32, American College of Surgeons Oncology Group (ACOSOG) Z0010, After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS), Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) and Milan trials confirmed a 95% to 99% success rate for identifying sentinel nodes, an average of two sentinel nodes, and an acceptable 8% to 10% false negative rate. These trials showed that sentinel node mapping was as accurate as axillary dissection in identifying patients who are node positive and showed a less than 1% risk of axillary recurrence after a negative SNB. Axillary dissection has now been abandoned in patients whose sentinel nodes are negative.

Several randomized trials have now addressed management of patients with positive sentinel nodes. The ACOSOG Z0011 trial randomized clinically node negative lumpectomy patients with primary tumors less than 5 cm and 1 to 2 positive sentinel nodes to axillary dissection versus radiation without further axillary surgery. Axillary ultrasound was not routinely used for eligibility. Patients with three or more positive nodes or gross extranodal extension were excluded. All patients received standard tangent radiation and some systemic therapy. At 6.3 years median follow up, the risk of axillary relapse was 0.5% after axillary dissection and 3.5% after sentinel node biopsy

RISK-REDUCING MASTECTOMY

Occult invasive cancer is found in 2% to 4% of risk reducing mastectomies in high risk women. This poses a problem for axillary staging after the fact. Some have advocated routine SLN biopsy for all risk reducing mastectomies, but it has been estimated that more than 200 contemporary procedures would need to be done to identify one patient with a positive SLN. It is reasonable to perform breast magnetic resonance imaging preoperatively and forego SLN biopsy in women with Breast Imaging Reporting and Data System 1 or 2 imaging. If an occult invasive cancer is identified on pathology, options would include axillary dissection, attempted lymphatic mapping and SLN biopsy postmastectomy, or ultrasound staging. Patient and tumor characteristics should guide the clinical decision.

AXILLARY RESTAGING FOR LOCAL RECURRENCE

Axillary assessment and management at the time of surgery for isolated local recurrence reduces axillary recurrence risk. Patients with local recurrence are likely to have already had SLN biopsy or axillary dissection as part of their initial treatment. This significantly reduces the SLN identification rate and increases the false negative rate. Nevertheless, lymphatic mapping can be attempted, even in patients who have had mastectomy, although this has not been systematically validated. Radiocolloid and blue dye can be injected subdermal. Imaging with a gamma camera is helpful in this setting as drainage may not be to the axilla. In any case, the axilla is opened and explored for radioactive, blue or suspicious palpable nodes.

AXILLARY REVERSE MAPPING

Axillary reverse mapping involves injection of blue dye into the upper arm and radiocolloid into the breast. Ideally, blue lymphatics and lymph nodes are preserved during sentinel node biopsy or axillary dissection. One institutional study that included 614 patients reported that arm nodes are also SLNs in 4% to 6%. The study found that 4.5% of axillary reverse mapping nodes harbored metastases. The data suggest that preservation of the arm nodes and lymphatics is associated with significantly reduced lymphedema risk (4.5% after axillary dissection) and a low rate of axillary recurrence (1%–2%).

AXILLARY STAGING IN THE ELDERLY

In general, breast cancer is treated less aggressively in elderly patients. Omission of radiation after breast conserving surgery in women over the age of 70 with small, node negative, estrogen receptor–positive tumors is common. Many surgeons are also beginning to omit SLN biopsy in patients older than age 70. There is no arbitrary age above which treatment guidelines can be modified. General health and anticipating remaining life should guide decisions. Sentinel node biopsy should be done if the results would influence decisions about adjuvant radiation or systemic therapies.

Suggested Readings

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Management of the Axilla in Breast Cancer

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AXILLARY DISSECTION

Modern axillary dissection includes clearance of level I to II nodes with sparing of important vessels and nerves. Axillary dissection remains the treatment of choice for patients with locally advanced breast cancers including those with inflammatory carcinoma or palpable nodes at the time of surgery. Such patients often require regional nodal radiation to reduce the risk of recurrence in level III and supraclavicular nodes.

Sentinel Node Biopsy

In the 1990s, improved understanding of breast anatomy recognized that breast lymphatic drainage is to a specific sentinel node. The sentinel nodes are identified by injection of radioactive and/or blue dye particles in subareolar or peritumoral tissue and excision of nodes that accumulate dye particles. In contrast to axillary dissection, lymphedema, chronic pain, or shoulder dysfunction are rare after sentinel node biopsy (SNB).

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Several randomized trials have now addressed management of patients with positive sentinel nodes. The ACOSOG Z0011 trial randomized clinically node negative lumpectomy patients with primary tumors less than 5 cm and 1 to 2 positive sentinel nodes to axillary dissection versus radiation without further axillary surgery. Axillary ultrasound was not routinely used for eligibility. Patients with three or more positive nodes or gross extranodal extension were excluded. All patients received standard tangent radiation and some systemic therapy. At 6.3 years median follow up, the risk of axillary relapse was 0.5% after axillary dissection and 2.3% after sentinel node biopsy

alone. Survival was no different in the omitted node versus axillary dissection arms. Of note, 27% of patients who underwent axillary dissection had additional positive nodes, suggesting that targeted radiation and systemic therapy was effective in controlling this extent of residual axillary node disease.

The AMAROS trial had a similar design and similar results. Patients undergoing lumpectomy or mastectomy for primary tumors less than 5 cm and 1 to 3 positive sentinel nodes were randomized to axillary dissection versus radiation that included regional and regional nodal radiation. Eighteen percent of patients underwent mastectomy and 7% of patients had 3 or more positive nodes. At 6.1 years median follow up, the risk of axillary recurrence was 0.4% after axillary dissection and 1.2% after SNB alone. Rates of lymphedema were measured at 13% for axillary dissection and 4% for SNB plus radiation. Like the ZO011 study, 33% of patients undergoing axillary dissection had additional positive nodes, again confirming the efficacy of radiation for controlling residual axillary node disease.

Histopathology Analysis of Excised Axillary Nodes

In patients undergoing axillary dissection, more often a single frozen section and stain stained slide is prepared from each node. More thorough analysis is generally performed on sentinel nodes, with each sentinel node sectioned at 2- to 3-mm intervals, and 1 slide made from each of these serial sections. Many centers use keratin immunohistochemistry (IHC) staining of sentinel nodes to identify small tumor deposits and to more easily identify invasive lobular cancer metastases.

These enhanced node pathology approaches have led to classification of nodal tumor deposits based on size. Tumor deposits greater than 0.2 cm are termed macrometastases, deposits greater than 0.02 to 0.2 cm are termed micrometastases, and deposits 0.02 cm or smaller are termed isolated tumor cells (ITCs). The ACOSOG Z0010 trial found no difference in survival in patients with ITCs identified only on IHC compared with patients without ITCs. In the current staging system, both nodes with macrometastases (N1) and micrometastases (N1mi[]) are classified as node positive, while nodes with ITCs are classified as node negative (N0(i+)).

AXILLARY IMAGING

Physical exam of the axilla may provide only limited information on node status because of patient habitus and anatomy. Ultrasound is the preferred imaging modality for assessment of axillary nodes. Suspicious node findings on ultrasound include a thickened or nodular cortex, loss of fatty hilum, a spherical shape and increased peripheral blood flow. Enlarged nodes may also be identified on breast magnetic resonance imaging (MRI) or computed tomography (CT) scans.

Axillary imaging has significant false positive and false negative rates, and clinical management should not be changed based on imaging alone. In the ACOSOG Z0011 trial, 641 breast cancer patients had axillary ultrasound after neoadjuvant chemotherapy and all had a complete axillary dissection. Only 21% of patients with suspicious axillary ultrasound were node positive on dissection and 57% of patients with a negative axillary ultrasound were node positive. Ultrasound-guided core- or fine needle biopsy may be used to perform diagnostic biopsy to confirm axillary metastasis. Placement of a marking clip during node biopsy can be used to guide excision of a positive node at the time of surgery.

It is important to note that axillary imaging is optional in patients with a negative clinical exam. Patients with nonpalpable nodes with suspicious findings on axillary imaging remain eligible for sentinel node biopsy and can safely be treated with axillary radiation rather than axillary dissection, as in the Z0011 and AMAROS trials.

MANAGEMENT OF THE AXILLA IN OLDER WOMEN

Several trials have shown that many older women with favorable, estrogen receptor (ER+) breast cancers do not require surgical staging of the axilla. Cancer and Leukemia Group B (CALGB) 9343 enrolled 636 women age 70 years and older with ER+ tumors of 2 cm or less. All received lumpectomy and 5 years of tamoxifen and were randomized to radiation or no radiation. Management of the axilla was at the discretion of the treating physician and 200 women in the radiation arm and 203 in the no radiation arm had no axillary surgery. At 12 years median follow up, the risk of axillary relapse was only 3% in women who had no axillary surgery and no radiation; there were no recurrences in women who received radiation. International Breast Cancer Study Group (IBCSG) 10-93 randomized 337 lumpectomy patients age 60 years and older who received tamoxifen and axillary dissection versus no axillary surgery. At 6.3 years median follow up, the risk of axillary recurrence was 1% after axillary dissection and 2% without axillary surgery.

The authors of these and other smaller studies concluded that axillary surgery did not contribute significantly to overall survival or to local control and could be omitted in older patients with favorable ER+ tumors who receive endocrine therapy.

Older patients with clinically palpable axillary nodes should undergo axillary dissection if they are fit enough for surgery. SNB should still be considered in older women with estrogen receptor negative (ER-) tumors if axillary node status will influence systemic therapy or radiation decisions. Frail elderly women may forego axillary surgery unless bulky disease requires excision for local control or symptom relief.

MANAGEMENT OF THE AXILLA IN PATIENTS WITH DUCTAL CARCINOMA IN SITU

Invasive cancer is found at definitive surgery in 10% to 20% of patients with an initial diagnosis of ductal carcinoma in situ (DCIS) on core biopsy. SNB can be performed as a second procedure after lumpectomy but is not possible immediately after mastectomy. As a result, SNB is recommended when mastectomy is performed for DCIS as it adds minimal morbidity and avoids the need for axillary dissection if invasive tumor is found on final pathology. SNB may be considered during lumpectomy for palpable DCIS or large areas of high grade DCIS, where an invasive component is more likely. SNB is routinely performed when core biopsy shows DCIS with any invasion.

When SNB is performed for DCIS or DCIS with microinvasion, micro- or macrometastases will be found in 1% to 2% of cases and ITCs will be present in approximately 10% of nodes examined with IHC. Micro- or macrometastases imply the presence of an occult invasive tumor and are managed as node positive disease. ITCs, however, are not associated with increased risk of local or distant recurrence in patients with DCIS and have no impact on prognosis.

MANAGEMENT OF THE AXILLA AFTER PREOPERATIVE NEOADJUVANT THERAPY

Neoadjuvant chemotherapy trials demonstrated that 35% to 43% of patients with documented positive nodes at diagnosis have no residual axillary disease when axillary dissection is performed after neoadjuvant therapy. A pathologic complete response (pCR) of axillary disease is more common in triple negative and human epidermal growth factor 2 (HER2) positive tumors. In all trials, women with ER+ disease were least likely to obtain a pCR with neoadjuvant chemotherapy or endocrine therapy. Residual disease in the axilla is an important predictor of locoregional and distant recurrence and guides decisions about subsequent systemic therapy and radiation.

For patients receiving neoadjuvant therapy, management algorithms are based on the patient's clinical exam and imaging results at presentation and are modified based on response to neoadjuvant therapy.

CLINICALLY NEGATIVE AXILLA

In the past, SNB was performed prior to neoadjuvant therapy due to concerns that response to therapy might alter lymphatic drainage patterns and reduce the accuracy of node mapping. However, multiple studies supported the use of sentinel node biopsy after neoadjuvant therapy in patients with no palpable axillary nodes at diagnosis. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 trial evaluated SNB after neoadjuvant chemotherapy in 428 patients, finding a 96.6% mapping success rate and a false negative rate of 10.2%, similar to that seen without neoadjuvant therapy. A meta-analysis summarizing 24 studies with a total of 1399 patients found an 89.6% sentinel node identification rate and an 8.4% false negative rate. These studies have confirmed that SNB after neoadjuvant therapy is feasible and accurate.

It is now standard practice to perform SNB after neoadjuvant therapy in patients who present with a clinically negative axilla and to base axillary management on the extent of residual disease. Axillary dissection is not required in patients who have no palpable axillary nodes at diagnosis and have a negative sentinel node after neoadjuvant therapy. Outside of a clinical trial, axillary dissection is performed for patients whose sentinel nodes are positive after neoadjuvant therapy, due to concerns that these positive nodes represent residual disease that benefits from complete surgical resection and radiation.

SNB is now only rarely performed before neoadjuvant therapy, as improved axillary ultrasound and needle biopsy techniques allow minimally invasive axillary node evaluation in patients where detailed pathology evaluation is required for treatment decisions.

Clinically Negative Axilla With Positive Axillary Imaging and Biopsy

Increasing use of axillary imaging at diagnosis identifies metastatic but imaging-negative axillary nodes. Needle biopsy can document that these nodes are pathologically positive, although nonpalpable. Although these patients previously would have undergone neoadjuvant therapy followed by SNB, imaging-based documentation of axillary tumor may lead to a recommendation for a complete axillary dissection that would otherwise have been avoided.

Three randomized controlled clinical trials addressed the question of axillary management in patients with documented positive nodes at diagnosis. The ACOSOG Z1071 evaluated the accuracy of SNB in women with stage II to IIIB disease. Positive axillary nodes were confirmed by fine needle aspiration or core needle biopsy prior to the initiation of therapy; the percentage of patients with palpable nodes at diagnosis was not reported. After neoadjuvant therapy the mapping success rate was 92.9% in patients with cN1 disease and 89.0% in patients with cN2 disease. The false negative rate was 12.6%. The SENTinel Neoadjuvant (SENTINA) trial found an 88.1% mapping success rate with a false negative rate of 14.2%. The Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) trial, which closed early when Z1071 results were published, had an 87.6% mapping success rate and a false negative rate of 8.9%.

In the Z1071 trial one third of patients had a clip placed in their positive sentinel node at the time of diagnostic biopsy. Retrieval of this clipped node during SNB resulted in a false negative rate of only 4.8%, compared with a false negative rate as high as 20% when the clipped node was not removed. Retrieval of a clipped node can be technically challenging but may be easier with seed-based localization techniques than with wire localization.

The Z1071 trial identified other factors that reduced false negative sentinel node results. Use of both radioisotope and blue dye mapping reduced the false negative rate, as did identification of at least three sentinel nodes.

These data support the use of SNB after neoadjuvant therapy for patients with no palpable nodes at diagnosis, where pretreatment axillary imaging identifies positive nodes. Dual tracer mapping should be used and positive nodes should be clipped and retrieved during SNB. Patients whose sentinel nodes are histologically negative after neoadjuvant therapy can be spared axillary dissection. Axillary dissection should be performed for patients whose nodes remain positive after neoadjuvant therapy.

These results are also being extended to include consideration of SNB in patients with palpable positive nodes at presentation whose nodes are no longer palpable after neoadjuvant therapy. Outside of a clinical trial, it may be reasonable to consider SNB in patients with only 1 to 2 positive nodes on initial imaging. The 2015 National Comprehensive Cancer Network (NCCN) guidelines acknowledge that SNB can be considered in patients with positive nodes if the axilla is clinically negative after neoadjuvant therapy.

Axillary dissection remains standard for patients with multiple positive nodes or bulky axillary disease at presentation, for patients with inflammatory cancer, and for patients with positive sentinel nodes after neoadjuvant therapy.

Ongoing Trials of Axillary Management After Neoadjuvant Therapy

Alliance Trial A11202 is evaluating the option of axillary radiation instead of axillary dissection in patients whose axillary nodes remain positive after neoadjuvant therapy. A11202 randomizes patients who become clinically node negative but whose sentinel nodes are positive after neoadjuvant therapy to axillary lymph node dissection (ALND) versus SNB plus axillary radiotherapy.

The NSABP B-51 trial is evaluating the extent of axillary radiotherapy required in women with stage II to III breast cancer whose nodes are negative after neoadjuvant therapy. Mastectomy patients are randomized to chest wall plus regional nodal irradiation versus no radiation, while lumpectomy patients are randomized to whole breast irradiation with or without nodal radiation. These studies will provide answers as to which patients are best suited for axillary dissection versus radiotherapy after neoadjuvant therapy. They will also provide information on whether treatment in the axilla should vary based on receptor subtype.

REPEAT SENTINEL NODE BIOPSY

Repeat sentinel node mapping and biopsy is possible in patients with a new ipsilateral primary cancer or a local recurrence after breast-conserving treatment. Mapping success rates are lower in such patients but if a sentinel node is identified, it is reliable for axillary staging. Several meta-analyses have found that mapping was successful in approximately 65% of patients, with success rates of 80% in patients with prior SNB but only 50% in patients with a prior axillary dissection. Dual tracer mapping should be used and a lymphoscintigram should be considered as up to a third of patients will have alternate drainage to internal mammary nodes or the contralateral axilla.

SENTINEL NODE BIOPSY IN PREGNANCY

Although the radiation dose administered for standard node mapping is low, approximately 1% of annual background exposure, sentinel lymph node biopsy during pregnancy remains controversial. NCCN guidelines state that radioisotope mapping can be used during pregnancy but the use of blue dye is contraindicated. American Society of Clinical Oncology (ASCO) guidelines still state that there is insufficient evidence to recommend SNB in pregnant patients. Generous hydration to facilitate urinary excretion of the isotope and use of a Foley catheter to reduce dwell time of isotope in the bladder may be useful in pregnant patients. Procedures should be discussed with the patient and her obstetrician.

TABLE 1 Patients Undergoing Primary Surgery

Ductal carcinoma in situ	• SNB with mastectomy • No axillary surgery during lumpectomy • Consider SNB during lumpectomy for palpable or large grade 3 DCIS lesions
Invasive breast cancer: node negative: lumpectomy	• SNB−: No further treatment • SNB+: Targeted radiation with systemic therapy • SNB+: 3 or more positive nodes, matted nodes, gross extracapsular extension perform axillary dissection
Invasive breast cancer: node negative: mastectomy	• SNB−: No further treatment • SNB+ • Post mastectomy chest wall and regional node radiation and/or ALND • ALND if results needed for decisions about post mastectomy radiation • ALND if more than 3 positive nodes, matted nodes, gross extracapsular extension
Invasive breast cancer: node positive: nodes, noisy or lumpectomy	• ALND for palpable nodes or multiple positive nodes at the time of surgery

ALND, Axillary lymph node dissection; +/−, ductal carcinoma in situ: −, negative; +, positive; SNB, sentinel node biopsy.

TABLE 2 Patients Undergoing Surgery After Neoadjuvant Systemic Therapy*

cN0 at presentation or cN0 with 1–2 positive nodes on imaging	• SNB after neoadjuvant therapy • No axillary treatment if SNB− • Axillary dissection if SNB+; or • Participation in a clinical trial of axillary management
cN1 at presentation with 1–2 palpable nodes, positive node biopsy	• Axillary dissection if still clinically node positive • Consider SNB if axilla becomes clinically node negative • SNB− then radiation • SNB+ then ALND; or • Participation in a clinical trial of axillary management
cN2 at presentation with 3 or more palpable or imaging positive nodes, positive node biopsy	• ALND; or • Participation in clinical trial of axillary management

*Treatment recommendations are changing for these patients, and participation in a clinical trial should be considered whenever possible.
ALND, Axillary lymph node dissection; −, negative; +, positive; SNB, sentinel node biopsy.

TABLE 3 Special Clinical Circumstances

Pregnant patient	Consider SNB with radiotherapy only
Elderly patient	No axillary surgery for women >70 years with ER+ tumor ≤2 cm who will receive endocrine therapy
Inflammatory breast cancer	ALND

ALND, Axillary lymph node dissection; ER+, estrogen receptor positive; SNB, sentinel node biopsy.

FUTURE DIRECTIONS

Genomic profiling of tumors increasingly informs decisions about the need for chemotherapy in ER+ breast cancer patients. Many ER+ patients with favorable genomic profiles are now treated with endocrine therapy alone, even if axillary nodes are positive. Axillary surgery may become unnecessary for patients with favorable ER+ tumors and clinically negative axillary exams if profiling of core biopsy specimens becomes routine. Surgical staging of the axilla still guides treatment decisions for ER− and HER2+ tumors. Improvements in axillary imaging will continue to influence axillary management.

SUMMARY: ALGORITHMS FOR MANAGEMENT OF THE AXILLA IN BREAST CANCER

Current management of the axilla in breast cancer aims to obtain staging information required for treatment decisions while minimizing interventions. Axillary dissection is avoided whenever possible but remains effective for treating bulky positive nodes (Tables 1 through 3).

SUGGESTED READING

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Inflammatory Breast Cancer

Pridvi Kandagatla, MD, and Lisa A. Newman, MD, FACS

Inflammatory breast cancer (IBC) accounts for only 1% to 5% of all new breast cancer cases. Its hallmark clinical presentation features an edematous breast, with prominent skin thickening. This unusual pattern of disease is typically evaluated as a separate biologic entity when compared to non-IBC because of its substantially higher rates of locoregional as well as distant organ failure rates and correspondingly lower survival rates. Population-based data from the Surveillance, Epidemiology and End Results program have demonstrated increasing IBC incidence rates in the United States over the past few decades and it is more common among African American compared to white American women. Median age at diagnosis is 49 to 55 years, typically occurring 5 to 10 years younger than non-IBC patients. Because of its inherently aggressive nature, IBC is typically managed with a rigorous multidisciplinary approach in terms of initial diagnostic workup as well as treatment, which usually includes neoadjuvant chemotherapy followed by modified radical mastectomy and postmastectomy radiation. Individualized adjuvant therapies will depend on tumor biomarker expression, response to primary systemic therapy, and the patient's menopausal status.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

As its name implies, IBC presents as an inflamed-appearing breast with generalized edema and skin thickening, which is often referred to as peau d'orange. The spectrum of IBC symptoms is broad: some patients have diffuse breast involvement associated with skin dimpling and nipple retraction, others have more subtle findings, with only faint central skin erythema, and these symptoms can be particularly challenging to discern in women with darker skin tones.

IBC can be categorized as one of three different types: primary IBC, secondary IBC, and locally recurrent breast cancer presenting as IBC. International IBC experts have defined primary IBC as those cases where the breast symptoms had a rapid onset (within 3–6 months) and where at least one third of the breast skin is involved. Secondary IBC implies the presence of an untreated/neglected breast cancer that progressed into an inflammatory state. Sadly, some patients will experience an inflammatory recurrence following appropriate treatment for an early stage breast cancer. Regardless of the prior cancer history, the clinical management of all three IBC patients is the same.

The most common condition that can masquerade as IBC is mastitis, and if other clinical symptoms suggest an infectious etiology (e.g., fever, history of previous mastitis) then it may be reasonable to give the patient a trial of antibiotics as initial management. If symptoms do not respond promptly within a week, however, then continued workup to rule out IBC is indicated. Rarely, congestive heart failure can present with unilateral breast edema and skin thickening; these patients will usually have other symptoms of cardiac dysfunction but nevertheless should be monitored for resolution of their breast findings as the cardiac condition is treated. Granulomatous mastitis and breast lymphomas can also mimic IBC; these conditions will also require diagnostic biopsy workup.

The initial imaging workup for a patient presenting with IBC symptoms should include a mammogram and targeted breast ultrasound; axillary ultrasound should also be performed when local resources allow, to permit more definitive assessment of regional involvement. Mammographic imaging should be bilateral to evaluate for asymmetric skin thickening and/or occult contralateral pathology. The involved breast may reveal diffuse malignant microcalcifications or multiple satellite tumors; however, some IBC patients will have skin involvement but no discrete tumors within the breast itself.

Diagnostic biopsy for IBC can be performed as a percutaneous core needle biopsy (usually with a 14- or 16-gauge device and at least 3 to 4 passes to extract an adequate amount of tissue) or a full thickness skin punch biopsy (using a 4- or 6-mm-diameter device). The choice between these two options is based on clinical judgment—patients with an obvious and highly suspicious palpable mass can be successfully biopsied by a core needle, but a punch biopsy might be preferable in situations where the skin findings predominate. Alternatively, a combination of these biopsy approaches can be offered, in which case the skin punch biopsy site serves as the point of entry for the core needle device. An image-guided percutaneous core needle biopsy can also be considered when resources are available, either in the form of a stereotactic biopsy if the mammogram provides a readily accessible target or as an ultrasound-guided biopsy of a mass lesion or suspicious axillary lymph node. If the percutaneous biopsy approaches are nondiagnostic in the setting of a patient that has persistent clinical findings suspicious for IBC, then it is appropriate to pursue a surgical incisional biopsy to resect a sample of skin and underlying breast tissue.

The histopathologic features supporting an IBC diagnosis is the presence of cancer cells within the dermal lymphatic plexus, and these tumor emboli account for the clinical symptoms. Dermal lymphatic involvement, however, is not an essential diagnostic feature. Any biopsy confirming the presence of invasive breast cancer associated with the clinical impression of IBC is adequate for establishing a diagnosis of IBC. The majority of IBC cases are high-grade tumors with invasive ductal features, but invasive lobular and other histopathologic patterns have been reported.

Immunohistochemistry evaluation of the invasive component of the diagnostic biopsy material is essential; the pathologist should ensure that biomarkers are not inadvertently assessed on an associated in situ component instead. American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines define any expression (≥1%) of either estrogen receptor or progesterone receptor as being hormone receptor positive and these cases will be referred for endocrine therapy. HER2/neu expression scores of 0 or 1+ are considered negative and 3+ as positive; cases with an intermediate score (2+) are tested amplification of the HER2/neu gene by fluorescent in situ hybridization (FISH). Patients with HER2/neu overexpressing IBC are candidates for targeted anti-HER2 therapy. Cases that are negative for all three biomarkers are described as triple-negative breast cancer (TNBC). IBC can feature any combination of these markers, and systemic therapy is planned accordingly. While frequency distributions of the various phenotypes varies widely across different studies, approximately half of IBC cases will be hormone receptor positive, 20% to 30% will overexpress HER2/neu, and approximately one quarter are TNBC. Additional markers can be performed selectively, based on institutional pathology preferences. IBC usually overexpresses the cell adhesion protein E-cadherin and the markers of proliferative activity such as Ki-67.

The American Joint Committee on Cancer (AJCC) TNM staging system automatically designates any IBC case as T4d (regardless of whether any discrete measurable tumor mass is present), nodal and metastatic status are categorized on the basis of clinical and imaging findings. The AJCC eighth edition staging system accounts for tumor grade and biomarker expression as well in assigning an overall clinical and/or pathologic stage for nonmetastatic IBC; these features will determine between an overall stage of IIIA, IIIB, or IIIC.

INITIAL STAGING WORKUP AND SPECIAL REFERRAL CONSIDERATIONS

Approximately one third of IBC cases will have clinically evident distant organ metastatic disease at time of diagnosis, and body

imaging to evaluate extent of disease is therefore routinely recommended. Options include computed tomography (CT) scans of the chest, abdomen and pelvis in conjunction with bone scan or positron emission tomography (PET) CT scan. PET CT imaging may be more challenging to schedule because of preauthorization policies of the third party payer. Brain imaging may be considered in cases where symptoms suggest neurologic involvement. If body imaging reveals foci suspicious for metastatic disease, biopsy of at least one site is usually recommended as a confirmatory procedure, and to reevaluate biomarker expression. Baseline evaluation with either echocardiogram or multigated acquisition scan is often necessary as well to assess cardiac function prior to exposing the patient to cardiotoxic chemotherapy.

Supplemental breast imaging (beyond the initial diagnostic mammography and ultrasound) can be considered as well. Breast magnetic resonance imaging (MRI) may clarify the extent of disease on the chest wall as well as in the contralateral breast. MRI has also been recommended as a sensitive strategy for monitoring response to neoadjuvant chemotherapy. Photographs of the breast entered into the electronic medical record can serve as a valuable strategy for documenting the baseline clinical status and subsequent treatment response.

Referrals for genetic counselling and testing are made on the basis of standard criteria regardless of IBC versus non IBC status. Young age at diagnosis (any phenotype, up to age 50 years), TNBC diagnosed up to age 60 years, bilateral breast cancer, family history of breast and/or ovarian cancer, and male breast cancer are all considered indications for genetic risk evaluation by the National Comprehensive Cancer Network.

As with non IBC, premenopausal IBC patients should undergo counseling regarding contraception that is non hormonally active, as a pregnancy would complicate treatment recommendations. Fertility preservation counseling should also be offered. Premenopausal IBC patients with hormone receptor-positive disease will be candidates for ovarian suppression as a component of their endocrine systemic therapy.

MANAGEMENT

General Management Considerations

IBC is considered inoperable at presentation, and primary treatment is in the form of systemic therapy. Selection of initial systemic therapy will be influenced by patient age and comorbidities, extent of disease imaging, and biomarker expression, but combination chemotherapy is typically recommended whenever feasible, in order to obtain prompt control of both locoregional and distant disease (macrometastatic or micrometastatic). Despite the adverse prognostic significance of the IBC diagnosis, curative intent multimodality therapy (neoadjuvant chemotherapy followed by surgery and postmastectomy radiation) is usually recommended when the baseline imaging is negative for macrometastatic foci to distant organs (Fig. 1). Elderly patients with multiple comorbidities may be considered for primary endocrine therapy if initial immunohistochemistry shows strong hormone receptor expression.

Patients with overt macrometastatic disease detected on baseline body imaging (stage IV IBC) are considered as having incurable disease, and a palliative treatment plan will be designed. This may involve radiation therapy to control symptomatic brain or bone metastases. Systemic therapy will be determined by biomarker expression as well as the patient's ability to tolerate general poly drug chemotherapy. Control of locoregional symptoms remains important in these patients, if not achieved with primary systemic therapy, then chest wall radiation or a palliative mastectomy may be considered. Young and physically fit patients with minimal distant organ involvement (oligometastatic disease) may be approached initially with aggressive neoadjuvant chemotherapy, followed by transition to a "pseudo" curative intent multidisciplinary treatment plan based on extent of response to the primary systemic therapy.

Preoperative Management

If the baseline body imaging is negative for overt metastatic disease, then a curative intent IBC management plan is indicated. This includes neoadjuvant chemotherapy (to address micrometastases), followed by modified radical mastectomy, postmastectomy locoregional radiation, and additional endocrine and/or targeted anti-HER2/neu therapy based on biomarker expression.

Neoadjuvant chemotherapy for curative intent treatment will usually include several cycles of an anthracycline and a taxane; conventional schedules are infused every 3 weeks, to maintain adequate activity of platelets, red blood cells, and white blood cells (which have a lifespan of approximately 3 weeks). Dose-dense schedules can improve efficacy by delivering altered doses at shorter intervals (every 1–2 weeks). Advances in bone marrow supportive therapies can improve eligibility for dose dense schedules. Chemotherapy induced alopecia is another expected adverse effect of regimens that are used for breast cancer, but recent prospective randomized clinical trials have proven the safety of scalp cooling technologies to reduce the incidence of this toxicity. These devices are costly and not typically covered by public or private health insurance plans.

Patients with HER2/neu overexpressing IBC will receive targeted therapy with trastuzumab in conjunction with the combination chemotherapy regimen, given as an infusion every 3 to 4 weeks for 1 year. Anti-HER2 therapy can exacerbate the cardiotoxicity of anthracyclines, and cardiac function therefore must be monitored. Dual-agent targeted therapy with pertuzumab in addition to trastuzumab can synergistically improve response rates.

More than three-quarters of patients receiving neoadjuvant chemotherapy will have a response that renders operable disease. Post-treatment response should be assessed with a follow up mammogram and ultrasound; selected patients may undergo a breast MRI as well. IBC patients were typically excluded from participating in prospective randomized trials of breast conserving surgery and sentinel lymph node biopsy. The well documented substantially higher rates of locoregional failure related to the high burden of diffuse microscopic skin and nodal involvement associated with IBC has therefore resulted in modified radical mastectomy being the mainstay of surgical management, regardless of the apparent extent of clinical response to neoadjuvant chemotherapy.

Surgical Management

Surgery is scheduled to occur 3 to 4 weeks after infusion of the final neoadjuvant chemotherapy course, and preoperative blood work should confirm adequate platelet count (preferably more than 75,000 per μL) and absolute neutrophil count (preferably at least 1,000 per μL). Ideally, surgery should be performed sooner than 12 weeks after final chemotherapy infusion, to minimize risk of disease progression. Frozen section analysis of the superior and inferior mastectomy skin edges may be considered to facilitate margin control in cases where residual, indeterminate skin changes persist. A standard level 1 and 2 axillary lymph node dissection is performed, along with resection of any suspicious level 3 tissue.

Immediate breast reconstruction is generally discouraged in IBC patients because of concerns that the increased complication rates of the more extensive surgery could delay completion of any necessary postoperative treatment. Furthermore, the postmastectomy radiation therapy that is indicated for IBC patients can compromise the cosmetic results of immediate reconstruction. Similarly, contralateral prophylactic mastectomy is also discouraged, and patients are recommended to prioritize the necessary treatment for the cancer-at-risk. Consideration of surgery to reduce the risk of a new primary tumor. Contralateral prophylactic mastectomy or contralateral reduction mammoplasty may be considered in patients with large, pendulous breasts if a unilateral mastectomy is expected to cause substantial symptomatic chest wall imbalance and/or quality of life disruption.

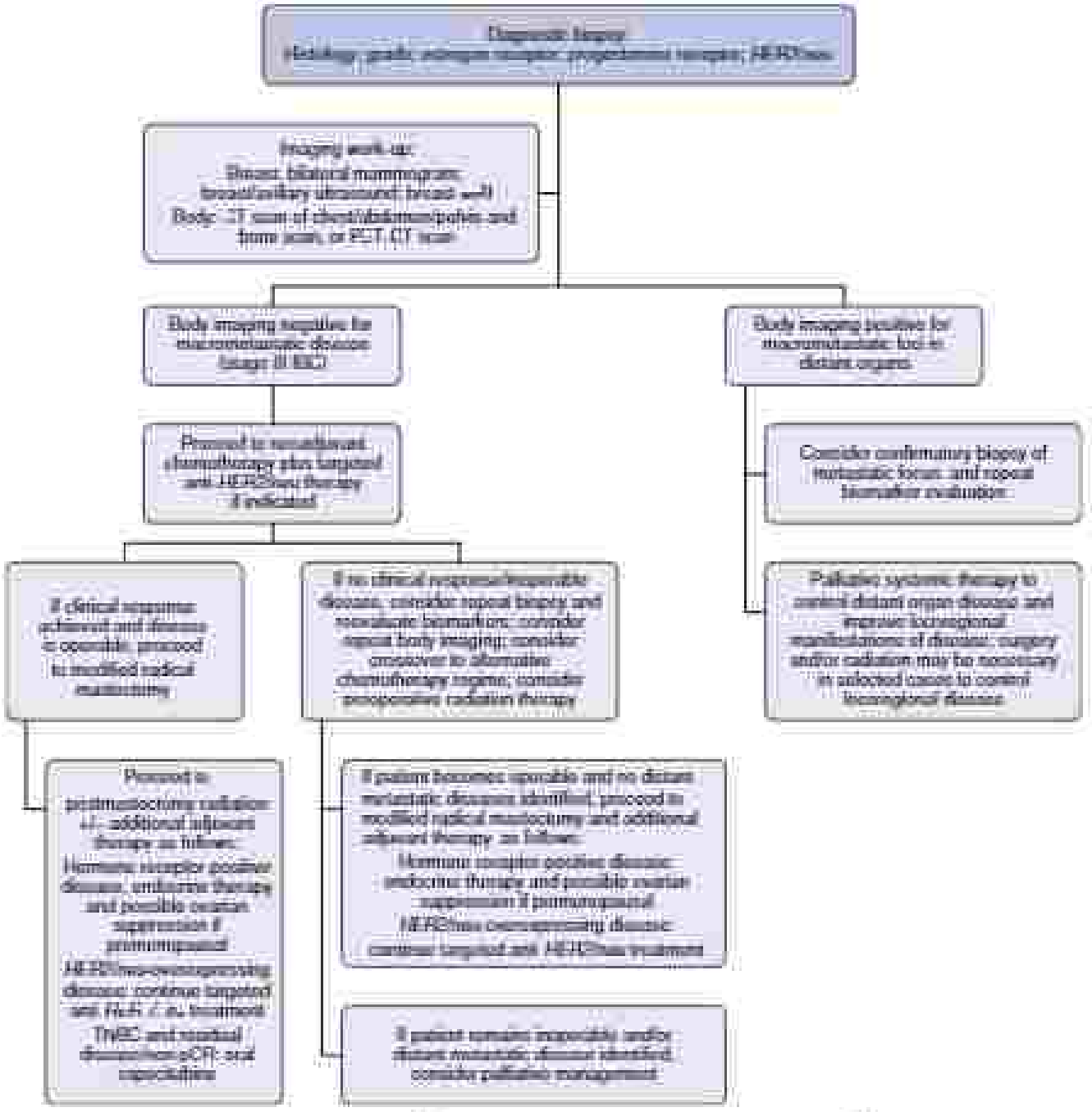

FIG. 1. Inflammatory breast cancer management algorithm. CT, Computed tomography; IC, inflammatory breast cancer; MR, magnetic resonance imaging; pCR, pathologic complete response; T/CT, positron emission tomography-computed tomography; TNBC, triple negative breast cancer.

Postoperative Considerations and Postoperative Management

The modified radical mastectomy surgical pathology specimen should be evaluated for extent of residual disease in the breast and lymph nodes. Immunohistochemistry to reevaluate hormone receptor and HER2/neu expression on residual malignant tissue is indicated. Evidence of treatment response (fibrosis, ghost cells) should also be documented. The presence of a pathologic complete response (pCR, no residual disease in the breast as well as axilla) is prognostically favorable but occurs in fewer than one third of cases. A complete response to neoadjuvant chemotherapy is more likely among tumors that are HER2 overexpressing and managed with targeted therapy, as well as cases of TNBC. Unfortunately, however, TNBC cases that do not achieve a pCR have a disproportionately worse outcome compared to non-TNBC cases with a non-pCR response; this is commonly described as the TNBC paradox. Recently, however, TNBC patients with a non-pCR following neoadjuvant chemotherapy were shown to benefit from receiving a 6 months of oral capecitabine as postoperative/adjuvant therapy, based on results from a prospective randomized trial conducted in Japan (Capecitabine for Residual Cancer as Adjuvant Therapy [CREATE]-X). This approach has been rapidly adopted elsewhere despite the fact that the number of IBC participants in this trial is unclear. Non-TNBC cases with complete biomarker driven adjuvant endocrine and/or targeted anti-HER2 therapy

Postmastectomy radiation is recommended for consolidation of locoregional management. These treatments typically begin 3 weeks after surgery, when the surgical drains have been removed and the patient is able to comfortably accommodate extremity positioning so that the arm is elevated up over the head. The radiation targets are designed with CT assistance to cover the soft tissue regions at highest risk for chest wall recurrence because of microscopic residual disease beyond the surgical resection field: the mastectomy skin flaps and underlying pectoralis musculature; the infraclavicular and supraclavicular regional nodes; the internal mammary chain is usually included as well. These treatments are usually delivered in daily fractions over 5 to 6 weeks to reach a cumulative dose of 5000 to 6000 rads. Left-sided postmastectomy radiation should include treatment planning that attempts to protect the heart, and clinical trials are underway to explore alternative imaging and radiation techniques to achieve this goal.

As noted previously, targeted anti-HER2/neu therapy is initiated during neoadjuvant chemotherapy for HER2 overexpressing cancers and continued to complete a 1 year course. Endocrine therapy is initiated after completion of neoadjuvant chemotherapy to avoid the risk of reducing chemotherapy effectiveness through its cytostatic effects. Tamoxifen (a selective estrogen receptor modifying agent) can be used in premenopausal or postmenopausal patients. Aromatase inhibitors can only be used in patients that have undergone natural menopause or in patients whose ovarian function has been ablated by surgical oophorectomy, pelvic radiation, or medical ovarian suppression. Advantages of medical ovarian suppression include its reversibility as well as its potential to protect fertility when administered during chemotherapy treatments. Tamoxifen is associated with an increased risk of venous thromboembolism, and so institution of this medication should be avoided until after surgery has been completed, or it should be withheld at least 2 weeks preoperatively to minimize postoperative deep vein thrombosis and pulmonary embolism complications.

Management of Chemoresistant Disease

IBC patients that appear to have clinically inoperable/unresectable disease following neoadjuvant chemotherapy can be considered for crossover to an alternative systemic therapy regimen. Repeating the body imaging may be useful in these patients to determine whether disease is progressing to distant organs; this information may influence the ultimate treatment goals and plans. Some patients will experience tumor necrosis that mimics chemoresistance, and follow up breast imaging may assist in distinguishing between these two situations. Repeat breast biopsies may also be indicated in these patients to confirm persistent disease and to reevaluate biomarker expression. Tumor heterogeneity may yield a phenotype that differs from the original biopsy and might influence choice of systemic therapy. Patients with definitively unresectable disease can be referred to receive preoperative radiation therapy in an attempt to improve resectability.

Mastectomy is occasionally indicated in IBC for palliative intent to control bulky or ulcerated disease that fails to respond to systemic therapy and/or radiation treatments. In these circumstances, assistance from the plastic surgery team may be necessary to provide latissimus dorsi flap or skin graft coverage of the resulting chest wall defect.

Prognosis

Contemporary multidisciplinary management of IBC has resulted in improved outcomes. For stage III IBC, rates of locoregional recurrence at 5 years range from 5% to 39% in patients receiving trimodality therapy (neoadjuvant chemotherapy, modified radical mastectomy, and postmastectomy radiation). Five year overall survival rates are 40% to 70%, and median survival times range from 2 to 4 years. Biomarker expression/phenotype and extent of response to neoadjuvant chemotherapy influence prognosis heavily. A recent series from the Mayo Clinic demonstrated that 5-year disease free survival was 36% for estrogen receptor–positive HER2/neu–negative IBC; 82% for HER2/neu–overexpressing disease; and 33% for triple-negative IBC. The prognosis of stage IV IBC remains particularly low, with fewer than 15% surviving 5 years.

SURVEILLANCE AND SURVIVORSHIP

IBC patients require long-term multidisciplinary follow-up. Clinical evaluation every 3 to 6 months is indicated to assess for any symptoms of chest wall, regional nodal, or distant organ failure. Contralateral mammography should be performed annually to screen for a new breast primary. Physical therapy is usually indicated to prevent and/or control lymphedema, which occurs in approximately 40% of patients undergoing an axillary lymph node dissection as well as postmastectomy radiation. Monitoring should also include assessments for impaired cognitive function, cardiac toxicity, and osteoporosis resulting from multidrug therapies.

FUTURE DIRECTIONS

Ongoing research seeks to identify additional biomarkers and technologies that may improve breast cancer outcomes. The role of these advances in IBC is uncertain, and warrants further study. Examples of such strategies include poly ADP ribose polymerase (PARP) inhibitors for patients with BRCA mutations; the addition of platinum agents to neoadjuvant chemotherapy regimens; and circulating tumor cells or cell free DNA as screening/surveillance tools. For locoregional management, lymphovascular bypass or alternative lymphatic grafting procedures can potentially reduce rates of lymphedema.

Suggested Readings

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Ductal and Lobular Carcinoma in Situ of the Breast

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Ductal carcinoma in situ (DCIS) of the breast and lobular in situ neoplasia (LISN) represent neoplastic cells within the basement membrane of the terminal ductal lobular units of the breast. DCIS is a nonobligate precursor for progression to invasive disease. While the etiology and pathogenesis of in situ neoplasia remains uncertain, DCIS has become a frequently detected histologic feature of breast screening programs. Currently, 20% to 25% of "breast cancer" detected by mammography is DCIS alone. Standard of care for DCIS follows the established treatments for invasive breast cancer: complete excision of the DCIS with a clear margin (potentially followed by breast radiotherapy and endocrine therapy) or mastectomy. LISN, usually detected as an incidental finding also via breast screening, does not present the same risk of progression to invasive disease and, contrary to popular belief, is not usually bilateral at presentation (Maxwell 2016) only the rare, pleomorphic, variant should be considered equivalent to, and treated like, DCIS.

DIAGNOSIS

The diagnosis of DCIS is usually made as an impalpable lesion detected by breast screening mammography demonstrating microcalcifications and/or tissue distortion (Fig. 1). More extensive DCIS may demonstrate a mass effect visible on ultrasound or present as a palpable lump. Magnetic resonance imaging may also be utilized to demonstrate the extent of DCIS. Confirmation of DCIS is best made by core needle biopsy with radiologic confirmation of the presence of microcalcifications in the core (Fig. 2) and subsequent histopathology (Fig. 3). The inevitable selective sampling of areas of DCIS may miss invasive disease in 10% to 20% of lesions, although the risk of under-calling may be reduced by the use of wide bore (7–9 gauge) vacuum assisted stereotactic guided needle biopsy. At the time of diagnostic biopsy, placement of one or more radiologic markers (Fig. 4) will facilitate subsequent localization for surgery. The pathology diagnosis of DCIS may be challenging with a spectrum of neoplastic changes ranging from benign atypical ductal hyperplasia via DCIS, through micro invasive penetration of the basement membrane to overtly invasive disease. The natural history of DCIS has been little studied, but if not operated on may develop into invasive disease (Maxwell et al., 2018). The likelihood and timing of invasive progression varies from low grade through intermediate and to greatest in high grade DCIS (Table 1). The risk of progression may be reduced by endocrine therapy.

Given the uncertainty of progression from DCIS to invasive disease, there are currently trials in progress around the world studying the potential for nonoperative intervention for those women with low risk of DCIS progression to invasive disease. The active surveillance trial in the United States, COMET (Comparing an Operation to Monitoring With or Without Endocrine Therapy) trial is restricted to women with low risk DCIS for progression to invasive breast cancer (criteria including age 40 years or greater, low- or intermediate grade DCIS, no palpable mass, estrogen receptor–positive DCIS). However, for the majority of women with DCIS, surgical management as outlined below remains guideline concordant care.

Surgical planning for DCIS should consider breast conservation surgery (segmental mastectomy) versus mastectomy and only where appropriate (at the time of mastectomy, not breast conservation) sentinel node biopsy (Ansari et al., 2008). The aim of modern surgery for DCIS is to excise the DCIS with an adequate margin (Morrow et al., 2016) to reduce the likelihood for future development of invasive disease or further occurrence of DCIS.

BREAST SURGERY

Segmental mastectomy (breast conservation surgery) or mastectomy are the key surgical options for surgery for DCIS (or pleomorphic lobular carcinoma in situ). LISN, unless of the rare, pleomorphic, variety does not require resection; use of core biopsy (including wide gauge vacuum assisted core) should ensure lobular invasive breast cancer is excluded. The choice of operation is made in discussion between the patient and her surgeon considering the relative size and site(s) of the DCIS, in relation to the size, shape, and volume of the breast. It may be technically possible to locally excise more than one region of DCIS, potentially to a maximum of three or four lesions, although the balance between multiple excision(s) and the potential for mastectomy with or without reconstruction should be considered.

BREAST CONSERVATION

For breast conservation (segmental mastectomy or wide local excision) the principles of excision of the DCIS, which is often impalpable, are to use a localization technique to maximize the opportunity for complete excision at a single operation with a currently recommended margin of 2 mm (Morrow et al., 2016).

Localization

Localization of the DCIS may be by use of one or more wires, seeds, or alternative localization techniques. These techniques aim to delineate the DCIS either by placing one marker in the lesion or by bracketing with two or more markers the DCIS to guide surgical excision.

Wire localization has historically been the principle method of localization for DCIS. Placement of one or more hooked wires by image guidance shortly before surgery can be achieved using the ipsilateral (mammographic) placement or, if a marker has previously been placed in the DCIS at the time of diagnostic core biopsy, using ultrasound to place the wire in the correct region if visible on ultrasound. Following deployment of the hooked needle via image guidance, the end of the wire passing out of the skin of the breast needs to be protected as the wire itself has the potential for displacement or accidental removal.

Recently, one or more markers placed in or demarcating the volume of DCIS to be resected has been practiced, as the marker seed can be placed the day (or more) before surgery and is less likely to be dislodged than a wire. In general, three categories of marker seed are in common usage: the radioactive Iodine 125 seed (which can be readily detected percutaneously over several days and months), a ferrous seed (Magseed; detected by use of a magnet probe) (Fig. 4) or microscopic radar detected reflector (SAVI SCOUT). Each technology has its advocates and detractors: the Iodine seed requires key radioactivity processes, protections and procedures to be in place; the Magseed probe cannot be used adjacent to ferrous surgical instruments (titanium or plastic retractors and instruments can be used) and the SAVI SCOUT® may be deactivated by the inadvertent close use of diathermy. Most surgeons who have moved from the use of wire guidance to seed localization (of whichever type) seem to prefer the seed localization method.

Using the seed based approach, a detector for whichever seed is deployed is used to identify the localized lesion and guide the resection. Prior to commencing the incision, care should be taken to identify the position of the seed or seeds and mark the skin of the breast (Fig. 5). Post seed placement mammograms and sometimes

FIG. 1 Ductal carcinoma in situ detected on mammography with the microcalcifications and right mass distortion reflecting the extensive ductal pathology.

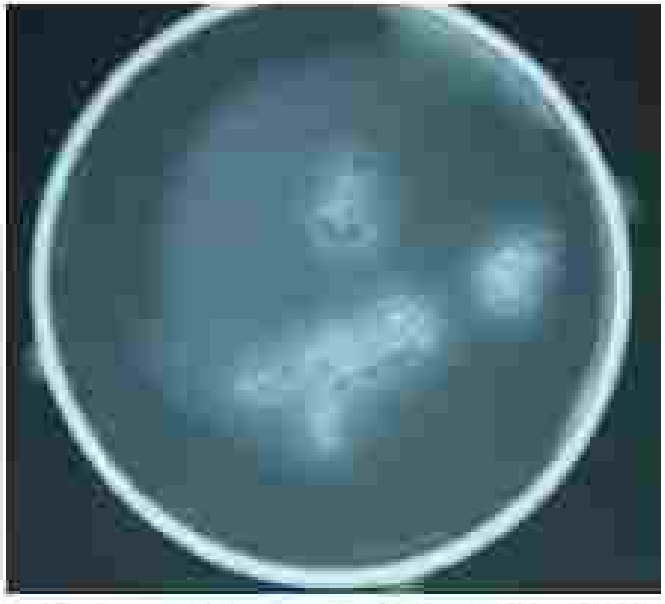

FIG. 2 Radiograph of cores demonstrating the microcalcifications and ductal carcinoma in situ.

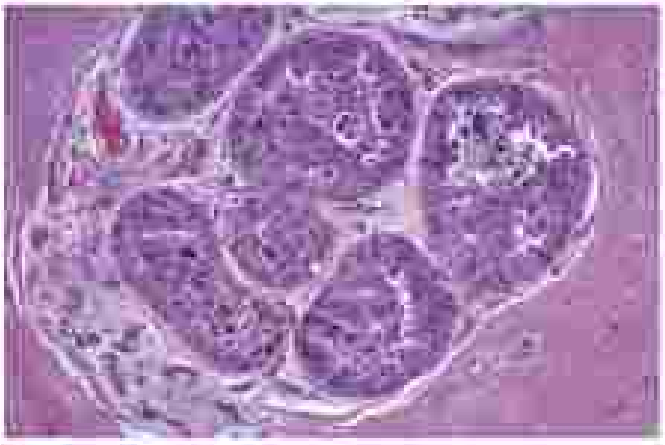

FIG. 3 Example of the pathologic appearance of ductal carcinoma in situ on hematoxylin and eosin staining.

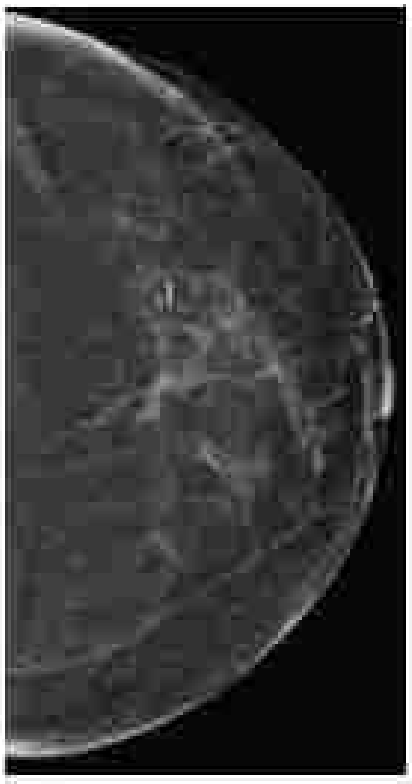

FIG. 4 Localized ductal carcinoma in situ with a marker clip and a negative seed (Pegseed).

the skin puncture wound from seed placement can be helpful to guide the approximate location of the seed or seeds and hence the tattoo for resection (see Fig. 5). The anticipated extent of the DCIS to be resected can then be outlined and thereafter the surgical incision placement determined (see Fig. 6).

Sentinel node biopsy should not be performed at the time of breast conservation in the setting of DCIS alone (Amant et al., 2008). Should there be an upgrade of the DCIS to identify invasive breast cancer, sentinel lymph node biopsy may be performed as a second procedure. This balances the low risk of upgrade (10%–20%) and need for a second procedure in such patients to perform a sentinel lymph node biopsy versus the unnecessary axillary surgery that would otherwise be conducted in the majority of women, with the risk of upper limb lymphedema of 4% to 10% even after sentinel lymph node biopsy.

Incision

In general, incisions can either be placed directly over the DCIS to be resected, preferably using skin lines (Fig. 6) (sometimes called Langer's lines or Dupuytren's lines), or placed distant from the lesion using the circumareolar junction between the areolar and breast skin (see Fig. 5 and Fig. 6). Rarely, however, they can be placed at the margin of the breast where it joins the chest wall laterally or inferiorly (see Fig. 6).

TABLE 1 Progression of Ductal Carcinoma in Situ (DCIS) to Invasive Disease (after Maxwell et al 2018)

Grade of DCIS	Cumulative incidence of invasion at 10 months	Cumulative incidence of invasion at 150 months
Low grade	10%	20%
Intermediate grade	20%	30%
High grade	40%	55%

Data from Maxwell AJ, Clements K, Hilton B, et al. Risk factors for the development of invasive cancer in unresected ductal carcinoma in situ. Eur J Surg Oncol. 2018;44:620–625.

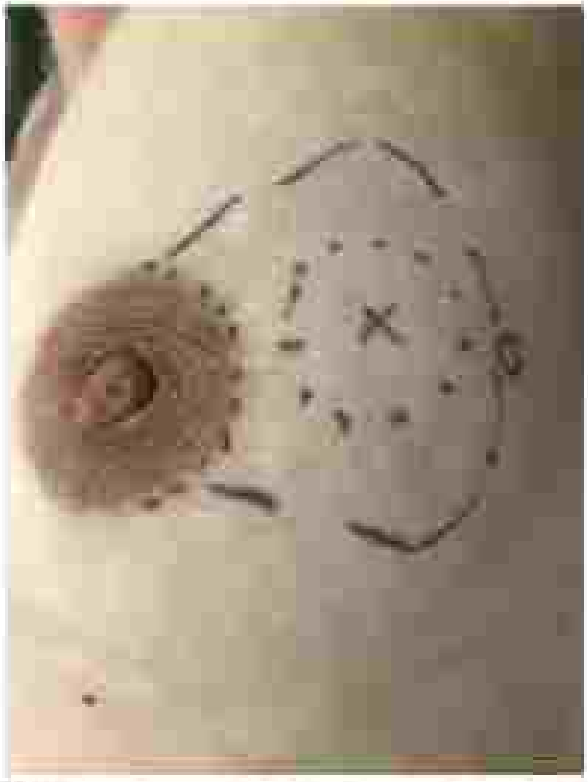

FIG. 5 Markings prior to surgical lesion demonstrating the detectable mass (marked x); the false circular impression where the mass disappears under gentle applied pressure on the skin; the skin puncture (pinch) from mass placement; the circumareolar incision mark and the extent of the breast skin flap to be raised to excise the area of ductal carcinoma in situ excision.

Incision placement does not need to be directly over the DCIS to be resected, with techniques to raise skin flaps and thus tunnel to the lesion technically possible (see Fig. 5), as for invasive disease. Great care is required when raising the flap to ensure that the overlying skin is not damaged and good visualization with gentle tissue retraction (Fig. 7) needed to ensure the correct tissue is targeted and removed. Either sharp or diathermy dissection may be employed to raise the flap and thus allow subsequent dissection around the local, used DCIS. Frequent use of the appropriate probe (Fig. 8) to detect the needle and ensure sufficient tissue is taken should be a primary concern, while identifying and securing bleeding points. Particular care is required with the hollow needle technique not to use suction (as the tissue may be aspirated into the suction apparatus) for this foreign

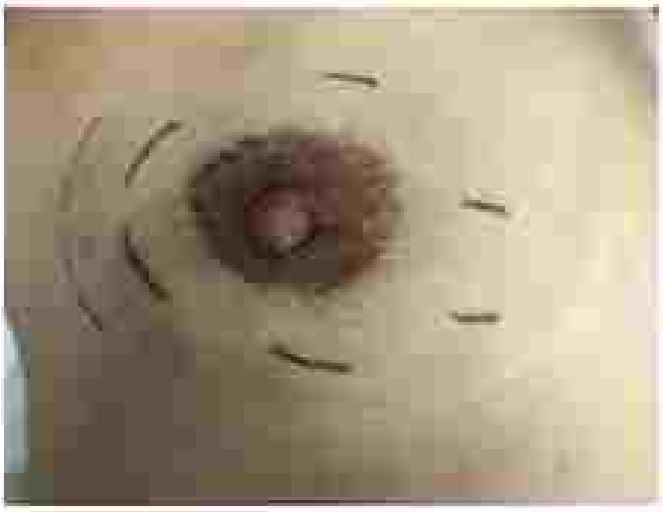

FIG. 6 Skin line markings around the breast. Note the direction of the final incision may be distinctly different from those secondly. Circumareolar and margin of lesion approaches are also marked.

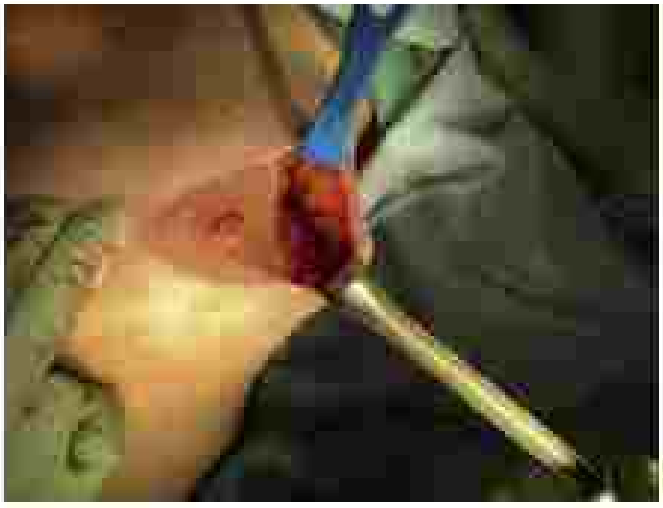

FIG. 7 Patient from Fig. 5 with the skin flap raised and the ductal carcinoma in situ already removed. This image also illustrates two different types of retractor: the *curved retractor (blue)* to avoid transection of diathermy to the skin and a *gentle retractor (for use with the hollow wire probe)*.

need, to use nonmetallic instruments, for the radio transmitter technique, not to place the diathermy too close to, and hence inactivate, the wire.

The relationship between the excision/resection, whether conducted with scissors or diathermy and the lesion should aim to completely excise the DCIS with ultimately a technically adequate margin (2 mm or more circumferentially) (Morrow et al., 2016), recognizing that there will rarely be a palpable lesion or margin to guide the surgeon's fingers. It is unusual to take the skin overlying the DCIS lesion or the needle tract in modern approaches to breast surgery. There is a very low risk of DCIS seeding along the needle tract and the resection of skin may distort the final cosmetic appearance of the breast. The resection may go down as far as the pectoral fascia, which will not be transgressed by the DCIS, if the lesion is posteriorly located in the breast, and may need to take the superficial tissue up to the subcutaneous fat and dermis for superficially placed DCIS.

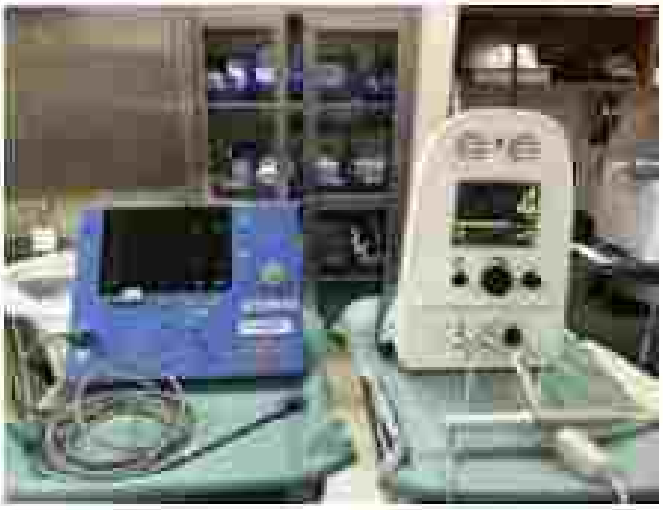

FIG. 8 Neoprobe seed detector which can detect iodine-125 seeds (left), and the Magseed detector (right), with the probe inside. ... Detector probe is used like pencil to detect seeds. The probe is placed into a plastic sheath to maintain sterility.

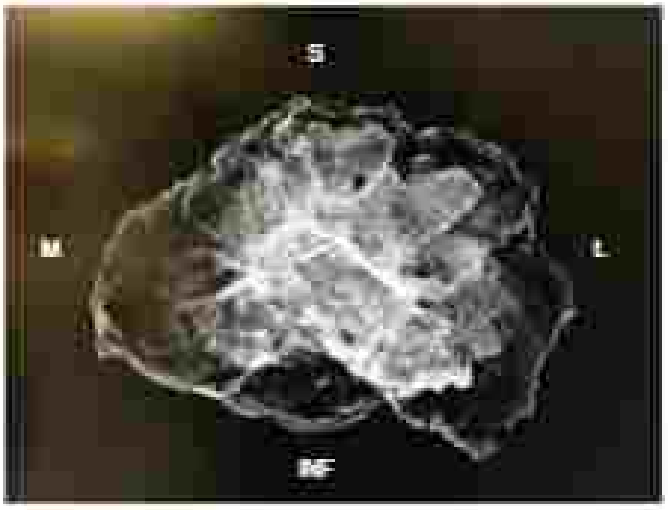

FIG. 10 Specimen radiograph of Fig. 9 demonstrating the centrally based steel and marker clip with wire margins. IN, inferior; L, lateral; M, medial; S, superior.

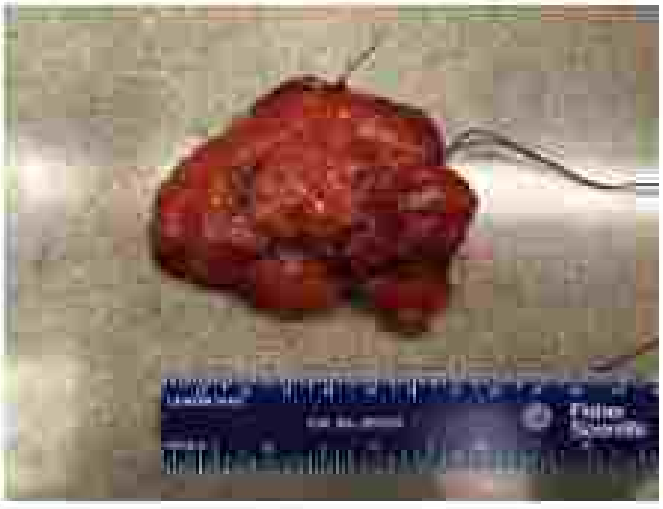

FIG. 9 Specimen oriented and marked with a short (superior) silk suture and long (lateral) suture for orientation.

Once removed, care is required to mark the orientation of the specimen for subsequent imaging and pathology orientation (Fig. 9). Some surgeons prefer to place the marking sutures or clips prior to finally removing the segment of breast to avoid errors of orientation as the tissue is removed from the breast. However, using the same markings and communicating to the pathology and imaging colleagues the markings used (e.g., short suture superior, long suture lateral), whether the lesion is from the left or right breast, and the position on a theoretical clock face on the breast are all helpful. The specimen should be imaged to ensure the model or wire is present in the specimen and for guidance for pathology (Fig. 10). It can be very helpful for the pathology team to section the resected mass and take further radiographs to demonstrate the likely resected margins, and whether any calcifications appear to be close to the margins. This may then guide the surgeon whether to take additional margins either guided by the imaging interpretation or possibly to perform cavity shavings if that is the practice of the surgeon operating.

Marking the site of the resection, once hemostasis has been established, is helpful if postoperative radiotherapy is to accurately target the resection bed. Either using several titanium based clips (e.g., Ingenuity clips) or a device inserted in place such as the Bmarq locator may facilitate such localization especially when the surgical skin incision is distant from the resection bed (see Fig. 5). These locators can usually be seen clearly on postoperative mammograms, CT planning for radiotherapy, and used to inform the design and delivery of postoperative radiotherapy if it is to be administered.

Tissue mobilization is often required to close the defect created by removal of the breast tissue harboring the DCIS. This can be achieved either by minor, local mobilization of the breast or by mobilization of the breast on the underlying chest wall and separating the breast from the overlying skin. Indeed, rotating breast tissue to fill the defect and using a few well placed absorbable sutures to maintain placement is usually effective in closing the defect while not creating skin tethering distortions. Alternatively, those who have undertaken experience to raise and place such a flap securely may deploy more advanced flap rotation techniques for larger defects, such as a lateral thoracoepigastric perforator flap.

Wound closure should employ dissolving sutures (e.g., 3.0 Vicryl) to appose the deeper tissues and the subcutaneous plane. Subcuticular sutures and/or skin glue (e.g., Dermabond) or paper adhesive strips complete wound closure. No drain should be necessary with this breast conservation approach and with support from a brassiere provided by the patient, normal upper limb movement and activities should be encouraged. By not using additional skin dressings, the patient may bathe as per normal from the next day.

Several experimental techniques are currently under investigation to provide intraoperative reassurance that resection margins around the DCIS are sufficient (at least 2 mm) (Morrow et al., 2016). These include preoperative injection of a "dye" that can be detected at the time of surgery to show involved margins; use of metabolomic profiling of the smoke plume from the diathermy; optical coherence tomography, either on the tissue bed or on the resected specimen to delineate up to 2 mm depth of clearance of the DCIS. All these techniques are under comparison with the gold standard of pathology of the resected margins, though the pathology examination may only actually consider some ~5% of the actual margin of resection. Some practitioners use touch preparation cytology of the resected margins or frozen section performed during the operative resection. This requires high quality, timely pathology support during the operative procedure.

Reoperation for a close margin (<2 mm) or positive margin (DCIS touching the surgical margin) is a relatively frequent occurrence reported in 10% to 60% of patients with DCIS who undergo breast

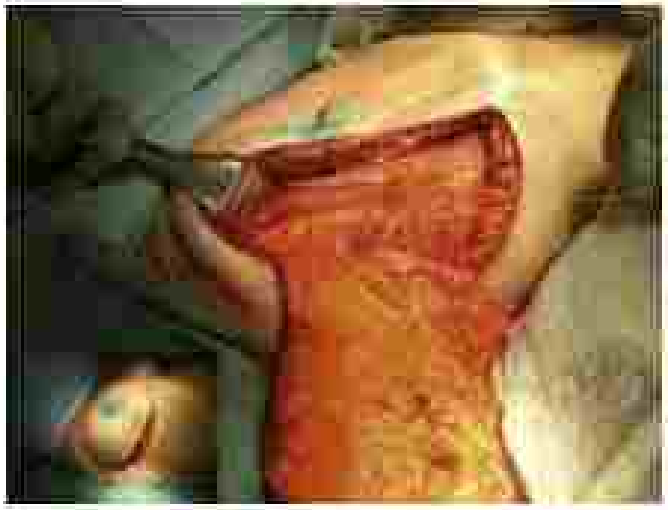

FIG. 11 Nipple-sparing mastectomy with intramammary incision and the blue dye in the breast skin ovoid from the sentinel lymph node biopsy technique. The sentinel node detected by blue dye and radioactive colloid is held by a suture for identification and subsequent excision.

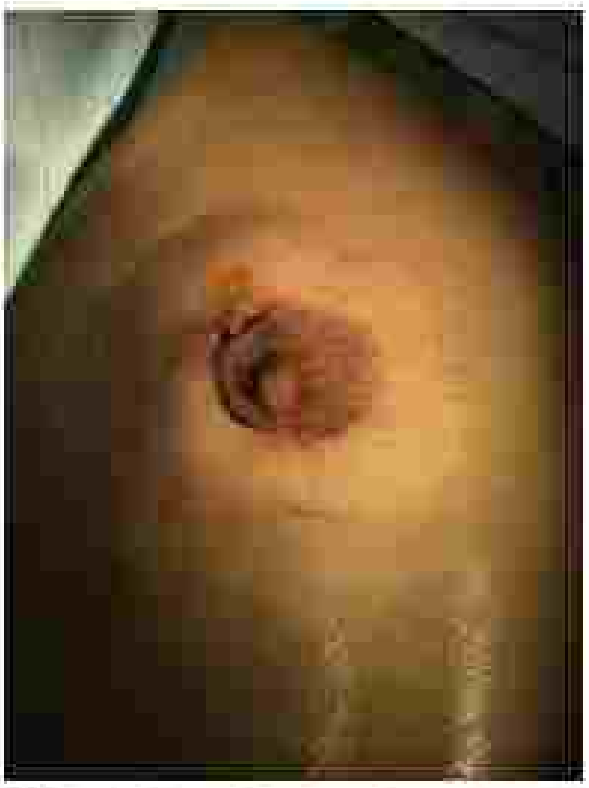

FIG. 12 Prior to final closure of the circumareolar wound, a cannula has been placed deep into the wound through which 10 mL of 0.25% bupivacaine was subsequently injected after final wound closure with subcuticular sutures and Dermabond skin glue, additional bupivacaine was inserted into the subcutaneous tissues.

conversation. This may be attributed to a disparity between the images and ultimate pathology report (Thomas et al., 2014), the lack of tactile appreciation by the surgeon at the time of the original surgery and/or failure to examine the resected specimen. Reoperation should be guided by the pathology report and focused on which, if any, margins require further resection or whether the DCIS is sufficiently extensive that a mastectomy will be required to completely resect the DCIS.

Mastectomy

Mastectomy may be performed either at the request of the patient (who may opt for bilateral mastectomy for symmetry or who is a breast cancer gene carrier) or due to the extent of DCIS present relative to the volume of the breast. The mastectomy may be either a simple mastectomy, or, if undergoing immediate reconstruction, a skin sparing mastectomy or nipple sparing mastectomy. Reconstruction may be via autologous tissue, tissue expander, or direct to implant. For skin sparing mastectomy, clearance of the DCIS in the breast from the skin and for nipple sparing mastectomy, a 2 cm margin on imaging between the DCIS and the nipple is recommended.

Prior to commencing a mastectomy, a sentinel lymph node biopsy should be discussed with the patient and, typically, a dual technique of technetium-99 colloid and blue dye is used. With the two injections performed before the mastectomy incision (of whichever sort) is made, the sentinel nodes are usually detectable and resectable though the mastectomy incision (whether a simple mastectomy, skin sparing mastectomy, or nipple sparing mastectomy) (Fig. 11). Mastectomy is usually the only indication for sentinel node biopsy in the setting of DCIS (Monti et al., 2018).

For skin sparing mastectomy, most appropriate where the patient has opted for a mastectomy and the DCIS impinges close to the nipple areolar complex, a circumareolar incision may be enlarged to form an elliptical incision incorporating resection of the nipple and areolar complex. It is, however, worth noting that central excision of the nipple areolar complex for DCIS involving tissues deep to the nipple and areola, rather than mastectomy, may be a good option to conserve the breast if the patient prefers. A nipple sparing mastectomy may be considered if the DCIS is no closer than 2 cm from the nipple, and thus unlikely to be involving the nipple areolar complex. For a nipple-sparing mastectomy, an inframammary incision may be preferred (see Fig. 11) to other approaches and can be extended superiorly along the lateral border of the breast to allow ease of access to the axilla for the sentinel lymph node biopsy (see Fig. 11), obviating the need for a separate axillary incision for the node procedure. Whichever type of mastectomy approach is used, great care is needed to aim to remove all the breast tissue but not compromise the subcutaneous blood supply to the skin of the breast and, if remaining, the nipple areolar complex. Immediate specimen radiographs should indicate that a wide margin has been achieved around the DCIS at mastectomy. If, on final pathology, the margins adjacent to the nipple or areolar are compromised, these structures can be excised as a second procedure. Postoperative radiotherapy is not indicated after mastectomy.

Anesthesia and Analgesia Considerations

Many patients will undergo their surgery using general anesthesia, which may be enhanced by local anesthesia placed to and around the wound at the time of surgery. This may be extended by regional blockade, potentially a paravertebral block or local nerve block, which is particularly effective for pain relief if a mastectomy is performed.

However, local anesthesia is very effective for the breast conserving (no approach in place of general anesthesia (bupivacaine 0.5% with the potential addition of intravenous sedation). Local anesthesia using long-acting agents such as 0.25% bupivacaine plain or in liposomal formulation (Exparel) instilled into the wound via temporary placement of a cannula deep into the extent of the surgical cavity (Fig. 12), and injected around the wound, on completion of the surgery to provide excellent analgesia alongside the use of oral agents.

Postoperative analgesia in conjunction with the use of local anesthesia or regional blockade may include acetaminophen or non-steroidal antiinflammatory drugs such as ibuprofen. In reality, few patients require opiate analgesia after breast conservation procedures for DCIS and even postmastectomy, pain may be well managed with little, if any, opioid analgesia.

Subsequent Management

Radiotherapy reduces the recurrence of DCIS and development of invasive breast cancer in the ipsilateral breast and hence patients undergoing breast conservation for DCIS should be considered for radiotherapy postoperatively. At the present time, intraoperative radiotherapy for DCIS is not recommended outside clinical trials. Marking the DCIS resection site at initial surgery using metallic clips will guide the radiation oncologist to the tumor bed, particularly if a tumor bed boost is warranted.

Endocrine therapy may also reduce the reoccurrence of DCIS or development of invasive breast cancer in the same breast and/or the contralateral breast whether tamoxifen (for premenopausal women) or aromatase inhibitor (for postmenopausal women). It may be prescribed following detection of estrogen receptors in the DCIS.

Recurrence of DCIS in the same breast may be managed by further local, segmental excision if the patient prefers, or mastectomy. Annual mammography is likely to detect further development of DCIS at an early stage or the development of an invasive breast cancer in the breast.

The surgical management of DCIS broadly reflects that of invasive breast cancer although the technical demands of local excision and the need for localization of the often impalpable DCIS may be greater than for invasive disease. Individual decision making between the breast conservation and mastectomy approaches should reflect patient preference and the extent of the DCIS. A circumferential 2-mm margin of resection around DCIS is desirable in the setting of breast conservation and the surgical techniques deployed will be selected from the wide range of current approaches now possible.

Suggested Readings

Ansari B, Ogston KN, Purdie CA, Johnston IH, Brown IC, Thompson AM. Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast. *Br J Surg* 2008;95:547–554.

Maxwell AJ, Clements K, Dodwell DJ, et al. The radiological features, diagnosis and management of screen detected bilateral neoplasia of the breast: findings from the Sloane project. *Breast* 2014;23:109–115.

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Advances in Neoadjuvant and Adjuvant Therapy for Breast Cancer

Cesar A. Santa-Maria, MD, MSCI

SYSTEMIC THERAPY IN EARLY-STAGE BREAST CANCER

Systemic therapy for early stage breast cancer consists of cytotoxic chemotherapy and targeted therapies including endocrine and anti-human epidermal growth factor 2 (HER2) neu therapies. While surgery remains the cornerstone of therapy for early stage disease, advances in systemic therapy can decrease the risk of recurrence by eradicating micrometastatic disease. Adjuvant chemotherapy first demonstrated a benefit over surgery alone in the 1970s, opening a field that has seen numerous successes and failures. This experience solidified the appreciation and expectation that adjuvant therapies should be recommended based on high level data in carefully designed clinical trials. Large organizations such as the National Comprehensive Cancer Network provide guidance for practitioners in this ever changing field.

The goal of this chapter is to highlight key aspects of systemic therapy for early stage breast cancer with practical clinical implications based on the available level of evidence. It is not meant to be an in-depth analysis of each specific area, rather a comprehensive, clinically oriented account of modern systemic therapy for early stage breast cancer.

ADJUVANT VERSUS NEOADJUVANT APPROACHES

Advantages and Limitations

While systemic therapy can eradicate micrometastatic disease, it can also substantially decrease breast tumor size when appropriate selection of therapy for specific breast cancer subtype is made. Chemotherapy can be administered preoperatively (neoadjuvant) or postoperatively (adjuvant), and there is no difference in terms of risk of distance disease recurrence or death.

Indications for a neoadjuvant approach are based on surgical considerations but may also serve to risk stratify patients. If surgery is contraindicated at diagnosis, and neoadjuvant therapy is not, neoadjuvant therapy may allow patients to delay definitive surgery until they are a suitable surgical candidate. Locally advanced breast cancers that may not be operable, may become operable if systemic therapy can shrink the tumor. Inflammatory breast cancer is a specific clinical presentation that benefits from a neoadjuvant approach. Patients with large breast cancers who are not a candidate for a breast conservation approach and desire this may also be considered for neoadjuvant therapy. Patients with clinically positive lymph nodes, where the standard approach would involve axillary lymph node dissection may become candidates for the more limited sentinel lymph node biopsy and dissection, which carries less lymphedema risk, if they have a good response to neoadjuvant therapy.

Patients with HER2 positive breast cancer and triple negative breast cancer (TNBC) with stage II and III disease in particular may undergo risk stratification, with neoadjuvant therapy, which may impact treatment options if they are left with residual disease. This is particularly critical since prognosis for the individual patient is heavily influenced by residual disease. The KATHERINE study found that patients with residual disease after neoadjuvant anti-HER2 based chemotherapy had decreases in recurrence rates when treated with trastuzumab emtansine. The CREATE X study found that adjuvant capecitabine for patients with residual disease could improve outcomes; this was largely observed in TNBC. Other ongoing studies in the residual disease space are ongoing and may help further delineate effective therapies for patients with residual disease. Of course patients with stage I disease may potentially have chemotherapy regimens (discussed further), and upfront surgery may be more appropriate. Nonetheless, the neoadjuvant approach allows us to risk stratify patients with HER2 positive breast cancer and TNBC and should be considered strongly in these patients.

Neoadjuvant therapy may be considered in certain clinical scenarios as well. If true pathologic stage may potentially affect the recommended systemic therapy, it may be warranted to proceed with primary surgery first, such would be the case in small HER2 positive tumors for example (discussed later). The neoadjuvant setting is one that lends itself to translational and clinical research questions abundant from

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Suggested Readings

Alvarez S, Anton HA, Portilla CA, Schanzer DL, Brown DC, Thompson AM. Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast. *Br J Surg* 2008;95:547–554.

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Maxwell AJ, Clements K, Dillon D, et al. Risk factors for the development of invasive cancer in contralateral ductal carcinoma in situ. *Eur J Surg Oncol* 2010;36(4):426–431.

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Neoadjuvant therapy may be considered in certain clinical scenarios as well. If true pathologic stage may potentially affect the recommended systemic therapy, it may be warranted to proceed with primary surgery first, such would be the case in small HER2 positive tumors for example (discussed later). The neoadjuvant setting is one that lends itself to translational and clinical research questions abundant from

before and after therapy, and pathologic complete response (pCR) rate is a clinical endpoint with possible survival implications. Therefore, when neoadjuvant clinical trials are available, oncologists should discuss with patients these options and see if this would be an appropriate avenue.

Neoadjuvant therapy should be avoided when there is unlikely to be a significant response to systemic therapy, such as the use of chemotherapy for luminal A–like hormone positive, and/or classical lobular carcinoma.

Pathologic Complete Response

After neoadjuvant therapy, some patients may achieve a pCR. For those with HER2 positive or TNBC, this may provide favorable prognostic information, as the risk of recurrence is significantly lower for the individual achieving a pCR. Indeed, this has served as a surrogate endpoint for neoadjuvant studies, and even accelerated Food and Drug Administration (FDA) approval. However, it is crucial to understand the difference between the individual achieving a pCR, and the ability of a drug in the setting of a clinical trial to improve the pCR rate; the latter does not always translate to better survival and recurrence endpoints. Examples are bevacizumab and lapatinib, where numerous studies demonstrated improvements in pCR, but when the confirmatory adjuvant studies were completed recurrence rates and survival endpoints were no better.

Neoadjuvant Endocrine Therapy

Neoadjuvant therapy may be an option for patients with estrogen receptor (ER) positive breast cancer, where there exists an indication to intent of improving surgical options and outcomes. There are, however, a few caveats. While adjuvant endocrine therapy is almost a universal recommendation for patients with ER positive breast cancer, there are phenotypes that are more endocrine sensitive than others, such as luminal A–like breast cancers. Treating a patient with a more aggressive phenotype ER positive breast cancer with neoadjuvant endocrine therapy should generally be avoided since these phenotypes are less endocrine sensitive. It is also important to consider that clinical response to endocrine therapy occur typically after many weeks, and regimens of at least 4 to 6 months are required to fully maximize clinical response. Pathologic complete response rates are exceedingly low with either chemotherapy or endocrine therapy, and indeed, the relevance of pCR in ER positive breast cancer is less well defined. Most patients with endocrine sensitive disease present with lower stage disease where upfront surgery is feasible, and more locally advanced disease where neoadjuvant approaches are typically considered, are usually associated with more aggressive, less endocrine sensitive phenotypes where chemotherapy may be more effective.

SYSTEMIC THERAPY ACCORDING TO BREAST CANCER SUBTYPE

Breast cancer is a heterogeneous group of diseases that arise in the breast. These can be classified into many subtypes based on molecular testing; however, clinically the ER, progesterone receptor (PR), and HER2 receptors are used to classify them. While there is some correlation between clinical and molecular subtypes, there is significant overlap. Therapy is based on clinical subtypes and may include chemotherapy and targeted therapy such as endocrine or anti-HER2 therapy.

Triple-Negative Breast Cancer

Cytotoxic chemotherapy was initially found to have anti-cancer effects over 100 years ago, and some of the earliest agents used were nitrogen mustards and anti folates. The first combination regimen evaluated in early stage breast cancer was cyclophosphamide with methotrexate and 5-fluorouracil, typically referred to as a first generation regimen. Substituting the methotrexate for an anthracycline was found to have better outcomes, and the FEC (5-fluorouracil, epirubicin, and cyclophosphamide) and FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) regimens were developed. These were found to be equivalent to doxorubicin and cyclophosphamide (AC), although AC is generally better tolerated. The addition of a taxane to AC was found to improve disease free survival (DFS) (hazard ratio [HR], 0.83; 95% CI, 0.79–0.87; $P < .00001$) and overall survival (OS) (HR, 0.85; 95% CI, 0.79–0.91; $P < .00001$), with an absolute improvement of 5% in DFS and 3% in OS. Dose density of the AC (every 2 week dosing with growth factor support), and taxane (either weekly or every 2 weeks) was found to be superior as well, which brings us to the current standard of care, dose dense AC/T. As there are no targeted agents currently approved in TNBC, dose dense AC/T is the standard of care for stages I to III (Table 1). Typically, patients with T1a/b do not have a significant benefit from chemotherapy, as the small size of their tumor portends a relatively favorable prognosis that chemotherapy is unlikely to substantially affect.

TABLE 1 Systemic Therapy for Early-Stage Triple-Negative Breast Cancer (TNBC)

Chemotherapy	Considerations
Anthracycline taxane regimens	• Anthracycline taxane regimens are standard of care for most patients with early stage TNBC • Dose dense A → paclitaxel weekly or dose dense (every 2 weeks) most common regimen in the United States
TC	• Not noninferior to anthracycline taxane regimens • May be considered when anthracyclines are contraindicated
Capecitabine	• May be considered in patients with residual disease after neoadjuvant chemotherapy
Carboplatin	• Typically added to the paclitaxel portion of AC/T • Can improve pCR, but effect on recurrence rates unknown • May have more activity in patients with BRCA mutations • Adds significant toxicity which may affect ability to complete standard therapy

AC, Doxorubicin and cyclophosphamide; AC/T, all standard chemotherapy (doxorubicin, cyclophosphamide, paclitaxel); pCR, pathologic complete response; TC, docetaxel with cyclophosphamide.

Because of the potential for serious toxicity from anthracyclines, including cardiomyopathies and secondary marrow neoplasms, anthracycline sparing regimens have been developed. Docetaxel with cyclophosphamide (TC) was compared to AC (not dose dense) and DFS rates favored TC, and OS was the same. A combined analysis of two trials evaluating TC versus an anthracycline and taxane regimen in HER2 negative early stage breast cancer found that 8 year DFS was 88.2% for TC and 90.7% for anthracycline and taxane regimen ($P = .08$) in the overall cohort. However, the benefit was especially noted in TNBC, where at all stages (stage I–III) anthracycline and taxanes was favored over TC. Only in the node negative ER positive subgroup did TC seem to do better.

Considering Carboplatin

Carboplatin has demonstrated efficacy in the metastatic setting, especially among patients with TNBC, in particular among patients with germline *BRCA* mutations. There have been numerous studies in the neoadjuvant setting that have confirmed that the addition of carboplatin to chemotherapy can improve pCR rates. The GeparSixto study evaluated the addition of carboplatin to neoadjuvant chemotherapy and found that overall it could improve the pCR rate; however, in those with BRCA mutations, the addition of carboplatin did not improve the pCR. Ongoing studies will confirm if there is a survival benefit. The addition of carboplatin does add toxicity and many patients are unable to complete all standard chemotherapy (AC/T) due to this toxicity.

Thus, in the meantime consideration of carboplatin should be on an individual basis, weighing the pros and cons of therapy (Table 1).

Capecitabine for Residual Disease

Although capecitabine has not been found to be a very active agent against TNBC in the metastatic setting, the CREATE X (Capecitabine for Residual Cancer as Adjuvant Therapy) study found it may improve outcomes in patients with residual disease after neoadjuvant chemotherapy. The CREATE X study included both TNBC and ER positive breast cancer, and randomized patients to 6 months of capecitabine or not and found there was benefit to DFS (HR, 0.70; 95% CI, 0.53–0.92; $P = .01$) and OS (HR, 0.68; 95% CI, 0.46–0.86; $P = .01$); however, this was mostly observed in the TNBC group. Although this was a relatively small phase III study and included heterogeneous disease (TNBC and ER positive); these data provide rationale to consider capecitabine in high risk patients (see Table 1). Ongoing studies are evaluating other agents in those with residual disease including carboplatin and immune checkpoint inhibitors.

Promise of Immunotherapy

Immune checkpoint blockade, especially against programmed cell death 1 or its ligand (PD1 or PD-L1, respectively) has shown modest benefits in the metastatic setting; however, early data in the neoadjuvant setting suggest significant activity. The IMPT2 study randomized patients to receive anthracycline taxane-based chemotherapy with or without the PD1 inhibitor pembrolizumab (during the taxane portion of therapy). Investigators found an unprecedented tripling of pCR rates with the addition of immunotherapy, and estimated pCR rate increased from 20% to 60%. A significant benefit was even observed in the ER positive subgroup. While other neoadjuvant studies adding immunotherapy to chemotherapy have not found the same degree of benefit (e.g., GeparSixtwo), a recent press release of KEYNOTE-522 (anthracycline/taxane study of chemotherapy with or without pembrolizumab) has claimed meeting its primary endpoint of pCR. We still need to await further data to evaluate the increase in anticancer benefit with toxicity.

Hormone Receptor–Positive Breast Cancer

Risk Stratification to Identify Need for Adjuvant Chemotherapy

While some ER positive breast cancers may benefit from adjuvant chemotherapy, many do not. Factors that can determine the net benefit from adjuvant chemotherapy include clinical and biologic characteristics. Clinically, age, comorbidities, and performance status are important factors to consider when considering the net benefit of adjuvant chemotherapy. Pathologically assessment of the primary (HR/PR, HER2 status, Ki-67, and grade can determine chemosensitivity. Gene expression platforms have been developed to determine the benefit of chemotherapy in ER positive breast cancer (Table 2).

Oncotype Dx (ODx) is a 21 gene expression panel that can provide a recurrence score (RS) between 0 and 100. This assay has been validated as a predictive and prognostic biomarker in numerous studies and is currently approved for use in ER positive lymph node–negative breast cancer. A score of 10 or less portends an excellent prognosis with endocrine therapy alone, and these patients should not be treated with chemotherapy. A score above 25 has been demonstrated to benefit from chemotherapy. Recently, the main results from the TAILORx (Trial Assigning Individualized Options for Treatment [Rx]) study were published where patients with scores between 11 and 25 were randomized to chemotherapy or not, followed by endocrine therapy. The primary endpoint of this noninferiority study demonstrated that in patients with an RS between 11 and 25, endocrine therapy alone was noninferior to chemoendocrine therapy. A subset analysis, however, suggested that women younger than 50 years derived benefit if they had an RS between 16 and 25; approximately a 6.8% decrease in distant recurrence between 11 and 25, and 1.8% with scores 16 to 20. The RxPONDER study is evaluating the benefit of chemotherapy in patients with ER positive lymph node positive disease.

The Mammaprint platform is a 70 gene expression panel that has also been prospectively validated; a score of high or low risk is generated. In the MINDACT (Microarray In Node-Negative Disease May Avoid Chemotherapy) study, investigators randomized patients with early stage breast cancer (any subtype and node status) with clinical high risk disease and molecular low risk disease to chemotherapy or not, finding that there was no significant benefit of chemotherapy in these patients. Strengths of this study were that it studied molecular risk in clinical risk, which included standard pathologic factors; it was also the only study where we have some prospective data in node positive disease. However, there are numerous limitations with the study including use of nonstandard chemotherapy (docetaxel with capecitabine), and a heterogeneous cohort (HER2 positive and TNBC included; lymph node positive disease included). Nevertheless, while ODx may have a higher level of evidence in ER positive node negative breast cancer, Mammaprint does provide prospective data, albeit limited, in ER positive node positive disease. Since HER2 positive and TNBC were a small subset of patients, there is currently insufficient data to apply to those patients.

However, the MINDACT study does provide additional information regarding the power of standard pathology in predicting benefit to adjuvant chemotherapy. Patients with clinical low risk disease did well whether or not their molecular risk was high, suggesting that these patients may not need genomic testing. While gene expression profiling can be valuable in assessing benefit from chemotherapy, it should be ordered with care, considering clinical and available pathologic information.

Optimizing Endocrine Therapy

Tamoxifen Versus Aromatase Inhibitors

Tamoxifen is a selective estrogen receptor modulator, which acts as an antagonist in breast cells. Studies have found that 5 years of adjuvant tamoxifen compared to no tamoxifen or shorter regimens can improve DFS. Tamoxifen can be administered to premenopausal women (see Table 2) and has also been studied in men with breast cancer.

TABLE 1 Systemic Therapy Options for Early Stage Hormone Receptor–Positive Breast Cancer

Treatment Type	Treatment Option	Considerations
Chemotherapy	• TC, e.g., (in node negative) • Anthracycline/taxane containing	• Standard pathology (ER/PR, HER2, grade, Ki-67) • Gene expression profiling (Oncotype Dx for ER positive, Mammaprint for low nodal burden)
Endocrine therapy	• Tamoxifen • Aromatase inhibitor	• Duration (5 vs. 10 years) • Addition of ovarian suppression (in high risk premenopausal)
Weight management	• None standard	• Universal recommendation for all breast cancer survivors • Includes diet and physical activity to achieve and maintain ideal body weight
Bisphosphonates	• Zoledronic acid • Clodronic acid	• No confirmatory studies • No standard schedule/duration

ER, estrogen receptor; LN, lymph node; PR, progesterone receptor; TC, docetaxel with cyclophosphamide.

Aromatase inhibitors (AI) can decrease circulating estrogens, thus "starving" cells that are dependent on estrogen. In postmenopausal women, 5 years of AI therapy is superior to tamoxifen (lower 10-year breast cancer mortality [HR, 0.85; 95% CI, 0.75–0.96]), and is generally the preferred agent for postmenopausal ER-positive breast cancer. There are three FDA-approved AIs: anastrozole, letrozole, and exemestane. While they are thought to be equally efficacious in terms of survival endpoints, due to differences in individual metabolism, patients may experience different side-effect profiles with the different drugs, especially AI-associated musculoskeletal symptoms. AI therapy alone may be inferior to tamoxifen in men with breast cancer; however, when a contraindication exists to tamoxifen, AIs may be used in conjunction with a gonadotropin-releasing hormone (GnRH) agonist.

Duration of Endocrine Therapy

A 10-year course of tamoxifen has been compared to a 5-year course in several studies. Two large randomized studies, the ATLAS and aTTOM studies, have found that a 10-year course may offer modest benefit compared to a 5-year course. In the ATLAS study 10 years of treatment compared to 5 years improved risk of recurrence (20.8% and 19% vs 18% and 20.8%, respectively; RR, 0.84; 95% CI, 0.76–0.90), breast cancer mortality (10.7% and 11.5% vs 9.7% and 11.5%, respectively; $P = .03$), and OS (Rs vs 21.1%, respectively; $P = .01$). The MA17 study evaluated 5 years of an AI after 5 years of tamoxifen, and found a benefit to the sequential approach (improved DFS locally/contralaterally [HR, 0.58; 95% CI, 0.45–0.76; $P < .001$], and risk of distant metastasis [HR, 0.68; 95% CI, 0.53–0.84; $P = .001$]). The study went on to have a second randomization (MA17R) to continue AI therapy for an additional 5 years versus placebo and found modest benefits in DFS with the 10 year AI course compared with placebo (90% vs 91%, respectively; HR, 0.66; $P = .01$), mostly in terms of contralateral prevention. Other extended AI studies have not demonstrated a benefit.

Adding Ovarian Suppression

Observations that chemotherapy-associated amenorrhea was associated with better outcomes in ER-positive early-stage breast cancer led to studies evaluating the role of medical ovarian suppression to addition to adjuvant endocrine therapy. The SOFT (Suppression of Ovarian Function) study randomized premenopausal women with early stage breast cancer to 5 years of tamoxifen, tamoxifen with ovarian suppression, or exemestane with ovarian suppression. Although initial reports did not find a difference in DFS between the tamoxifen alone versus with ovarian suppression arms, a recent update demonstrated a modest benefit with longer follow up; at 8 years, DFS was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with AI plus ovarian suppression ($P = .006$). Subgroup analysis demonstrated the majority of the benefit was seen in patients who were treated with chemotherapy. Indeed, authors presented a subpopulation Treatment Effect Pattern Plot (STEPP) analysis demonstrating benefit was mainly observed in high risk patients (see Table 2). It is important to note that the addition of ovarian suppression did come at the cost with higher toxicity, and long-term studies assessing effects on quality of life and bone health (AIs and ovarian suppression can both decrease bone density) are required.

Additional Adjuvant Considerations

Weight Management

Obesity and low physical activity are associated with a higher risk of breast cancer, and weight gain after diagnosis of breast cancer is associated with a higher risk of recurrence. The mechanisms between "energy excess" states and breast cancer is likely multifactorial including inflammatory cytokines and immune cells, adipocytokines, and excess hormones. The Women's Intervention Nutrition Study (WINS) found that a dietary intervention associated with weight loss could decrease the risk of breast cancer recurrence by 24% at 5 years. The Breast Cancer Weight Loss (BWEL) study is now confirming if weight loss can improve outcomes in patients with breast cancer. At the minimum, oncologists should recommend a healthy lifestyle including a balanced diet, physical activity, and attainment of an ideal body weight.

Benefit of Bisphosphonates

Bisphosphonates are a class of drugs approved for osteoporosis indications including osteopenia, hypercalcemia of malignancy, and decreasing fractures in patients with bone metastases. Numerous studies have been conducted using various different bisphosphonates and various schedules inconsistently finding possible benefit in terms of breast cancer recurrence. A large meta-analysis was conducted and found, especially in patients who were post-menopausal, bisphosphonates could improve rates of recurrence (RR, 0.86; 95% CI, 0.78–0.94; $2P = .002$), distant recurrence (RR, 0.82; 95% CI, 0.73–0.92; $2P = .0003$), especially bone metastases (RR, 0.72; 95% CI, 0.60–0.86; $2P = .0002$). Limitations with this study included use of various bisphosphonates, dosing regimens and schedule, as well as varied adjuvant chemotherapy and endocrine therapy treatment. The most well studied bisphosphonates are zoledronic acid and clodronic acid. Since definitive data from adequately powered and designed confirmatory trials are unlikely to occur in this class of mostly generic medications, oncologists may consider bisphosphonate therapy in close consultation with their patients, reviewing the pros and cons of therapy. Of note, postmenopausal women with ER-positive breast cancer are often prescribed AI therapy, which can decrease bone density, and many patients end up being prescribed bisphosphonates for bone density–related indications.

HER2-POSITIVE BREAST CANCER

Trastuzumab in HER2-Positive Breast Cancer

The development of trastuzumab, a monoclonal antibody targeting HER2, changed the treatment landscape of HER2-positive breast cancer. The Neoadjuvant Herceptin trial demonstrated that adding trastuzumab to chemotherapy increased pCR rates from 30% to 65% (OR for pCR 2.97; 95% CI, 1.41–5.03; $P = .0002$), and decreased relapse rate from 20% to 12% (RR for relapse 0.67; 95% CI, 0.48–0.94). Indeed, numerous large randomized studies have consistently demonstrated the addition of trastuzumab to chemotherapy improved not only DFS but overall survival as well. The Breast Cancer International Research Group (BCIRG) conducted one of these studies, where patients with HER2-positive early-stage breast cancer were randomized to AC/T, AC/T with trastuzumab, or docetaxel with carboplatin and trastuzumab (TCH). With 10 years of follow up, both trastuzumab-containing arms have shown DFS and OS benefit compared to the AC/T arm; however, outcomes between AC/T with trastuzumab were not significantly different than with TCH (AC/TCH HR, 0.78; 95% CI, 0.61–0.85; $P < .001$; TCH HR, 0.76; 95% CI, 0.65–0.89; $P < .001$). This is a particularly interesting observation, given the potential serious toxicity of doxorubicin (cardiomyopathy and secondary marrow neoplasms).

Duration of Trastuzumab

Initial studies with trastuzumab prescribed 1 year of trastuzumab, somewhat arbitrarily. Therefore, it was unclear if longer durations would improve outcomes. The Herceptin Adjuvant (HERA) trial randomized patients to 1 versus 2 years of trastuzumab and found no difference in DFS (HR, 0.99; 95% CI, 0.82–1.16). Various studies have looked at shorter durations of trastuzumab therapy, as may be more cost effective and possibly limit trastuzumab-related cardiotoxicity. Shorter 9-week regimens have been studied but have either not shown noninferiority or have not been reported yet. Three studies have examined 6 month regimens were noninferior to 12 month regimens; however, only one (PERSEPHONE) has reported that 6 months may be noninferior to 12 months. The PERSEPHONE study was a noninferiority study designed to allow a 5% margin in DFS benefit and found that indeed 6 months was noninferior to 12 months of trastuzumab (HR, 1.05; 95% CI, 0.88–1.25; 95th percentile, 1.22; noninferiority HR, < 1.30). In the current age, where trastuzumab-related cardiotoxicity has not been found to be as clinically relevant long term, the noninferiority margin may not be congruent with overall best outcomes. In addition, subgroup analysis demonstrated that

TABLE 3 Anti-HER2 Therapy for HER2-Positive Breast Cancer

Clinical Risk Stratification	Treatment Considerations
Small HER2-positive	• TH
Intermediate risk	• TCH • ACT with trastuzumab has equivalent DFS but more toxicity
High-risk HER2-positive	• TCHP or ACTHP • Strongly consider neoadjuvant trastuzumab emtansine for residual disease • May consider neratinib, especially if no pertuzumab or trastuzumab-emtansine given, and HR positive

ACT, doxorubicin, cyclophosphamide, paclitaxel; ACTHP, as addition to ACT plus trastuzumab and pertuzumab; DFS, disease-free survival; ER, estrogen receptor; H, H, docetaxel, carboplatin, trastuzumab; HCP, TCH plus pertuzumab; TH, paclitaxel and trastuzumab.

those with HR-negative disease, who underwent neoadjuvant therapy or who were treated with anthracycline-sparing regimens (as most patients commonly are now) tended to do better with the 12 month regimen. Thus, 12 months of trastuzumab remains the standard of care (Table 3).

Pertuzumab in High-Risk HER2-Positive Breast Cancer

Crosstalk between HER2 and HER3 as a resistance mechanism for anti-HER2 therapy led to the development of a monoclonal antibody targeting HER3, pertuzumab. The NeoSPHERE and TRYPHENA studies demonstrated that the addition of pertuzumab to trastuzumab-based chemotherapy regimens in early HER2-positive breast cancer could improve pCR rates significantly. The APHINITY study, a large phase III study randomizing patients to trastuzumab-based chemotherapy with or without pertuzumab, sought to assess if there was a DFS benefit. While the results of the intention-to-treat analysis demonstrated a very modest, albeit statistically significant, benefit in terms of DFS (94.8% in pertuzumab, 93.2% in placebo), a more pertuzumab benefit was seen in node-positive disease (HR, 0.77; 95% CI, 0.62–0.96; $P = .02$). Therefore, pertuzumab and trastuzumab-based chemotherapy is considered a standard approach for high-risk HER2-positive early breast cancer (see Table 3).

Trastuzumab-Emtansine for Residual Disease

Patients with HER2-positive breast cancer who do not achieve a pCR are at a higher risk of recurrence. The KATHERINE study found that invasive disease-free survival was significantly higher in patients receiving trastuzumab emtansine than trastuzumab alone (HR, 0.50; 95% CI, 0.39 to 0.64; $P < .001$). Even though the presented results are only the initial interim analysis, overall survival was trending positive, and the FDA granted approval as this has quickly become a standard of care.

Integration of Tyrosine Kinase Inhibitors

While trastuzumab and pertuzumab demonstrated that an improvement in pCR could lead to better survival outcomes, not all agents necessarily validate this relationship. Lapatinib, a small molecule tyrosine kinase inhibitor (TKI) against the intracellular domain of HER2, was found to improved pCR rates across multiple studies; however, the confirmatory Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimization (ALTTO) study did not demonstrate a DFS benefit in patients treated with lapatinib.

Although lapatinib did not result in DFS benefit in confirmatory studies, neratinib, a next-generation oral HER2 TKI, has been shown to provide DFS benefit. The ExteNET study randomized patients with early-stage HER2-positive breast cancer to receive neratinib for 1 year after the completion of trastuzumab-based chemotherapy. Investigators found that treatment with neratinib resulted in better DFS in the intention-to-treat analysis (HR, 0.73; 95% CI, 0.57–0.92; $P = .0083$), although this was mostly in ER-positive HER2-positive disease (HR, 0.66; 95% CI, 0.49–0.88; $P = .0043$). A major limitation of this study was that it did not include patients treated with pertuzumab, thus we do not know if neratinib would have the same benefit in patients who received pertuzumab. Furthermore, 40% of patients experienced grade 3 diarrhea (defined as ≥7 bowel movements by a day and/or incontinence, and/or requirement of intravenous fluids for at least 24 hours, and/or hospitalization). Although subsequent studies found that prophylaxis with antidiarrheals could improve rates of severe diarrhea, the toxicity limits integration into practice.

Deescalating Strategies in Small HER2-Positive Breast Cancers

Given the excellent prognosis that anti-HER2 therapy can provide patients with HER2-positive breast cancer, deescalation studies have been conducted to determine if less therapy can still provide excellent outcomes. A single-arm phase two study evaluating paclitaxel with trastuzumab found that patients with small (≤3 cm) HER2-positive breast cancer can experience very low rates of recurrence (at 3 years, 98.2% free from invasive disease; 95% CI, 97.6–98.8). Longer follow-up demonstrated continued excellent prognosis. Although this has not been confirmed in a randomized phase three study, it has been widely adopted given the very low recurrence rates observed and lower toxicity (see Table 3).

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Management of Recurrent and Metastatic Breast Cancer

Mufaro Lazar, MD, Sawsri Bhattacharya, DO, and Theodore N. Tsangaris, MD, MBA

Nothing challenges the surgeon and the multidisciplinary breast care team more than recurrent breast cancer. Today, recurrent breast cancer is treated by a team of physicians including a surgical oncologist, plastic surgeon, medical oncologist, and radiation oncologist. The advancements in breast imaging, surgical technique, systemic treatment and radiation therapy contribute to improved local, regional, and systemic control of recurrent or metastatic breast cancer. Recurrent and/or metastatic breast cancer presents in the following three scenarios: (1) local recurrence after breast conservation or mastectomy, (2) regional recurrence to regional lymph node basins, and (3) systemic metastatic disease.

LOCAL RECURRENCE AFTER LUMPECTOMY OR MASTECTOMY

Recurrence in the ipsilateral breast or to the chest wall after mastectomy is classified as local recurrence. Ipsilateral breast tumor recurrence (IBTR) after breast conservation today has an incidence of 4% to 9%. The majority of local recurrences happen at the original lumpectomy site or close to the site.

In contrast, 1% to 3% of patients undergoing a mastectomy will have a chest wall or nodal recurrence 10 years after surgery. Locoregional recurrence isolated to the chest wall occurs in 50% to 70% of these patients and only one third of these patients have synchronous distant disease. However, chest wall recurrences can represent a significant source of morbidity for breast cancer patients causing bleeding, ulceration, and pain.

Needless to say, local recurrence is disappointing and often disheartening to both patient and surgeon. However, local recurrence should not be considered the instigator of a patient's demise but an indicator of potential systemic disease. Here a pragmatic approach is wise. It is essential to perform re-staging scans with a computed tomography (CT) scan/bone scan or a positron emission tomography/CT (PET/CT) scan. Systemic disease in combination with local recurrence is common and represents a different scenario than local recurrence alone.

REGIONAL RECURRENCE

Tumor occurring in the axillary, infraclavicular, supraclavicular, or internal mammary lymph node basins is considered regional recurrence.

METASTATIC RECURRENCE

The treatment of metastatic breast cancer is tailored by the expression of the estrogen receptor, progesterone receptor, HER2/neu protein, PD-L1 status on the tumoric cell, and germline BRCA1 or 2 status. Other factors affecting prognosis include location of metastases, age, performance status, and values of the patient. The treatment of metastatic breast cancer is palliative, and it is essential that the goals of care are addressed from the beginning. The treatment of metastatic breast cancer includes treatment with oral chemotherapy agents (CDK4/6 inhibitors, Lapatinib, Xeloda, PARP [poly(ADP-ribose) polymerase] inhibitors), cytotoxic intravenous (IV) chemotherapy, antibody-directed therapy (e.g., ado-trastuzumab or trastuzumab), endocrine therapy, and immunotherapy agents (atezolizumab). Only 22% of metastatic breast cancer patients are alive at 5 years, underscoring the importance of developing novel therapies to improve survival.

Regardless of the type of recurrence (local, regional, or metastatic), the approach to the patient and the disease remains similar. Recurrence should be considered a systemic issue and the whole patient should be attended to. The two most important principles to consider when dealing with recurrent breast cancer are (1) fully understanding the implications of recurrent breast cancer for that individual and (2) carefully, thoughtfully, and realistically formulating a treatment plan. A one-size treatment for recurrent local, regional, or systemic disease does not fit all.

DIAGNOSIS AND STAGING

When a patient presents with signs and symptoms of a local, regional, or metastatic recurrence it should initiate a compulsive and complete diagnostic workup cascade. Included in this workup are the following elements:

- Complete history and physical examination
- Breast imaging (mammography, ultrasound, breast magnetic resonance imaging [MRI])
- Metastatic workup (CT of the chest, abdomen, and pelvis, bone scan; PET/CT scan)
- Core biopsy for tissue diagnosis
- Bloodwork to assess anemia, renal insufficiency, and synthetic liver function

MANAGEMENT OF LOCAL RECURRENCE AFTER BREAST CONSERVATION

Local Excision

The standard textbook answer of "mastectomy for all local recurrences after breast conservation" may no longer be appropriate. In fact, the surgeon's role may be to only provide material for pathologic diagnosis and tumor markers. Usually, however, some form of surgical therapy is appropriate. Factors that would influence local excision versus completion mastectomy include:

- Size of the recurrence
- Location of the recurrence
- Single versus multicentric disease in the breast
- Tumor prognostic and predictive markers including estrogen receptor, progesterone receptor, and HER2 status
- Time interval between initial treatment to the recurrence
- Age of patient
- Comorbidities
- Cosmetic considerations
- Presence or absence of metastatic disease
- Prior radiation
- Patient preference

For small recurrences, after many years, near the *old* tumor site, with favorable prognostic markers and no evidence of metastatic disease, a lumpectomy with or without additional radiation therapy may be perfectly appropriate. Based on the results of the NRG Oncology Radiation Therapy Oncology Group (RTOG) 1014 contradictions may be feasible in some cases. RTOG 1014 was a prospective phase II study of 30 conformal external beam partial radiation following repeat lumpectomy in patients with an IBTR following prior breast conserving therapy (BCT) (lumpectomy and whole breast radiation). Skin, fibrosis, and breast pain toxicity was acceptable at the 1 year follow up.

Mastectomy

If a mastectomy is necessary or the patient's preference, it can be a challenge after prior surgery and radiation therapy (Fig. 1). Care must be taken when creating the skin flaps as radiation can result in a diminished blood supply leading to skin necrosis. Also, radiation changes can make it difficult to identify the plane between the breast tissue and subcutaneous fat. It is important to achieve negative margins in the area of the recurrence. This may require excision of skin or a portion of muscle in the area of the tumor. If the patient desires breast reconstruction, this is also challenging in the face of prior surgery and radiation. An autologous tissue flap, such as deep inferior epigastric, transverse rectus abdominis myocutaneous, or a latissimus dorsi myocutaneous flap, is usually recommended. Implant based reconstruction can be performed but it has a higher complication and failure rate. The involvement and contributions of the plastic surgeon in this case should not be understated.

TECHNICAL POINTS FOR MASTECTOMY FOLLOWING BREAST-CONSERVING THERAPY

After a lumpectomy and radiation therapy, a mastectomy with or without reconstruction for IBTR recurrence can be challenging. Our institutional experience finds us using a modified radiation mastectomy incision instead of the more traditional horizontal ellipse for patients who require mastectomy after IBTR recurrence (Fig. 2).

Advantages

- The skin closure after mastectomy is usually under less tension.
- This incision provides excellent exposure.
- This approach is committally superior as it eliminates the dog ears and redundant skin and soft tissue at the edges.
- The inferior flap can be deepithelialized and be used as an autologous covering and protection over the tissue expander.
- Extremely versatile for the plastic surgeon and the patient's reconstructive options.
- This incision is cosmetically in harmony with a contralateral breast reduction mammoplasty that many women undergo at the time of definitive reconstruction to achieve symmetry.

Disadvantages

- Corners of the incision on the superior flaps are susceptible to vascular compromise.
- Technical learning curve.

MANAGEMENT OF LOCAL RECURRENCE AFTER MASTECTOMY

Local recurrence following a mastectomy is less common, about 1% to 5%, and is associated with a higher rate of distant disease as well as a worse prognosis. Core needle biopsy or skin punch biopsy can be used to confirm tissue diagnosis and test receptor status. The patient should undergo staging studies to rule out distance metastatic disease. Resectability can be assessed by physical exam, ultrasound, CT chest, or MRI. A simple local resection may be all that is necessary. Consideration should be given to neoadjuvant chemotherapy or hormonal therapy if the size of the recurrence would make surgical resection difficult. Plastic surgery may be helpful in helping to close or cover a defect. Following surgery, the patient should be referred to radiation oncology.

MANAGEMENT OF THE AXILLA

With the wide acceptance of the sentinel lymph node (SLN) biopsy as the standard of care versus axillary dissection in staging breast cancer patients, a completely new class of patients with local recurrences is emerging. This begs the question, what do we do with the ipsilateral axilla in the patient who recurs locally? The answer to the question may lie in the very reason SLN biopsy is now standard of care. The axilla provides prognostic and staging information with some therapeutic benefit. If one accepts that local recurrence is prognostic in and of itself, then excessive surgical attention to the axilla is superfluous and carries unnecessary morbidity. With MRIs and high definition ultrasound the status of the axilla may be well known to the surgeon and multidisciplinary team. However, there may be a time when another SLN biopsy or axillary dissection is appropriate. If a prior SLN procedure yielded 10 or fewer lymph nodes there is a good chance (70%–75%) that another SLN procedure would identify a SLN. Other factors that affect the ability to identify a SLN biopsy include prior surgery, radiation, location of prior tumor, and recurrent tumor location. Preoperative lymphoscintigraphy should be performed to understand the patient's current lymphatic drainage. Regardless, the need for axillary sampling should be carefully discussed so that unnecessary morbidity can be avoided. If not to control known regional disease or to direct systemic therapy, then the axilla should be left alone.

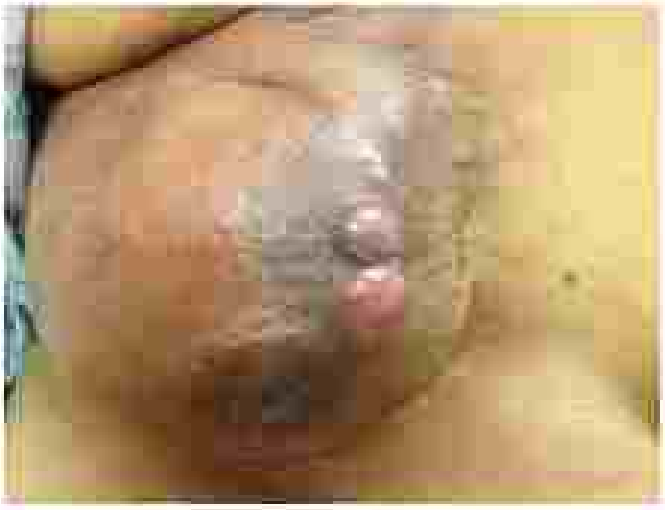

FIG. 1 Locally advanced recurrence in a patient with a history of prior breast conservation.

METASTATIC DISEASE

The aim in treatment of metastatic breast cancer is not cure, but prolonging survival, alleviating symptoms, and maintaining quality of life.

PRINCIPLES OF TREATMENT FOR METASTATIC BREAST CANCER

The estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), programmed death ligand 1 (PD-L1), and germline *BRCA* status are important in determining a treatment plan. A treatment plan is tailored to the individual patient and the medical oncologist must weigh the risks and benefits of oral chemotherapy agents, cytotoxic chemotherapy, endocrine therapy, immunotherapy, and biologic agents. Factors such as symptoms, medical comorbidities, performance status, previous exposure to chemotherapy, menopausal status, and disease location are carefully considered before a regimen is chosen.

The average metastatic breast cancer patient is richer with decades of life and often has many medical comorbidities. It is important to assess each patient's medical problems and assess the patient's performance status before embarking on chemotherapy. Also, many patients with metastatic breast cancer are heavily pre-treated with adjuvant chemotherapy often with an anthracycline. The lifetime dose of an anthracycline is

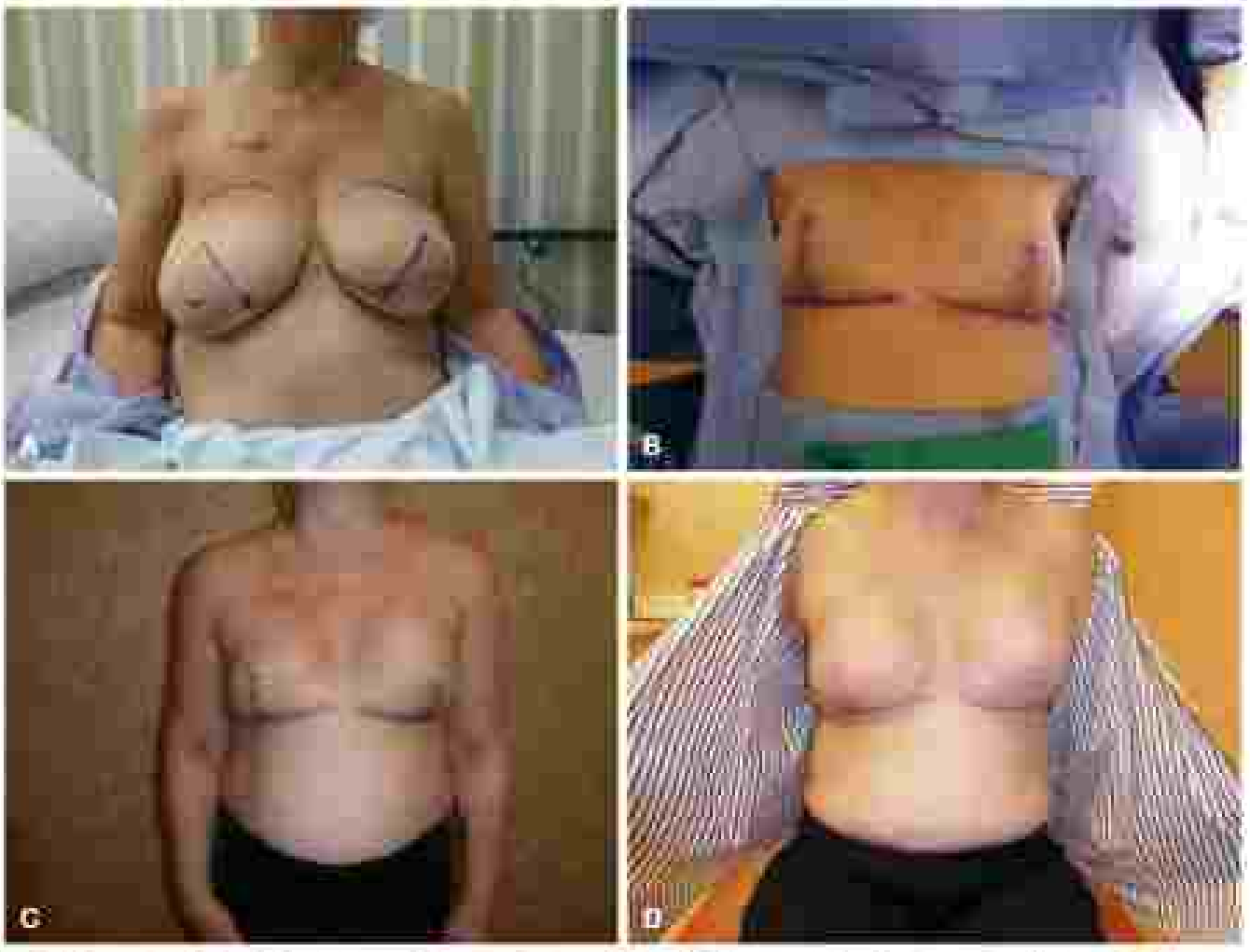

FIG. 2 (A) Preoperative marking for mastectomy via Wise pattern reduction technique. (B) Operative photo of mastectomy via Wise pattern reduction technique. (C) One week postoperative photo. (D) After tissue expanders are changed to permanent silicone implants.

about 300 mg/m², thus limiting the ability to further treat with this regimen. Additionally, patients may have had coronary artery disease, thus limiting the use of an anthracycline. Liposomal doxorubicin or eribulin is often a suitable alternative. If a patient has HER2 positive disease, it is important to perform an echocardiogram prior to starting trastuzumab or ado-trastuzumab regimens. Many females also have concurrent type 2 diabetes with concurrent neuropathy, which further limits the ability to treat with a taxane-based regimen.

The location of metastatic disease can affect survival. Patients with metastatic lesions in the chest wall, liver, or lymph nodes may have prolonged progression free survival in comparison to those with hepatic and or lymphangitic pulmonary disease, who tend to have shorter progression free survival and overall survival. The term visceral crisis is used to describe patients with lymphangitic lung metastases, bone marrow replacement, cardiomyopathy, meningitis, or significant liver metastases. In these cases, cytotoxic chemotherapy is preferred as it will lead to rapid disease control. Patients with liver dysfunction have a very poor prognosis, with limited treatment options due to synthetic dysfunction. In these situations, low dose taxanes, eribulin, carboplatin/cisplatin, and gemcitabine are often used for disease control.

CDK4/6 Inhibitors

The interaction of cyclin D with CDK4 and CDK6 facilitates hyperphosphorylation of the retinoblastoma (Rb) gene, which leads to progression through the G1 checkpoint to the S phase of the cell cycle. Alterations in the cyclin D-CDK4/6-Rb pathway have been described in many malignancies and are associated with endocrine resistance in breast cancer. Treatment with a CDK4/6 inhibitor (ribociclib, palbociclib, and abemaciclib) is now considered first line therapy for patients with metastatic hormone receptor positive breast cancer and has resulted in a significant improvement in quality of life, progression free survival, and overall survival. Multiple key trials showing this in combination with hormonal therapy include the PALOMA 2, PALOMA 3, MONALEESA 2, MONALEESA 7, MONARCH 2, and MONARCH 3 trials.

PARP Inhibitors

For patients with a germline BRCA1 or 2 mutation, PARP inhibitors including olaparib and talazoparib were recently approved for the treatment of metastatic breast in patients with germline BRCA1/2 mutations, based on the results of the OlympiAD trial and more recently the EMBRACA trial. The initial study that led to olaparib approval demonstrated that olaparib given at 300 mg by mouth twice a day improves progression free survival in patients with metastatic breast cancer with a BRCA1/2 mutation with a response rate of 59.9% in the olaparib group and 28.8% in the standard therapy group (single agent chemotherapy with capecitabine, eribulin or vinorelbine in 21-day cycles). The median progression free survival was significantly longer in the olaparib group than in the standard therapy group (7.0

months vs. 4.2 months; hazards ratio [HR] for disease progression or death, 0.56; 95% confidence interval [CI], 0.43–0.80; $P < .001$). Olaparib is an effective treatment for patients with metastatic breast cancer with a BRCA1/2 mutation.

Cytotoxic Chemotherapy

Treatment with single agent or combination based cytotoxic regimens can lead to improved disease control. Single agent chemotherapy regimens are reserved for patients with a low burden of disease. Combination based regimens are given to patients with symptomatic disease with need for rapid disease control. Agents often used include taxanes (paclitaxel and docetaxel), platinums (cisplatin and carboplatin), anthracyclines (erlotinib, doxorubicin, or liposomal doxorubicin), and anti metabolites (capecitabine and gemcitabine). When choosing a suitable cytotoxic chemotherapy option, a patient's comorbidities must be carefully examined including renal function, liver function, residual neuropathy, and anemia. Patient preferences such as frequency of therapy and side effect profile must also be considered.

Immunotherapy

For patients with triple negative breast cancer, immunotherapy in combination with cytotoxic chemotherapy has potential to provide durable treatment. By harnessing the immune system's ability to recognize cancer related antigens, immunotherapy can induce targeted immune responses against cancer cells. Recently, the IMpassion130 trial showed that treatment with atezolizumab, an immunotherapy agent that is a PD-L1 inhibitor, in combination with cytotoxic chemotherapy with nab-paclitaxel (Abraxane) resulted in meaningful progression free survival for patients with metastatic triple negative breast cancer with tumor infiltrating lymphocytes expressing PD-L1 greater than 1% (Schmid et al., 2018). Among the PD-L1 positive tumors, the median overall survival was 25.0 months with the combination of cytotoxic chemotherapy and immunotherapy versus 15.5 months with nab-paclitaxel alone (HR, 0.62; 95% CI, 0.45–0.86). This trial recently led to Food and Drug Administration approval of the first immunotherapy drug in combination with cytotoxic chemotherapy in the treatment of patients with metastatic triple negative breast cancer.

CONCLUSION

Recurrent and metastatic breast cancer patients are a heterogeneous group of patients for whom the experienced breast surgeon seeks the support of his or her multidisciplinary team. Today there is no one size fits all treatment. Advanced diagnostic surgical techniques and medicines have greatly impacted this special group of patients. Improved quality of life as well as longevity should be the goal.

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Management of Male Breast Cancer

Samuel Sarmiento, MD, MPH, MBA, Michael McCall, BS, and Mahran Habibi, MD, MBA

Male breast cancer (MBC) is a rare disease. In 2018, the number of men with breast cancer was around 2550 compared to 266,120 in females, slightly less than 1%. The lifetime risk of developing MBC is about 1 in 1000. There is some evidence that the incidence has been increasing since the 1980s. This may be due to the increasing prevalence of associated risk factors. The risk of MBC is increased by those conditions that increase the effects of estrogen (cirrhosis, obesity, exogenous estrogens) or decrease the effects of testosterone (testicular malignancy, infection, trauma, 5α-reductase inhibitors, or Klinefelter's syndrome [XXY]) and is especially increased for genetic predisposition. The estimated proportion of MBC associated with BRCA mutations varies widely (4%–40%), but for men with BRCA mutations the cumulative absolute risk of MBC by age 70 years is estimated to be 1.2% for *BRCA1* (a relative risk 12 times that of non-mutation carriers) and 6.8% for *BRCA2* (a relative risk 42 times that of noncarriers). The evidence linking MBC to other gene mutations (CHEK2, AR, CYP17, PTEN) is suggestive but inconclusive. Most MBCs are ductal in origin; 75% of cases in the National Cancer Database were infiltrating ductal carcinomas. Most tumors are invasive but about 2% are in situ, and more than 90% are hormone receptor (HR) positive.

The prognosis of MBC appears to be worse than for female breast cancer but is comparable when corrected for stage of disease (most MBC is detected as a mass, not by mammography). Data from the 31,995 MBC diagnoses between 2004 and 2014 revealed a 5-year survival of 75% (95% confidence interval [CI], 0.74–0.76). Unfortunately, more than half of MBCs were seen as advanced disease (Stages III–IV), but with a trend toward earlier diagnosis in the more recent series, about 80% of MBCs have been seen with local or regional disease. MBC inhabits a unique diagnostic and treatment landscape as its rarity precludes most randomized controlled trials; however, it has a very common corollary to female breast cancer that provides a large source of related data to extrapolate from and apply. Historically, much of the diagnosis and treatment of MBC stems from what we know about female breast cancer. In recent years some investigative efforts have begun to establish MBC as its own entity.

DIAGNOSIS

MBC most commonly presents as a painless, unilateral breast mass. The tumorous onset contributes to the advanced stages of disease at diagnosis that is typical of MBC. Some men may experience bloody nipple discharge, skin changes in the nipple and areola, or suspicious axillary adenopathy, which often brings them to care earlier. The differential must include gynecomastia, as it is a fairly more common cause of breast masses in men. However, these masses will typically be tender and transient. Mammography and ultrasound should be used to investigate a potential mass. If these suggest a benign diagnosis, observation alone is sufficient, as most masses will resolve spontaneously in 2 to 3 months. A core biopsy is not necessary unless the mass persists or has particularly suspicious physical findings. In the case that mammography and ultrasound suggest a more pathologic lesion, a core biopsy of the breast lesion, punch biopsy of the nipple and areola, or ultrasound (US) guided fine-needle aspiration of axillary nodes is appropriate. Excisional biopsy is required for no more than 5% to 10% of patients, mainly those in whom the core biopsy is nondiagnostic or discordant with imaging

months vs. 4.2 months; hazards ratio [HR] for disease progression or death, 0.56; 95% confidence interval [CI], 0.43–0.80; $P < .001$). Olaparib is an effective treatment for patients with metastatic breast cancer with a BRCA1/2 mutation.

Cytotoxic Chemotherapy

Treatment with single agent or combination based cytotoxic regimens can lead to improved disease control. Single agent chemotherapy regimens are reserved for patients with a low burden of disease. Combination based regimens are given to patients with symptomatic disease with need for rapid disease control. Agents often used include taxanes (paclitaxel and docetaxel), platinums (cisplatin and carboplatin), anthracyclines (erlotinib, doxorubicin, or liposomal doxorubicin), and anti metabolites (capecitabine and gemcitabine). When choosing a suitable cytotoxic chemotherapy option, a patient's comorbidities must be carefully examined including renal function, liver function, residual neuropathy, and anemia. Patient preferences such as frequency of therapy and side effect profile must also be considered.

Immunotherapy

For patients with triple negative breast cancer, immunotherapy in combination with cytotoxic chemotherapy has potential to provide durable treatment. By harnessing the immune system's ability to recognize cancer related antigens, immunotherapy can induce targeted immune responses against cancer cells. Recently, the IMpassion130 trial showed that treatment with atezolizumab, an immunotherapy agent that is a PD-L1 inhibitor, in combination with cytotoxic chemotherapy with nab-paclitaxel (Abraxane) resulted in meaningful progression free survival for patients with metastatic triple negative breast cancer with tumor infiltrating lymphocytes expressing PD-L1 greater than 1% (Schmid et al., 2018). Among the PD-L1 positive tumors, the median overall survival was 25.0 months with the combination of cytotoxic chemotherapy and immunotherapy versus 15.5 months with nab-paclitaxel alone (HR, 0.62; 95% CI, 0.45–0.86). This trial recently led to Food and Drug Administration approval of the first immunotherapy drug in combination with cytotoxic chemotherapy in the treatment of patients with metastatic triple negative breast cancer.

CONCLUSION

Recurrent and metastatic breast cancer patients are a heterogeneous group of patients for whom the experienced breast surgeon seeks the support of his or her multidisciplinary team. Today there is no one size fits all treatment. Advanced diagnostic surgical techniques and medicines have greatly impacted this special group of patients. Improved quality of life as well as longevity should be the goal.

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characteristics. All biopsy diagnoses of MBC should include determination of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor–2 (HER2). As with female breast cancer, a preoperative workup for distant metastases (by positron emission tomography/computed tomography [PET/CT] or CT and bone scan) is indicated only for locally advanced disease (stage III) or suspicious symptoms.

TREATMENT

Preoperative Considerations

Although surgery is the appropriate initial treatment for most MBC, neoadjuvant chemotherapy or hormonal therapy should be considered. The indications for neoadjuvant chemotherapy are the same as for women: advanced T or N stage (T3 to T4 tumors, including inflammatory cancer, or N2 to N3 nodes). The main limitation of neoadjuvant chemotherapy is that almost all MBC is ER positive, and this tumor subtype is not particularly responsive to neoadjuvant chemotherapy, with rates of pathologic complete response of 10% or less. For the same reason, neoadjuvant hormonal therapy makes sense for locally advanced MBC, especially in the setting of advanced age or significant comorbidities. Most patients respond to hormonal treatment with tamoxifen or aromatase inhibitors; the typical duration of response is in the range of 1 to 2 years, and those who progress often will respond to a change in hormonal agent.

Breast Conservation

Although historically, mastectomy was the method of choice in managing MBC, in a select group of patients, partial mastectomy can be done with similar outcomes.

The rationale for mastectomy for MBC has been the paucity of data in breast conserving surgery (BCS). The extent of excision required to obtain negative margins for BCS in women is significant and for most men could easily approach the volume of the entire breast. Further, the delivery of tangential field radiotherapy (RT) to the much smaller male breast raises concerns about exposure to the chest wall, lung, and heart, although these concerns are substantially reduced by contemporary techniques of CT guided treatment planning, they are eliminated altogether by the performance of mastectomy, after which RT is required only for locally advanced disease. Finally, even for men who wish to preserve the nipple as part of a nipple sparing mastectomy, the proximity of most MBC to the nipple and areola renders this approach unsound from both a cosmetic and an oncologic perspective. Despite these, a 2010 National Surgical Quality Improvement Program (NSQIP) study showed 15.9% of men had BCS, which suggests significant progress in surgical technique for MBC.

Mastectomy

Mastectomy remains the most common surgical technique for patients with MBC. The incision is dependent on body habitus. For most men, separate breast and axillary incisions are not needed and especially for those with a laterally placed nipple and areola, a single oblique elliptical incision encompassing both breast and axilla is reasonable (Fig. 1). For certain bulky or locally advanced cancers, a single incision will allow en bloc resection of the breast in continuity with the intervening soft tissues, lymphatics, and axillary nodes, but because these patients will all receive postmastectomy RT (PMRT), the benefit of this approach in local control is debatable. The mastectomy is done through a transversely oriented elliptical incision sufficient to encompass all of the breast and tumor tissue. The incision should widely encompass any areas of skin, nipple, or areolar involvement. For men with marked obesity or gynecomastia, the incision will be comparable to that required for a female mastectomy, whereas for those who are thin, the incision rarely needs to encompass the nipple and areola but should be long enough to avoid dog ears at the time of skin closure. Skin flaps are elevated peripherally sufficient to remove all breast tissue and any gynecomastia. The extent of this dissection again varies widely and is highly dependent on body habitus, but in general, the skin flaps in MBC do not need to be as thin as for women. In obese patients, as one nears the edges of the breast the skin flaps should be thickened gradually to avoid a sharp drop off differently at the periphery of the operative defect. The breast is dissected from the underlying pectoralis major muscle, removing the pectoral fascia and, if muscle invasion is found, the adherent portion of the pectoral muscle. The surgical specimen is oriented with sutures for noting of the margins by the surgical pathologist and handed off. Resection of the entire pectoralis major (i.e., radical mastectomy) is almost never required in the current era, but partial muscle resection is indicated for all patients with muscle invasion.

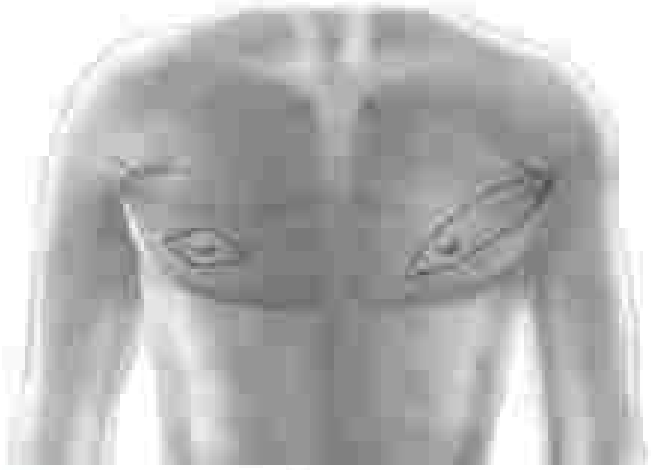

FIG. 1 Suggested incision (dotted line) for mastectomy with axillary staging in male breast cancer.

Axillary Management

Management of the axilla in MBC is comparable to that in female breast cancer. Sentinel lymph node (SLN) biopsy is appropriate for all operable invasive MBC with clinically negative axillary nodes (cT1-3N0). Because most men with a core biopsy diagnosis of ductal carcinoma in situ also have a palpable mass, invasion cannot be ruled out and SLN biopsy makes sense for them as well. Because patients with MBC do not fall within the eligibility of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (which showed that patients with one or two positive SLNs having BCS with whole breast RT do not require axillary lymph node dissection [ALND]), we recommend intraoperative pathologic assessment of the SLN and ALND for patients who are SLN positive. For patients who are clinically node positive we recommend a stepwise approach. First, if metastasis is confirmed preoperatively by fine needle aspiration or core biopsy, we recommend ALND. Second, if metastasis cannot be confirmed by preoperative needle biopsy, we recommend SLN biopsy with intraoperative assessment and, if positive, ALND. Finally, when metastasis cannot be confirmed at the time of SLN biopsy, surgical judgment prevails, and it is reasonable to proceed to ALND on the basis of intraoperative suspicion alone, recognizing that the possibility of a false positive clinical and intraoperative lymph node examination must be balanced against the consequences of leaving gross axillary disease behind. For men who will receive neoadjuvant chemotherapy for locally advanced disease, we recommend axillary staging upfront by US guided fine needle aspiration, not SLN biopsy. Because about 40% of patients with positive axillary nodes will convert to node negative, we recommend SLN biopsy with intraoperative assessment after chemotherapy at the time of definitive surgery and ALND for those with positive SLN.

Perioperative Management

Wound closure is straightforward. Even for tumors that have required an extensive skin excision, primary wound closure is virtually always possible by elevating the skin flaps superiorly toward the clavicle and inferiorly onto the abdomen. We recommend closed suction drainage for mastectomy, and we instruct all patients in shoulder exercises to maintain or restore range of motion. There is no evidence to support any of the "standard" recommendations for the avoidance of lymphedema, and patients are encouraged to use their arms as normally as possible.

Postoperative Management

Postoperative consultations should include referral to genetic counseling (BRCA testing is appropriate for all patients with MBC and especially appropriate if there is a family history of breast or ovarian cancer), to medical oncology (the criteria for adjuvant hormonal therapy and chemotherapy in MBC are the same as with female breast cancer), and to radiation oncology (for patients with more locally advanced disease requiring PMRT). Plastic surgical consultation is also reasonable for the small minority of men who are bothered by loss of the nipple; nipple reconstruction by a local skin flap and tattooing gives excellent results in appropriate patients. It is vital to recognize that cosmetics are important to some male patients. NSQIP data shows 8% of men opted for immediate reconstruction and another 13.9% chose BCS even in the setting of the challenges with the procedure discussed previously.

Postoperative follow up for MBC, as for female breast cancer, should also include regular physical examination. Unlike female breast cancer, contralateral MBC is very rare and there are no data to support screening of the contralateral breast by mammography; however, patients may be unconvinced of this (in fact, NSQIP data shows 6.7% of men choosing contralateral prophylactic mastectomy) and mammography every 2 to 3 years is a reasonable compromise. As with female breast cancer, there are no data to support routine screening for distant metastases, but further workup is indicated for all new and persistent complaints suspicious for metastatic disease. ER positive breast cancers in women have a long natural history, with as many breast cancer events in years 5 to 10 as in years 0 to 5, and relapses beyond 10 years are not rare. The same is probably true for men, and because 90% of MBC are ER positive there is a strong rationale for lifelong surveillance of all MBC.

Suggested Readings

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A Surgeon's Practical Guide to Breast Imaging

Ashley L. Hoppe, MD, Christine E. Taul, MD, and Rachel F. Brem, MD, FACR, FSBI

Breast imaging is a constantly evolving, technology-driven specialty that is often in the spotlight due to the impact of breast imaging on mortality reduction, cost, and direct patient care. Additionally, breast imaging is the only subspecialty in radiology that is regulated by the federal government. This results in breast imagers undergoing annual evaluation with regard to image quality and radiation dose, as well as requiring an annual practice audit that allows physicians to objectively evaluate their practice against established benchmarks. The interaction of the breast radiologist and breast surgeon plays an integral role in the optimal diagnosis and treatment of the breast cancer patient as well as the identification and surveillance of patients at elevated risk for breast cancer. This chapter is a guide for the surgeon to better understand the wide array of imaging modalities utilized by the radiologist and their indications; the terminology of the standardized lexicon and the techniques of percutaneous, image-guided procedures as well as known localization prior to surgery. A discussion of breast cancer screening will also be provided, as screening has become controversial and thus relevant to any provider caring for women.

Breast Cancer Screening

Current Recommendations and Controversy

Breast cancer is the second leading cause of cancer-related death in women and was the cause of death in an estimated 40,610 women in the United States in 2017. It is well established that breast cancer is a treatable disease when detected early, with a vast amount of data demonstrating up to 45% reduction in mortality over the last 30 years—a laudable accomplishment achieved by both improved screening and improved therapies. While there are many factors that can increase a woman's risk for breast cancer, approximately 75% of breast cancers occur in women who have no risk factor other than being a woman. Despite the indisputable evidence supporting screening mammography, there remains significant controversy stemming from the interpretation of the data, varying opinions on risk versus benefit, and the potential harms of mammography (false positives, patient anxiety, overdiagnosis, and radiation exposure).

There are numerous organizations that have released recommendations and guidelines for breast cancer screening, among them the American College of Radiology (ACR), Society of Breast Imaging (SBI), the American Cancer Society (ACS), and the United States Preventive Services Task Force (USPSTF), all of whom agreed until about 10 years ago that all women over the age of 40 should be routinely screened with annual mammography. Since then, the ACR, SBI and American College of Obstetrics and Gynecology (ACOG) have continued to support this screening schedule, maintaining that this is not only the most effective method to save the most lives, but also has the additional benefit of reducing aggressive surgery and chemotherapy treatments by decreasing the number of women diagnosed with advanced disease. It is important to note that the organizations

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that have differing recommendations from that of annual screening beginning at age 40 (maintained by the ACR, SBI and ACOG) all concur that annual screening beginning at age 40 will save the most lives, though have tempered their recommendations due to the harms of mammography. As of 2015, the ACS recommends that women of average risk be given the opportunity to begin annual screening at age 40 to 44 (qualified recommendation) and should undergo annual screening mammography starting at age 45 to age 54 (strong recommendation) and that women 55 and older be given the option for annual or biennial screening (both qualified recommendations). These updated and qualified recommendations are based on uncertainty regarding the benefits and risk and the patients' values and preferences. The USPSTF updated its guidelines in 2016, stating that women should undergo biennial screening from age 50 to 74, that screening prior to age 50 should be an individualized decision, and that there are no data to support screening in women over the age of 74, not because of data demonstrating lack of efficacy, but rather due to the lack of studies that included women over the age of 74. When considering the recommendations of organizations that recommend screening begin at age 50 it must be noted that over 23% of all breast cancers in the United States occur in women in their 40s, further emphasizing the need to begin annual screening at age 40. The USPSTF states that with their current recommendations, 81% of the achieved mortality reduction will be maintained. Of course, the corollary to this is by following the USPSTF recommendations there is an expected 19% increase in mortality from breast cancer.

The two most significant noted harms of mammography are the anxiety women experience from false positive mammograms and the radiation dose. With regard to anxiety, studies have definitively demonstrated that the anxiety that occurs as a result of a false positive outcome, whether it be a false positive mammogram necessitating additional imaging or a false positive finding resulting in a minimally invasive breast biopsy, is transient, with no long-lasting consequences. Furthermore, the radiation dose from a mammogram is stringently limited by law and is equivalent to four round trips across the United States via airplane, with no demonstrable case of cancer ever documented as a result of a mammogram. These issues should be considered when discussing screening mammography with women.

Technology and Data Reporting

Recent advances in technology have resulted in marked changes in mammography. The transition from analog to digital mammography resulted in increased detection of breast cancer in women under 50, premenopausal women, and in women with dense breast tissue. More recently, digital breast tomosynthesis, commonly referred to as three dimensional (3D) mammography, has been introduced, which uses a low dose x-ray system to create multiple planar images of each breast that are reconstructed into a set of 3D images, thus reducing the masking effect of overlapping fibroglandular tissue. Studies demonstrated that tomosynthesis modestly increased cancer detection over digital mammography, with a concomitant significant decrease in recall rate, thereby addressing one of the most cited harms of mammography, the false positive rate. However, studies evaluating tomosynthesis have not all been consistent, with some, largely from Europe, demonstrating no impact on cancer detection and variable impact on the false positive rate. Recently, a large multiinstitutional study from the United Kingdom has demonstrated a lower biopsy rate and a higher positive predictive value of biopsy in women undergoing tomosynthesis as compared to full field digital mammography. Initially, tomosynthesis was Food and Drug Administration (FDA) cleared for two dimensional (2D) plus 3D mammography, thereby having a higher radiation dose, albeit still within the federally allowable limit. More recently, the FDA has cleared tomosynthesis with a synthetic 2D image, a 2D like image obtained from reconstituted 3D data. This approach is increasingly being integrated into clinical practice, thereby harnessing the benefits of tomosynthesis while utilizing a lower dose of radiation. The studies evaluating the sensitivity of the reconstructed 2D image are limited, but the data supports equal accuracy of both types of 2D images, whether directly obtained or reconstructed from 3D data. From the patient's perspective, acquisition of tomosynthesis is no different than 2D digital mammography. Currently, virtually all insurance carriers cover tomosynthesis for both screening and diagnostic mammography.

All mammographic reports require a BIRADS (Breast Imaging Reporting and Data System) assessment, a lexicon that was created to provide a standardized terminology to assist in the communication of breast imaging findings. BIRADS assessments consist of numbered recommendations (I through 6, given for both screening and diagnostic imaging (Table 1). A screening mammogram consists of a standardized set of images performed similarly on all patients and should only receive one of three assessments: BIRADS category 1 (normal), category 2 (benign, with the mammogram demonstrating a pathologically benign finding such as a fibroadenoma, diffuse fibrocystic calcifications, or a stable mass), or category 0 (needs additional evaluation). BIRADS categories 3, 4, and 5 are used exclusively with diagnostic mammography, with BIRADS 3 used for findings with a less than 2% risk of malignancy where a short term follow up is recommended to assess interval growth. BIRADS 4 and 5 are similar in that both recommend a tissue diagnosis, with the difference being the likelihood of malignancy. BIRADS 4 is a broad category used for findings with a more than 2% but less than 95% likelihood of malignancy, while BIRADS 5 is reserved for lesions with a 95% or greater likelihood of malignancy, and for which a benign pathology diagnosis would be considered discordant and not accepted. BIRADS 6 is used in women with biopsy proven cancer. After treatment for breast cancer, and with no evidence of residual disease, the BIRADS assessment returns to categories 0 to 5.

TABLE 1: BIRADS Final Assessment Categories

	Category	Management	Likelihood of Cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	N/A
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably benign	Short interval follow up	>0% but <2%
4	Suspicious	Tissue diagnosis	>2% but <95%
5	Highly suggestive of malignancy	Tissue diagnosis	>95%
6	Known biopsy proven malignancy	Surgical excision when clinically appropriate	N/A

BIRADS, Breast Imaging Reporting and Data System; N/A, not applicable.

Screening Versus Diagnostic Mammography

Screening mammography is for women with no signs or symptoms of breast cancer. The indications for diagnostic mammography include assessment of clinical findings (such as palpable abnormalities, focal pain, nipple discharge, or skin retraction or discoloration), the workup of a finding on a screening mammogram (callback), or for short-term interval follow-up of BIRADS 3 findings. Of note, the use of diagnostic mammography for women with a personal history of cancer is variable, and is at the discretion of the facility, the referring physician and patient preference without definitive recommendation. The Affordable Care Act (ACA) mandates coverage of screening mammography with no deductible or copay. In contrast, diagnostic mammography is subject to possible deductibles and copays dependent on the patient's individual insurance coverage. Women with implants, strong family history of breast cancer, and/or prior benign breast biopsies may have once opted for an annual diagnostic mammogram, where all imaging required was performed at the time the patient presented. In addition, with the significant change in financial considerations following the implementation of ACA and without direct standards, there has been a shift in women opting to undergo screening mammography, likely due to the financial considerations.

Other differences in screening and diagnostic mammography include the frequent use of batch reading for screening, which may be read the same day the examination is performed or days later. Women who undergo diagnostic evaluation will obtain the imaging necessary for triage and will not be recalled on another day, as the findings will be evaluated during the diagnostic examination. Additionally, women who present for a diagnostic mammogram who require ultrasound will obtain that study at the time of the diagnostic mammogram.

High-Risk Screening

There are numerous reasons a woman is at increased lifetime risk for breast cancer; a situation that results in the need for supplemental screening to optimize detection of early, curable breast cancer. Various risk assessment models have been developed to calculate a woman's lifetime risk for breast cancer, with factors such as age, ethnicity, genetics, history of chest irradiation, family history of breast or ovarian cancer, as well as personal history of breast cancer and atypia taken into account. It is noteworthy that these risk assessment models, of which the Gail and Tyrer-Cuzick are the most commonly employed, have substantial variability in risk determination due to the variability in factors utilized. Another significant risk factor that has gained attention more recently is breast density, a factor not traditionally included in the currently used risk models (although the most recent updated version of Tyrer Cuzick now includes density). Breast density is determined by a subjective assessment of the amount of fibroglandular tissue on the mammogram, with four BIRADS categories, A through D, ranging from least to most dense (Fig. 1). The only way to determine breast density is with a mammogram. Approximately 40% of American women have dense breast tissue, defined as heterogeneously or extremely dense, or BIRADS categories C and D. Both breast tissue and breast cancers are white on a mammogram. Therefore, dense breast tissue decreases the sensitivity of mammography from approximately 85% in all women to ≤50% in women with dense breast tissue. Furthermore, dense breast tissue is an independent risk factor for developing breast cancer, with the risk of breast cancer to women having extremely dense breasts (category D) being fourfold higher than those with fatty breasts (category A), and a nearly twofold increased risk of breast cancer when comparing dense (BIRADS density C and D) to nondense breast tissue (BIRADS density A and B). Therefore, having dense breast tissue both decreases the sensitivity of mammography as well as independently increases the risk of breast cancer.

With 40% of American women having dense breasts, women with dense breast tissue constitute the largest population of intermediate-risk women. Breast density has also become a political issue, with over 36 states and the District of Columbia enacting laws that require women be informed of their breast density. There is variability among the state-mandated information women must receive, with some requiring women to be informed of additional screening that can detect mammographically occult breast cancer. In two states and the District of Columbia, there is mandated insurance coverage of adjunct screening in women with dense breast tissue. Studies have demonstrated that while screening mammography detects 2 to 7 breast cancers in 1000 women screened, screening breast ultrasound in women with dense breast tissue can detect an additional 2 to 7 cancers per 1000 women screened. Of note, mammographically occult

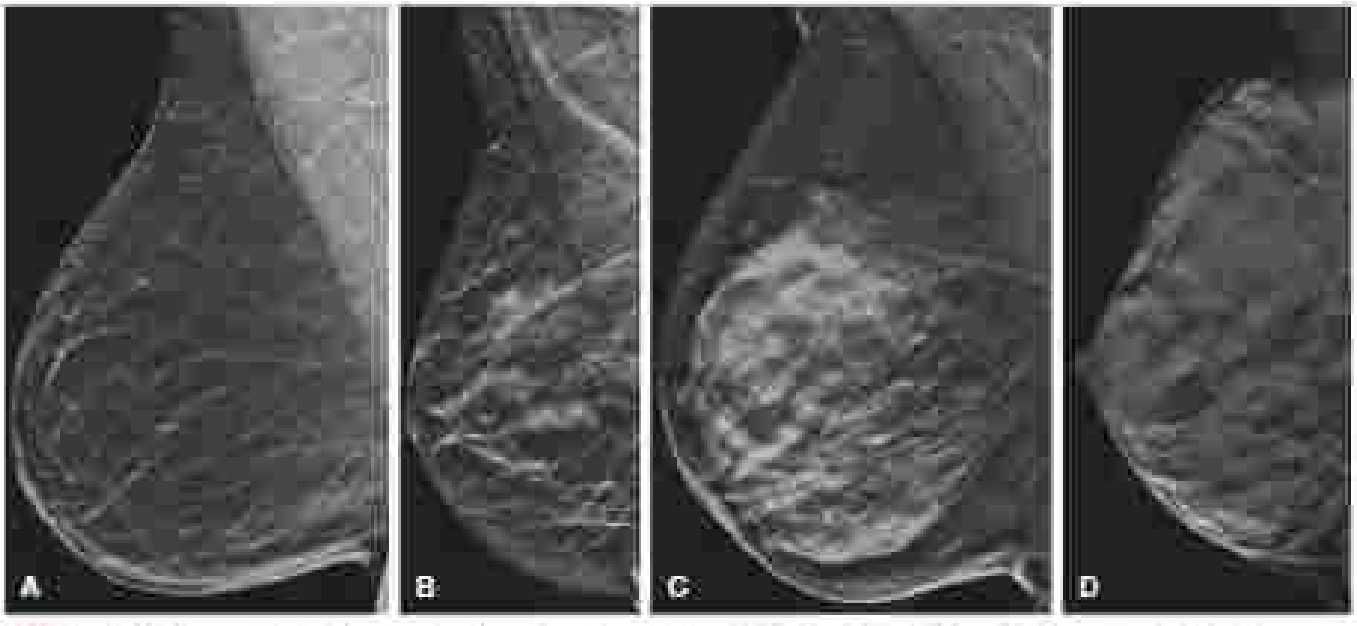

FIG. 1 Examples of the Breast Imaging Reporting and Data System density categories using a synthetic two-dimensional mammogram in the right mediolateral oblique projection. (A) Almost entirely fatty. (B) Scattered areas of fibroglandular density. (C) Heterogeneously dense. (D) Extremely dense.

cancers detected with screening breast ultrasound are frequently small, invasive, node-negative cancers. When widespread screening breast ultrasound began, there was concern that the rate of additional cancer detection would not be sustained. However, this has not been the case. Studies have continued to demonstrate that screening ultrasound detects an additional 2 to 4 cancers per 1000 women screened in subsequent years, nearly doubling the rate of cancer detection. Studies have also evaluated magnetic resonance imaging (MRI) and molecular breast imaging (MBI) as adjunct screening modalities in women with dense breast tissue. These technologies detect more cancers than screening breast ultrasound; however, they are much higher cost and require an injection and therefore are currently not in widespread use in screening women with dense breast tissue.

Currently, there is no consensus on how to screen women at intermediate risk for breast cancer, which includes women with dense breast tissue, a history of atypia, a personal history of breast cancer, and some women with a family history of breast cancer. While breast ultrasound is the most commonly used supplemental screening, While initial studies demonstrated the added benefit of screening-based ultrasound using a hand-held technique by a radiologist, this method has limitations of scanning time and operator dependence. More recently, the development of screening 3D automated whole breast ultrasound (ABUS) has been shown to be a promising technique to circumvent the limitations of hand-held ultrasound. ABUS allows for uncoupling of image acquisition from interpretation, with the breast imaged using a specialized, long field of view ultrasound probe in a standardized, reproducible method, which can later be reviewed in entirety by the interpreting radiologist. Although this is a relatively new technology, it is a promising solution to the increasing need for additional screening. One of the most significant limitations of screening breast ultrasound is the false-positive rate. Recent developments in enhanced sonographic tissue characterization utilizing technology such as sound speed and transmission ultrasound, in addition to reflective imaging, will likely allow for a substantial decrease in the false positive rate, possibly with an increase in sensitivity. Additionally, artificial intelligence is being developed to improve both the sensitivity and specificity of lesions detected with breast ultrasound.

MRI has a very high sensitivity for breast cancer, over 95% for invasive breast cancer and slightly lower for the detection of ductal carcinoma in situ. MRI is used for numerous clinical indications including as a problem-solving tool in women with palpable findings with no mammographic or sonographic correlate, evaluation of extent of disease, and additional foci in women with newly diagnosed breast cancer, evaluation of response to neoadjuvant chemotherapy, evaluation of silicone implant integrity, and the most frequent indication, surveillance of high-risk women (Fig. 2A). The American Cancer Society recommends that women with a lifetime risk of breast cancer of 20% or greater undergo annual supplemental surveillance for breast cancer with MRI. This includes women with genetic mutations that are associated with a predisposition for breast cancer such as BRCA 1 and 2, untested first-degree relatives of women with known genetic mutations, women with a history of mantle radiation for Hodgkin's during adolescence, as well as women with syndromes such as Li-Fraumeni, Cowden, and Carney, which increase the risk for breast cancer. With recent advances in the understanding of genetic mutations, the number of mutations that are associated with increased predilection for breast cancer is increasing and the number of mutations of unknown significance is decreasing. Recent studies have demonstrated that women who are found to have atypical ductal hyperplasia (ADH) under the age of 50, and who have multiple foci of ADH have a greater than 20% lifetime risk of developing breast cancer and should undergo annual surveillance with MRI. It has also been shown that women with a personal history of breast cancer have substantially more cancers detected with annual MRI. Although these indications are not routinely recommended, it is likely that the population of women for whom MRI surveillance is recommended will likely be expanded.

With the increased use of screening MRI, abbreviated MRI, which utilizes fewer sequences resulting in a shorter, more cost effective,

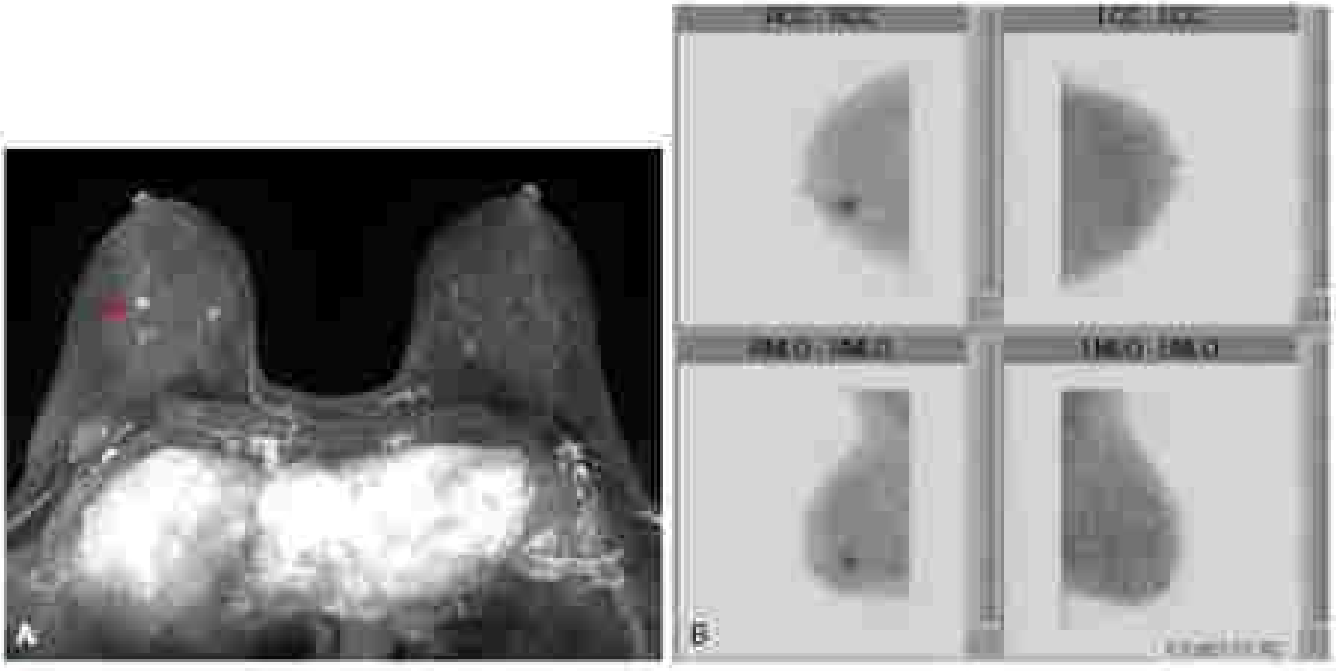

FIG. 2—(A) A maximum intensity projection image of a screening breast magnetic resonance imaging performed on a 48-year-old woman with *BRCA*-gene mutation demonstrating an 8-mm irregular enhancing mass in the right breast (arrow) at 1 o'clock. This was later biopsy-proven to be a grade 2 invasive ductal carcinoma, and node negative following definitive surgical management. (B) Standard screening molecular breast imaging images in a 41-year-old high-risk female demonstrating focal radiotracer uptake in the lower right breast, with subsequent ultrasound-guided biopsy demonstrating a grade 1 invasive ductal carcinoma.

better ultrasound examination has been shown in single institutional studies, to be equally effective in screening high risk women. There is an ongoing large, multiinstitutional trial evaluating abbreviated MRI protocols. Increasingly, abbreviated MRI protocols are being utilized to screen high risk women with MRI, however, the definitive ability of abbreviated MRI to equally detect breast cancer awaits the results of the trial.

MBI, also called breast specific gamma imaging (BSGI) is a physiologic imaging modality that uses 99m Tc sestamibi. Sestamibi uptake is increased in vascular and hypermetabolic tissue. The sensitivity of MBI has been shown to be comparable to MRI with slightly greater specificity. For women in whom MRI is contraindicated (i.e., women with renal insufficiency, implanted devices, claustrophobia and body habitus that precludes MRI imaging), having MBI has been extremely helpful and may be the only physiologic imaging modality available to them. The sensitivity of MBI in detecting cancer and high risk lesions in women at increased risk for breast cancer is comparable to MRI. MBI also has equal sensitivity in women with dense and non-dense breasts. In challenging clinical situations such as implants, and silicone injections, MBI can be extremely helpful in detecting otherwise occult cancers. In addition, MBI has detected additional foci of occult cancer in 7% to 10% of women with newly diagnosed cancer. Of course, radiation is always a concern. Initially, the dose used in MBI studies was 20 to 30 mCi. More recently studies have shown no difference in the ability to detect and diagnose cancer using 5 to 8 mCi, resulting in a radiation dose comparable to two mammograms, albeit the radiation is full body and not limited to the breast. Several studies have evaluated MBI for screening women with dense breasts and have reported detecting more cancers than that detected with ultrasound screening (Fig. 28). Nevertheless, the issue of injection and radiation remains, and MBI is generally used as a problem-solving tool and in women with newly diagnosed breast cancer.

MRI is commonly used for the workup of clinically suspicious abnormalities in the face of negative mammography and ultrasound, such as palpable findings, and pathologic nipple discharge (Fig. 3). The use of galactography, or ductography is decreasing. In women with new onset pathologic nipple discharge, a negative mammogram and ultrasound is generally followed by evaluation with MRI, which provides higher sensitivity than ductography and uses a noninvasive approach. Furthermore, evaluation with MRI does not require the ability to extract the nipple discharge. When initially introduced, MRI was predominantly used as problem solving tool. However, with time, the indications for MRI have shifted and the current most common indication is surveillance in high risk women.

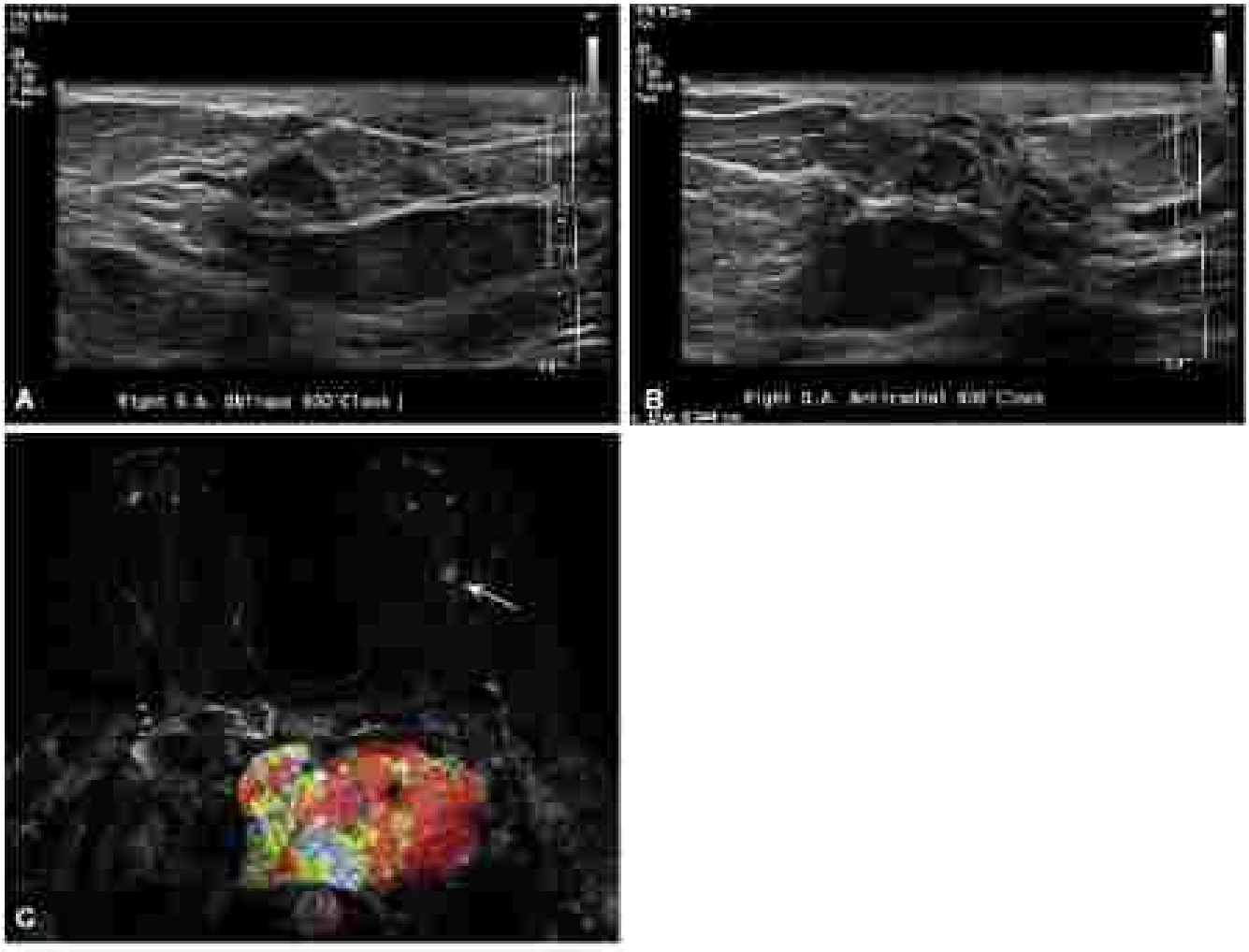

FIG. 3 Oblique (A) and sagittal (B) sonographic images of a solitary intraductal mass in a 55-year-old woman who presented with unilateral, bloody, spontaneous nipple discharge, later biopsy-proven to be an intraductal papilloma. (C) Contrast-enhanced magnetic resonance image with color kinetic overlay performed on a 51-year-old woman with spontaneous and clear nipple discharge in the left breast, which demonstrates a subcentimeter heterogeneously enhancing mass in the central left breast, also later biopsy proven to be a papilloma.

The use of MRI in women with newly diagnosed breast cancer varies greatly and is controversial. Studies have demonstrated that MRI detects additional foci of breast cancer in approximately 18% of women with newly diagnosed breast cancer, 7% in the ipsilateral breast, and 3% in the contralateral breast. In our institution, all women with newly diagnosed breast cancer obtain physiologic imaging with either MRI or MRI prior to definitive surgery. In other institutions, MRI in women with newly diagnosed breast cancer is reserved for women with dense breast tissue where the sensitivity of mammography is decreased, in women with invasive lobular carcinoma, which can be more difficult to detect with mammography and ultrasound or in other clinical situations. Recent studies have demonstrated that the preoperative use of MRI in women with newly diagnosed breast cancer not only results in higher rates of negative margins but increases survival. The concerns regarding the routine use of MRI in women with newly diagnosed breast cancer include the decision to change conservative therapy to a mastectomy as a result of the MRI finding, and the cost of detection of *false positives* that require biopsy prior to determination of definitive *optimal* surgical approach. Currently, there are no definitive recommendations regarding MRI in women with newly diagnosed breast cancer.

IMAGE-GUIDED PROCEDURES

Breast Biopsy

There are over 3 million breast biopsies performed in the United States annually. The vast majority, if not all, are optimally approached with minimally invasive tissue acquisition. Minimally invasive breast biopsy is more cost effective, less invasive, and better tolerated by the patient than open surgical biopsy. The vast majority of breast biopsies (i.e., 70% or more) result in benign findings, thereby further emphasizing the need for minimally invasive breast biopsy. Additionally, studies have shown that women who undergo minimally invasive breast biopsy that demonstrate malignancy have higher rates of negative margins at lumpectomy, thereby improving the patient experience and decreasing the cost of care.

Image-guided minimally invasive breast biopsy can be performed by ultrasound, mammogram (stereotactic), MRI, and gamma guidance. In our practice, following all minimally invasive breast biopsies, with the consent of the patient, a marker is placed at the site of biopsy. There are an increasing number and types of biopsy markers available, varying in shape, size, and material. Markers are most frequently made of titanium or a stainless steel alloy, although newer markers made of carbon are available. There are numerous purposes for the routine placement of the marker, including confirmation of ultrasound biopsy with a targeted mammographic finding, marking a site of benign biopsy so that repeat biopsy is not recommended at a later time, and marking a site of malignancy or atypia for identification for localization prior to surgical excision. This is especially important if the imaging evidence of the targeted lesion is removed or altered by the biopsy itself, or the patient undergoes neoadjuvant chemotherapy, which can render the cancer invisible by imaging. In our practice, we utilize different shaped markers in women with multiple biopsies to definitively identify a specific biopsy site. Other considerations include the signal void of the marker on MRI, with some markers being difficult to identify on MRI and others resulting in a large signal void that can obscure substantial areas of the breast. The selection of the type and shape of biopsy marker is important and should be carefully considered.

The patient experience and the time and difficulty of a biopsy can vary by the guidance method used. Minimally invasive breast biopsy utilizing ultrasound guidance is generally quick, allows for real-time imaging of the biopsy device, and is generally performed with the patient supine, generally the most comfortable position for the patient. It is for these reasons that ultrasound guidance is the modality of choice for any lesion visualized with ultrasound. If a lesion is seen with mammography and is not sonographically visible, which is frequently the case with microcalcifications, stereotactic biopsy is used. Stereotactic biopsy can be performed with the patient prone or upright, depending on the equipment available. More recently, the introduction of minimally invasive biopsy with tomosynthesis guidance allows for the targeting and accurate biopsy of lesions seen only with tomosynthesis and not visible on 2D mammography. This situation is becoming increasingly frequent with the growing use of tomosynthesis and detection of subtle areas of architectural distortion not previously appreciated with 2D mammography. MRI guided biopsies are reserved for findings seen only by MRI, as MRI guided biopsies are more time consuming, involve an additional injection of intravenous gadolinium, and are less comfortable for the patient. Of note, MRI biopsy can be performed bilaterally with availability of appropriate biopsy coils. With the increasing availability of MRI, gamma guided biopsy can be performed and is similar to MRI biopsy, although the patient is comfortably seated during the procedure. If a lesion is initially visualized with mammography, correlation with ultrasound must be attempted to confirm that the same lesion is being visualized in both imaging modalities. Furthermore, it is imperative that correlation with the postprocedure mammogram be performed to ensure accurate lesion targeting. No minimally invasive biopsy is complete without radiologic-pathologic concordance. If the pathology obtained for a lesion is discordant, then re-biopsy is required. Both surgical and minimally invasive breast biopsy obtain accurate pathology in 98% of biopsies. It is for this reason that, aside from well-circumscribed masses found to be fibroadenomas and cysts with complete resolution, we choose to obtain a 6-month follow-up of all lesions biopsied to evaluate for interval change and to identify the 2% of missed lesions. The imaging modality used to target the lesion should be utilized to evaluate the lesion at the 6-month interval to confirm its stability.

Localization

Preoperative needle localization is an integral component of breast imaging and is a collaborative procedure between the breast imager and breast surgeon. Localization is typically performed by the radiologist prior to lumpectomy for malignancy, or prior to excisional biopsy for high-risk lesions such as atypia, complex sclerosing lesions, tubular carcinoma in situ and papilloma, among others. The traditional method of localizing nonpalpable breast lesions has been by image-guided wire placement immediately prior to surgery. This has many disadvantages, including wire displacement, suboptimal positioning of the wire entry point related to the planned surgical incision, and the risk of a vasovagal reaction during the procedure with the patient not eating or drinking for extended periods prior to the localization. Furthermore, preoperative wire localization must be performed the same day of the surgery and therefore presents workflow and scheduling challenges in terms of timing of the localization and the surgery. The need to transport the patient from radiology to surgery with the wire protruding from the breast is challenging, particularly as there may not be adjacency of the radiology department and the operating room. As a result of these limitations, new techniques have been developed and are rapidly replacing wire localizations. Currently, the most widely used alternative to radioactive seed localization (RSL), which involves placing a small metallic radioactive (I^{125}) seed into the lesion, either by mammographic or sonographic guidance. The surgeon can then accurately localize the lesion in the operating room by way of a hand-held gamma probe. Not only does this provide major logistical advantages for the surgeon, but it is also more convenient for the patient as this can be done up to 7 days prior to surgery. Although RSL has significant advantages over wire localization, the use radioactive materials results in Nuclear Regulatory Council stringent oversight and extensive regulations that can make implementation difficult. Several nonradioactive devices have recently been introduced with advantages similar to RSL, though without the stringent regulatory issues. These include Localite, which uses a radiofrequency localizer; Magseed, which is a paramagnetic steel and iron oxide seed; and SentiMag, which uses a radar

localization system. These devices are placed similar to the approach used with radioactive seed and then detected in the operating room by specialized probes. Until recently, the ability to detect deeply situated localization devices has been challenging. Additionally, the FDA has recently cleared the Localite for long-term placement, for up to a year, as long as there is the intent to remove it surgically. Another consideration of the surgeon during the selection of a nonradioactive, nonwire localizing device is the size of the probe used during intraoperative detection, as this can vary widely. In certain clinical situations it is also possible for the surgeon to localize the biopsy site with intraoperative ultrasound during surgery.

Multidisciplinary Care

Optimal care of the breast cancer patient requires a multidisciplinary approach throughout the care cycle. From the time of abnormal mammogram or clinical finding, the interaction of the entire breast "team" can include, though is not limited to, the breast surgeon, imager, pathologist, oncologist, plastic surgeon, genetic counselor, social worker, physical medicine, psychologist, complementary medicine, survivorship practitioners, navigators, nurses, and others, resulting in overall improved care. From the time of an abnormal mammogram to the subsequent additional appointments, the value of navigation has been well established. The navigator has become an integral component of the breast imaging center resulting in coordinated and efficient care, helping patients understand their pathology, and partnering with them for appointments, support, and guidance. In our practice, every patient who has a diagnosis requiring surgery, whether it be a high-risk lesion requiring excision or a patient with a diagnosis of breast cancer, is partnered with a navigator. This results in improved patient experience, and a more efficient and compassionate approach to the care of women with breast disease. The ability to later review what was discussed during the initial appointment when told of a breast cancer diagnosis is invaluable to the patient.

The interaction of the breast imager and breast surgeon can impact the surgical approach with imaging rendering insight into the possibility of nipple sparing during mastectomy, the opportunity for conservative therapy dependent on extent of disease and additional foci of disease identified, as well as a collaborative decision regarding optimal screening protocols for high-risk women. The interaction of the medical oncologist and the imager during neoadjuvant chemotherapy can impact the choice of regimens, further emphasizing the critical importance of the multidisciplinary team. Furthermore, with the average age at breast cancer diagnosis decreasing, we are seeing younger women with fertility concerns and women diagnosed during pregnancy, underscoring the need for multidisciplinary care. Finally, as we continue to gain knowledge regarding the vast amount of genetic factors associated with both increased risk of and care of the women with breast cancer, the multidisciplinary approach, which includes an ever expanding cadre of specialties, is critical.

CONCLUSION

Breast imaging is a rapidly evolving field that is intimately associated with breast surgery, and the best outcomes for the patient result from the combined, multidisciplinary efforts of the breast care team. Optimization of patient care can be achieved when each subspecialist has an appreciation and basic knowledge of each other's fields and maintains an open line of communication.

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Genetic Counseling and Testing

Michele A. Gadd, MD, and Kevin Hughes, MD

Genetic testing for hereditary cancer syndromes has evolved significantly since the identification of the *BRCA1* and *2* genes in 1994 and 1995, and the mapping of the human genome in 2003. Technologic advances in genetic science and the Supreme Court ruling in 2013, preventing genes from being patented, paved the way for direct to consumer genetic testing. For several hereditary cancer syndromes, genetic testing provides an opportunity to identify high-risk individuals and take action before they develop cancer. In an increasing number of cases, however, the discovery of a less well-characterized genetic mutation is not as informative and the future of the individual's health less certain. Thus the issue of who to test and how best to counsel patients regarding their cancer risks is an increasing challenge to healthcare delivery.

MECHANISM OF CANCER DEVELOPMENT

More than 100 genes have been identified with activating or inactivating mutations that can increase the risk of cancer, and many more will be found in the near future. The majority of these genes are tumor suppressor genes, in which the protein produced by the gene actively works to prevent the development of cancer. Tumor suppressor genes tend to be organ specific, each preventing cancer in a subset of organs (or leading to cancer in that subset when inactivated through mutation), thus establishing a spectrum of susceptible organs for each syndrome. The responsible gene (or genes) has been identified for the major hereditary cancer syndromes (Table 1). These genes tend to be predominantly inherited. This means a single mutation in one of the two paired genes causes cancer susceptibility but tend to behave recessively at the cellular level. Therefore not every cell of the specific organ will become cancerous. As humans, we have two sets of genes, one inherited from each parent (Fig. 1). When a germline tumor suppressor gene has an inactivating mutation, the other copy of the gene continues to function normally. It is only when the second gene is damaged by a somatic event and loses function that the cell begins to accumulate other mutations, eventually leading to cancer. This is known as the Knudson two-hit hypothesis and helps to explain why most patients with a mutation develop cancer sometimes in a single organ but often in multiple organs.

A small number of genes, such as the *RET* gene, which causes multiple endocrine neoplasia type 2 (MEN2), are exceptions. Oncogenes are the mutant form of proto-oncogenes, the genes that regulate cellular proliferation and apoptosis. In cancers involving oncogenes, a single germline mutant gene can drive cancer development without a second hit causing the cancer to often develop at a very young age. This helps explain the need for thyroidectomy in children younger than 5 years in some cases of MEN2.

IDENTIFICATION OF THOSE AT RISK

To identify patients with a hereditary predisposition to cancer, it is critical to take a thorough family history. A pattern of multiple cancers associated with a specific syndrome, occurring in a single bloodline, is the key to identifying families who are more likely to harbor a germline mutation associated with a specific syndrome. The second hallmark of hereditary cancer is young age at diagnosis. Cancers diagnosed in young adults are more likely to be hereditary because the first mutation is already present at birth. Multiple cancers in a single individual is a third indicator, and an unusual cancer, such as male breast cancer or medullary thyroid cancer, is the fourth indicator of hereditary cancer. In addition, the threshold required for testing drops significantly in groups with an established high probability of mutation, such as Ashkenazi Jewish individuals, who may be eligible for testing even without one of these indicators. If any of these indicators are observed in the family history, genetic testing should be considered. Guidelines, such as those established by the National Comprehensive Cancer Center (NCCN) or the United States Preventive Services Task Force, provide examples of notable patterns, whereas risk models (e.g., BRCAPRO, Tyrer Cuzick) can be helpful for quantifying risk and setting thresholds for testable families.

Identifying individuals who are at risk for hereditary cancer is critical and can occur at multiple stages in the patient's care. Within your practice, you will find potential mutation carriers among (1) patients who do not have cancer, (2) patients with newly diagnosed cancer, and (3) patients being followed for past cancers. It is critical to have a system in place to identify high-risk individuals in each of these categories.

Patients Who Do Not Have Cancer

Ideally, mutation carriers should be identified before the development of cancer. It is good medical practice to take a family history for each patient. A strong family history should indicate the need to consider genetic testing. If testing is positive, the patient can be placed on a management strategy that either prevents cancer or aids in earlier diagnosis. In the past, it was recommended that a living affected relative be tested first, to identify the family specific mutation. If testing of a relative can be accomplished expeditiously, this remains the ideal approach because it provides the entire family with clinically actionable information. However, because testing has become more accessible and the cost decreased, it is becoming more common to test patients, whether or not they have cancer, as long as the family history supports an increased risk.

Patients With Newly Diagnosed Cancer

Among patients with a newly diagnosed cancer, more immediate identification of the mutation status may be critical because this information may have implications for treatment.

Patients Being Monitored for a Past Cancer

Follow-up cancer patients may not have had testing at diagnosis. Even some of those tested in the past may have undergone less comprehensive testing than is available today. Updating family history and readdressing additional testing should be part of continued cancer care. For those who tested negative on past screening, even within the last few years, updating their testing with new gene panels may be recommended.

Relatives of Mutation Carriers

When a patient with a hereditary syndrome is identified, it is extremely important to make the patient aware of the need to inform other family members. Close to half of the patient's close relatives, and a high proportion of more distant relatives, may have the mutation and be unaware of the risk. Although informing other family members can be difficult for patients dealing with a new diagnosis, the implications for their relatives can be great.

GENETIC TESTING PANELS

Once a patient has been identified as appropriate for genetic testing, the next decision is which test to order. Labs can now test multiple

TABLE 1 Examples of Hereditary Cancer Syndromes and Their Associated Genes

	Breast	Ovarian	Colorectal	Uterine	Melanoma	Pancreatic	Stomach	Prostate	Leukemia
HEREDITARY BREAST AND OVARIAN CANCER SYNDROME									
BRCA1	+	+				+		+	
BRCA2	+	+			+				
LYNCH SYNDROME									
MLH1		+	+	+		+	+		
MSH2		+	+	+		+	+		
MSH6		+	+	+		+	+		
PMS2		+	+	+		+	+		
FAMILIAL ADENOMATOUS POLYPOSIS SYNDROME									
APC		+				+	+		
LI-FRAUMENI SYNDROME									
TP53	+	+	+	+	+	+	+	+	+
COWDEN'S SYNDROME									
PTEN	+		+	+	+				
PEUTZ-JEGHERS SYNDROME									
STK11	+	+	+	+		+	+		
HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME									
CDH1	+		+				+		

cancer gene smaller panels (analogous panel testing). These panels may be organ directed, representing multiple genes that are related to a single organ system, or they may be pan-cancer panels, sometimes covering several or even all known cancer genes. The advantage of these panels is that it is no longer necessary to limit the test to a small subset of genes, and it is far less likely that the responsible gene will be missed. The disadvantage is that many panels include less well-studied genes with fewer evidence-based guidelines regarding preventive and early detection to share with patients. Keeping these limitations in mind, it is now more common to move directly to panel testing unless a known gene mutation has previously been identified to exist in a family. In the latter case, single site mutation testing remains a reasonable option. Surgeons should be involved in this process, ideally referring the patient to a genetics expert for testing. For surgeons who choose to do their own genetic testing, it is important to provide pre-test and post-test counseling, in keeping with the recommendations of the American Society of Clinical Oncology (ASCO). This entails carefully reviewing the ASCO elements of informed consent with patients before testing and counseling patients regarding the implications of their results after testing is completed.

INTERPRETATION OF RESULTS

Mutations or variants in cancer susceptibility genes can be classified into one of five categories: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, and pathogenic. Benign or likely benign variants basically should be ignored and generally are not reported. Pathogenic mutations, which include deleterious mutations, should be treated appropriately, whereas mutations that are likely pathogenic (suspected deleterious) should be managed based on the family history and the clinical situation, although a low threshold for action may be appropriate (Fig. 2). Mutations that occur in the population and are not associated with cancer are categorized as polymorphisms; some have been reported in the past and others may not. These mutations do not alter management. The results that are most frustrating for patients and clinicians are the VUS. A VUS means that although there is indeed a change in the DNA sequence of the gene, the change may or may not be cancer causing. These variants are seen more commonly in newer, less well-studied genes, such as *PALB2*, but can still be found, although less commonly, in extensively tested genes, such as *BRCA1* or *BRCA2*. Patients with a VUS should be managed based on the family history and the clinical situation, as if the VUS had not been found. Over time, most VUS mutations will be reclassified, at which time the lab involved usually will notify you and you, in turn, should inform the patient. A recent 20-year retrospective study of 1483 VUS demonstrated that the chance of "upgrade" (reclassification to suspected or deleterious) was less than 3% (Slavin et al.).

The number and variety of genes that cause cancer, together with our rapidly accumulating knowledge of cancer genetics, has made it virtually impossible for anyone to know what every gene mutation in every gene means in terms of cancer risk or how it should be managed. One must consider the penetrance and clinical spectrum of that specific gene mutation and then determine the management options that apply to the individual patient. The laboratory generally provides suggested management guidelines but one may still need to go to the literature to learn more. The NCCN and many specialty societies have produced excellent guidelines for many of the major cancer syndromes. Counseling patients about management often requires a multidisciplinary approach. It is important to identify a set of consultants in your area to whom you can refer the patient. For *BRCA* mutations, experts in gynecologic oncology, medical oncology, and breast surgery are helpful, whereas for Lynch syndrome, experts in gynecologic oncology, medical oncology, gastroenterology, and colorectal surgery are helpful.

There is a website, Adv2MetOnc, available to assist with calculating the risk of cancers associated with a deleterious mutation. The tool was developed by the Jiayu Mendel Lab at Dana-Farber Cancer Institute and the Hughes Lab at Massachusetts General Hospital. Reliable studies for each gene are used to convert results into clinically

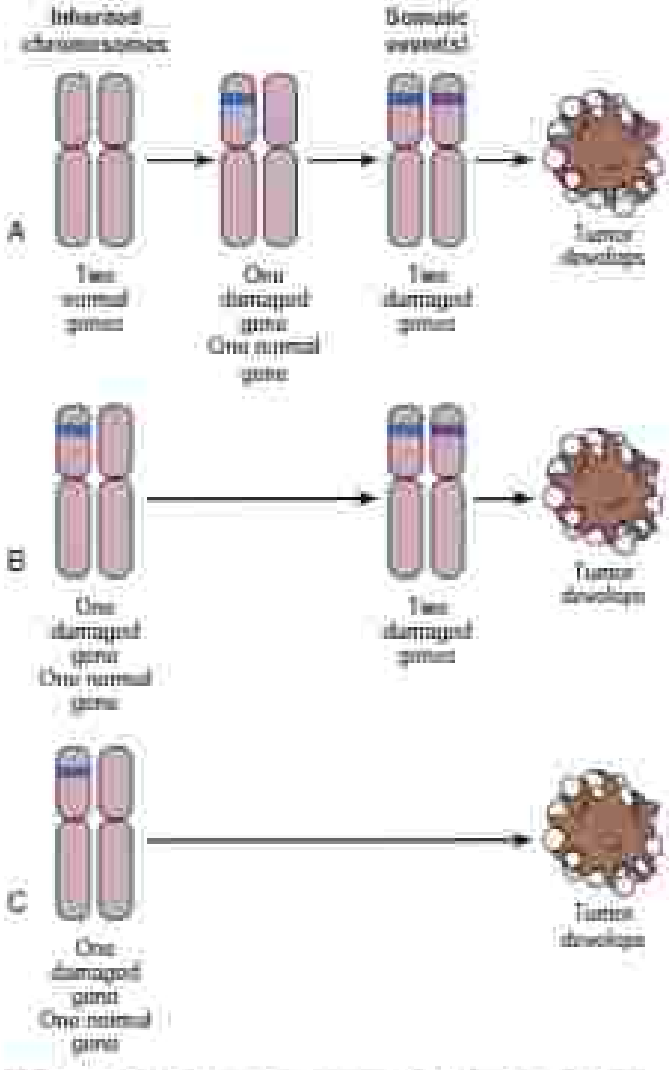

FIG. 1 (A) In sporadic cancers, two mutations in the same gene need to occur before developing cancer. These events generally take decades to occur. (B) In the major hereditary cancer syndromes the responsible gene (often a tumor suppressor gene) is inherited and already damaged. When the second gene is damaged, the loss of function leads to cancer. This can still be generally occurs at an earlier age. (C) When the inherited mutated gene is an oncogene, cancer develops without a second mutation. In this case, cancer may develop in childhood.

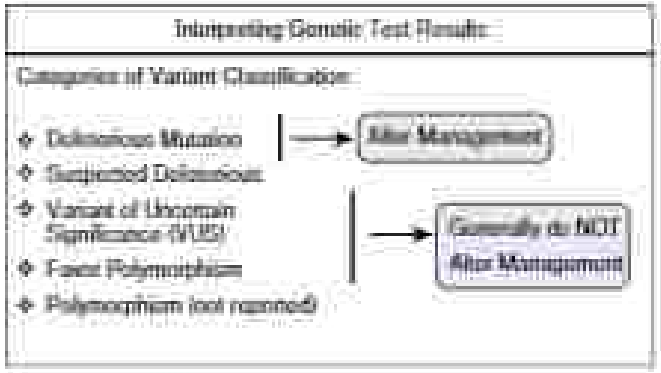

FIG. 2 Interpreting genetic test results.

relevant absolute risk estimates. The database is updated often and is considered a work in progress.

CANCER SYNDROMES

Breast and Ovarian

The majority of patients with hereditary breast and ovarian cancers have mutations in either the breast cancer type 1 or 2 susceptibility genes (*BRCA1* and *BRCA2*). Mutations in these genes are associated with approximately 10% of women with familial breast cancer and women with ovarian cancers. *BRCA* mutations are also associated with an increased incidence of prostate, male breast and pancreas cancers. Components of the patient's history that should lead one to consider genetic testing are listed in Box 1. Guidelines for screening and prevention for *BRCA1* and *BRCA2* carriers are listed in Box 2. Mutations in other genes such as *TP53*, *PTEN*, *CHEK2*, and *PALB2* occur less often and are associated with varying penetrance and risk (Table 2).

BOX 1 Risk Factors for Hereditary Breast and Ovarian Cancer

Breast cancer before age 50 years
Multiple primary breast/ovarian cancers
Triple negative breast cancer
Male breast cancer at any age
Ovarian cancer at any age
Ashkenazi Jewish ancestry
Early onset pancreas or (metastatic) prostate cancer
Relatives of a *BRCA* mutation carrier

BOX 2 Guidelines for Screening and Prevention for *BRCA1/2* Carriers

Risk training and education and regular monthly BSE starting at age 18 years
Semiannual clinical breast exam starting at age 25 years
Annual breast MRI screening starting at age 25 and mammogram age 30 years
Discuss option of prophylactic mastectomy
Recommend ovary/fallopian tube removal from age 35 for *BRCA1* and age 40–45 years for *BRCA2*
For those who have not elected ovary/fallopian tube removal: consider vaginal US and Ca 125 every 6 months starting at age 25 or 5–10 years earlier than earliest age of first diagnosis of ovarian cancer
Consider chemoprevention options for breast and ovarian cancer
Consider investigational imaging and screening studies

BSE, breast self exam; MRI, Magnetic resonance imaging; US, ultrasound.

Colorectal

It is estimated that 20% to 30% of colorectal cancers are familial and that there is a 5% to 10% chance of relating the cancer to a known genetic syndrome. Greater than 20 genes have been identified and linked to hereditary colon cancer risk (Table 3). Identifying individuals with a mutation associated with early colorectal cancer is critical for prevention and early detection. Most panel tests today include genes associated with increased colorectal cancer risk. Comprehensive cancer panel testing should be considered when there are overlapping syndromes being considered. The best understood are the high penetrance genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, EPCAM) responsible for Lynch syndrome and the high penetrance gene (*APC*, *MUTYH*) responsible for Familial Adenomatous Polyposis/MUTYH associated polyposis. Patients with hereditary colorectal syndromes are at risk of earlier cancer development, metachronous

TABLE 2 Panel Testing

Hereditary Breast and Ovarian Cancer Syndrome	Hereditary Breast Cancer, High-Risk Panel	Hereditary Breast Cancer, Moderate-Risk Panel	Hereditary Gynecologic Cancers, High-Risk Panel
BRCA1	*BRCA1*	*ATM*	*BRCA1*
BRCA2	*BRCA2*	*CHEK2*	*BRCA2*
	TP53	*MRDH*	*TP53*
	PTEN	*RAD51*	*PTEN*
	STK11	*PALB2*	*PMS2*
	CDH1	*MRE11A*	*MLH1*
	PALB2	*NBN*	*MSH2*
		NF1	*MSH6*
		RAD50	*EPCAM*
		RAD51C	

TABLE 3 Genes Associated With Inherited Risk of Colorectal Cancer

Gene	Syndrome
HIGH PENETRANCE	
APC	Familial adenomatous polyposis, Attenuated familial adenomatous polyposis
MSH2, MLH1, PMS2, MSH6, EPCAM	Lynch syndrome
MUTYH (biallelic)	MUTYH-associated polyposis
SMAD4, BMPR1A	Juvenile polyposis
STK11	Peutz–Jeghers syndrome
PTEN	Cowden's disease
TP53	Li–Fraumeni syndrome
MODERATE/UNCERTAIN PENETRANCE	
ATM	
AXIN2	
CDH1	
CHEK2	
GALNT5	
GREM1	
MSH3	
MUTYH (monoallelic)	
NTHL1	
POLE, POLD1	

TABLE 4 National Comprehensive Cancer Network Surveillance Recommendations for Hereditary Colorectal Cancer Syndromes

Syndrome	Site	Age to Begin Surveillance (y)	Surveillance Interval (y)	Procedures
HNPCC	Colon	20–25 or 2–5 y before earliest colorectal cancer diagnosis	1–2	Colonoscopy
	Endometrial and ovarian	No evidence to support	1	Consider annual endometrial sampling Consider prophylactic TAH/BSO after childbearing No evidence to support ovarian screening
	Urinary tract	30–35	1	Consider annual urinalysis
	Small bowel and gastric	30–35 No evidence to support	3–5	Consider EGD with ascendent duodenoscopy in at-risk individuals
Familial adenomatous polyposis	Colon Upper GI	10–15 20–25 Earlier if colectomy at <20	1 1–3	Flexible sigmoidoscopy or colonoscopy EGD with complete visualization of the papilla Surveillance by Spigelman staging Consider CT or MRI for small bowel if duodenal polyposis advanced
	Thyroid	Late teenage years	1	Annual thyroid exam, consider annual ultrasound
	Intra-abdominal desmoids	No evidence to support	1	Annual abdominal exam Consider CT or MRI 1–2 y after colonoscopy then every 5–10 y or symptom based
Attenuated familial adenomatous polyposis	Colon Upper GI Thyroid	Late teenage years 20–25 Earlier if colectomy at <20	2–3 1–3 1	Colonoscopy EGD with complete visualization of papilla Annual thyroid examination and thyroid ultrasound
MUTYH-associated polyposis	Colon Upper GI	25–30 30–35	2–3 1–3	Colonoscopy EGD with complete visualization of the papilla
Serrated polyposis syndrome	Colon	40 10 y before earliest CRC diagnosis	1–3	Colonoscopy

CT, Computed tomography; EGD, esophagogastroduodenoscopy; HNPCC, hereditary nonpolyposis colorectal cancer; MRI, magnetic resonance imaging; TAH/BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

cancers, and extracolonic manifestations. Guidelines for surveillance are listed in Table 4.

Pancreatic

Approximately 10% to 20% of cases of pancreatic cancer are associated with inherited predisposition (two first-degree relatives affected). Pancreatic cancer is a component of hereditary breast ovarian syndrome, Lynch syndrome, familial adenomatous polyposis, familial atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, hereditary pancreatitis and Li-Fraumeni syndrome (see Table 1). A high proportion of patients with pancreatic cancer with a family history of a variety of solid tumors will likely carry a pathogenic mutation in a known cancer predisposition gene. Relatives of an individual with pancreatic cancer found to carry a mutation in a high-risk gene may benefit from screening.

Melanoma

Approximately 7% to 12% of melanoma occurs in patients with a strong family history of melanoma. About 40% of familial melanoma is attributed to the inheritance of a mutation in a highly penetrant predisposition gene (Fig. 3). Other well-known predisposition genes may increase susceptibility to melanoma but with lower penetrance.

SUMMARY

Genetic testing is a critical part of medical practice today, especially among specialists who treat cancer. It is imperative that we identify patients at risk, facilitate their testing and know to whom to send the patients for up-to-date information on how to manage dealing with the associated cancer risks. Whether surgeons opt to test their own patients or refer them to a genetic counselor, the surgeon must be involved intimately in the management of the genetic syndrome that ultimately is revealed. Changes in management prompted by the results of genetic testing can have a meaningful impact on the lives of affected individuals and their families.

Acknowledgment

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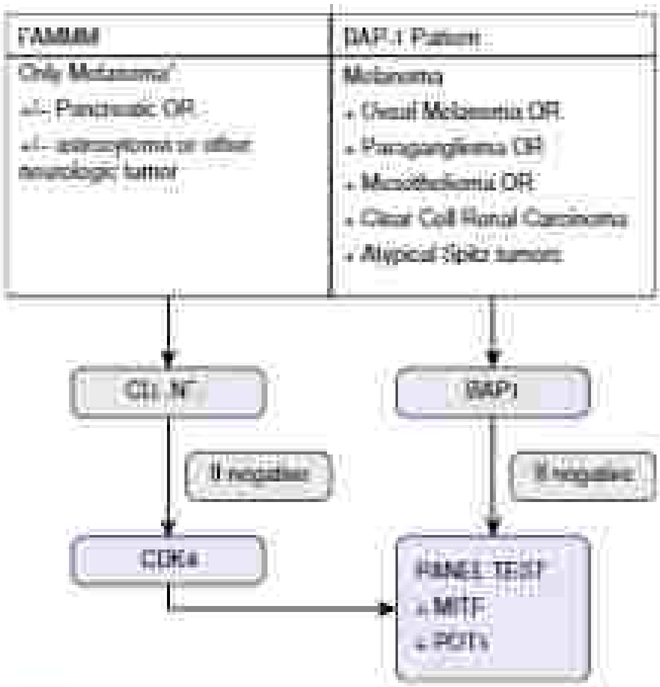

FIG. 3 Genetic testing in melanoma dominant cancer syndromes. *Pedigree with three primary melanomas in first- or second-degree relatives in areas with high-melanoma incidence or two primary melanomas in a low-incidence area. FAMMM, Familial atypical multiple mole melanoma syndrome.

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Contralateral Prophylactic Mastectomy

Amanda Kupstas, MD, and Judy C. Boughey, MD, FACS

CONTRALATERAL PROPHYLACTIC MASTECTOMY

The question of whether to perform a risk reducing contralateral prophylactic mastectomy (CPM) on a patient with unilateral breast cancer is complex and a topic of increasing interest. The most recent guidelines do not recommend CPM for women with unilateral breast cancer who are of average risk for developing contralateral breast cancer (CBC). However, rates of CPM continue to rise despite these recommendations. It is not hard to imagine why this trend is continuing. Patients tend to have an exaggerated perspective of their risk of contralateral cancer. Meanwhile the surgical complications, psychosocial impact, and economic implications may not be fully understood and symmetry and patient perception of control seem to dominate the decision. An evidence-based approach understanding individual risk of CBC, CPM outcomes, and patient values must be employed and a recommendation should be offered.

RISK OF CONTRALATERAL BREAST CANCER

Average-Risk Patient

CPM offers a risk reduction of breast cancer development of 90% to 95%. This impressive number can be misleading if it is not taken into the context of the individual patient's absolute risk. The risk of CBC in the average risk patient with unilateral breast cancer is reported to be 0.6% per year in historic series and 0.2% to 0.5% per year in contemporary series in patients receiving adjuvant therapies for their index breast cancer. For the majority of patients, the absolute risk of CBC is low, and therefore the risk reduction from CPM is small and does not warrant an aggressive surgical approach.

Young Age and Family History of Breast Cancer

Two important factors found to be associated with increased risk for a CBC are young age at diagnosis and family history. The WECARE study (Women's Environmental Cancer and Radiation Epidemiology Study) described 10-year cumulative risk of developing CBC in these subgroups. Patients younger than 45 years at diagnosis who had an affected first-degree relative had a risk of 9% to 13% compared to

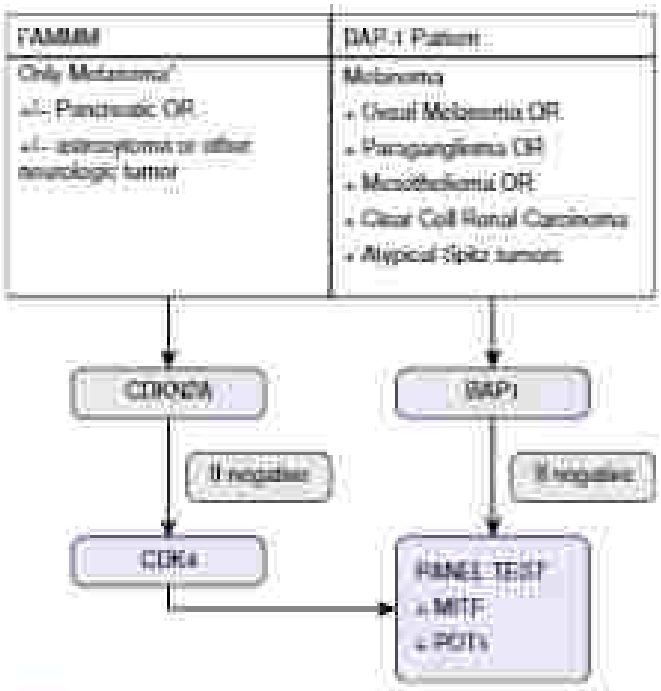

FIG. 3 Genetic testing in melanoma dominant cancer syndromes. *Subjects with three primary melanomas in first- or second-degree relatives in areas with high melanoma incidence or two primary melanomas in a low-incidence area. FAMMM, familial atypical multiple mole melanoma syndrome.

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3.7% to 8.6% in patients older than 45 years. Young patients with a first-degree relative with bilateral cancer had a risk of 4% to 13%.

Gene Mutations

BRCA1 and BRCA2 and High Penetrance Gene Mutations

The risk for patients with highly penetrant deleterious gene mutations of developing a CBC is considerable. Carriers of *BRCA1* and *BRCA2* deleterious mutations have a relative risk of CBC ranging from 10 to 30 times that of average risk women and a lifetime risk of 40% to 80%. Other less common but highly penetrant mutations include *TP53* (Li-Fraumeni) and *PTEN*, which confer a lifetime risk of 50% to 90% for development of CBC. For patients with *BRCA1* and *BRCA2* mutations and breast cancer, consideration of CPM and bilateral salpingo-oophorectomy (after child bearing, if desired) is recommended. The other highly penetrant mutations are far rarer but confer a significant risk and CPM should be considered in their management.

Low-Penetrance Gene Mutations

As our understanding of hereditary breast cancer evolves beyond *BRCA1* and *BRCA2*, and panel testing is becoming more popular, the significance of other low- to moderate-penetrance alleles is being brought into question. While *BRCA1* and *BRCA2* account for the cancer risk in the majority of women with multiple affected family members, families with a less strong family history are more likely to have low-penetrance alleles, such as *CHEK2*, *PALB2*, *ATM*, and *BRIP1*, which each have been found to confer a two- to threefold increased risk of breast cancer. Typically, the patients found to have these mutations are already categorized as high risk based on their family history. Little is known about the risk of CBC associated with these mutations, so there is not adequate evidence to recommend CPM based on the presence of these mutations alone.

Prior Chest Wall Irradiation

Patients who have undergone treatment with chest wall irradiation for Hodgkin's lymphoma and other malignancies have an incidence of breast cancer of 30% by the time they reach 50 years of age. Their risk approaches that of *BRCA* mutation carriers. Current national guidelines recommend breast cancer screening 8 years after completion of treatment or at 25 years of age. CPM should be considered in the treatment of women with breast cancer who have been previously treated with chest wall irradiation given the increased risk.

Breast Density

Breast density is a significant risk factor for the development of breast cancer increasing the lifetime risk of breast cancer by 4.6 times for a women with greater than 75% breast density compared to a woman with 5% breast density. A version of the Gail model risk assessment tool modified to include breast density (>75% dense) resulted in improved predictive value of the risk assessment tool. Breast density also poses a particular challenge to surveillance and can contribute to increased biopsies and imaging. This might be considered for the patient who has significant surveillance anxiety.

Characteristics of the Primary Cancer

It is intuitive that the biology of the index cancer will influence the risk of CBC. Some model based studies suggested lobular histology in particular as a risk factor. A recent study by Langagaard et al. reported an increased risk of CBC in patients with invasive lobular compared to invasive ductal histology. Other proposed characteristics include multicentricity and presence of other high risk lesions in the primary affected breast. While some may advocate for magnetic resonance imaging in these patients, these factors are not an indication for CPM in the context of the current knowledge.

ONCOLOGIC OUTCOMES

Risk Reduction and Survival

CPM consistently provides a 90% to 95% reduction of risk regardless of the patient population. However, it does not eliminate risk of breast cancer development. Additionally, this risk reduction has not translated to a survival benefit. Multiple retrospective studies found no significant association between CPM and breast cancer–specific survival. In the studies that did find a statistically significant improvement in breast cancer–specific survival there is a question of whether a healthier, younger cohort in the CPM group may confound the data. With regards to overall survival, many studies demonstrated that there was no benefit with CPM. Two studies that found an overall survival benefit in the CPM group appeared again to be confounded by patient selection bias, with a healthier CPM cohort. Overall, patients should be counseled that there is no definitive evidence that CPM improves survival.

Recurrence of the Primary Cancer

Concern regarding recurrence of the primary cancer locally and as metastatic disease is a major concern of patients undergoing treatment. While CPM protects against a new cancer in the contralateral breast it offers no protection against recurrence of the index tumor and in most cases risk of recurrence of the primary tumor exceeds the risk of development of a CBC.

Contralateral Prophylactic Mastectomy and Adjuvant Therapy

Delays in systemic therapy and radiation therapy can potentially interfere with the chemo- free survival benefit provided by adjuvant therapy. Time to initiation of chemotherapy is longer in patients undergoing mastectomy with reconstruction than mastectomy without reconstruction. Additionally, since CPM increases the complication rate associated with surgery, there is concern that this could contribute to delay to adjuvant therapy. This is a particular concern for patients with advanced stage disease and aggressive tumor biology. In these cases, if CPM is warranted it may be advisable to consider performing it in a delayed fashion.

NONONCOLOGIC OUTCOMES OF CONTRALATERAL PROPHYLACTIC MASTECTOMY

Surgical Complications

The surgical complications evaluated in most studies pertaining to CPM include hematoma, infection, flap necrosis, delayed wound healing, and also those related to reconstruction (implant loss, nipple necrosis, and microvascular thrombosis of free tissue flaps). Regardless of whether the patient has reconstruction or not, CPM has been shown to double the risk of complications. Complications related to reconstruction including additional unanticipated procedures must be considered as well. One series estimated a 40% to 60% risk of complications over the course of reconstruction, with an estimated 32% requiring an additional unanticipated surgery. Patient dissatisfaction with CPM was found to be linked to the requirement of subsequent procedures (anticipated or unanticipated). This should therefore be included in the counseling process when reconstruction is desired.

Psychosocial Impact and Satisfaction

Psychosocial impact is difficult to study and it is hard to predict how a patient will respond to their surgical treatment. Studies evaluating long term satisfaction, which analyze the variables that contribute to the level of satisfaction, provide some insight. After a mean of 20 years after CPM 90% of women were satisfied or very satisfied with their decision to undergo CPM.

"Peace of mind" in the perception of risk reduction is described as being the most common motivating factor for CPM as well as the

most likely cause of satisfaction with treatment. The second most common reason was cosmetic outcome or symmetry. While most women were content overall with their treatment many reported dissatisfaction with body image, poor cosmetic outcomes, wound/pain related complications, and sexual changes. An open discussion taking into consideration the patients values and the possible psychosocial impact of the procedure can help reduce dissatisfaction and allow the patient to be better prepared for the informed decisions they make.

Surveillance and Cost-Benefit Analysis

Equality in distribution continues to be a challenging public health issue. Several model based studies have evaluated cost effectiveness and quality adjusted life years (QALYs) across the financial benefit of CPM. Three factors that were found to influence the results are the patient's age, risk level of breast cancer, and quality of life. For patients with hereditary cancer syndromes, CPM was cost effective over surveillance and it provided more QALYs. Zendejas et al. found the cost of unilateral mastectomy (UM) and surveillance of the other breast and CPM are equivalent in women age 40 and younger, however, the CPM group provided more QALYs. In a recent study by Kerkvy et al. UM and CPM were compared and there was a clear advantage to UM with respect to cost and quality. For young patients and those with a high risk of breast cancer without a known deleterious mutation there is a questionable quality advantage but this relies heavily on quality of life assumptions.

SURGICAL CONSIDERATIONS

Types of Mastectomy

A simple mastectomy can be offered for patients who do not wish to undergo reconstruction. An elliptical incision is made incorporating the nipple areola complex and the majority of the extra skin overlying the breast. The breast tissue, nipple areola, and extra skin is resected. The edges are approximated to create a smooth flat surface, which is ideal for use of a prosthetic as desired. Due to the operation of choice for the therapeutic mastectomy in patients with inflammatory breast cancer or locally advanced cancers with skin involvement. Advantages include lower rate of complications and usually no requirement for subsequent procedures and reoperation.

For women who desire reconstruction the two most common options are skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM). The primary difference being in NSM the dermis and epidermis of the nipple areolar complex (NAC) is preserved, while in skin sparing the NAC is excised with the specimen. Women with bloody nipple discharge or with central tumors close to the NAC should not undergo NSM on the therapeutic side, although may still consider NSM for the CPM. Gould et al. report complication rates are higher for NSM than SSM (36% vs 9%).

Nipple necrosis can occur in 10% to 20% of patients but actual nipple loss as a result is only 2% to 3%. Nipple necrosis may also occur secondary to presence of ductal carcinoma in situ or malignancy in the retroareolar tissue on final pathology in up to 4% of patients. The patient should be counseled explicitly that there is loss of sensation of the breast and nipple despite preservation of the skin and NAC. While preservation of the nipple can give excellent natural looking results, nipple reconstruction and tattooing can be offered, if desired, for patients who undergo SSM.

Options for Reconstruction

The involvement of an experienced plastic surgeon early on in the decision process is invaluable. When the patient's motivation for CPM with reconstruction is driven by a desire for symmetry other options such as mastopexy, augmentation, and reduction mammoplasty should be discussed and offered. These offer the ability to achieve symmetry without loss of the breast and result in less sensation loss and a more natural texture to the breast. There is no reconstruction

BOX 1 Points for Patient Counseling

- CPM decreases the risk of CBC by 90%–95%
- CPM offers no survival benefit
- CPM does not protect against recurrence of the primary cancer
- CPM doubles the chance of a surgical complications
- CPM with reconstruction may require multiple procedures and possible reoperation
- CPM results in severely decreased or loss sensation of the once living skin and nipple if preserved
- CPM results in the inability to breast feed
- CPM may impact sexuality and body image
- 10% of patients who undergo CPM regret their decision
- Alternatives to CPM for risk reduction include chemoprevention, BSO, and surveillance

Modified from Boughey JC, et al. Contralateral prophylactic mastectomy (CPM) consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. Ann Surg Oncol 2010;17(5):1320–7310.
CPM, Contralateral prophylactic mastectomy; BSO, bilateral salpingo-oophorectomy.

method that is superior for every woman. Individualized counseling will improve patient satisfaction.

If the decision is to proceed with CPM the two general options for reconstruction are autologous and autoplastic reconstruction. Autologous reconstruction consists of free flaps like the deep inferior epigastric perforator flap and rotational flaps such as the transverse rectus myocutaneous flap. Autologous reconstruction options provide an excellent cosmetic outcome that closely resembles the natural breast. They do require a longer initial hospital stay and may be associated with more short-term complications. Alloplastic reconstruction usually consists of tissue expander placement, with a second procedure to exchange the tissue expander to a permanent implant. Consultation direct to implant reconstruction can be performed.

Sentinel Lymph Node Surgery

Sentinel lymph node (SLN) surgery in prophylactic mastectomy is not recommended because of the low risk of occult malignancy and increased complication rate. The risk of occult malignancy in the contralateral breast is only 1.8% and the chance of axillal positivity in that case is only 1.3%. By meta-analysis, the risk of lymphedema after SLN surgery alone was found to be 5.6%. Therefore, routine SLN surgery in all patients undergoing CPM is not recommended. However in cases where a suspicious lesion is identified in the contralateral breast and malignancy is not excluded by preoperative percutaneous biopsy, SLN surgery should be done at the time of surgery.

COUNSELING AND SHARED DECISION MAKING

Optimizing Informed Consent

The surgical consultation should first include a discussion of the facts. A surprisingly large number of women who considered and underwent CPM were unaware it did not improve survival. Over half did not know that CPM did not completely eliminate the risk of breast cancer or risk of distant metastases. As mentioned previously, the value of poor or mild and perception of risk of the patient is one of the most important factors influencing the decision to have CPM. Any discrepancies between perceived risk and the actual individualized risk of the patient should be reconciled. The potential psychosocial impact should be discussed. If reconstruction is desired, discussion of possible complications and the need for multiple anticipated and unanticipated procedures may be necessary. Box 1 summarizes major points that should be addressed during the consultation.

BOX 2 Summary of Recommendations

- CPM should be discouraged in women at average risk
- CPM should be offered to *BRCA* carriers along with RSO after childbearing
- CPM can be considered in patients with other gene mutations, young women with a history of mantle radiation, and young women with a strong family history without a gene mutation
- CPM can be considered for women who desire symmetry or a change in the size and shape of their breasts
- CPM can be considered for women who have extreme risk–related anxiety, have had surveillance failure, or have dense breasts

Modified from Boughey JC, et al. Contralateral prophylactic mastectomy (CPM) consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. Ann Surg Oncol. 2010;17(10):2631. CPM, Contralateral prophylactic mastectomy; RSO, bilateral salpingo-oophorectomy.

Importance of Shared Decision Making

A survey-based study by Jagsi et al. demonstrated almost half of women, including both high risk and average risk, received no recommendation for or against CPM. Of the women who were advised against CPM (37%) almost all followed the physician's recommendation (97.9%). This suggests the physician's recommendation can be an important contributing factor. While the decision is very personal and must take into consideration the patient's values it is important to ensure the patient has a clear understanding of their options and to overcome misconceptions and offer a recommendation.

Rates of Contralateral Prophylactic Mastectomy in the United Kingdom

Rates in the United Kingdom are significantly lower than in the United States. All the same variables that contribute to the individual decision to undergo CPM are similar, including poor understanding of actual risk, and fear of recurrence. One key difference is that private health insurers and some National Health Service commissioners in the United Kingdom will not fund CPM with the exception of *BRCA* carriers. Also, breast surgeons are trained in oncoplastic procedures as part of their training, which can be employed to improve symmetry without reconstruction.

CONCLUSION

As more and more patients are asking about CPM for the treatment of their breast cancer the physician must be equipped with the knowledge to help patients arrive at the right decision for them. An evidence-based shared decision method is the best approach. (Box 2).

SUGGESTED READINGS

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MARGINS: HOW TO AND HOW BIG?

Hiram S. Cody III, MD

Negative margins of excision optimize local control in breast conserving surgery (BCS) and are the subject of an extensive literature. Two recent meta-analyses concluded that for invasive cancer that local control following BCT with whole breast radiotherapy (RT) was not improved by margins wider than "no tumor in ink," and for ductal carcinoma in situ (DCIS) that local control was optimized by margins of 2 mm and not significantly improved by wider margins. The apparent simplicity of these recommendations is deceptive. Local control is a function of many variables beyond margins width, including preoperative imaging, image guided tumor localization, surgical technique, pathologic processing, tumor extent, tumor biology, radiotherapy, systemic therapy (chemo and hormonal), and patient preferences regarding cosmesis and benefit versus risk. Since many of these are modifiable by surgeons and their multidisciplinary colleagues, this chapter is the composite of a long personal experience and the consensus protocols of our Breast Disease Management Team at Memorial Sloan Kettering Cancer Center.

PREOPERATIVE IMAGING

Prior to surgery, it is not sufficient to rely on written reports. An in person review by the surgeon of all imaging with the radiologist—preferably breast specialized—is particularly helpful (1) to fully define the extent of all abnormalities seen on mammography and/or ultrasound (US), (2) to take additional views and perform additional biopsies as necessary, (3) to establish imaging fiducials concordance for all biopsy sites, (4) to confirm the position of any localizing clips placed at the time of core biopsy, and (5) to jointly plan for localization of nonpalpable lesions. We strongly discourage routine breast magnetic resonance imaging (MRI) prior to BCT. MRI false positives for submammary true positives, but require additional core biopsies, delay surgery, may increase the extent of excision, and almost always

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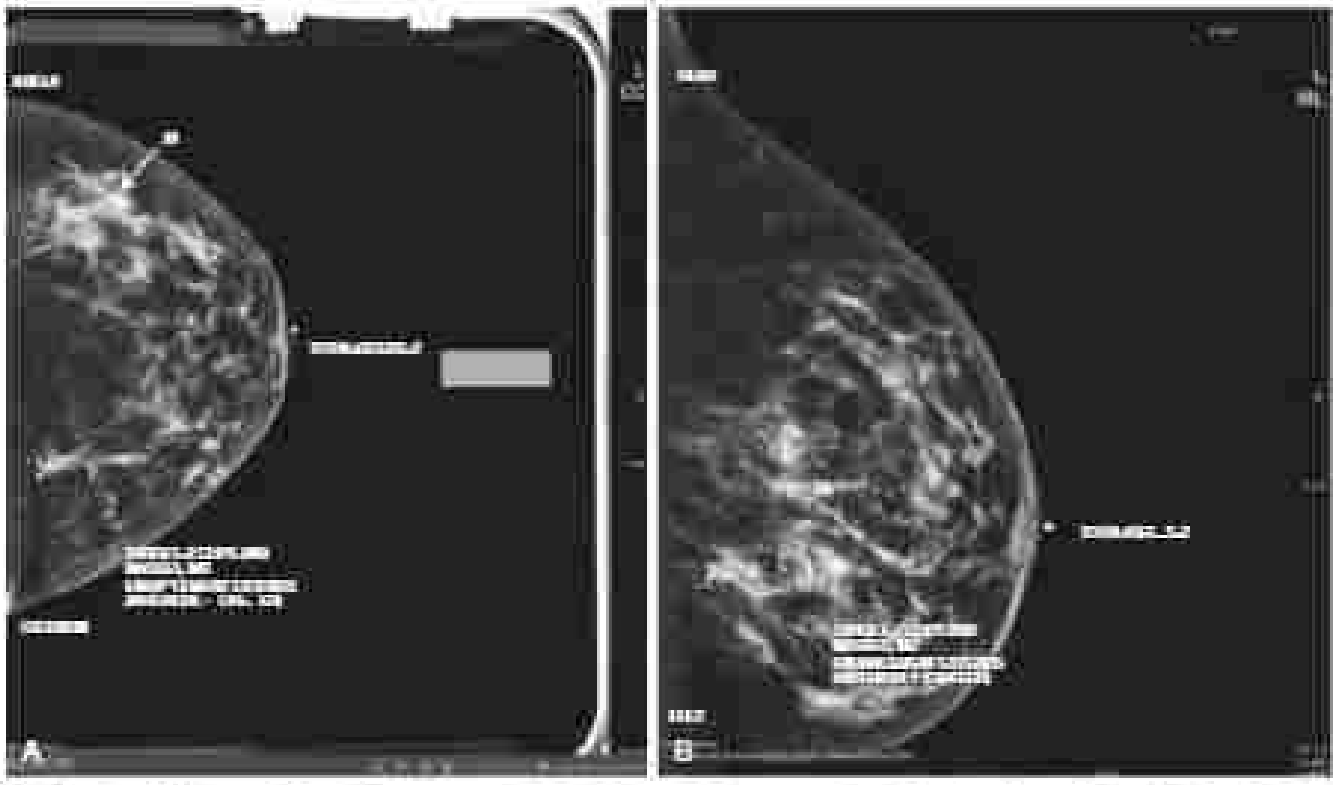

FIG. 1 Craniocaudal (A) and mediolateral (B) mammography of the left breast following preoperative localization with two I-125 seeds. The radiologist's annotations indicate irradiation, the site of a previous benign biopsy at 3 o'clock, the site of a microcalcific biopsy at 9 o'clock showing ductal carcinoma in situ (DCIS) despite short course and the site of focal MRI enhancement requiring anatomy from which an MRI-guided biopsy showed DCIS. I-125, radioactive; MRI, magnetic resonance imaging. (*C. Vince Alcalá, J. Mango, MD.*)

require a follow-up MRI at 6 months and longer. There are no convincing data to suggest that MRI reduces the rates of positive margins, reexcision or local recurrence, and MRI may be associated with an increased rate of mastectomy. To be sure, MRI—*done selectively*—makes sense whenever mammography and US fail to clearly delineate the extent of the lesion, especially for patients with *dense* breasts or following neoadjuvant chemotherapy.

IMAGE-GUIDED LOCALIZATION

For nonpalpable lesions we currently use radioactive (I-125) seed localization, for which the results are comparable to those of traditional wire localization, and which can be placed by the radiologist under mammographic or US guidance prior to the day of surgery, allowing flexible scheduling and minimizing operating room (OR) delays. We place one seed for small lesions, "bracket" larger lesions with multiple seeds, and confirm seed position with a post-localization mammogram. Annotation of the films by the radiologist, especially in patients with multiple abnormalities, is particularly helpful in the OR (Fig. 1A and B). "Head First," "Medial Lateral," "site of cancer," "Site of nipple," "Displaced clip," and so forth help to minimize errors of orientation.

SURGERY

Preliminaries

In the OR prior to starting surgery, we review the patient's medical record (especially the pathology report), review and display all necessary imaging studies, and conduct a time-out confirming laterality, procedure, and number of I-125 seeds with all members of the OR team. Once prepped and draped, we use a gamma probe to localize the "hot spot" corresponding to each I-125 seed and mark the overlying skin.

Incision

The first step in obtaining negative margins is proper incision placement. We typically make a circumareolar or a (diametric incision to the natural (Kraissl) skin lines, which is sufficient to allow excision of the cancer under direct vision and is designed to maximize skin sparing should a completion mastectomy be required. I only excise skin if the tumor is adherent, having found that many patients with dimpling do not have skin involvement; elliptical skin excisions, especially in the 12:00 to 6:00 axis of the breast, and even if limited in extent, can cause striking asymmetry. Many difficulties with specimen margins result from a well-intentioned incision placed to optimize cosmesis but far from the tumor, leading to tunneling, inadequate exposure, piecemeal excision, and positive margins. For excision of multiple lesions (for example, one site with cancer and another with atypical ductal hyperplasia [ADH]), the initial incision should be placed closest to the cancer and will often suffice for removal of the additional sites.

Benign but Possibly Malignant Lesions

Except for fibroadenomas, which can simply be enucleated and submitted without orientation, all other benign conditions requiring surgery (bloody nipple discharge, ADH, imaging/histologic discordance, subareolar abscess, etc.) should be regarded as potentially malignant and excised conservatively but as an intact specimen, oriented, imaged (if appropriate), inked, and processed as a possible cancer. For the minority that prove malignant, most will be DCIS and the initial excision may be sufficient to avoid a reoperation.

Malignant Lesions

Malignant lesions require an intact excised specimen, orientation, specimen radiograph (for nonpalpable lesions), and inking of the

specimen margins. There is no single "right" way to do this, and each institution's protocol should represent a consensus of radiologist, surgeon, and pathologist. The overall goal is to minimize the rate of reexcision while maximizing local control.

Our current reexcision rate of about 10% is based on a very favorable experience of more than 10 years with the following technique:

1. Conservative excision of the cancer
2. Specimen radiograph to confirm lesion/clip/seed retrieval
3. Excision of separate specimens from each face of the excision cavity
4. Orientation of each specimen with a single suture on the outermost face
5. Inking by the pathologist of only the outermost/sutured face of each margin specimen
6. Sectioning and submission of all specimens for permanent sections

Although this technique is often referred to as cavity shave, the margin specimens should be sufficiently thick (at least 5–10 mm) to assess the distance from tumor to ink, and with enough surface area to honestly represent the circumference of the cavity, not tiny portions of it. In taking margin specimens, one should go as wide as possible consistent with an acceptable cosmetic result. My preference is to begin the initial excision in the subdermal plane, eliminating the need to submit a specimen of anterior margin, and to extend the separate posterior margin specimen to the pectoral fascia, eliminating the need to reexcise for a positive posterior margin. Our technique avoids the use of multicolored inks, which can bleed into each other giving ambiguous results. It allows the surgeon to control specimen orientation and labeling at the moment of excision, and clearly delineates the source and site of each margin specimen for the pathologist. Clear communication between surgeon and OR staff is essential, with the surgeon naming each specimen for the scrub nurse and circulator, and with a confirmatory "read back" from the circulator to the surgeon.

Although intraoperative margin assessment by touch prep cytology or frozen sections may reduce rates of reexcision, most institutions, ours included, have found the logistics of intraoperative margin assessment to be prohibitive. Investigation of electrical impedance and fluorescent devices for immediate intraoperative margin assessment is ongoing and benefit remains unproved.

INTERPRETATION OF THE PATHOLOGY REPORT

The pathology report contains a wealth of information beyond margin width, all bearing on the adequacy of excision. Our reports include the following:

1. Width of margin: "positive (tumor on ink), close (<1 mm), or exact width in mm"
2. Extent of positive or close margins: "positive/close along a broad front, positive/close in 3 of 6 slides, or locally positive/close"
3. Size of initial excision and of each margin specimen: "3 × 4 × 1 cm"
4. Tumor burden in each margin specimen: "in the superior margin specimen, tumor is present in 3 of 6 slides"
5. Invasive cancer type/size in each margin specimen: "the superior margin specimen contains a 5 mm focus of invasive ductal carcinoma"
6. DCIS type/size in each margin specimen: "the superior margin specimen contains a single 3 mm focus of intermediate grade DCIS"
7. Presence/extent of lymphovascular invasion (LVI).

In discussing the pathology report with the patient, I find it very helpful to draw out a simple diagram of the breast, indicating the location of the tumor excision and the margin specimens, drawing the extent of tumor in each, and then discussing whether to reexcise.

WHEN TO REEXCISE

On one hand, reexcision is never required for margins beyond "no tumor on ink" (for invasive cancer) or 2 mm (for DCIS). On the other hand, reexcision is almost always required for patients with positive or locally positive margins (tumor on ink). Exceptions to this rule include (1) a positive anterior margin of the initial excision biopsy at the subdermal plane, (2) a positive posterior margin if the initial excision was carried to the pectoral fascia, or (3) positive margins at the breast periphery (i.e., whenever there is no breast tissue beyond the margin site). Careful documentation of these details in the operative note can help avoid reoperation.

The decision to reexcise for margins between 0 and 2 mm is the most problematic, is subject to the greatest variation between surgeons, and cannot be made on the basis of margin width alone. Especially for patients with DCIS, reexcision of margins of less than 2 mm need not be mandatory. I am in general much more influenced by tumor burden (a composite of specimen size, tumor size, and the extent of tumor in each margin) than by margin width. One must also find a balance between those patient and tumor characteristics associated with increased risk of ipsilateral breast tumor recurrence (IBTR) and those treatment factors that act to reduce the risk of IBTR. Among the former are younger age, larger tumor, higher grade, triple negative/ (human epidermal growth factor receptor 2) HER2+ subtype, LVI, nodal metastasis and genetic predisposition. Among the latter are breast RT and systemic adjuvant therapy: chemotherapy, anti-HER2 therapy, and hormonal therapy. Multidisciplinary input from the medical and radiation oncologist may help to reach a decision in borderline cases. Finally, the decision must be shared with the patient, some will prefer to err on the side of more surgery and others will not.

I do not perform post-BCT mammography routinely, but for all patients who need reexcision and whose tumors presented as microcalcifications, mammography is required to identify and localize any suspicious residual calcifications prior to reoperation.

HOW TO REEXCISE

Following localization of any residual calcifications, reexcision is best done within a few weeks of the first operation, when the excision cavity is easily opened. I reopen the previous incision without resecting it. The margin in question is simply grasped and resected, going from subdermal plane to pectoral fascia, and taking as much tissue as possible, at least 5 to 10 mm, within the limits of cosmesis. The specimen is oriented and submitted for inking as done at the initial procedure. For patients with layered wound closures or healed excision cavities, one can be guided by the presence of subcutaneous sutures, or surgical clips.

SPECIAL CIRCUMSTANCES

Isolated Tumor Foci or Lymphovascular Invasion at the Margin

Margin specimens sometimes contain an isolated focus of tumor at the margin ("the specimen measures 3 × 3 × 1 cm and there is a 1 mm focus of DCIS at the inked margin in 1 of 4 slides"). Here the disease is clearly low volume and not contiguous with the tumor site. In the mastectomy era, about 20% of patients harbored such foci in the other quadrants of the breast and these foci were the justification for mastectomy. In the era of BCT these foci are the rationale for whole breast RT, which clinical trials show is very effective in eradicating occult multicentricity. Accordingly, I generally recommend against reexcision for such noncontiguous low volume "incidentalomas." LVI is clearly associated with an increased risk of IBTR (and of distant metastasis) but, as stated previously, when found as noncontiguous isolated foci does not require reexcision.

UNEXPECTEDLY EXTENSIVE DISEASE

Some patients have surprisingly extensive disease, typically DCIS—extending to all margins and which was not apparent on preoperative evaluations. Postoperative MRI is very useful in this setting: it can identify those patients with extensive residual disease who should undergo mastectomy and, if negative, allows the option of reexcision for those patients in whom it can be done with acceptable cosmesis. For patients with unexpectedly extensive disease and a responsive tumor subtype (estrogen receptor, progesterone receptor negative, HER2+), another reasonable option is to proceed directly to chemotherapy (including anti HER2 agents), and then perform the resections. Rates of pathologic complete response for this subtype exceed 50%, allowing BCT for some patients who would otherwise have required mastectomy. Patients will have their own preferences and many will opt for mastectomy regardless but for those who prefer BCT mastectomy need not be automatic.

MORE THAN ONE SITE OF DISEASE

BCT is feasible for a highly selected group of patients with multicentric (typically two small foci in separate quadrants) or multifocal cancers (multiple foci in the same quadrant). For multicentric tumors, I excise each site separately and take additional margins from each site in the usual fashion. For multifocal tumors, I try to encompass all sites within a single excision specimen. When a two site excision results in a single cavity, I document the relationship of the two sites and their margins to each other ("the inferior margin of the 2 o'clock site was contiguous with the superior margin of the 8 o'clock site") aiming to avoid a reexcision if either or both of the contiguous margins were reported positive.

MARGINS POSITIVE FOR BORDERLINE LESIONS

ADH and classic lobular carcinoma in situ (LCIS) are not cancers, and therefore when present at specimen margins do not require reexcision. Reexcision makes sense for truly borderline lesions ("almost ADH bordering on DCIS") or for patients with pleomorphic LCIS, an unusual variant of LCIS for which natural history data are inadequate, but which, unlike classic LCIS, may behave more as a true cancer than a marker of risk.

POSITIVE MARGINS IN MASTECTOMY

Few topics arouse more debate for the multidisciplinary team than this one. Should one reexcise and, if so, where and how? Are we treating the pathology report or the patient? As for anterior margins in BCT, the first consideration is whether the mastectomy skin flaps were dissected in the subdermal plane, outside the superficial fascia of the breast, leaving no visible breast tissue on the flap. This can be challenging, especially in thin patients where the breast tissue is very close to the skin or in nipple sparing mastectomy (NSM) where meticulous placement may limit exposure but can always be done and is the responsibility of the operating surgeon. After removal of the breast specimen, I find it very helpful to "critique" the flaps with my assistants and take additional specimens wherever the flaps are too thick or there seems to be residual breast tissue. *The time to do this is the first operation, not by guesswork at a reoperation.* The second consideration relates to taking of the mastectomy specimen. The anterior surface is fatty, irregular, and, in thin patients, very close to the underlying breast parenchyma and the posterior surface comprises the pectoral fascia. Anteriorly, ink runs into the interstices of the specimen, generating a falsely "positive" anterior margin. Posteriorly, there is no breast tissue beyond the pectoral fascia.

"Positive" mastectomy margins are a rare event in my practice and for the above reasons I do not reexcise when I have performed the initial operation. For a positive anterior margin, precise localization is impossible, the benefit of reoperation is unproved, and the added risk of local recurrence, independent of other tumor characteristics, is unclear. For a positive posterior margin, gross muscle invasion is obvious at the first procedure and addressed upfront by taking additional tissue, whereas microscopic disease at the pectoral fascia is insignificant. Patients with mastectomy margins positive for invasive cancer or with muscle invasion typically receive post mastectomy RT, for which local control is excellent whether one reexcises or not.

Occasional patients will present with positive margins after a poorly done mastectomy with thick skin flaps and obvious residual breast tissue. In this setting, I do recommend reoperation, aiming to re-dissect the skin flaps throughout. This is also my practice when such patients present metachronously with post mastectomy local recurrence.

NIPPLE-SPARING MASTECTOMY

NSM appears to be a safe procedure in properly selected patients, with short term local control comparable to that of conventional mastectomy techniques. In our own practice we typically recommend NSM for the good risk patient with a smaller breast and minimal ptosis, having surgery for prophylaxis or for a stage 0 to II cancer more than 2 cm from the nipple. The main challenge in NSM is exposure, which through a typical unilateral or reframmamary incision can be limited, especially in the more medial and superior aspects of the breast, where removal of all breast parenchyma is particularly important, especially for patients with genetic predisposition or larger tumors. A second challenge is removal of all the subareolar breast parenchyma by dissecting in the subdermal plane and by taking a "nipple margin," inverting the nipple and shaving off the remaining ductal tissue up to the level of the dermis. The nipple margin specimen is often so small that it is best evaluated by permanent section, not frozen. NSM is a setting where the conundrum of positive mastectomy margins is more likely for the above reasons, and if all visible breast parenchyma has been carefully removed at the initial surgery I see little value in reoperation. For patients with a positive nipple margin, we recommend removal of the nipple, although in many patients the areola can be spared.

CONCLUSIONS

Surgical margins in BCT should be managed in a standardized fashion, representing a consensus of radiologist, surgeon, and pathologist. In general, positive margins require reexcision and negative margins do not. For patients with intermediate margins of 0 to 2 mm, especially for DCIS, the decision to reexcise should be multivariate and multidisciplinary, taking into consideration patient, tumor, and treatment characteristics and should not be based on margin width alone.

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Breast Reconstruction Following Mastectomy: Indications, Techniques, and Results

Asad A. Khan, MD, MPH, PhD, and Gadge D. Pierson, MD

Breast cancer remains the most common cancer in women and is the second most common cause of cancer death in women. The American Cancer Society estimates that in 2019 there were 268,600 new cases of breast cancer, representing a 0.4% increase in incidence. The Agency for Healthcare Research and Quality estimates the rate of mastectomy to be at 90 per 100,000 and increasing. The steepest increases in mastectomy rates have been for bilateral procedures, which have been driven, in part, by the increased uptake of genetic screening for *BRCA1/2* mutations and the evolving role of contralateral risk–reducing mastectomies in non-BRCA breast cancer patients. The demand for breast reconstruction therefore continues to increase, and the beneficial effects of reconstruction on quality of life and self-esteem patient-derived outcomes are now well established. Decision making in breast reconstruction is a shared process between the surgeon and patient, and no one type of reconstruction is universally suited. The approach to reconstruction is bespoke and considerations that influence decision making will include the timing of adjuvant therapies (particularly radiotherapy), the availability of donor tissues, the management of the contralateral breast and, most important, patient preference.

PREOPERATIVE CONSIDERATIONS

Mitigating Perioperative Risk

As with any surgery, modifiable perioperative risk factors should be identified well ahead of time and optimized to minimize the risk of complications. In patients with cancer, it is essential to have a clear plan for venous thromboembolism prevention and this may entail preoperative (for example, cessation of tamoxifen), perioperative (heparin, sequential compression devices, fluid management), and postoperative (early ambulation, sequential compression devices, ongoing heparin) strategies.

Patients who are smokers should be counseled about the increased surgical risks attributable to smoking and encouraged to cease any and all forms of nicotine, including smoking, vaping, and second-hand smoke. From a reconstructive perspective, the effects of smoking in diminishing cutaneous blood flow are well established and wound-related complications and infections, particularly in the context of implant-based reconstructions, can be disastrous.

Obesity

Body mass indices greater than 25 kg/m^2 are associated with an increase in perioperative complications and higher rates of reconstructive failure both in implant-based and autologous reconstructions. Again, patients should be counseled as to the increase in risks attributable to obesity and offered support to reduce their weight before reconstruction when feasible, especially for prophylactic mastectomies and in later stages when timing is not urgent.

BREAST RECONSTRUCTION

Although reconstruction is often considered separately from ablative surgery, it is influenced heavily by the requirements of tumor excision and the delivery of adjuvant therapies. For this reason, it is imperative that surgical decision making between both oncologic and reconstructive teams is communicated clearly and effectively to present coherent and cohesive treatment options to the patient (Fig. 1). No one form of reconstruction is superior and the approach must be tailored to the patient. In some cases, no reconstruction may be the best way forward; therefore, this should not be discounted from the surgical armamentarium. In reaching the optimal surgical plan, there are many additional forms of patient information and support that are available in most healthcare systems. Breast reconstruction awareness events, the opportunity for patients to talk to other patients who have undergone differing forms of reconstruction, and Internet-based resources are increasingly important in shared decision making and are championed by all professional organizations. These tools are also instrumental in leading patients control of their cancer management and guiding them to arrive at the best choice of reconstruction for them.

Effect of Mastectomy Incision Choice and Skin Flap Thickness on Reconstruction

The choice of mastectomy incision is predicated by whether the nipple is to be preserved or removed with the breast. For skin-sparing mastectomies, a transverse or vertical elliptical incision encompassing the nipple-areolar complex is chosen and closed primarily after mastectomy as is most commonly used when an implant-based reconstruction is planned. If an immediate autologous breast reconstruction is planned, skin-sparing mastectomy can also be performed through a periareolar incision. For nipple-sparing mastectomies, an inframammary, lateral, or partial periareolar incision may be used and as the decision making must be communicated clearly between ablative and reconstructive teams. Most centers find that inframammary incisions give the best results and the incisions are not easily seen. From a reconstructive perspective, the choice of incision should: (1) facilitate tension-free skin closure over an implant if required or (2) allow adequate access to recipient vessels for free tissue transfer (commonly, the internal mammary at the level of the second or third costal cartilages or thoracodorsal vessels).

In performing a mastectomy, the surgical oncologist is faced with the challenge of removing a tumor while preserving the blood supply to the skin of the breast. The latter comes from a variety of cutaneous perforating vessels from the internal mammary, the thoracodorsal vascular axis, and the lateral intercostal perforators that run in the subcutaneous tissues. In removing the glandular portion of the breast, however, these are often interrupted and the skin is then reliant on blood flow from the more tenuous subdermal plexus. Although it is sometimes possible to identify a clear anatomical plane between the glandular and subcutaneous portions of the breast and so preserve the perforating vessels, this is not always the case. Factors such as neoadjuvant chemotherapy may obscure this plane, or a very superficial large tumor may necessitate a thinner mastectomy flap to be taken. The subdermal vascular supply is also very sensitive to disruption from mechanical stresses (e.g., retraction) and environmental temperature; therefore, thin flaps, particularly in large-breasted patients, are at higher risk of skin necrosis. This risk may be compounded by patient factors such as smoking, diabetes, and previous radiotherapy. This is particularly problematic in patients undergoing implant-based reconstructions because it may lead to implant exposure, infection, or extrusion. Prolonged wound care and healing by secondary intention may also delay the delivery of adjuvant therapies. Although this risk is still applicable to autologous reconstructions, the sequelae are less severe because the necrotic skin can be excised and the resultant defect skin grafted to achieve wound healing. It is not always possible to predict the extent of skin necrosis at the time of mastectomy; however, more recent technologies such as indocyanine green perfusion imaging of mastectomy skin flaps may aid in the diagnosis. If skin

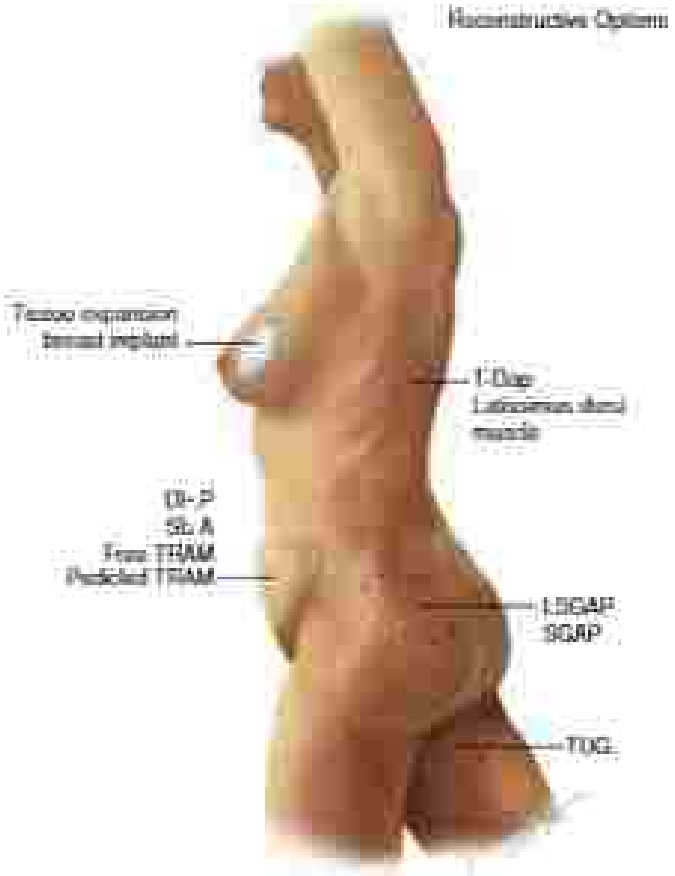

FIG. 1 Most common breast reconstructive options. IEP, Deep inferior epigastric artery perforator; LSGAP, lateral superior gluteal artery perforator; SGAP, superior gluteal artery perforator; SEA, superficial inferior epigastric artery; TAP, transverse abdominis myocutaneous; TDG, transverse upper gracilis.

to felt to be of dubious viability require measures such as warming, the application topical vasodilators, consideration of sildenafil, and possibly hyperbaric oxygen therapy may mitigate the final amount of skin necrosis.

Te Timing of Reconstructioo

Definitive breast reconstruction can be performed at the time of mastectomy (immediate), at a later time (delayed), or a temporizing tissue expander can be placed at the time of mastectomy with a view to performing a definitive autologous reconstruction at a later date (delayed-immediate, or staged). From the plastic surgeon's perspective, the optimal timing is driven largely by the requirements for postmastectomy radiotherapy because this increases significantly the complication profiles of both implant based and autologous reconstructions. The decision to delay definitive reconstruction may also be chosen by the patient as the decision making processes can be complex and patients may elect to defer these until their cancer treatment is complete.

Immediate Breast Reconstruction

Immediate reconstruction at the time of mastectomy is preferable for most patients and can entail placement of a tissue expander, direct-to-implant, or autologous reconstruction. Many centers deliberately avoid immediate autologous reconstruction if it is known, a priori, that radiotherapy will be required after the mastectomy. Immediate reconstruction offers excellent aesthetic outcomes because the breast envelope is preserved and can shape the reconstructed breast to give a more natural aesthetic. Overall, patients require fewer surgical procedures and a shorter, cumulative hospital stay. Disadvantages include the need to overcome scheduling problems to bring together ablative and reconstructive teams and a longer operative time, particularly for immediate autologous reconstructions. The stability of mastectomy skin flaps is a greater consideration in the immediate setting because of the risk of flap ischemia as mentioned previously.

Delayed Breast Reconstruction

Delaying reconstruction offers the benefit of being able to deliver adjuvant therapies (e.g., radiotherapy) without the problems of radiation induced fibrosis compromising the reconstructed breast. It may also be the preferred option for patients who are undecided as to what form of reconstruction they wish to pursue. The disadvantages of delayed reconstruction include somewhat inferior aesthetic outcomes compared with immediate reconstructions because of the loss of the breast envelope. This may make implant based reconstruction more challenging because it necessitates a period of tissue expansion to restore the breast envelope before it will accommodate an implant of the desired size. Delayed autologous reconstructions usually also require a greater import of donor site skin to restore the breast envelope so the final reconstruction will have a larger skin paddle than an immediate.

Delayed-Immediate (Staged) Breast Reconstruction

The delayed immediate paradigm aims to circumvent the problems associated with loss of the breast envelope encountered with delayed reconstructions. A temporizing tissue expander is placed at the time of mastectomy to maintain the skin envelope over the course of adjuvant radiotherapy. Once this is complete, if the envelope has contracted it can be expanded gently to accommodate an implant, or the expander can be removed and replaced with autologous tissue. This latter route is perhaps more preferable because of the significant risks of both short- and long-term reconstructive failure with implant-based reconstructions in the irradiated breast.

RECONSTRUCTIVE TECHNIQUES

Breast reconstruction is often a staged process consisting of three or more stages. The first stage aims to recreate the breast mound by the import of either autologous tissue or an implant. The second stage addresses the symmetry of the breasts and may require the addition (or removal) of volume from either the reconstructed breast or the contralateral side. The final stage entails further revisions and refinements, nipple reconstruction, and/or tattooing.

Implant-Based Reconstruction

Techniques in implant based reconstruction have evolved over time resulting from the availability of newer adjunctive technologies that help achieve robust implant coverage. Implant based reconstruction is traditionally performed as a two-stage procedure. Stage 1 places a tissue expander (most often with an integrated injection port) into a subpectoral pocket and, once this is healed, the patient returns to the clinic and begins the process of expansion by the injection of saline into the expander port. Once the desired volume is achieved the patient is scheduled for stage 2, which is removal of the expander and exchange for a fixed volume implant. The disadvantages of this paradigm include a longer treatment time (expansion can take up to 3 months) and multiple procedures, a slightly higher risk of expander related complications (infection, rotation/malposition, rupture, exposure); however, the two stage paradigm offers much better control over breast size and, proponents argue, pain less stretch on fresh mastectomy flaps. Although tissue expanders have traditionally been

placed in the subpectoral plane, there is increasing popularity with prepectoral (subcutaneous) placement.

Single-stage implant-based reconstruction has grown in popularity and feasibility because of the advent of acellular dermal matrices (ADMs). ADMs are animal-derived biologic sheets of dermis that support revascularization by ingrowth of blood vessels from adjacent tissues and ultimately integrate into the skin. Their use in breast reconstruction has largely obviated the need for tissue expansion because they can provide coverage of the implant either in part (e.g., lower pole coverage for implant placement in the subpectoral plane) or in total (e.g., in prepectoral implant placement). Although the one-stage paradigm offers the opportunity for immediate implant–based reconstruction, it is absolutely reliant on healthy mastectomy flaps to achieve implant coverage and prevent exposure, and some studies have shown a slightly higher overall failure rate with direct-to-implant techniques. Many surgical oncologists deliberately make the skin very thin for oncologic reasons, making it highly risky to place a direct-to-implant owing to the likelihood of some skin necrosis.

Types of Implants

Implants consist of a silicone shell containing either silicone or saline. The cohesiveness of the gel in modern-day implants is high, meaning that the gel can retain its shape to a greater degree, resulting in less of a cosmetic deformity and leakage in case of rupture. Implant shells can be either smooth or textured, where the surface of the implant has a coarse texture applied to it. There is some evidence to suggest that capsular contracture rates are lower with textured implants. The degree of texturing can vary from so called nanotexturing to macrotexturing as is the case with polyurethane implants. In shape, implants are either round or anatomical, and the choice of which implant is best suited to a patient depends on factors such as base width, implant coverage, and the desired projection. Most implant manufacturers will offer a variety of implant choices that offer a range of base widths, heights, and projections in both smooth and textured prostheses.

Acellular Dermal Matrices

ADMs are derived from either bovine or porcine dermis and are available in a variety of dimensions and thicknesses. As a biologic, they support the ingrowth of blood vessels and connective tissue and so become integrated into the body over time. In the context of breast reconstruction, their use is primarily for providing soft tissue reinforcement and thereby better implant coverage for prepectoral breast reconstruction, or lower pole coverage in subpectoral reconstruction. They are particularly useful for defining the implant pocket when the normal anatomical boundaries have been transgressed to achieve tumor clearance. Complications specific to the use of ADMs include increased seroma rates and cutaneous hypersensitivity resulting in the appearance of a red breast, which can mimic an implant infection.

Implant-Related Complications

Implant Rupture

US Food and Drug Administration–mandated studies have quantified the implant rupture rate, for breast reconstruction, to be as high as 10% at 10 years. These rates do vary by implant type and by whether they are being used in the context of primary reconstruction or revision reconstruction. The majority of ruptures, particularly with newer generation devices, are often silent but may also present with changes in breast shape/volume, capsular contracture, palpable lumps (breast or axilla), and pain. The gold standard investigation for diagnosing implant ruptures is magnetic resonance imaging; however, high-resolution ultrasound examination is sometimes performed in the first instance as a screening test.

Capsular Contracture

This is defined as the presence of a pathologic, fibrous capsule around the implant that can result in palpable, visible, or painful distortion of the breast. Breast implant capsules are a normal physiologic response to the insertion of foreign material, but in some instances, this response becomes exaggerated. Risk factors that increase the risk of contracture include implant infection, hematoma, radiotherapy, and implant rupture. Capsular contracture rates from US Food and Drug Administration postapproval studies range from 10% to 15% at 10 years but vary between implant manufacturers. The capsular contracture associated with radiation treatment is actually combined with fibrosis of the skin, subcutaneous tissue, pectoralis muscle, intercostal muscles, and the ribs, and should therefore be thought of as a regional radiation fibrosis rather than simple isolated capsular contracture, as would be seen in breast augmentations.

Breast Implant–Associated Anaplastic Large Cell Lymphoma

Recognized by the World Health Organization as a new form of peripheral T cell non-Hodgkin's lymphoma in 2016, breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a lymphoma arising within the capsule of breast implants and is currently thought to arise in relation to textured devices. The true incidence is unknown, but current estimates place it between 1 in 3407 to 30,000 women with textured implants. The etiology of BIA-ALCL remains elusive but toxic activation of the immune system in relation to either subclinical infection, inflammation, or response to foreign material is considered the underlying drive for lymphomagenesis. Patients commonly present with late-onset effusions of the breast (on average, 7 years after insertion), or, less commonly, with a lump. BIA-ALCL is anaplastic lymphoma kinase negative and CD30 positive. For disease confined to the capsule, capsulectomy alone is curative but adjuvant therapies, such as chemotherapy (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) or monoclonal antibodies (brentuximab vedotin, anti-CD30) may be required if extracapsular spread is evident.

Implant Infections

Implant infections can arise in the early postoperative period or even much later as a result of systemic bacteremia from any other cause (e.g., urinary sepsis, dental work). Most commonly, patients will present with a red breast and a history of pyrexia or feeling generally unwell. Implant infections should be managed by systemic antibiotics, and if no improvement then explantation of the implant and irrigation of the pocket before closure over closed suction drainage. In exceptional circumstances, it may be possible to irrigate and replace the implant in the immediate setting, but infection rates are high and patients must be counselled accordingly.

Autologous Reconstruction

Autologous breast reconstruction is gaining in popularity because of the problems associated with implant-based reconstructions for cancer. Autologous reconstruction is most commonly performed following the completion of radiotherapy because this is known to be harmful to normal tissues and leads to volume loss, fat necrosis, and contracture. The primary advantage of autologous reconstruction is that prosthetic devices are not used and reconstructions have a more natural feel as they are made of vascularized tissue. Disadvantages relate to the management of the donor site and include long scars, delayed healing, seroma formation, and possible muscle weakness. Although autologous reconstructions require a greater investment of time at the time of reconstruction, over a lifetime they offer better outcomes and incur less of a healthcare and economic burden than implant-based reconstructions.

Donor tissue can be obtained from a variety of anatomical sites but in the current era the first line in autologous reconstruction is an abdominally based free flap such as the deep inferior epigastric artery perforator (DIEP), muscle sparing transverse rectus abdominis myocutaneous, free TRAM (fTRAM), or superficial inferior epigastric artery (SIEA) flap. Other donor sites for free tissue transfer include

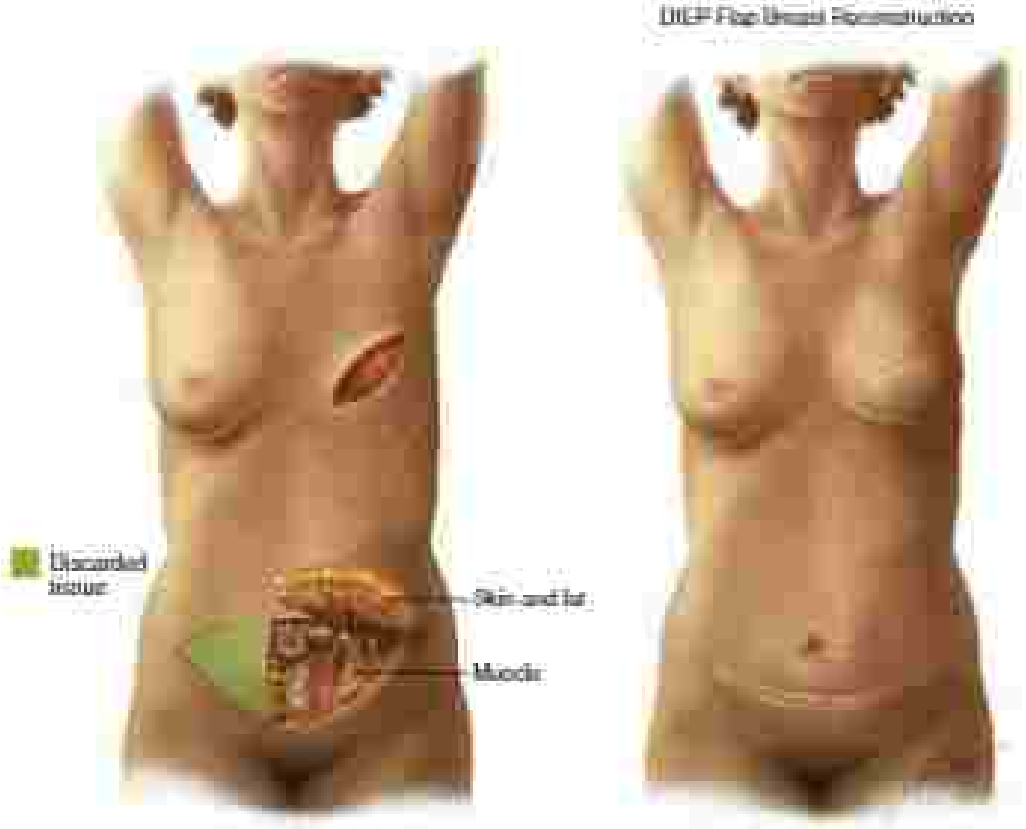

FIG. 2. Deep inferior epigastric artery perforator flap illustration.

the thigh (transverse upper gracilis [TUG], profunda artery perforator flaps), the buttock (superior gluteal artery perforator [SGAP] or inferior [IGAP]), or the back (lumbar artery perforator). In addition, the latissimus dorsi myocutaneous and pedicled TRAM flaps remain valuable fall back options if the above microsurgical options are not feasible or have failed.

Abdominal Free Flaps (DIEP, Muscle-Sparing TRAM, fTRAM, SIEA)

With the exception of the SIEA flap, all other abdominal free flaps derive their blood supply from the deep inferior epigastric artery (Fig. 2). The skin of the abdomen is supplied by perforating blood vessels from this axis that traverse the rectus abdominis muscle in a predictable manner. Depending on the pattern of supply, the skin/fat of the abdomen can be raised on the deep inferior epigastric artery with a varying degree of accompanying muscle. In the majority of patients, it is possible to raise this flap without sacrificing muscle because the perforator supply is robust enough to supply the flap on one to two perforators of suitable caliber. Consequently, donor site morbidity is minimized by preserving the musculature to reduce the risk of later bulge/hernia. In some instances, however, the caliber of perforators is too small and as, to ensure adequate blood supply to the flap, some or all of the rectus muscle must be included. Both sides of the abdomen can be harvested to reconstruct both breasts at the same time, or both sides can be used to reconstruct one breast where greater volume is required. In rare cases, the dominant blood supply to the abdomen comes not from the deep inferior epigastric artery but from the superficial system (SIEA). In these cases, the flaps can be raised on the SIEA without violating the anterior rectus fascia at all; however, SIEA flaps are at higher risk of developing fat necrosis and their blood supply is not as predictable as that from the deep system. Abdominal flaps can also be raised with cutaneous nerves that pierce the anterior rectus fascia to supply the overlying skin. These can be coapted to nerves at the recipient site with a view to restoring protective and proprioceptive sensation to the breast. The incidence of abdominal bulge/hernia is reported to range from 1% to 3% for DIEP flaps to up to 20% with TRAM flaps. It is therefore recommended that where muscle is taken, a formal permanent mesh repair is performed to reduce the risk of this. The resultant donor site scar from an abdominal flap harvest is designed to stay as low as possible based on the perforator location seen on three-dimensional computed tomography angiogram or magnetic resonance imaging angiogram and extends from hip to hip.

While the flap is being raised, the breast pocket is created and recipient vessels exposed (Fig. 1). Most commonly the internal mammary artery and vein (internal mammary vessels) are used as recipients and can be exposed either by removal of the second, third, or fourth costal cartilage or by dissection at the interspace. Other recipient vessels that can be used are the thoracodorsal vessels in the axilla. Microvascular anastomoses between flap and recipient vessels usually proceed by first connecting the veins using a venous coupling device before then performing a handsewn anastomosis of the artery under the microscope. The flap is then inset and shaped to match the contralateral side and the patient recovers. Free flaps require intensive monitoring for the first 48 to 72 hours postoperatively to ensure that the vascular supply (inflow and outflow) are maintained.

Thigh Free Flaps

The thigh is currently regarded as the second line choice for autologous tissue when the abdomen is unavailable and offers a discrete donor site scar in the groin crease. The TUG myocutaneous flap is based on perforating blood vessels traversing the gracilis muscle to supply the overlying skin. The flap is raised to include the gracilis muscle on the descending branch of the medial circumflex femoral artery. The profunda artery perforator flap is also raised from the medial thigh but sits posteriorly to the TUG flap. It is supplied by the perforating branches (second or third) of the profunda artery that pierce adductor magnus posterior to the gracilis. The advantage of this over the TUG is that it usually offers a longer pedicle, however, both medial thigh flaps usually offer only a small amount of volume for insetting and bilateral flaps (or an implant) can be required to achieve greater reconstructed volume. The disadvantage of the thigh

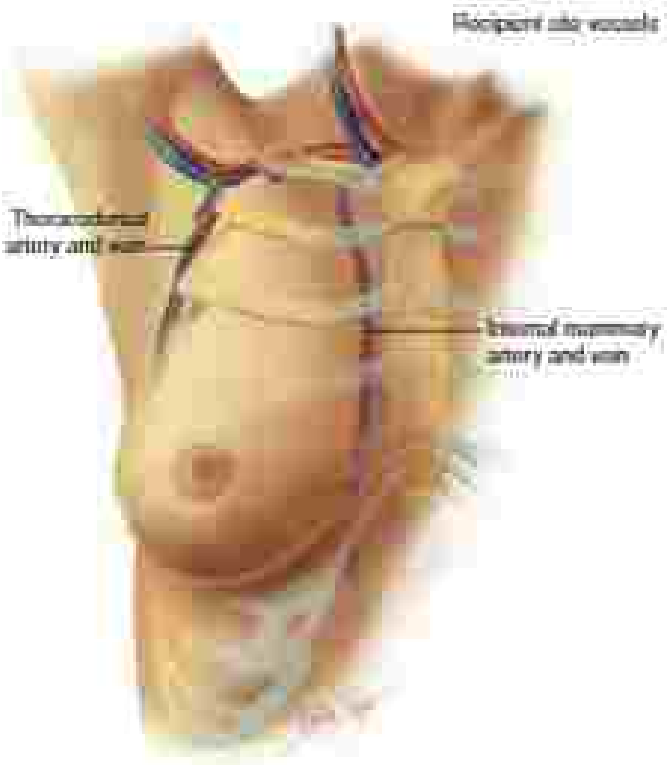

FIG. 3 Most common recipient vessels for autologous microvascular breast reconstruction.

donor site is that it can be difficult to heal, is prone to wound breakdown, and prolonged seroma formation.

Gluteal Free Flaps

Gluteal flaps are based on perforators from either the superior or inferior gluteal arteries. These flaps are not as popular as they once were because they have been superseded by medial thigh flaps. Advantages of the GAP flaps are that they offer a discrete gluteal scar; however, raising the flaps is very challenging, the pedicle length is always short, and the quality of the fat being transferred is much more rigid than abdominal or medial thigh fat and lacks the feel of a breast. In addition, GAP flaps are logistically challenging because they require the patient to be turned intraoperatively.

Pedicled Flaps for Breast Reconstruction

Latissimus Dorsi

The latissimus dorsi flap is raised from the back as a myocutaneous flap pedicled on the thoracodorsal artery. Various design options for the cutaneous element exist but most commonly the skin paddle can be designed transversely below the tip of scapula to be hidden in the bra line when closed. For breast reconstruction specifically, the extended latissimus dorsi flap is preferred where the muscle is raised with overlying fat and with discrete pockets of fat (e.g., scapular) to enhance the volume for transfer. More recently, immediate lipofilling of latissimus flaps has become popular because this can also increase significantly the volume for transfer; alternatively, the latissimus can be used in combination with a breast implant to achieve volume. Advantages of this procedure include a shorter operative time and reliability but, on its own, the latissimus flap rarely provides sufficient volume to reconstruct a breast. The donor site can be problematic with prolonged seroma drainage and larger studies suggest that there may be some degree of upper limb weakness attributable to it. In addition, the latissimus flap can be at risk of developing challenging animation deformities if the thoracodorsal nerve is not identified and cut at the time of surgery.

TRAM Flap

TRAM flaps are designed from the lower abdomen in the same way as DIEP/TRAM flaps, however, they are raised pedicled on the costal origins of the rectus abdominis. The blood supply to these flaps comes from the superior epigastric artery, but the cutaneous supply from this axis is not as robust as the deep inferior epigastric artery system. The incidence of fat necrosis and partial flap loss is consequently higher in these flaps and so the volume of tissue that can be transferred reliably is less. Abdominal wall weakness is inherent in this procedure because the entire rectus muscle is harvested.

Lipofilling

Fat grafting, fat transfer, or lipofilling has become a very useful tool in the second stage breast reconstruction to deal with minor contour deformities, or to add volume or soft tissue coverage over implants. It is also very good for managing skin changes after radiation; recent data suggest that fat grafting reduces inflammation and hypoxia in irradiated tissues. The volumes of fat that can be transferred are limited and, typically, 50% to 80% of the transferred volume will be resorbed with time, hence the requirement for multiple stages of lipofilling to achieve the desired clinical goals.

Lipofilling is performed by harvesting fat from suitable donor site areas (not the abdomen if an abdominal free flap may be used) using traditional wet liposuction techniques. The lipoaspirate is then processed to separate the cellular fat components (consisting of adipose-derived stem cells and adipocytes) from the oil and blood components. This can be achieved by centrifugation (Coleman's technique) or longer techniques using commercial devices that wash away the fat and aspirate the undesired elements. The cellular fat component is then loaded into syringes and injected using a blunt lipofilling cannula. The fat is deposited in multiple layers (subcutaneous, superficial, subfascial) within the target areas to gradually build up the volume. Advantages of the procedure are that it can be performed in the day case setting and works very well where retention is good. Disadvantages include unpredictability with outcome and the need for multiple procedures. There is also a theoretical risk that the transfer of stem cells into a resected tumor bed might encourage recurrence but this has not been borne out in larger clinical studies. Some centers have reported complete breast reconstruction with multiple sessions of serial fat grafting, thus obviating the need for implants and/or flaps in certain select patients.

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Adrenal Incidentaloma

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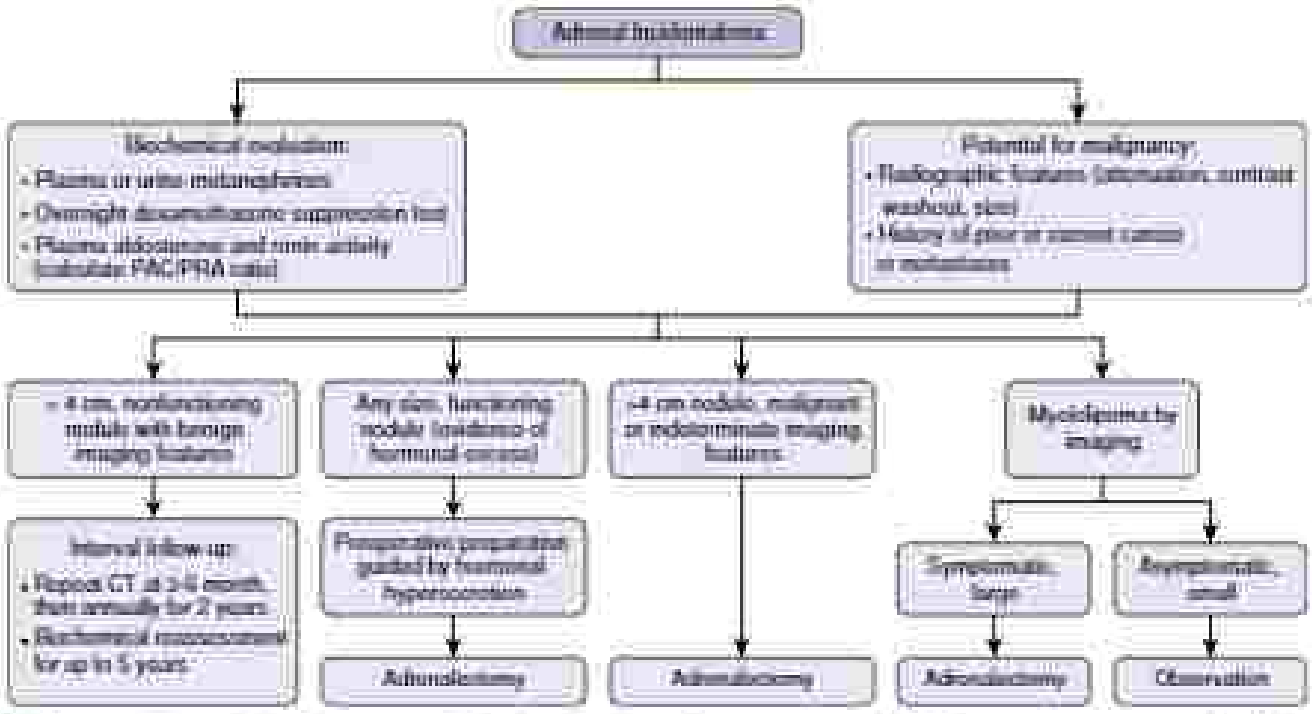

FIG. 1 Algorithm for the evaluation and [illegible] a patient with [illegible] CT, [illegible] to age [illegible] years, [illegible] plasma renin ratio.

TABLE 1 Imaging Features That May Help to Distinguish Benign and Malignant Adrenal Lesions[a] in Identical [illegible]

	Benign		Malignant	
Imaging Features	Lipid-Rich Adenoma	Lipid-Poor Adenoma	Adrenocortical Carcinoma	Pheochromocytoma or Extra-adrenal Paraganglioma
Noncontrast CT	<10 HU	< 10 HU	> 10 HU	> 10 HU
CT scan with contrast	<30 HU; rapid washout of contrast (> 50%)	<30 HU; rapid washout of contrast (> 50%)	> 30 HU; no rapid washout of contrast	> 30 HU; No rapid washout of contrast
Size	Usually <3 cm	Usually <3 cm	Usually > 5 cm	Variable size
Growth rate	Usually stable	Usually stable	Usually significant growth	Usually significant growth

CT = computed tomography, HU = Hounsfield unit.

CT scans today are done with contrast enhancement and therefore unenhanced attenuation measurements cannot be obtained unless dual imaging was originally performed, and (2) up to 30% of adenomas are lipid poor and, hence, have attenuation values greater than 10 HU (Table 1).

Another imaging feature that can prove useful in the characterization of adrenal nodules when contrast-enhanced CT scans are performed is a phenomenon termed contrast washout, in which adenomas take up the intravenous contrast rapidly but also rapidly lose the contrast medium on delayed images. Malignant lesions usually enhance rapidly but have a slower washout of the contrast medium. Lipid poor adenomas, which have higher HU measurements similar to malignant lesions on unenhanced CT, show a rapid contrast washout on contrast-enhanced CT, just like the lipid rich adenomas. Thus, contrast washout kinetics allows a distinction to be made between lipid poor adenomas and malignant lesions. Studies have shown that a relative contrast washout of 50% or greater on the 10-minute delay images of a contrast-enhanced CT has a 98% sensitivity and a 100% specificity for characterizing adenomas (Fig. 1).

Fine-Needle Aspiration Biopsy

The role of fine-needle aspiration (FNA) biopsy has a very limited role in the diagnostic evaluation of the adrenal incidentaloma. Mansfield and Meschia showed in their retrospective analysis that cytopathology from an FNA biopsy was unhelpful in distinguishing between benign and malignant primary adrenal lesions. Its value was largely in the diagnosis of metastatic carcinoma to the adrenal gland in patients with a nonadrenal primary malignancy.

Other studies evaluating the role of FNA biopsy in the adrenal incidentaloma concluded that the FNA biopsy rarely changed management and was associated with a significant risk of complications (including hematoma, pain, error or delay in diagnosis, and inadvertent biopsy of a pheochromocytoma with resulting severe hypertension) and subsequent increased difficulty of adrenalectomy. Vandewiele and Thompson et al. specifically noted biopsy-related complications in 25% of their patients who underwent FNA biopsy of their adrenal tumors. In light of this, we typically recommend not performing an adrenal FNA biopsy. We find that clinicians can almost always make the decision to proceed with adrenalectomy based on clinical, biochemical, and radiologic assessment alone.

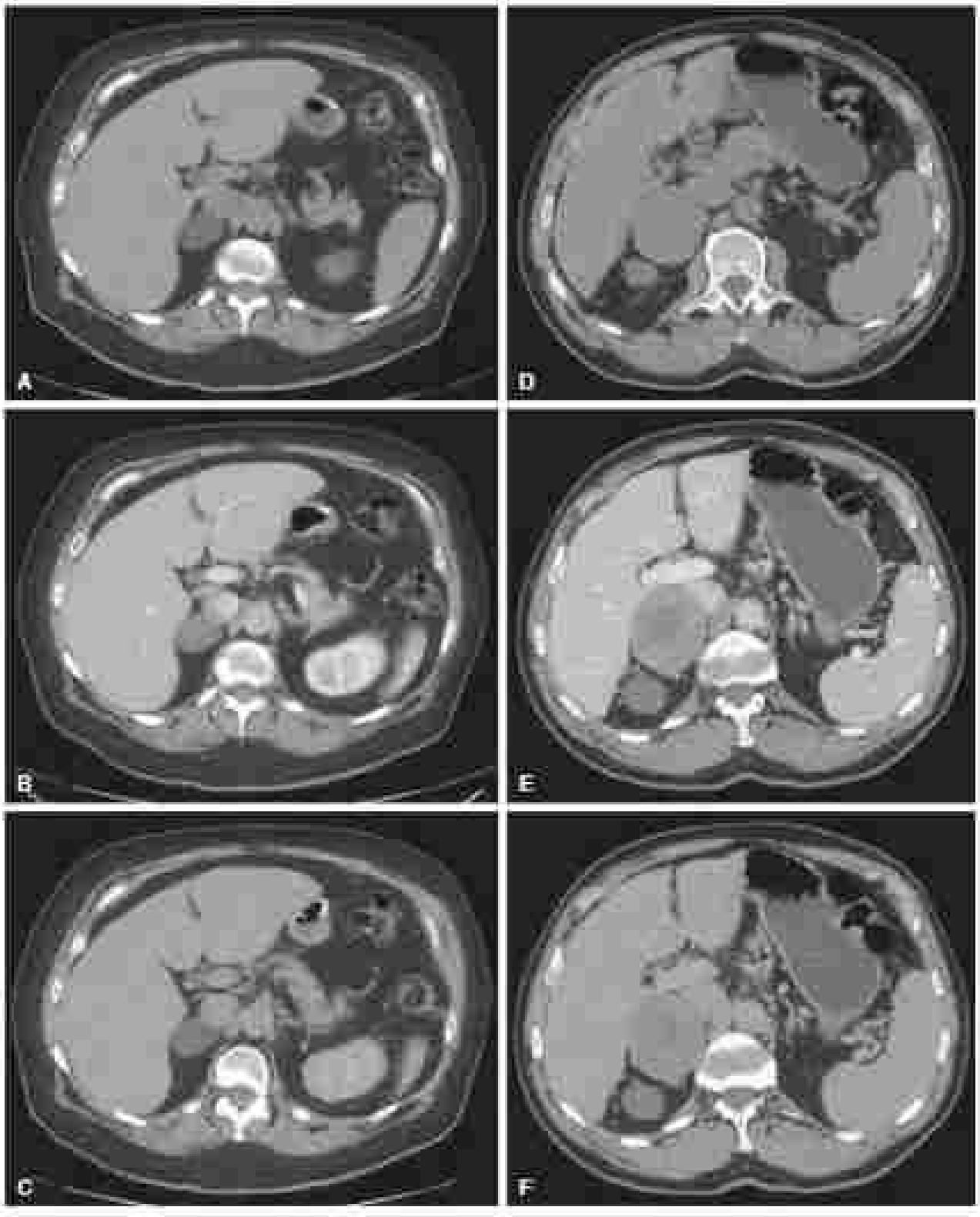

FIG. 2. Cross-sectional computed tomography scans showing a benign adrenal adenoma and an adrenocortical carcinoma. (A) Noncontrast image of a benign adenoma showing a homogeneous lesion with an low attenuation of −3 Hounsfield units (HU). (B) Contrast-enhanced computed tomography scan (portal venous phase) showing rapid contrast uptake with attenuation of 61 HU. (C) Contrast-enhanced computed tomography scan (delayed phase) showing rapid contrast washout with attenuation of 52 HU (relative contrast washout of 39.2%). (D) Noncontrast image of an adrenocortical carcinoma showing a high attenuation lesion (47 HU). (E) Contrast-enhanced computed tomography scan (portal venous phase) of an adrenocortical carcinoma showing a heterogeneous lesion with attenuation of 72 HU. (F) Contrast-enhanced computed tomography scan (delayed phase) showing slow contrast washout with attenuation of 71 HU (relative contrast washout of 1%).

Assessment for Adrenal Hormone Excess

Hormone assessment is critical to the workup of an adrenal incidentaloma as biochemically active lesions should undergo resection (Fig. 1). Several factors should be considered when performing a biochemical evaluation in a patient with an adrenal nodule, including patient age, sex, medications, and limitations of assays or varying reference ranges of tests. With these important considerations in mind, we recommend performing the following tests on all patients with a new adrenal incidentaloma.

Screening for Hypercortisolism

If no clinical features of hypercortisolism, an overnight 1 mg dexamethasone suppression test should be performed. Here, the patient is instructed to take 1 mg of dexamethasone the night before a blood draw. Serum cortisol levels are checked the following morning between 8 AM and 9 AM. In normal individuals, the cortisol level should suppress to less than 1.8 μg/dL. A cortisol level above 5 μg/dL after administration of dexamethasone is usually diagnostic of hypercortisolism. Cortisol levels between 1.8 and 5 μg/dL should spur further workup for possible hypercortisolism. The patient usually undergoes confirmatory testing with an adrenocorticotropic hormone (ACTH) level as well as a 24-hour urinary cortisol level or a midnight salivary cortisol level. An elevated urinary cortisol and a low or suppressed ACTH level further support the diagnosis.

Screening for Hyperaldosteronism

Plasma potassium, aldosterone, and renin activity are measured and a ratio of plasma aldosterone concentration to the plasma renin activity is calculated. A ratio of more than 20 while not taking mineralocorticoid receptor antagonists such as spironolactone should spur further confirmatory testing with aldosterone suppression testing: either a saline infusion test or a 24-hour urinary aldosterone test while the patient maintains a high sodium diet. Patients should be off mineralocorticoid receptor antagonists for 4 weeks before testing.

Once primary hyperaldosteronism is confirmed, it is important to differentiate idiopathic hyperaldosteronism from bilateral cortical hyperplasia. Adrenal vein sampling for aldosterone and cortisol is recommended for all patients with bilateral adrenal nodules, a unilateral nodule less than 1 cm, normal appearing glands, or age older than 45 years to determine if there is unilateral aldosterone hypersecretion which would be amenable to surgical management.

Screening for Pheochromocytoma

The simplest screening test to rule out pheochromocytoma is measurement of plasma free metanephrines (metanephrines and normetanephrines). False-positive results, primarily with the normetanephrine component of the assay, can occur. If either the metanephrine or normetanephrine is elevated mildly, then further testing with 24 hour urine for catecholamines and fractionated metanephrines should be done to confirm or rule out this diagnosis.

Screening for Sex Hormone-Secreting Tumors

Screening for virilizing or feminizing tumors is only performed if suggestive clinical features or suspicion for adrenocortical carcinoma is present. Plasma dehydroepiandrosterone sulfate levels should be measured. Elevated levels are concerning for an adrenocortical carcinoma. 17 β-estradiol can also be checked if clinical features of feminization are noted in men and postmenopausal women only.

Management

In patients with a unilateral adrenal incidentaloma, surgery is usually indicated for the following:

- A hormonally active tumor
- A hormonally inactive tumor size greater than 4 cm and/or radiographic imaging features
- Any tumor, hormonally active or otherwise, with a rapid growth rate on serial imaging
- Known or suspected adrenocortical carcinoma
- Large, symptomatic myelolipomas
- Metastatic tumors

Laparoscopic adrenalectomy (transabdominal lateral approach) or retroperitoneoscopic approach) is the preferred approach for most patients with incidentalomas who require adrenalectomy. The exception is the patient with a large suspected adrenocortical carcinoma (greater than 10 cm) because of a greater difficulty in removing these tumors laparoscopically and the potentially increased risk of breaching the tumor capsule leading to higher local recurrence rates. Either the transabdominal lateral or the retroperitoneoscopic approach can be considered for incidentalomas depending on local surgical expertise. The retroperitoneoscopic approach has the advantage of avoiding entry into the abdominal cavity particularly in patients who may have had prior intraabdominal operations and provides the most direct route to the adrenals. It is more difficult in patients with larger tumors (>4–5 cm) and who are obese (BMI >35); however. A laparoscopic approach appears to be appropriate for selected patients with adrenal metastases, provided the surgeon has substantial experience in performing laparoscopic adrenalectomy. Long-term follow-up studies of resection of adrenal metastases are lacking, however, so these patients should be approached with caution. Removal of an intact specimen with negative surgical margins should be the primary goal regardless of the nature of the underlying lesion.

Perioperative Management

The perioperative management is critical to the success of most adrenal operations and avoiding hormonal complications.

Patients with pheochromocytomas require pharmacologic preparation with an alpha adrenergic receptor blocker such as phenoxybenzamine or doxazosin for 1 to 3 weeks preoperatively to avoid intraoperative blood pressure instability. Therapy is started at a low dose and titrated upwards to achieve normotension. Occasionally, β-adrenergic blockade is given in addition to α-blockade for control of persistent tachycardia, arrhythmias, or hypertension. It should only be started after adequate α-blockade. Other important aspects of preoperative care for this group of patients include encouraging a high sodium diet and liberal fluid intake to counteract the catecholamine-induced intravascular volume depletion. Additionally, clinicians should consider screening patients diagnosed with pheochromocytomas for genetic syndromes. Postoperatively, phenoxybenzamine is discontinued and close monitoring for hypotension and hypoglycemia is instituted. Other antihypertensive medications should be resumed only if it appears the patient has underlying essential hypertension. The exception to this rule is in the instance of long-standing beta adrenergic receptor blocker therapy, where abrupt discontinuation perioperatively is not advised.

Patients with hypercortisolism generally need preoperative optimizing of the specific comorbidities associated with their disease such as hypertension, diabetes, dyslipidemia, infections, and poor physical fitness. These patients also benefit from venous thromboembolism prophylaxis perioperatively because they are at significantly increased risk of developing thromboembolic complications. Hypercortisolism also increases the risk of wound complications and stress ulcer formation so perioperative prophylactic antibiotics and perioperative stress ulcer prophylaxis should be given. Further, these patients may undergo a period of adrenal insufficiency after adrenalectomy and should be given supplemental glucocorticoids perioperatively. In uncertain cases, a morning plasma cortisol level and/or ACTH stimulation tests on postoperative day 1 may be obtained and glucocorticoid replacement therapy initiated if the cortisol level is low.

Patients with hyperaldosteronism are almost always treated preoperatively with a mineralocorticoid receptor antagonist, such as spironolactone. Some might still require potassium supplementation. In the postoperative period, mineralocorticoid receptor antagonists

are stopped and close blood pressure monitoring is initiated. Other antihypertensive medications are reduced or stopped to maintain normotension. Sawka et al. showed that factors such as having one or more relatives with hypertension as well as the preoperative use of two or fewer antihypertensive medications were associated with postoperative resolution of hypertension. In our experience also, patients who have had longstanding hypertension are generally unable to be weaned off all antihypertensive medications postoperatively and normotension without drug treatment may never be achieved in this group, likely because of the vascular remodeling that occurs. Additionally, postoperative potassium supplementation is withdrawn (including in the multivitamin intravenous fluids). The Endocrine Society clinical practice guidelines for management of primary aldosteronism recommend measurement of serum potassium and aldosterone levels the morning after surgery as an early indication of biochemical response.

Follow-up of Adrenal Incidentalomas

Recommended Follow-up if Adrenal Adenoma Was Performed

In the immediate postsurgical period, it is imperative to review the surgical pathology report to ensure concordance with the preoperative diagnosis. In the long term, patients with pheochromocytomas should undergo annual biochemical testing with plasma metanephrines to identify possible recurrence which can occur in up to 16% of patients with benign disease. Patients with hypercortisolism often require glucocorticoid therapy postoperatively. The replacement is weaned under the guidance of an endocrinologist when the hypothalamic-pituitary-adrenal axis has recovered, typically within 6 to 18 months in most adults. In all of these patients, blood pressure monitoring and antihypertensive medication wean remains important as normotension could take several months to achieve.

Recommended Follow-up of an Incidentaloma if Surgery Was Not Performed

Patients with nonfunctioning adrenal incidentalomas that have benign radiographic features with sizes smaller than 4 cm do not need to have immediate surgery. In these patients, the recommended follow up is repeat cross sectional imaging with CT at 3 to 6 months and then annually for the next 1 to 2 years. A recent cost effectiveness analysis showed that more frequent imaging or a longer duration of imaging surveillance is without incremental benefit and is not cost effective. Biochemical screening is recommended annually for up to 5 years. Surgical excision should be considered for lesions that increase in size or have emerging evidence of hormonal hyperactivation. Beyond the initial 5-year period, the expert guidelines do not address what the subsequent follow up should be for a stable, hormonally inactive adrenal incidentaloma.

Suggested Readings

[illegible]

Management of Adrenal Cortical Tumors

Barbra S. Miller, MD

Adrenal tumors are increasingly being diagnosed, currently with a prevalence of 4% to 10% due to the surge in use of multiple imaging modalities. With this, the rate of adrenalectomy nearly doubled in just over a decade. Adrenal nodules of cortical origin are most commonly found incidentally on imaging studies pursued for various unrelated reasons. Adenomas, metastases to the adrenal gland, pheochromocytomas, myelolipomas, angiomyolipomas, cystic neoplasms, cysts, lymphoma, and abscesses/infections of various origin have been described. Adrenocortical carcinoma (ACC) is an extremely rare malignancy with an incidence of 1 to 2 per million in the population. As classic pheochromocytoma is of medullary origin, there will be limited further discussion of this type of adrenal tumor. Adrenocortical nodules may also be identified if suspicion of adrenal hormone excess is noted based on patient history, physical examination, or laboratory studies and imaging pursued as a result.

Formal evaluation of a patient with an adrenal nodule begins with taking a complete personal and family history and performing a full physical examination. Specific evaluation of an adrenal nodule is completed by seeking evidence of adrenal hormone excess and characterizing tumor appearance by imaging studies. The history should focus on onset of any hypertension, electrolyte abnormalities, signs or symptoms associated with hypercortisolism (Cushing disease or syndrome), pheochromocytoma, or primary aldosteronism (Conn) syndrome. Changes in secondary sexual characteristics may indicate the presence of a virilizing or feminizing tumor. Signs and symptoms suggestive of primary aldosteronism may include hypertension, generalized edema, weight gain, muscle cramping due to hypokalemia, and weakness. Signs and symptoms consistent with hypercortisolism may include weight gain, hypertension, impaired glucose tolerance and diabetes, thinning of the skin, easy bruising, central adiposity, development of a buffalo hump, striae, proximal muscle weakness, and change in fat distribution from the periphery to the abdomen. Signs and symptoms associated with pheochromocytoma may include hypertension, episodic palpitations, diaphoresis, sudden onset headaches, pallor, anxiety, or feeling of doom. These may be exacerbated in certain situations or after eating certain foods. A family history should be taken to investigate the possibility of a genetic mutation driving development of an adrenal abnormality. This will also prompt possible investigation for other disease processes that may be part of a particular genetic syndrome (multiple endocrine neoplasias, von Hippel-Lindau, neurofibromatosis, etc.). Patients should be questioned about a previous history of malignancy or any signs or symptoms, which may lead to consideration of recurrent metastatic disease or a previously undiagnosed malignancy.

Biochemical evaluation of an adrenocortical nodule in most should be carried out in a systematic fashion. In patients found to have evidence of adrenal hormone excess, 25% have subclinical disease. Biochemistry commonly obtained as part of the hormonal evaluation can be noted in Table 1. If there is suspicion for adrenal hormone excess based on laboratory results, adrenal specific imaging should then be pursued if not done already, the most common being an adrenal protocol computed tomography (CT) scan (Fig. 1) with magnetic resonance imaging (MRI) as an alternative modality. Routine CT of the abdomen or of the chest will not adequately evaluate an adrenal abnormality. Table 2 lists characteristics and criteria to differentiate benign from indeterminate adrenal masses. Various washout percentages, most commonly 50% to 60%, have been proposed as cutoffs to differentiate lipid poor benign adenomas from potentially malignant adrenal tumors. An alternative imaging modality to MRI. A 16% loss of signal between in- and out-of-phase images

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Suggested Readings

Kamel IR, Raman SS. Cross sectional imaging work-up of adrenal masses. World J Radiol. 2010;2(12):466–472.

Zeiger MA, Thompson GB, Duh QY, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocrine Practice. 2009;15(suppl 1):1–20.

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Formal evaluation of a patient with an adrenal nodule begins with taking a complete personal and family history and performing a full physical examination. Specific evaluation of an adrenal nodule is completed by seeking evidence of adrenal hormone excess and characterizing tumor appearance by imaging studies. The history should focus on onset of any hypertension, electrolyte abnormalities, signs or symptoms associated with hypercortisolism (Cushing disease or syndrome), pheochromocytoma, or primary aldosteronism (Conn) syndrome. Changes in secondary sexual characteristics may indicate the presence of a virilizing or feminizing tumor. Signs and symptoms suggestive of primary aldosteronism may include hypertension, generalized edema, weight gain, muscle cramping due to hypokalemia, and weakness. Signs and symptoms consistent with hypercortisolism may include weight gain, hypertension, impaired glucose tolerance and diabetes, thinning of the skin, easy bruising, central adiposity, development of a buffalo hump, striae, proximal muscle weakness, and change in fat distribution from the periphery to the abdomen. Signs and symptoms associated with pheochromocytoma may include hypertension, episodic palpitations, diaphoresis, sudden onset headaches, pallor, anxiety, or feeling of doom. These may be exacerbated in certain situations or after eating certain foods. A family history should be taken to investigate the possibility of a genetic mutation driving development of an adrenal abnormality. This will also prompt possible investigation for other disease processes that may be part of a particular genetic syndrome (multiple endocrine neoplasias, von Hippel Lindau, neurofibromatosis, etc.). Patients should be questioned about a previous history of malignancy or any signs or symptoms, which may lead to consideration of recurrent metastatic disease or a previously undiagnosed malignancy.

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is consistent with a benign nodule or mass. In the case of an indeterminate lesion, positron emission tomography (PET) CT may also be used to help differentiate between a benign and potentially malignant mass; however, one should be aware of the pitfalls for various cancers in terms of ^{18}F-FDG avidity. Adrenal cancer is ^{18}F-FDG avid and whereas renal cell cancer is not particularly ^{18}F-FDG avid. Some centers in Europe are using ^{11}C metomidate PET imaging as well as urinary steroid profiles to help differentiate between benign and malignant primary adrenocortical tumors. Imaging evaluation of adrenal masses and differentiation of benign versus potentially malignant adrenal lesions is extremely important because it helps inform the selection of an appropriate operative procedure as surgery for benign adrenal tumors and primary ACC is different.

ROLE OF FINE-NEEDLE ASPIRATION

There is a very limited role for fine-needle aspiration (FNA) of adrenal nodules. The ability to discriminate between benign adrenal tumor and ACC is poor, and the undesirable possibility of seeding the needle tract with tumor has been reported. Treatment should be based on biochemical and radiologic imaging characteristics. The most common circumstance for which FNA may be considered in patients with adrenal masses is (1) patients who are poor operative candidates and need a diagnosis to guide additional treatment, (2) patients with suspected metastatic disease in which the adrenal mass is the most easily accessible metastatic tumor deposit, (3) suspected adrenal lymphoma or abscess/infection due to an infectious etiology (tuberculosis, histoplasmosis) which are often bilateral, (4) patients with presumed unresectable ACC and without evidence of hormonal excess where tissue confirmation is necessary to guide neoadjuvant or palliative chemotherapy. FNA in other situations is not particularly helpful. If FNA of an adrenal mass is pursued, pheochromocytoma must be ruled out before biopsy because hypertensive crisis may result.

TABLE 1 Initial Biochemical Evaluation of Adrenal Tumors

Routine	Consider
Metabolic panel	17-OH progesterone
Aldosterone	17-OH pregnenolone
Renin	11-deoxycortisol
Plasma or 24-hour urine metanephrine and normetanephrine levels	Progesterone
1 mg DST with 0800 ACTH, cortisol	Androstenedione
24-hour urine free cortisol	Estradiol
DHEAS	FSH
Testosterone (total or bioavailable)	LH

ACTH, Adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; FSH, follicle stimulating hormone; LH, luteinizing hormone.

DECISION TO OPERATE

The decision to proceed with adrenalectomy is based on imaging characteristics, size, and evidence of hormone excess.

Imaging Characteristics and Size

Tumor size alone should not dictate the need for adrenalectomy. In the past, tumor size greater than 4 or 6 centimeters alone was used as a cutoff given an increase in rate of malignancy; however, more recently, imaging characteristics (taking into account washout percentages) are considered in combination with size. A purely nonfunctional tumor with benign imaging characteristics greater than 4 to 6 cm does not necessarily need resection based on size alone. Follow-up imaging should be obtained 6 to 12 months later to assess for change in size or imaging characteristics. Myelolipomas and other benign adrenal tumors may grow to fairly large sizes without causing significant symptoms. Local symptoms of compression in the form of pain or early satiety are not well studied, but tumors can grow to become quite large and result in minimal to no symptomatology. If a benign-appearing tumor reveals evidence of growth, resection is indicated. A decision to pursue resection for benign-appearing nonfunctional tumors reaching 6 to 10 cm may also be made because tumors of this size are still potentially amenable to a minimally invasive approach. With growth, an open approach is more likely needed simply to remove the tumor through an incision because mobilization of an adrenal tumor is to be avoided to allow for adequate pathologic examination. Patient age and comorbidities should also be taken into consideration to aid in the decision-making process regarding resection of benign nonfunctional tumors. In those patients who are young, continued follow-up over many years adds to medical costs, and the patient may prefer resection sooner rather than later, especially while still healthy and with few comorbidities. Patients with adrenal cysts need to be considered in a slightly different manner. Pure cysts without evidence of a solid component can often be

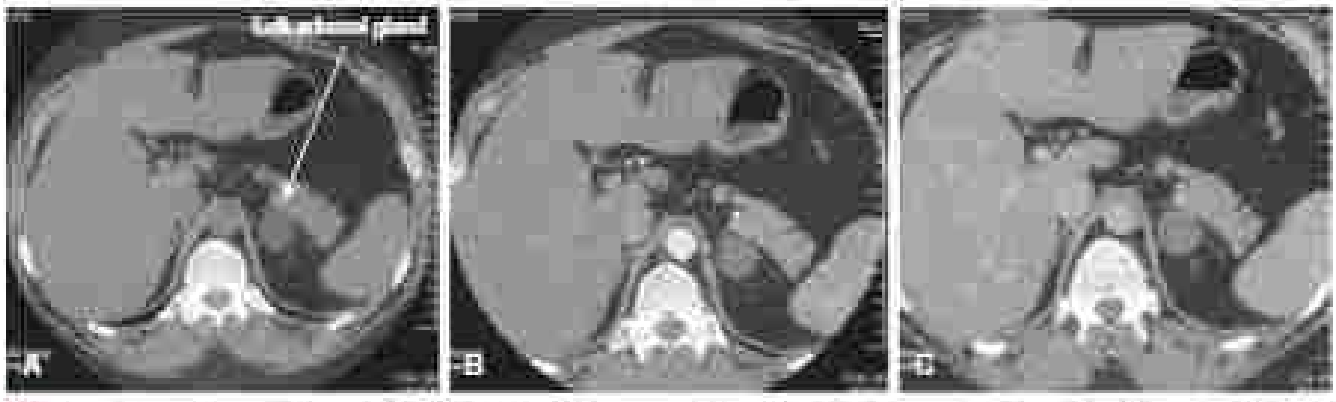


FIG. 1 Adrenal protocol computed tomography (CT) scan. (A) Initial noncontrast CT scan with thin cuts through the adrenal gland is obtained. If the nodule or mass is homogeneous Hounsfield units (HUs) are calculated. If HUs within the nodule are <10, contrast is administered and HUs again measured shortly thereafter (B) and again at 15 minutes (C). A washout percentage is then calculated.

TABLE 2 Imaging Characteristics Utilized to Differentiate Benign From Potentially Malignant Adrenal Tumors

Characteristic	Benign	Indeterminate
Size (cm)	<4 cm if other benign internal characteristics	>4–6 cm if other indeterminate characteristics
Unenhanced CT (Hounsfield units)	≤10	>10 and washout % indeterminate
Percentage washout on CT (if homogeneous tumor)	>60%–40%	<60%–40%
MRI chemical shift	≥50%	<50%
Internal attenuation	Homogeneous	Heterogeneous
Calcification	Absent	Present
Necrosis	Absent	Present
Borders	Regular	Irregular
Invasion of adjacent structures	Absent	Present
Intravascular tumor thrombus	Absent	Present
Lymphadenopathy	Absent	Present
6-NC-PET CT: Tumor SUV	<3.4	>3.4
6-NC-PET CT: Tumor/liver SUV ratio	<1.45	>1.45

CT, Computed tomography; 6-NC-PET CT, 6-beta-iodine-131-iodomethyl-19-norcholesterol positron emission computed tomography; MRI, magnetic resonance imaging.

observed. If small cysts less than 4 to 6 cm are noted to be slowly growing and all other imaging characteristics are otherwise benign, aspiration with injection of ethanol can be considered. The long-term durability of this approach is about 30%, with decreased success rates as cyst size increases. Cysts with a solid component harbor a small risk of malignancy, whereas those with cystic areas within a larger, more solid tumor, the risk of malignancy is even higher because fluid-filled portions may be due to tumor necrosis. Pheochromocytomas may show evidence of necrosis and fluid.

Biochemically Functional Versus Nonfunctional

Those patients with overt hormone excess due to a unilateral adrenal tumor are most often offered surgery as opposed to medical management. For those with hypercortisolism, the management of those with biochemical evidence of subclinical hormone excess can be more difficult from a decision-making standpoint. Most patients with subclinical hypercortisolism will be diagnosed by a one-milligram dexamethasone suppression test. For those with AM cortisol levels greater than 3 μg/dL, resection should be considered, whereas those with AM cortisol levels 1.8 to 3 μg/dL may be able to undergo surveillance. The decision for operation in these patients should be made in the context of the severity of other potential disease processes that may be attributable to hypercortisolism, such as hypertension, diabetes, weight gain, and bone density loss. Studies reporting outcomes of patients with subclinical hypercortisolism do show benefit after adrenalectomy; however, many of these studies have methodologic flaws, and accurately differentiating patients with subclinical disease from those with overt hypercortisolism can be difficult. For those with hypercortisolism due to bilateral excess adrenal production (adrenocorticotropic hormone dependent or independent disease and other types of hyperplasia), the decision for unilateral (starting with the largest adrenal) versus bilateral adrenalectomy should be made jointly with an endocrinologist.

Patients with primary aldosteronism need further evaluation to determine whether surgical resection is appropriate. Assuming the aldosterone level is greater than 15 ng/dL and the renin level is suppressed, an aldosterone/renin ratio greater than 30 suggests the diagnosis. Certain medications should be held before testing because it can affect the renin level most often. Confirmatory tests such as saline suppression tests and others may be pursued. The Endocrine Society published guidelines detailing the biochemical evaluation of these patients. CT imaging has found to be poor in terms of specificity for unilateral versus bilateral excess aldosterone secretion from the adrenal glands. Specificity averages about 40% to 50%. Therefore, once a clear biochemical diagnosis has been made, adrenal vein sampling should be pursued in most patients to determine the unilateral or bilateral nature of the excess hormone production. Understanding how to interpret these studies is critical, as is having an interventional radiologist with high success of entering the left adrenal vein and especially the right adrenal vein.

Aside from those with hormone excess, the decision for operation should also be based on the physical status of the patient and existing comorbidities. Some patients can be easily medically managed, and this may be more appropriate in patients with significant comorbidities. Patients with metastatic disease to the adrenal glands should be evaluated carefully to their overall prognosis as well as future planned therapy should be taken into consideration. Those with metastatic disease may be better served by other treatment modalities. Some malignancies are quite radiosensitive, and in the situation of an aggressive cancer with poor prognosis, radiation therapy or other types of local interventions may be more appropriate; however, these are not recommended as first- or second-line therapy.

For those with suspected or obvious ACC, a chest CT should be obtained as part of the routine preoperative evaluation to evaluate for metastatic disease. In those with metastatic disease, resection is usually delayed in favor of chemotherapy and mitotane, with a select few being able to undergo resection if all sites of disease can be addressed in some form or fashion (medical or procedural). Those with locally invasive tumors where an R0 resection would be unlikely may also benefit from neoadjuvant chemotherapy and mitotane for a period of time.

PREOPERATIVE CONSIDERATIONS

The individual patient's anatomy should be carefully studied when selecting an operative approach. The operative approach is not solely based on size alone, but also includes prior surgical history, concern for malignancy, need for access to other intra-abdominal organs, planned concomitant procedures elsewhere in the peritoneal cavity, cardiac and pulmonary status in terms of toleration of a lateral or

TABLE 3 Anatomic Features to Consider When Choosing Between Laparoscopic and Retroperitoneoscopic Adrenalectomy

Characteristic	Laparoscopic Approach	Retroperitoneoscopic Approach
Tumor size	<10 cm	<7–8 cm
BMI (kg/m^2)	Any BMI	<45
Subcutaneous adipose depth at twelfth rib	>5–6 cm	<5–6 cm
Retroperitoneal fat	Abundant	Sparse
Tumor position (anterior/posterior) relative to kidney	Any position	Adrenal gland in posterior or neutral position to plane of kidney
Position of adrenal gland in relation to renal vasculature	Any position	Separated and superior
Position of twelfth rib in relation to kidney	Rib overlies lower one third of kidney	Rib overlies upper two thirds of kidney
Previous upper abdominal surgery	No	Yes
Stage 3 or 4 renal insufficiency	Yes	No

BMI, body mass index.

TABLE 4 Medications Used to Decrease Excess Production of Adrenal Hormones

Type of Hormone Excess	Primary Medication	Alternative Medications
Cortisol	Metyrapone	Ketoconazole, mitotane, etomidate, mifepristone (ACC)
Aldosterone	Spironolactone	Eplerenone, amiloride
Testosterone	Spironolactone	
Estrogen	Tamoxifen	Raloxifene, anastrozole, letrozole, exemestane

ACC, Adrenocortical carcinoma.

prone position, body habitus, and position of the adrenal gland with respect to the renal vasculature and upper pole of the kidney from the standpoint of selecting an anterior or posterior approach. Important anatomic features to consider when choosing between a laparoscopic and retroperitoneoscopic approach are listed in Table 3.

An attempt to control hormonic excess and correct electrolyte abnormalities should be pursued if possible. Medications to assist in curbing excess hormone production are listed in Table 4. For those with primary aldosteronism, hypertensive control or hypertension is often best achieved with spironolactone or eplerenone. Creatinine, sodium, and potassium levels should be closely followed while titrating these medications. In addition to potassium supplementation, hypokalemia (which occurs in ~50% of patients) may also be controlled in part with amiloride. If patients are found to be hypokalemic in the preoperative area, lower doses than normal should be given due to the potential for rebound hyperkalemia in the postoperative setting.

In patients with hypercortisolism, exercise and consumption of a high-protein diet should be encouraged before surgery as much as possible given muscle deterioration due to the disease process. If time permits, several months of preoperative treatment with one of the previously listed medications can be helpful in better controlling the quantity of cortisol excess. During surgery, patients with overt hypercortisolism should be given stress dose steroids. If undergoing a bilateral adrenalectomy, stress dose steroids can be given after resection of the first adrenal gland. A standard stress dose steroid regimen is 50 to 100 mg of intravenous hydrocortisone every 8 hours. This is then tapered over several days to a lower maintenance dose until return of function of the hypothalamic–pituitary axis, which can take months to a year. Those with suspected subclinical disease may forego stress dose steroids if testing of the hypothalamic–pituitary–adrenal (HPA) axis is planned for the morning after surgery in the form of an early morning cortisol level or formal cosyntropin stimulation test.

OPERATIVE APPROACHES

Adrenalectomy may be accomplished by utilizing a number of approaches. Most commonly for small benign tumors, a laparoscopic transperitoneal approach is preferred. An alternative approach, for those with experience in adrenal surgery, is the posterior retroperitoneoscopic approach. The spleen and liver do not need to be mobilized, and blood loss is often diminished due to increased insufflation pressures and the need for less mobilization of overlying structures. This approach also allows for access to both adrenal glands without repositioning, reprepping, and redraping during bilateral laparoscopic transperitoneal adrenalectomy. Postoperative pain can be less and recovery quicker. However, the retroperitoneoscopic approach does not allow for multivisceral resection or adequate access to the peritoneal cavity. Those with significant renal insufficiency may experience further worsening of their glomerular filtration rate due to the increased insufflation pressures. Robotic assistance may be used for either laparoscopic or retroperitoneoscopic approaches. For those patients with larger tumors not amenable to a purely laparoscopic or laparoscopic hand-assisted approach, tumors concerning for primary adrenocortical carcinoma, prior surgery in the upper retroperitoneum, or those needing multivisceral resection or concomitant retroperitoneal procedures, an open transabdominal approach using a subcostal or midline incision is usually pursued. Although used frequently in the past, the open posterior approach is rarely used anymore but remains a useful approach, especially in those who have undergone prior surgery in the upper quadrants. Finally, a thoracoabdominal approach to the adrenal glands may also be used but is rarely needed except in the situation where access to the chest and abdomen is required or there has been significant prior surgery in the area and an open posterior or posterior retroperitoneoscopic approach is not possible. Most often, these situations involve patients with extensive invasive or recurrent malignant adrenal tumors.

Right Laparoscopic Transperitoneal Adrenalectomy

The patient is placed in left lateral decubitus position at a 45 degree angle as shown in Fig. 2A so that the abdomen and flank are

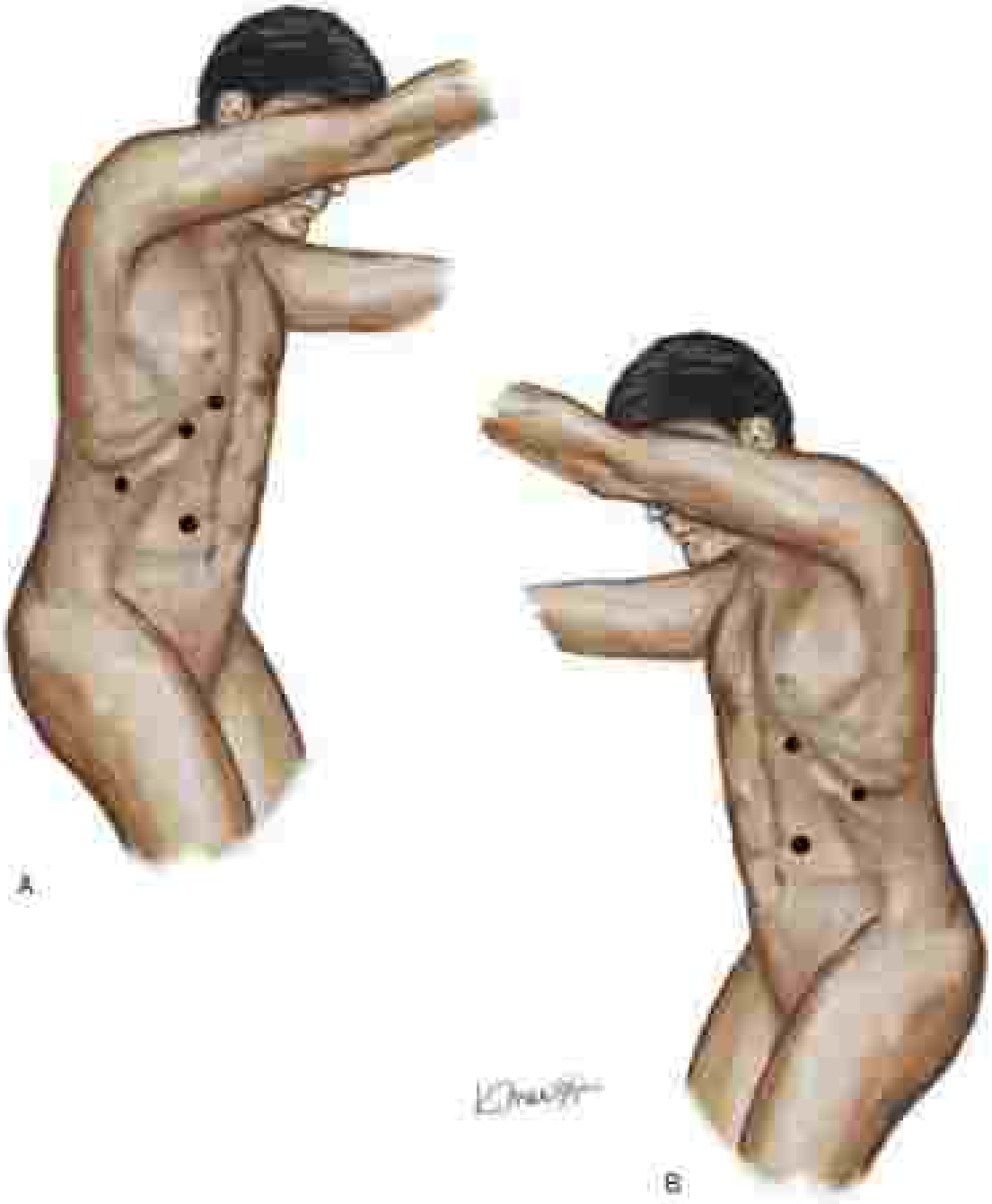


FIG. 2 Patient positioning and port site placement for (A) right laparoscopic adrenalectomy and (B) left laparoscopic adrenalectomy (Patient illustration from www.colorimagery.com Copyright Elsevier Inc. All rights reserved.)

accessible if conversion to an open procedure is necessary. The space between the ribs and pelvis is extended. Port sites are established using standard techniques for access. On the right side, four ports (occasionally more) are most often placed, one of which is for retraction of the liver. The triangular and coronary ligaments of the right lobe of the liver are divided and the liver is retracted medially. The upper pole of the kidney is identified and the space between it and the adrenal gland is identified. The vena cava is also identified. Intraoperative ultrasound can be useful for identifying the adrenal gland when abundant retroperitoneal fat is present. The attachments of the perinephrinal fat are released from the upper pole of the kidney using standard techniques, most often ultrasonic dissection. It is critical to identify and remove the most inferior extent of the adrenal gland, which sometimes overlies the renal vasculature as even a small amount of hormonally functional tissue can lead to postadrenal disease. Once the inferior attachments have been released, some of which may include small vessels coming off the renal artery or renal vein, the dissection continues superomedially along the vena cava until the adrenal vein is identified. Options for ligating and dividing the adrenal vein include ultrasonic instruments, clips, and sometimes a stapler if access is difficult or the vein is wide. The more superior attachments medially and laterally are then released and the adrenal gland is removed. Port sites are closed in standard fashion.

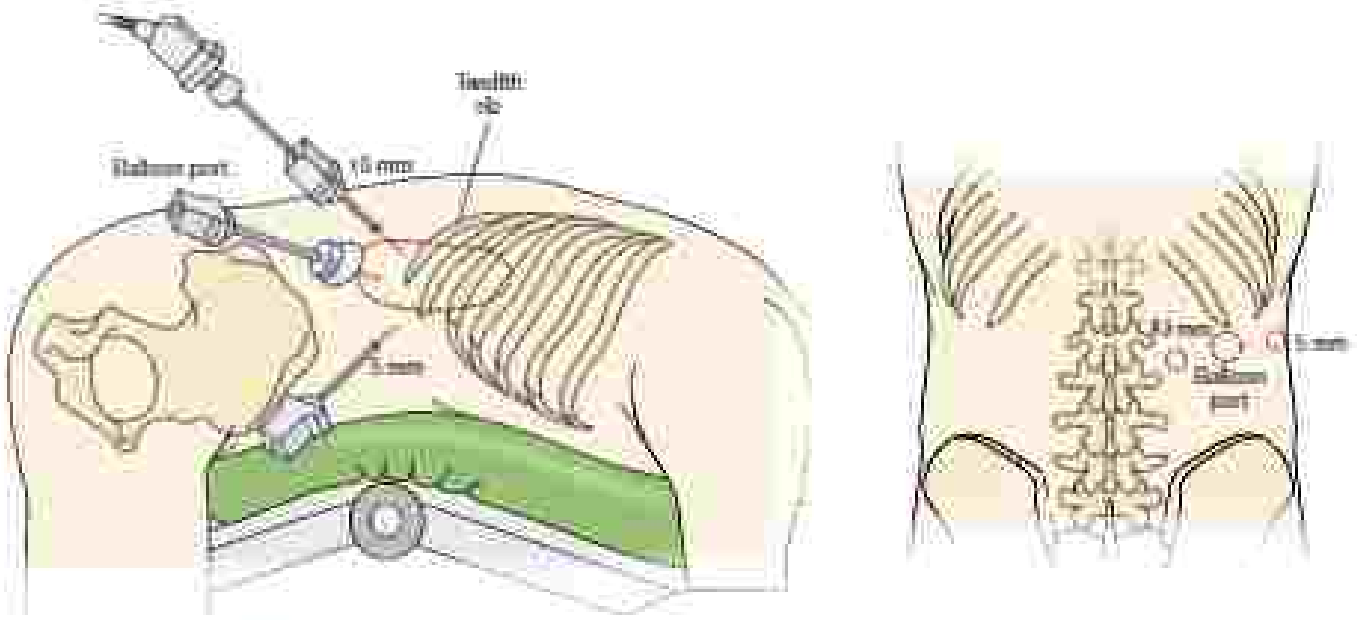


FIG. 3 Patient positioning and port-site placement for posterior retroperitoneoscopic adrenalectomy.

Left Laparoscopic Transperitoneal Adrenalectomy

Three ports (occasionally four or more) are most often required for left adrenalectomy (Fig. 3B). The splenocolic ligament is divided and the colon mobilized inferiorly and medially. The remaining splenic attachments are then mobilized to the esophageal hiatus so that the spleen will remain mobilized, often without the need for a retractor. Left adrenalectomy is then carried out in similar fashion to the right side. The left adrenal vein is usually identified in the 7 o'clock position. This may be visualized on preoperative imaging in many cases. A communicating branch may course longitudinally from the adrenal vein to the phrenic vein along the medial aspect of the adrenal gland. Attachments of the adrenal gland to the surrounding tissue are ligated and divided and the adrenal gland is removed.

Posterior Retroperitoneoscopic Adrenalectomy

The patient is placed in a prone position as shown in Fig. . An initial incision is made near the tip of the twelfth rib. Blunt dissection into the retroperitoneal space is pursued. The retroperitoneal fat is bluntly swept from the musculature using a finger, allowing for placement of a 5-mm port near the tip of the eleventh rib laterally and a 10-mm port medially at the lateral edge of the erector spinae muscles ~30 degrees inferior to the original incision. The retroperitoneum is insufflated to a pressure of 20 to 22 mm Hg. This can be increased if needed to assist with control of oozing or bleeding up to ~28 mm Hg. More tissue is bluntly dissected from the posterior musculature and the dissection carried medially and superiorly. As dissection and exposure proceed, the tone of the liver will be seen superolaterally. It is important not to dissect into the peritoneal cavity because visualization becomes extremely difficult with loss of insufflation of the retroperitoneal space. Once the adrenal gland is identified, dissection should proceed from an inferior to superior fashion. On the right side, surgeons should proceed with caution during the medial dissection until the vena cava is clearly identified because it will be compressed due to increased insufflation pressure. Because the right adrenal vein often emanates from the posterolateral aspect of the vena cava, it will be visualized more anteriorly in this approach than in a traditional laparoscopic approach given the prone positioning. The adrenal vein is ligated and divided and the remaining attachments released. The adrenal is removed, the fascia of the middle port site reapproximated and the wounds closed.

A similar approach is taken for left retroperitoneoscopic adrenalectomy. The tone of the spleen is identified superolaterally, and dissection is carried out as described. The left adrenal vein can be more difficult to identify than the right adrenal vein due to the proximity of the left renal vein to the renal hilum and a more posterior position when compared with the traditional transperitoneal approach.

With all laparoscopic and retroperitoneoscopic procedures, it is important to avoid disturbing the capsule of the adrenal gland because this will lead to bothersome oozing during the case, which may obscure visualization. Some literature supports that partial adrenalectomy is appropriate in select situations. This should be very carefully considered and performed by a high-volume adrenal surgeon because there are nuances to the decision making and conduct of the operation.

Right Open Adrenalectomy

Because open adrenalectomy is most often performed for malignant tumors, this section will describe the operative approach from an oncologic standpoint. Although a midline incision can be made, a wide right subcostal incision extending to the left side is favored because of an improved ability to retract the ribs and mobilize the liver, providing exceptional access to the adrenal gland, kidney, and vena cava. The peritoneal cavity is inspected to a systematic fashion. Intraoperative ultrasound scanning of the liver and evaluation of the adrenal vein and vena cava for tumor thrombus may be performed. The attachments to the liver are divided and the right lobe of the liver rotated medially. A retractor (Omni or Thompson) is placed to provide exposure. Through the surface of the posterior peritoneal lining, the kidney and the adrenal gland are able to be appreciated. If the tumor is found to be invading the posterior aspect of the liver, a rim of normal liver may be resected en bloc as part of the anterior margin. As delineated in Fig. , dissection occurs inferiorly over the superior half of the kidney, taking the posterior peritoneal lining and any fat over the superior half of the kidney to provide an ample inferior margin. This is continued to the plane found between the adrenal gland and kidney. If there is any concern for the invasion of the kidney, removal of a portion of the capsule of the kidney, partial or complete nephrectomy may be performed depending on the extent of suspected invasion because one does not want to create a plane between tumor and the surface of the

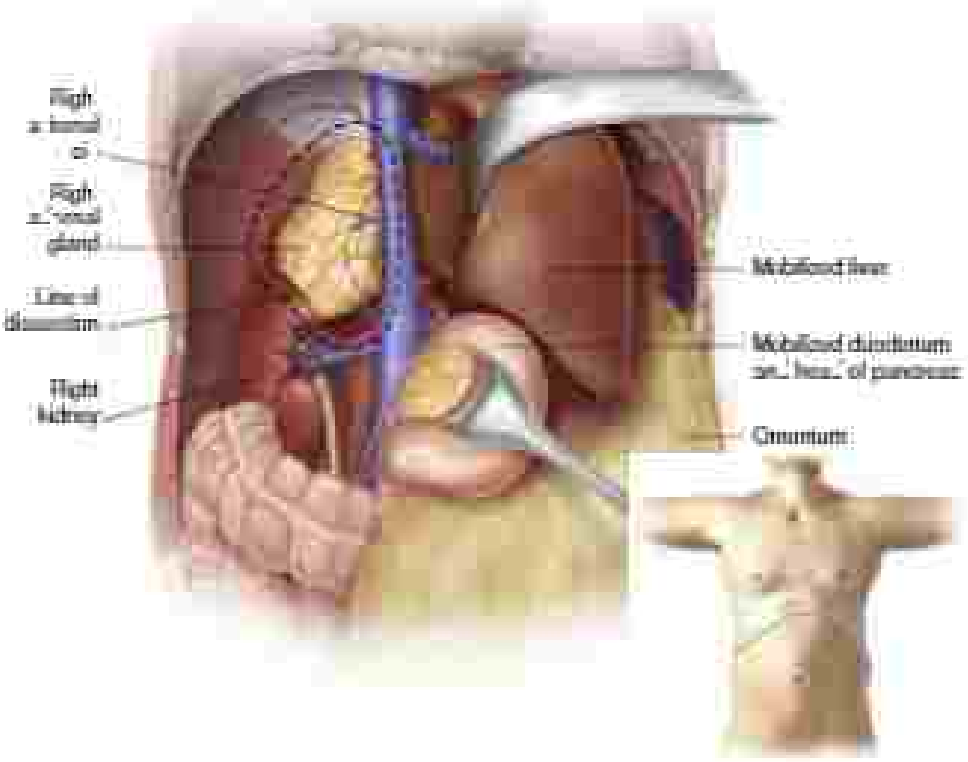


FIG. Use of [illegible] incision to access the left renal vein and adjacent adrenal. Upper A shows the abdominal compartments to be entered.

kidney where none exists, allowing for microscopic dissection and demonstration of tumor. The dissection is continued laterally to the abdominal sidewall, and all [illegible] fat over the psoas muscle is taken as part of the specimen and preserved with the specimen. The posterior adrenal gland is then separated from the diaphragm using electrocautery. The diaphragmatic muscle fibers attached to the adrenal gland are left attached to the specimen. The specimen is then removed and sent to pathology. Hemostasis is confirmed and the wound is closed in standard fashion.

Laparoscopic Adrenalectomy

The patient is placed in lateral decubitus position. A 12-mm trocar is placed in the umbilicus using the Veress technique. Pneumoperitoneum is established and maintained at 15 mm Hg. Two 5-mm trocars are placed in the upper abdomen, one in the midclavicular line and one in the anterior axillary line. The liver is retracted superiorly and the spleen inferiorly. The lateral peritoneal attachments are incised, and the adrenal gland is identified. Dissection proceeds from lateral to medial, with the adrenal vein ligated and divided last. The adrenal gland is placed in a specimen bag and removed through the umbilical port. Hemostasis is confirmed and the trocars are removed under direct vision. The fascial defects are closed with sutures, and the skin incisions are closed with subcuticular sutures.

Laparoscopic Retroperitoneal Adrenalectomy

The patient is positioned in lateral decubitus position. A 12-mm trocar is placed in the midaxillary line at the level of the 12th rib. Pneumoperitoneum is established and maintained at 15 mm Hg. Two 5-mm trocars are placed in the upper abdomen, one in the midclavicular line and one in the anterior axillary line. The liver is retracted superiorly and the spleen inferiorly. The lateral peritoneal attachments are incised, and the adrenal gland is identified. Dissection proceeds from lateral to medial, with the adrenal vein ligated and divided last. The adrenal gland is placed in a specimen bag and removed through the umbilical port. Hemostasis is confirmed and the trocars are removed under direct vision. The fascial defects are closed with sutures, and the skin incisions are closed with subcuticular sutures.

Open Posterior Adrenalectomy

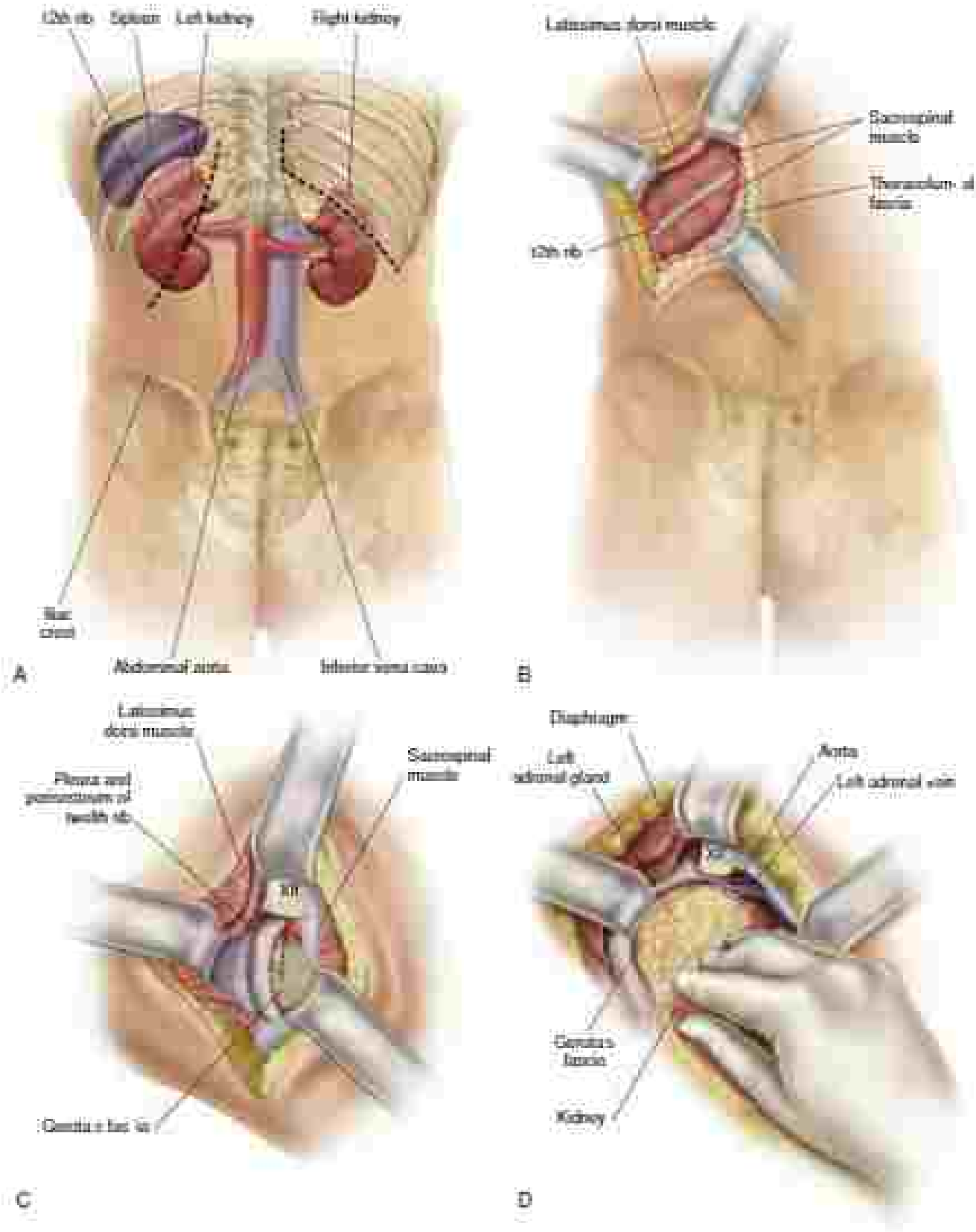
The patient is placed in prone position. A curvilinear or angled incision is made as shown in Fig. 5 from medial to lateral over the twelfth rib. The twelfth rib is identified and removed. The retroperitoneum is entered. It is important to sweep the retroperitoneal fat from superior to inferior and from medial to lateral. Because of the location, the pleural cavity may be inadvertently entered and may be sutured closed. Using hand held retractors to retract the ribs and musculature, the kidney is identified and retracted inferiorly with the surgeon's hand and the adrenal gland identified medially and superior to the renal hilum. Adrenalectomy is performed, albeit from a dorsal approach, in standard fashion. The wound is closed in multiple layers, making sure not to injure the neurovascular bundle of the eleventh and twelfth ribs.

Open Anterior Transperitoneal and Thoracoabdominal Approach

The patient is positioned as shown in Fig. . An incision is made and the pleural cavity is entered. The costal margin is transected using bone cutters. The diaphragm is divided to enter the peritoneal cavity, making sure not to injure the phrenic nerve. A small rim of diaphragm attached to the rib is preserved for later reapproximation. The abdominal cavity is then entered. Resection is then carried out in a similar approach to open adrenalectomy.

ADRENALECTOMY IN THE SETTING OF A GENETIC SYNDROME

In those patients with adrenal tumors resulting from a genetic mutation, patients should be referred to a genetic counselor. Ideally, those suspected of having a possible genetic mutation would undergo this testing in the preoperative setting as knowledge of the specific mutation can impact preoperative testing and conduct of the operative. Adrenal tumors may be found in patients with MEN 1, MEN 2, or found in patients with Cushing syndrome or [illegible] nodulosis.


12th rib
Spleen
Left kidney
Right kidney
Iliac crest
Abdominal aorta
Inferior vena cava
A
Latissimus dorsi muscle
Sacrospinal muscle
12th rib
B
Latissimus dorsi muscle
Sacrospinal muscle
Pleura and peritoneum at twelfth rib
Quadratus lumborum
C
Diaphragm
Left adrenal gland
Aorta
Left adrenal vein
Quadratus lumborum
Kidney
D

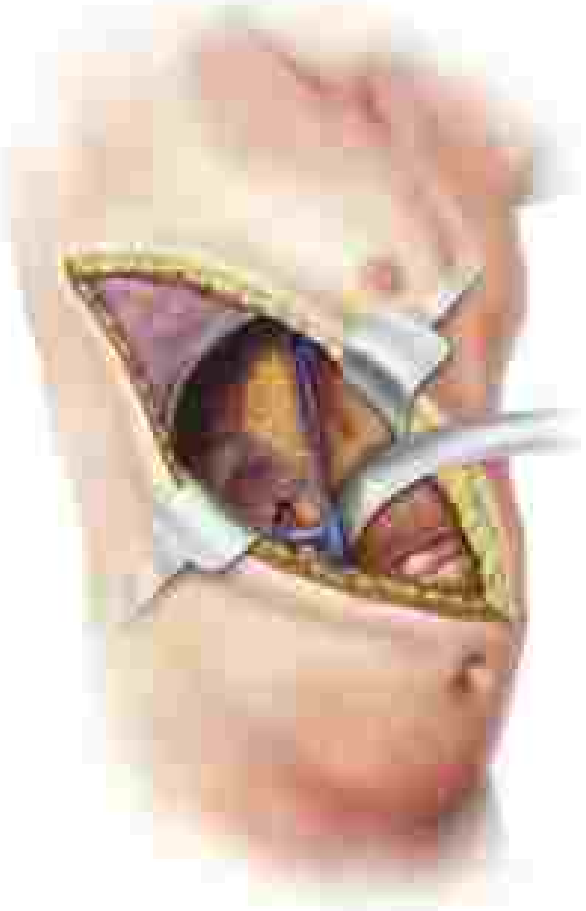


FIG. 6 Exposure of the right adrenal gland via transabdominal approach. An incision is made between the ribs and carried to the midline and inferiorly toward the umbilicus.

Pheochromocytoma is associated with MEN 2A, MEN 2B, neurofibromatosis, and von Hippel-Lindau syndromes. Partial adrenalectomy may be pursued in some of these patients depending on the size of the tumor, as well as the position of the tumor in relation to the draining vasculature. Approximately 20% of a normal adrenal gland is required for continued cortical function. Patients who are potential candidates for partial adrenalectomy should be referred to a surgeon with expertise in the disease process, decision-making process, and the nuances of partial adrenalectomy.

ADRENALECTOMY IN PREGNANCY

As with other diagnoses necessitating surgery during pregnancy, it is best if adrenalectomy is delayed until after delivery. Should surgery be required, it is best performed during the second trimester. Most commonly, adrenal disorders encountered during pregnancy include pheochromocytoma, Cushing's syndrome, and adrenal cortical carcinoma, all of which are extremely rare. For those with Cushing's syndrome, the scant amount of literature available suggests adrenalectomy during the second trimester. For those with pheochromocytoma, α- and β-blockade can be pursued and adrenalectomy performed after delivery or at the time of delivery.

POSTOPERATIVE CONSIDERATIONS

Patients undergoing adrenal surgery may require various levels of care depending on the diagnosis and operation performed. Most patients can be managed in a routine inpatient setting. Some cases can be done in an outpatient setting; however, this is only in highly selected situations. For those with evidence of hormone excess, most patients will need monitoring in the hospital for 24 to 48 hours to assess electrolytes, volume status, and blood pressure. For those with primary aldosteronism, all antihypertensive medications and home potassium supplementation regimens should be discontinued after surgery to allow for determination of cure and to assess the need for reinstitution of any of these medications. It can take weeks to months for the body to reestablish a new baseline blood pressure, and patients are encouraged to continue monitoring blood pressure after surgery for optimal titration of medications.

For those patients with overt signs of hypercortisolism, postoperative steroid supplementation will almost always be required. A normal daily total dose of hydrocortisone is 15 to 30 mg, depending on the patient. The total dose is divided two to three times daily, giving a larger dose in the morning and smaller dose to the mid- or late afternoon to replicate the normal diurnal rhythm. Administering steroids at night can adversely affect the normal sleep pattern. Patients with severe hypercortisolism may exhibit signs of steroid withdrawal even when normal replacement doses of steroids are given. Higher-than-normal daily doses of hydrocortisone may be required in the postoperative period, and weaning of steroids should be managed by an endocrinologist. In general, prednisone should not be used for steroid replacement because it increases the length of time for recovery of the HPA axis. For those patients with subclinical production of excess cortisol, these patients may or may not require postoperative steroids. It is recommended that perioperative administration of dexamethasone (Decadron), which may be given during surgery for prevention of postoperative nausea and vomiting, be avoided in these patients because it may impact testing of the HPA axis the morning after surgery.

Any patient undergoing adrenalectomy, whether unilateral or bilateral, should be warned about the possibility of developing Addisonian crisis and the need for steroid supplementation to prevent or treat this life-threatening situation. Warning signs and a management plan are ideally discussed in advance with the patient and their family. The chance of this occurring is dependent on the diagnosis, extent of surgery, and amount of residual adrenal tissue.

SUGGESTED READINGS

[illegible]

[illegible]

[illegible]

Wade ME, Alwaise F, Wenger EA, et al. Outcome comparison in adrenalectomy: results of 5-9 procedures in [illegible]

Williams TA, Lenders JWM, Mulatero P, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort. [illegible]

MANAGEMENT OF PHEOCHROMOCYTOMA

William M. Brigode, MD, Emil [illegible] Hirall r, MD, and
[illegible] A [illegible], MD, MEd

BACKGROUND

Pheochromocytomas and paragangliomas (PPGL) are rare chromaffin neoplasms with the potential to synthesize, store, metabolize, and secrete catecholamines. The term pheochromocytoma is limited to tumors that arise from within the adrenal medulla (10%), whereas paragangliomas are similar extraadrenal tumors that arise anywhere from skull base to scrotum along the path of the embryologic neural crest cells in the autonomic ganglia. The incidence ranges from [illegible] to 8 per million people annually. Although rare, a higher prevalence is reported on autopsy, suggesting these tumors are underdiagnosed and may contribute to premature death secondary to a number of cardiovascular and metabolic complications associated with functional PPGLs, including hypertension and diabetes.

Pheochromocytoma was previously described as the rule of 10 tumor: 10% malignant, 10% bilateral, 10% multifocal, 10% pediatric, 10% without hypertension, 10% incidentally discovered, 10% extraadrenal (paraganglioma), and 10% familial. However, with an increased understanding of the inheritance patterns and genetics, it has become clear that a significant percentage of patients with these tumors has a genetic predisposition. Researchers continue to identify genetic associations in up to 35% of these tumors, which may have clinical implications as they are at higher risk for extraadrenal, bilateral, and malignant disease (Table 1).

CLINICAL PRESENTATION

Patients with PPGL may experience a wide range of symptoms related to catecholamine and catecholamine metabolite excess. The symptom triad of paroxysmal headaches, palpitations, and excessive sweating is classically described but is infrequently present. Anxiety, lightheadedness, tremors, fever, heat intolerance, pallor, abdominal pain, nausea, vomiting, blurred vision, dyspnea, chest pain, and feelings of impending doom are some of the many symptoms experienced. These "spells" may occur at varying intervals and may be incited by anxiety or exertion. Metabolic disturbances such as weight loss and glucose intolerance may also occur. Hypertension is frequently present in these patients, and patients with severe or therapy-resistant hypertension should be screened for PPGL to avoid delays in diagnosis. PPGLs are rare in older adults, most commonly presenting in the fourth to fifth decades of life. They are typically found in children, except in patients with hereditary forms of the disorder. Patients with hereditary syndromes will be symptomatic at a younger age than patients with sporadic disease. Additionally, those with hereditary syndromes are more likely to have extraadrenal tumors and have multiple or bilateral lesions.

DIAGNOSIS

Any patient with symptoms consistent with episodic catecholamine excess or refractory or severe hypertension resistant to multiple antihypertensive drugs should undergo biochemical workup. Similarly, any patient with an incidentally discovered adrenal mass should be tested because up to 10% of adrenal incidentalomas are found to have a biochemical profile consistent with pheochromocytoma. Plasma-free fractionated metanephrine and normetanephrine or 24-hour urine fractionated metanephrine and normetanephrine are the main diagnostic tests for PPGL. Because paragangliomas are extraadrenal by definition, they typically do not secrete epinephrine due to the lack of phenylethanolamine *N*-methyltransferase (PNMT). The high sensitivity and specificity of 24-hour urine testing make it the preferred initial test in most patients. Wide specificity and sensitivity ranges are reported and differ by laboratory, as well as the diagnostic threshold used. Values greater than four times the upper limit of normal are considered diagnostic whereas diagnosis may still be made with higher sensitivity using a cutoff of two times the upper limit of normal. Lower laboratory levels may make the diagnosis more difficult to obtain, and numerous food products and medications are associated with false-positive results (Box 1). High-risk patients, especially those with a hereditary syndrome predisposing them to PPGLs, should be screened with plasma metanephrine testing; this has a higher sensitivity but is associated with a false-positive rate as high as 10%. Testing after a period of supine rest and an overnight fast can limit false-positive results. For patients with borderline elevations in catecholamine metabolites, clonidine suppression testing, or chromogranin A measurements may be performed as confirmatory tests. Because of the prevalence of associated genetic syndromes, any patient with confirmed paraganglioma should participate in the shared decision-making process for genetic testing, and a strong recommendation is made for counseling in all patients with pheochromocytoma.

IMAGING AND LOCALIZATION

Localization should only be performed after the diagnosis of PPGL has been confirmed biochemically. Computed tomography (CT) and magnetic resonance imaging (MRI) are adequate for localization in the majority of cases and have thus become the mainstays of PPGL localization. Both modalities provide excellent anatomic information that can be used to assist operative planning.

Adrenal protocol CT uses thin cut noncontrast and phased intravenous (IV) contrast images to assess enhancement and washout. CT characteristics of pheochromocytomas include homogeneity in smaller lesions with Hounsfield units greater than 10 and commonly in the 40 to 50 range on noncontrast CT. Pheochromocytomas enhance vigorously with IV contrast with less than 60% washout. Larger tumors are more likely to display heterogeneity, calcifications, or cystic areas (Fig. 1).

T2 MRI, pheochromocytomas have a hyperintense "light bulb" signal intensity on T2 weighted imaging due to the vascularity and water content. The MRI signature is often capable of discriminating pheochromocytomas from other types of adrenal tumors, and MRI is superior to CT in detecting extraadrenal lesions. Reported sensitivity of magnetic resonance imaging is as high as 100% in some series. MRI imaging for PPGL does not require contrast and does not expose patients to ionizing radiation, making it the preferred imaging choice in children and pregnant or lactating women (Fig. 2).

Functional imaging has improved specificity over CT and MRI in PPGL and plays a large role when localization is inconclusive or when multiple lesions or metastatic disease are present. I-131 metaiodobenzylguanidine (MIBG) is the classic functional imaging used to confirm and localize PPGLs. It is frequently an unnecessary addition to the workup but has increased utility in suggesting malignancy in large pheochromocytomas, in localizing lesions not found on CT or MRI, and for localizing paragangliomas. Positron emission tomography (PET)/CT is an advantageous alternative in malignant and metastatic disease, or when other localization modalities are inconclusive. A variety of isotopes are used in PET for PPGL, such as 18-F fluorodihydroxyphenylalanine, 18F-3,4-dihydroxyphenylalanine, 18F-metaiodobenzylguanidine, and 68Ga-DOTA. Improved CT resolution with functional nuclear scintigraphy imaging technology provides outstanding three-dimensional anatomic information.

TABLE 1 PPGL-Associated Genes and Genetic Syndromes

Syndrome	Gene
Multiple endocrine neoplasia type 2A (MEN2A)	*RET*
Multiple endocrine neoplasia type 2B (MEN2B)	*RET*
von Hippel-Lindau syndrome (VHL)	*VHL*
Neurofibromatosis type 1 (NF1)	*NF1*
Paraganglioma syndrome 1 (PGL1)	*SDHD*
Paraganglioma syndrome 2 (PGL2)	*SDHAF2*
Paraganglioma syndrome 3 (PGL3)	*SDHC*
Paraganglioma syndrome 4 (PGL4)	*SDHB*
Paraganglioma syndrome 5 (PGL5)	*SDHA*
Carney triad	unknown; *SDHC* hypermethylation
Carney-Stratakis syndrome/Carney dyad	*SDHB/SDHD/SDHC*
Pacak-Zhuang paraganglioma polycythemia syndrome	*EPAS1/HIF2A*
Fumarate hydratase (FH)	*FH*
MYC-associated factor X (MAX)	*MAX*
Transmembrane protein 127 (TMEM127)	*TMEM127*

EPAS1/HIF2A, Endothelial PAS domain protein 1/hypoxia-inducible factor 2A; *PPGL*, pheochromocytoma and paraganglioma; *RET*, ret proto-oncogene; *SDH*, succinate dehydrogenase; *SDHAF2*, succinate dehydrogenase complex assembly factor 2.

BOX 1 Food and Medications Associated with Falsely Elevated Catecholamine Levels

Tricyclic antidepressants
Monoamine oxidase inhibitors
Norepinephrine reuptake inhibitors
Selective serotonin reuptake inhibitors
Antipsychotics (e.g., haloperidol, chlorpromazine)
Antiemetics (e.g., metoclopramide, prochlorperazine)
Antimicrobials with dextromethorphan
Amphetamines, methylphenidate
Pseudoephedrine
Cocaine
Ketamine
Opioids
Nitrates
Antibiotics (e.g., linezolid)
Corticosteroids
Weight loss supplements (e.g., bethanechol, phenylethylamine)
Chocolate
Beer and wine
Cured/smoked meats
Aged cheese
Yogurt and sour cream
Fermented soybean and fish products (e.g., tofu, soy sauce, fish sauce)
Nuts (e.g., peanuts, coconut, Brazil nuts)
Certain fruits (e.g., raspberries, red plums, pineapple, banana, figs)
Certain vegetables (e.g., avocado, eggplant, fava beans, snow peas, green beans, sauerkraut)
Antihypertensive supplements with yohimbe bark extract
Chewing tobacco

PREOPERATIVE MANAGEMENT

Operative preparation for pheochromocytoma and paraganglioma patients requires optimization of blood pressure, treatment of tachycardia, and restoration of normal circulating blood volume. Because of the risks associated with both chronic catecholamine excess and hypertension, preoperative cardiac evaluation is justified for medical optimization in all patients who undergo surgical intervention. Perioperative antihypertensives are mandatory for all patients with catecholamine-secreting tumors before the initiation of anesthesia to reduce intraoperative hemodynamic instability and avoid wide swings in blood pressure and heart rate.

Alpha-adrenergic antagonists are the first-line agents because of their ability to combat hypertension, reduce vascular resistance, and help restore normal blood volume. In preparation for operative resection, α blockade should begin 1 to 2 weeks before the planned surgical date. The standard initial regimen is phenoxybenzamine 10 mg twice daily. The dose can be increased by 10 to 20 mg every 3 days to a goal blood pressure of less than 130/80 mm Hg while sitting, orthostatic hypotension, and the sensation of a "stuffy nose." Numerous alternative regimens have been described, including selective α1-adrenergic antagonists or calcium channel blockers (Table 2). For patients with resistant hypertension, nitroprusside therapy may be added, but this medication is associated with a fourth-side-effect profile. Its use is often limited to refractory and metastatic disease. For patients with tachycardia, β-adrenergic antagonists should be added to control heart rate. However, β blockers are should be reserved until at least 2 days after the initiation of α blockade. β-Blockers should never be used in the absence of α-adrenergic antagonists because they would result in unopposed α-adrenergic catecholamine stimulation. The goal heart rate is 60 to 65 beats/min, and medications are titrated to symptoms. Chronically high catecholamine levels lead to vasoconstriction and an overall decrease in circulating blood volume. Three days after commencement of α blockade, a high-salt (3 g/day) diet is recommended to help restore circulating fluid volume. Normalization of circulating blood volume before surgery in PPGL patients reduces the hypotension associated with tumor removal.

Management of PPGL during pregnancy is particularly difficult and is associated with a 60% maternal mortality rate and up to a 50% fetal death rate. On diagnosis, α-adrenergic antagonists should be initiated immediately and elective third-trimester Cesarean section should be performed because vaginal delivery is contraindicated due to potentially catastrophic massive catecholaminic release. Combined adrenalectomy with Cesarean section versus early postpartum resection is generally preferred. Tumor removal should be avoided during the first trimester because of the high risk of miscarriage, but there is the possibility of adrenalectomy in the second trimester.

INTRAOPERATIVE MANAGEMENT

Preparation and excellent communication with the anesthesiologist are essential components of PPGL management during surgery. To augment volume restoration, 1 to 2 L of resuscitative fluids are given before surgery. Adequate IV access and arterial monitoring are required before administration of anesthesia. Multiple vasoactive medications should be prepared and available in anticipation of blood pressure lability. Alpha or calcium channel blockade should continue, although esmolol or sodium nitroprusside is used for intraoperative blood pressure swings. Ephinephrine and norepinephrine are drugs of choice for intraoperative hypotension. A particularly important communication point is at the ligation of the adrenal vein. The surgeon and anesthesiologist should communicate closely during this event to prepare for potential rapid and significant hypotension, which can be treated with vasopressors as needed.

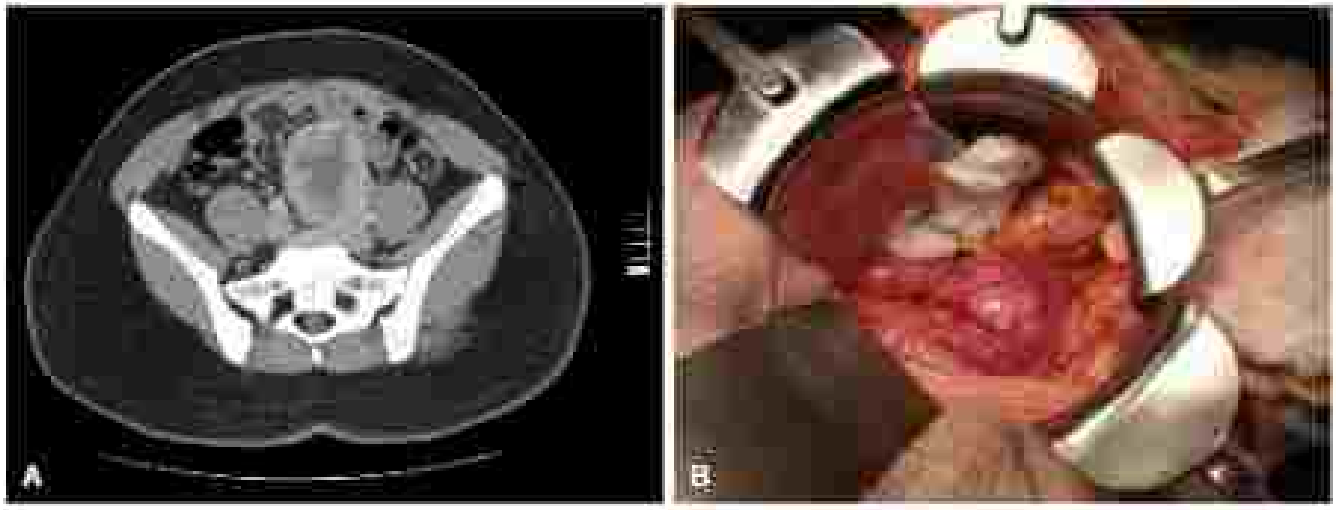


FIG. 1 (A) Paraganglioma in the aortic bifurcation, intravenous contrast-enhanced computed tomography shows heterogeneity and Hounsfield units greater than 10 with areas of necrosis. (B) Vessel anatomy of the IVC must be noted at the time of operation.

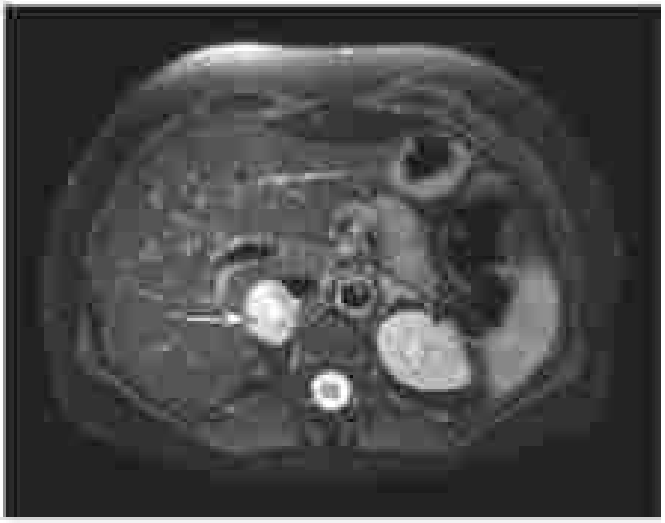


FIG. 2 Pheochromocytoma imaging of a right pheochromocytoma. 123-iodine imaging reveals a "right-hot" hypermetabolic appearance with heterogeneity.

TREATMENT AND SURGICAL APPROACH

Although medical management can be used to control symptoms, operative removal is the mainstay of treatment. Surgical resection for localized PPGL is the only curative treatment option, and operative debulking has a major role even in widely metastatic disease. Resection extent is based on disease locality, size, and potential for malignant or metastatic disease. Adrenalectomy is the standard resection for unilateral sporadic tumors localized to the adrenal gland. Subtotal adrenalectomy may have a role in sparing adrenal cortex for patients with bilateral pheochromocytomas and tumors associated with familial disease to avoid adrenal insufficiency and steroid dependence. When a cortex sparing procedure is planned, at least one third of a well-perfused cortex should be preserved. A multidisciplinary and multimodality therapeutic plan is required for malignant or metastatic disease.

Surgical removal of PPGL can be divided into transabdominal or retroperitoneal approaches. Within each category, laparoscopic, robotic, and open techniques may be used. Minimally invasive resection is the procedure of choice for most PPGLs and is feasible in the vast majority of patients. The minimally invasive approach results in decreased operative times, decreased blood loss, decreased need for blood transfusion, decreased analgesic requirements, shorter stays in the intensive care unit, shorter hospital stays, and faster return to work when compared with an open approach. Additionally, there are decreased surges in catecholamines during tumor manipulation with laparoscopic versus open adrenalectomy for pheochromocytoma. Open approaches are typically reserved for larger, locally advanced, malignant, or metastatic tumors, and intraoperative conversion from

TABLE 2 Preoperative Pharmacologic Management of PPGL

Nonselective α-adrenergic receptor antagonist	
Phenoxybenzamine	10 mg bid, increase by 10–20 mg every third day to goal
Selective α-adrenergic receptor antagonist	
Prazosin	1 mg, three times daily, increase to max 12 mg/day
Terazosin	2–10 mg/day
Doxazosin	1–16 mg/day
Calcium channel blocker	
Nifedipine	30–90 mg/day
Verapamil	180–540 mg/day
Nicardipine	60–120 mg/day
Amlodipine	10–20 mg/day
β-Adrenergic receptor antagonist[a]	
Atenolol	12.5–25 mg, 2–3 times daily
Metoprolol	25–50 mg, 2–4 times daily
Metoprolol XL	25–200 mg per day
Propranolol	20–80 mg, 1–3 times daily
Tyrosine hydroxylase inhibitor	
Metyrosine	250 mg, 4 times daily, increase 250–500 mg every third day to goal or maximum of 4 g/day

bid, two times daily; IVC, pheochromocytoma and paraganglioma.
[a]Labetalol and carvedilol are contraindicated due to ratio of α- to β-receptor antagonism.

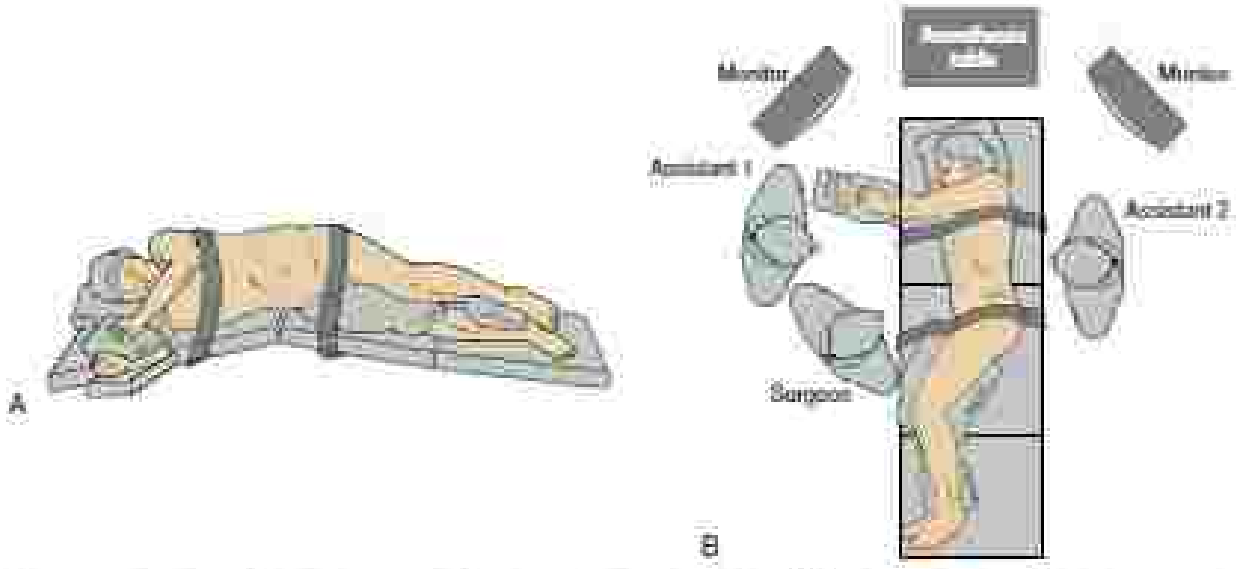


FIG. 3 Patient positioning for transabdominal laparoscopic adrenalectomy. (A) The patient is placed in lateral or mid-flank decubitus position with the table flexed to create a wide gap between the costal margin and the iliac crest. (B) Operative room setup and monitor placement.

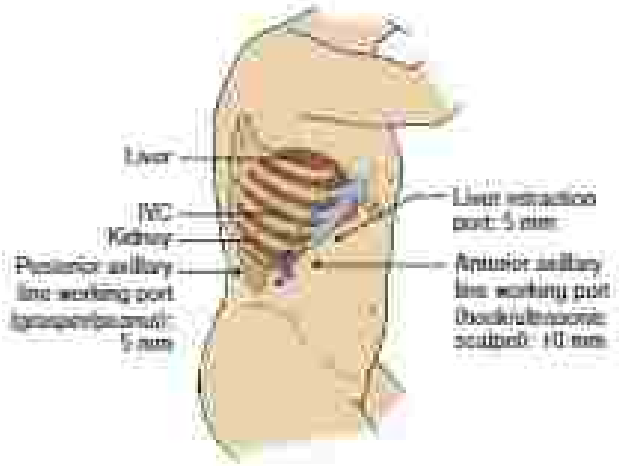


FIG. 4 Right transabdominal adrenalectomy (single-site laparoscopic approach): port placement.

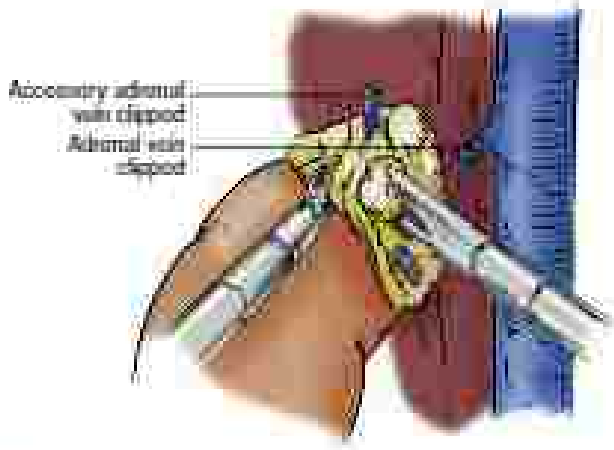


FIG. 5 (A) In a right-sided laparoscopic adrenalectomy, the liver is retracted to expose the gland. The lateral border of the inferior vena cava is dissected to encounter the short right adrenal vein. The accessory adrenal vein at the anterior border of the liver has the potential for significant bleeding.

a minimally invasive to open procedure may be required when malignancy or metastasis are suspected. Regardless of approach, complete tumor resection is a key component to outcomes of PPGL. The choice of operative approach ultimately depends on patient characteristics, anatomy and location of the tumor(s), sporadic versus hereditary nature of disease, and surgeon preference and comfort with each technique.

Transabdominal Laparoscopic Adrenalectomy

The transabdominal laparoscopic technique is the most commonly performed approach used for patients without obvious signs of malignancy or metastatic disease. Key technical maneuvers in any adrenalectomy for pheochromocytoma are minimal tumor manipulation and early control and division of the adrenal vein. The lateral decubitus position is used with the patient's hips rotated to expand the distance between the costal margin and the iliac crest (Fig. 3). After the peritoneal cavity is accessed, a 30-degree laparoscope is used. Port placement varies depending on the laterality of the tumor. A right adrenalectomy requires four trocars placed 2 cm inferior and parallel to the costal margin in the midclavicular line, and anterior axillary, mid-axillary, and posterior axillary lines (Fig. 4). Liver retraction is performed through the most medial port, then the lateral triangular ligament is divided to gain access to the right adrenal gland. The plane superior to the adrenal gland is dissected medially along the inferior border of the liver until the inferior vena cava (IVC) is encountered. During dissection of the lateral aspect of the IVC caudally from the liver, the short right adrenal vein will be identified draining directly into the IVC, where it is divided with clips or an energy device (Fig. 5). It is imperative to coordinate with the anesthesia team during this step. The arterial supply to the adrenal gland can be controlled with a vessel sealing device along its medial aspect, then the gland with the periadrenal fat can be circumferentially freed from surrounding tissue. Leaving the lateral attachments intact until near complete dissection facilitates exposure of the more important hilar structures. The position of the renal artery and vein must be

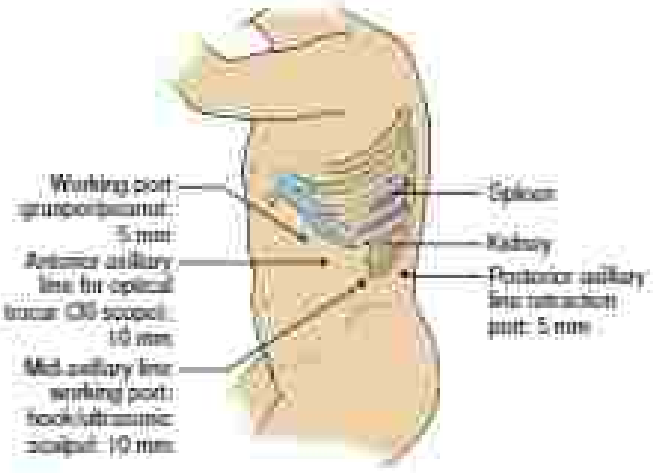


FIG. 6 Left [illegible] approach for adrenalectomy: [illegible]

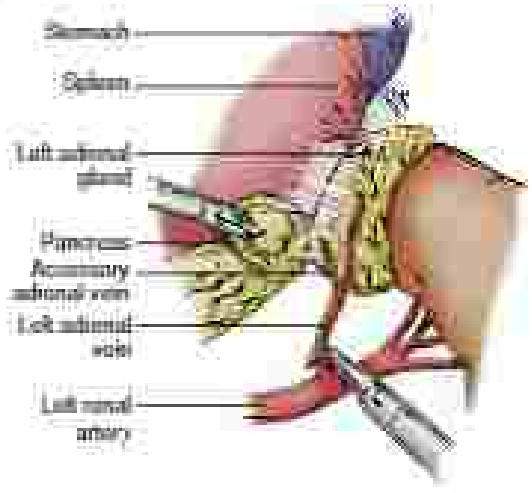


FIG. 7 [illegible] adrenalectomy. Right adrenal gland. After the gland has been [illegible] the adrenal vein is ligated and divided. The gland is then removed from the retroperitoneal space. The [illegible] adrenal vein.

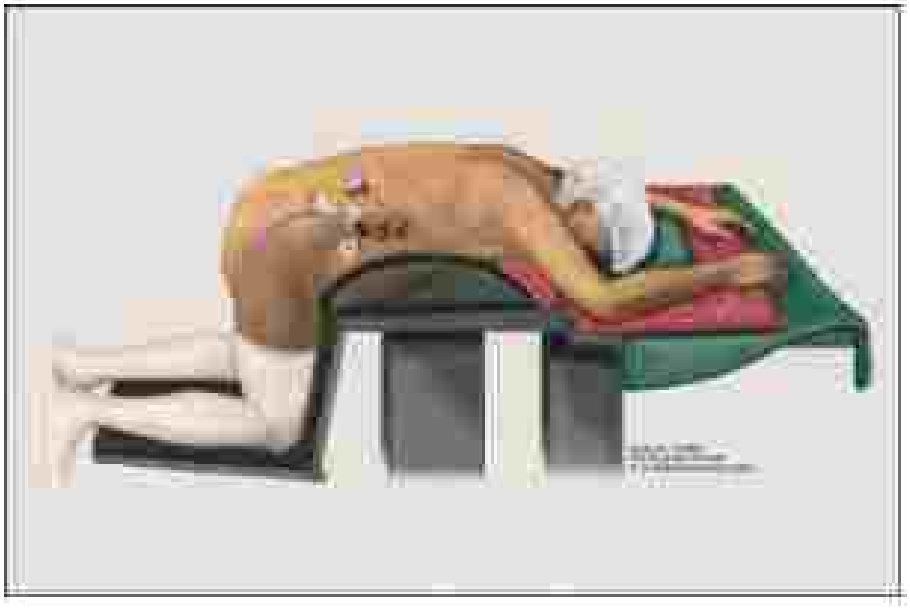


FIG. 8 Position and port sites for transperitoneal laparoscopic adrenalectomy. Previous patient with the patient in the prone adductor position. An inset highlights the abdomen in left, anteriorly, showing retroperitoneal pressure. Three ports are placed [illegible] on the middle axillary line, about at the tip of the twelfth rib. [illegible]

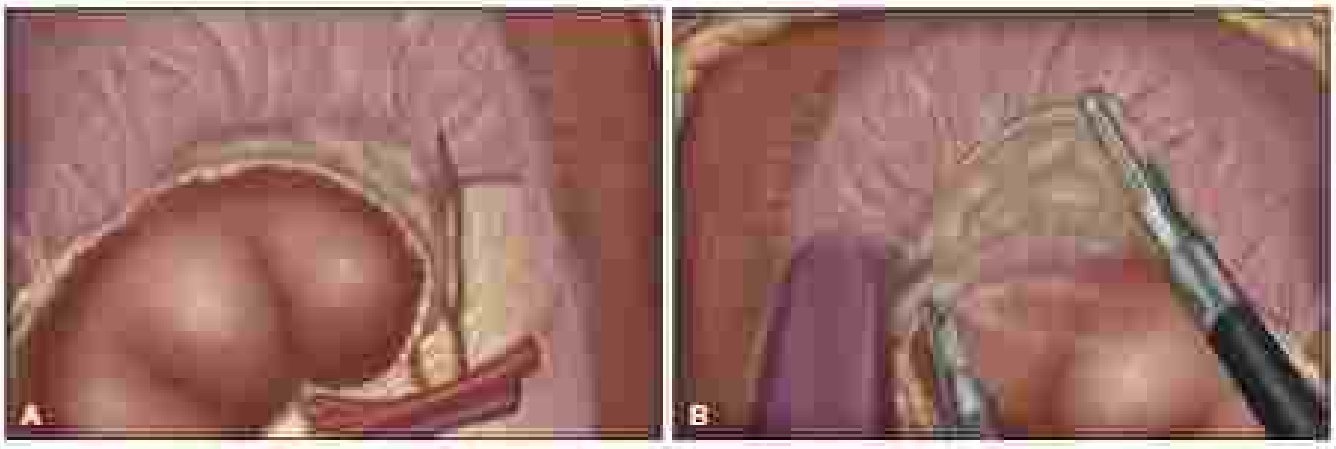


FIG. 9 *Local anatomy of retroperitoneoscopic adrenalectomy.* Posterior view of retroperitoneoscopic adrenalectomy. After the retroperitoneal dissection space is created, paraspinous muscles are swept medially and the peritoneum laterally prior to clearance of the superior pole of the kidney. The borders of the adrenal gland are appreciated, and the adrenal vein is divided before dissection of the gland from adjacent tissue. The left adrenal vein drains into the left renal vein (A), whereas the right adrenal vein drains into the IVC. (From Lobo DN, Scott-Coombes DM, Stanley MC, et al. Retroperitoneoscopic surgery with reference to laparoscopic surgery. Surg Endosc 2004;18:1412.)

placed inferiorly to the adrenal gland under direct vision so as not to injure the vena cava and artery. The adrenal vein is then identified and clipped with small vascular clips. The adrenal gland is then dissected free from the surrounding tissue, and the adrenal vein is divided between clips. Care must be taken to avoid injury to the adrenal vein, which can result in significant hemorrhage. Small accessory adrenal veins may be encountered and divided between clips. Because the adrenal gland is highly vascular, the adrenal vein should be divided before manipulation of the adrenal gland to avoid excessive release of catecholamines during surgery. After the adrenal vein is divided, the remainder of the adrenal gland is dissected free from the surrounding tissue. The retroperitoneum can be closed primarily, avoiding undue tension on the closure.

Open Approach

Open adrenalectomy procedures are used for large tumors, malignancies, or locally invasive tumors. The high recurrence rate after laparoscopic adrenalectomy for malignant tumors has led some surgeons to perform open adrenalectomy for malignant tumors. The adrenal gland is approached via a subcostal incision, a flank incision, or a thoracoabdominal incision. Open adrenalectomy is rarely performed for pheochromocytoma because of the risk of massive hemorrhage during manipulation of the tumor. Open adrenalectomy may be necessary for large tumors, tumors with local invasion, or tumors with vascular thrombus. Open adrenalectomy for pheochromocytoma should be performed with the same principles as laparoscopic adrenalectomy. Meticulous dissection of the adrenal vein before manipulation of the adrenal gland is essential. After the adrenal vein is ligated, the remainder of the adrenal gland is mobilized. Open adrenalectomy can be performed safely, avoiding undue release of catecholamines.

PERIOPERATIVE MANAGEMENT AND COMPLICATIONS

Morbidity and mortality rates for patients who are appropriately managed preoperatively and undergo elective laparoscopic surgery are low. In addition, patients are monitored in the intensive care unit for 24 hours and can be discharged on the second postoperative day. With adequate preoperative preparation, intraoperative pressure and resuscitation are rarely required for more than a few hours. Vital signs should be monitored frequently, and hemodynamic parameters and plasma levels should be monitored for 24 hours after operation. Most patients have an uneventful postoperative hospital course and are discharged on reduced dosages of antihypertensive drugs that can usually be withdrawn in most patients. Adrenal insufficiency is uncommon in patients who undergo unilateral adrenalectomy but should be expected in patients who undergo bilateral operations including cortical sparing techniques. Stress dose steroids with a rapid taper to oral corticosteroids may be implemented for patients at risk. Disease surveillance should commence for all patients who undergo surgical resection for PPGL, with perioperative serum or urinary metanephrine measurement approximately 2 to 6 weeks after removal to ensure biochemical cure. If preoperative metanephrines were normal, chromogranin A can be used as an alternative screening test for recurrence. When metanephrines remain elevated despite presumed surgical cure, imaging should be obtained 3 months after the operation. Follow-up is required for at least 10 years and should be lifelong if high risk for recurrence such as patients who are young, have a large or extraadrenal tumor, or have an associated genetic cause of the PPGL. Standard monitoring includes yearly screening for local or metastatic recurrence or new tumors with plasma or urinary metanephrines and imaging tests every 1 to 2 years.

RECURRENT, MALIGNANT, AND METASTATIC DISEASE

Up to 14% of PPGLs are malignant. Malignancy is more common in hereditary disease, paragangliomas, and tumors larger than 5 cm. There are no reliable histologic methods to differentiate benign and malignant in PPGLs. The diagnosis of malignancy in PPGL is based mainly on behavior and can be defined by the presence of metastatic disease. Additionally, there are multiple pathologic features and genetic tests that are used in an attempt to predict behavior. The Pheochromocytoma of the Adrenal gland Scaling System is one such scoring system that has been created to stratify patients using 12 features that include mitoses, necrosis, cellularity, and invasion.

A multidisciplinary approach should be taken to the treatment of recurrent, malignant, or metastatic PPGL. Functional imaging by PET/CT with novel radionuclides provides exceptional assessment of disease (Fig. 10). Complete surgical resection when possible is the optimal treatment modality and is associated with durable survival despite high accompanying recurrence rates. Metastatic options are rarely curative, with 5-year survival rates ranging from 40% to 60% depending on the site of metastasis. When an R0 or R1 resection is not feasible, tumor debulking may still be of benefit for symptom palliation and reduction of catecholamines. Combination systemic chemotherapy (cyclophosphamide, vincristine, dacarbazine),

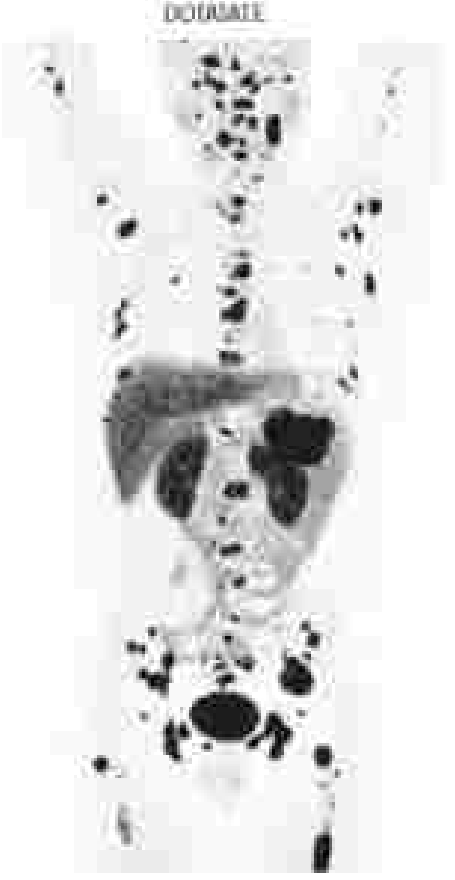


FIG. 10 Functional imaging of a patient with recurrent metastatic pheochromocytoma. ^{68}Ga dotatate positron emission tomography/computed tomography has superior accuracy for metastatic disease as pictured by the extensive number of lesions identified.

[illegible] MIBG, targeted therapeutics, radiotherapy, radiofrequency ablation, cryoablation, and arterial embolization are options in the treatment metastatic disease with a focus on symptom relief and reducing tumor burden.

SUMMARY

PPGLs are rare catecholamine secreting tumors that can occur throughout the body and frequently lack the classic triad of paroxysmal headaches, palpitations, and sweating. They are associated with an increasingly recognized number of genetic mutations and hereditary testing should be considered in this patient population. The most useful diagnostic testing includes plasma or 24 hour urinary metanephrines, whereas CT and MRI are the most commonly used diagnostic imaging modalities. Surgical removal is the mainstay of treatment and can be performed via minimally invasive techniques with excellent results. Therapy for hereditary and metastatic disease requires a multidisciplinary approach.

SUGGESTED [illegible]

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MANAGEMENT OF THYROID NODULES

Jonathon O. Russell, MD [illegible]

BACKGROUND

Thyroid nodules are highly prevalent in the United States and are found in more than 50% of adults in some studies. Whereas a majority are benign, 5% to 15% may be malignant. Arguably due primarily to the increased use of medical imaging, the diagnosis of thyroid nodules and thyroid cancer has grown rapidly in recent decades, contrastingly, death from thyroid cancer remains rare and has increased only slightly during that same period.

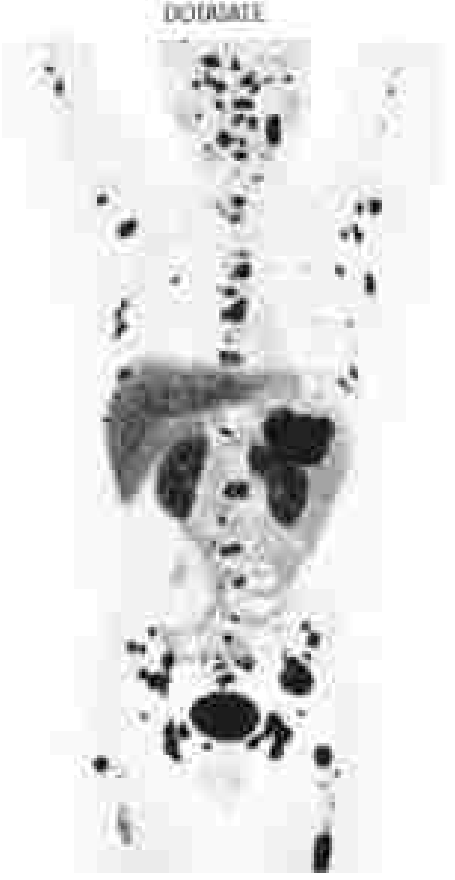
Because a majority of thyroid nodules will be benign and a majority of malignant tumors will demonstrate indolent behavior, surgeons and clinicians must have a thorough understanding of the most appropriate diagnostic and treatment techniques. Any intervention must add value to that individual patient while minimizing harm. To that end, recent advancements in both the diagnosis and treatment of thyroid nodules focus primarily on reducing overtreatment and minimizing morbidity.

DIAGNOSIS

When a thyroid nodule has been identified, regardless of the method of identification, the diagnostic algorithm is clear and begins with thyroid function testing. In general, thyroid stimulating hormone and T4 are sufficient and will lead to a diagnosis of a euthyroid, hypothyroid, or hyperthyroid state. The next step is imaging. Hyperthyroid patients will infrequently have cancer, and scintigraphy is generally the next step. "Hot" nodules (those demonstrating increased activity on scintigraphy) will so rarely be malignant that further invasive diagnostic testing is not generally indicated. Cold nodules in the setting of hypothyroidism may require ultrasound scanning to determine whether further investigation is appropriate. For euthyroid and hypothyroid patients, however, ultrasound scanning is the most appropriate next step.

ULTRASONOGRAPHY

Because ultrasonography is noninvasive and inexpensive, does not expose patients to ionizing radiation, best characterizes thyroid nodules for consideration of biopsy, and is readily available, it is the next step in the diagnostic algorithm of hypothyroid or euthyroid patients with thyroid nodules. Both the size and characteristics of the nodule are important to determine the risk of a clinically relevant malignancy. In general, nodules less than 1 cm do not require fine needle



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SUGGESTED READINGS

Sato K, Ignatiadis P, Krajewski K, et al. Pheochromocytoma and paraganglioma: imaging characteristics. Cancer Imaging. 2013;13:533–542.

Taïeb D, Kaliski A, Boedeker CC, Martucci V, et al. Current approaches and recent developments in the management of head and neck paragangliomas. Endocr Rev. 2014;35(5):795–819.

Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(5):1915–1942.

MANAGEMENT OF THYROID NODULES

Jonathon O. Russell, MD, and Ralph P. Tufano, MD, MBA

BACKGROUND

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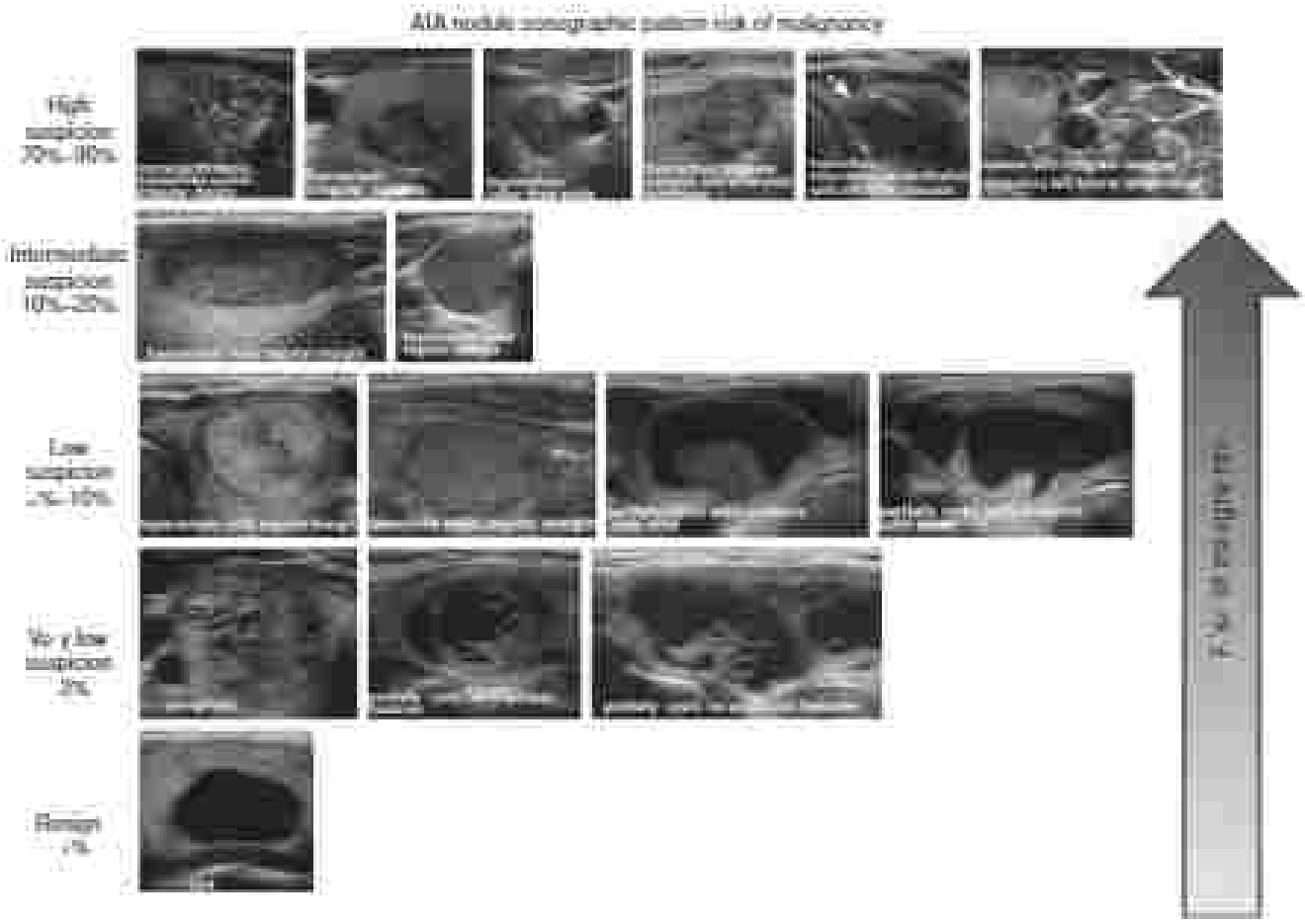

FIG. 1 Sonographic findings aid in risk stratification of thyroid nodules. [illegible]

aspiration (FNA), and only a repeat ultrasound should be scheduled in 6 to 24 months. For nodules more than 1 cm, however, certain high-risk features guide the necessity of more invasive diagnostic techniques (Fig. 1). Hypoechoic lesions, those with irregular borders, microcalcifications, and more are concerning signs of malignancy. Depending on a combination of such features, FNA may be warranted at size criteria between 1 to 2 cm. Both the American Thyroid Association and American College of Radiology have proposed classification systems that guide the timing of FNA in thyroid nodules.

FINE-NEEDLE ASPIRATION

For patients with nodules meeting criteria for biopsy, FNA is the next step in the diagnostic algorithm. The Bethesda Criteria represent a standard diagnostic criteria to be used by all cytopathologists in reporting FNA results. Table 1 demonstrates each of the six criteria, risks of malignancy, and recommended next steps.

MOLECULAR TESTING

As noted in Table 1, each FNA result is recognized as demonstrating only a probability of malignancy on final pathologic study. Historically, Bethesda III and IV lesions, due to their low but real risk of malignancy, were referred for diagnostic lobectomy. This led to a high rate of diagnostic surgery with benign final pathology. In the hopes of avoiding these unnecessary surgeries when otherwise clinically possible, patients and surgeons may opt to send additional FNA material for molecular testing. Such testing may increase or decrease the probability of malignancy, but each has limitations. Because of the expense and additional FNA passes required, it is our practice to limit molecular testing to those patients who are motivated to avoid surgery and do not have symptoms or other surgical indications. Because long-term follow-up will be required in this patient population, the explanation of these molecular tests and their limitations is a crucial responsibility for a modern thyroid surgeon.

NONINVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES

Since the release of the 2015 American Thyroid Association guidelines, an additional pathologic classification for some thyroid nodules has been created. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) represents a subset of thyroid nodules with almost no risk of metastatic spread, and it is therefore no longer considered a malignancy. The diagnosis requires a complete histopathologic review of the entire nodular capsule to ensure there is no invasion. This means that it is indistinguishable from other follicular lesions on FNA, and surgical intervention is therefore required to differentiate these lesions from well-differentiated thyroid cancers as of this writing. Because it is no longer considered malignant, some recent authors have demonstrated that the probabilities of malignancy noted in Table 1 are lower (because a subset of tumors previously defined as malignant are now considered benign). Some early reports suggest that this change in the classification of pathology has also affected the positive and negative predictive values of some of the molecular testing mentioned previously, because they were designed in an era where NIFTP was still considered a cancerous finding.

TABLE 1 2017 Bethesda System for Reporting Thyroid Cytopathology: Diagnostic Categories and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy if NIFTP Is CA	Risk of Malignancy if NIFTP Is Not CA	Clinical Management
Nondiagnostic or unsatisfactory	5–10	5–10	Repeat FNA with ultrasound guidance
Benign	0–3	0–3	Clinical and sonographic follow up
Atypia of undetermined significance or follicular lesion of undetermined significance	6–18	10–30	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm or suspicious for a follicular neoplasm	10–40	25–40	Molecular testing, lobectomy
Suspicious for malignancy	45–60	50–75	Near total thyroidectomy or lobectomy[b]
Malignant	94–96	97–99	Near total thyroidectomy or lobectomy[c]

Modified from Baloch ZW, Cooper DS, Randolph GW, et al. Overview of diagnostic terminology and reporting. In: Ali SZ, Cibas ES, editors. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. New York: Springer; 2018.

CA, carcinoma; FNA, fine needle aspiration; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

[a] Actual management may depend on other factors (e.g., clinical, sonographic) besides the FNA interpretation.

[b] Some of these have recommended molecular analysis to assist the type of surgical procedure (lobectomy vs. total thyroidectomy).

[c] In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

TREATMENT RATIONALE

Treatment recommendations have trended toward less intervention in recent years because thyroid nodules are ubiquitous, most cytologically indeterminate nodules will ultimately return as benign on surgery, and even the few cancers are unlikely to cause death. As mentioned previously, FNA of subcentimeter nodules is discouraged during the diagnostic stage. During the treatment stage, lobectomy is now encouraged as a potential treatment for differentiated thyroid cancers if one or less in the appropriate clinical scenario. Prophylactic central neck dissection is generally discouraged for early stage differentiated thyroid cancers, except in specific situations and in the hands of high volume thyroid surgeons.

This last point deserves further consideration: to help a patient with a nodule that is unlikely to cause harm, the morbidity must be very low. High volume surgeons (variably defined, but generally more than 20 thyroidectomies per year) have superior outcomes. Any surgeon should constantly consider his or her own volume, outcomes, and adverse events. Additionally, at least in cases of cancer, completeness of resection is an important prophylaxis against long term complications. Radioactive iodine and other adjuncts do not compensate for inadequate surgery. The equipoise between the morbidity of the treatment and the disease process are considered repeatedly in this chapter.

OBSERVATION TRIALS

Given the above, some patients who are poor surgical candidates may instead be best served with watchful waiting. Taking this one step further, and based mainly on the Japanese experience with observation of papillary microcarcinomas (defined as 1 cm or less, most institutions have begun to offer active surveillance for some indeterminate and suspicious for malignancy thyroid nodules that are small (usually <1 cm) and meet other careful inclusion criteria but who would otherwise be surgical candidates. In most of these studies with long term follow up, 10% to 20% will ultimately progress to require surgery, but delayed surgery appears to be successful in early trials with no risk for decreased disease control. Although it remains to be seen how safe and effective this approach will be in a Western population, it clearly underscores the point that most thyroid nodules, even small thyroid cancers have a generally indolent clinical course. At this time, observing indigent or indeterminate lesions should be done as part of a multidisciplinary evaluation process requiring extensive patient education and engagement. Tumors that are near the recurrent laryngeal nerve, have radiographic evidence of aggression, or have other concerning features are generally not candidates for this approach.

SURGERY

Surgery remains the mainstay of treatment for most patients with symptomatic, cytologically indeterminate, or malignant thyroid nodules. In addition to the general risks of any surgical intervention, hypoparathyroidism and permanent vocal fold injury remain the chief concerns of thyroid surgeons. As above, both complications are less common among high volume surgeons and when completing lobectomy rather than total thyroidectomy.

Before surgery, confirmation of normal vocal fold mobility provides information that may alter the surgical plan, and we advocate preoperative laryngeal examination. Most high volume thyroid surgeons will use a nerve monitoring device for all thyroid surgery. Arguments against this are primarily financial. On the other hand, the potential to modify surgery intraoperatively and thus avoid a disastrous bilateral vocal fold palsy is a primary motivator for those who use the device. Additionally, intraoperative feedback of nerve health allows near instant technical modification that may help some surgeons avoid temporary vocal fold weakness.

Additional technology that is commonly used in thyroid surgery includes vessel sealing technologies of various types. Although the specific device may not be important, provided the appropriate technique and settings are used, thermal energy devices have become the norm among high volume thyroid surgeons. They have been demonstrated to have an excellent safety profile while decreasing operative times in most series.

Beyond these technological advancements, the surgical technique has changed little for more than 100 years. A transverse cervical incision is designed in a skin fold above the sternal notch. Flaps are raised, the linea alba (midline raphe) is identified and divided, and the strap muscles can be separated. The soft tissue is elevated off of the gland itself, and the trachea below and the larynx above are identified. In cases of malignancy, it is important that surgeons remove any pyramidal lobe, which may extend as high as the hyoid. This can be done by grasping the pyramidal lobe with a pickup and performing a fine hand dissection with electrocautery beginning superiorly, such that an inferiorly based pyramidal lobe pedicle is created. This maneuver also facilitates identification of the cricoid and removal of the Delphian lymph node, which then ensures clear visualization of the cricothyroid space laterally. We mobilize this tissue bluntly with an elevator and thus identify and preserve the external branch of the superior laryngeal nerve while simultaneously isolating the superior pole vessels (Fig. 2). The superior pole is then followed inferiorly to a point above the expected insertion of the recurrent laryngeal nerve (RLN).

FIG. 2. The external branch of the superior laryngeal nerve should be preserved; identification and dissection may facilitate this preservation.

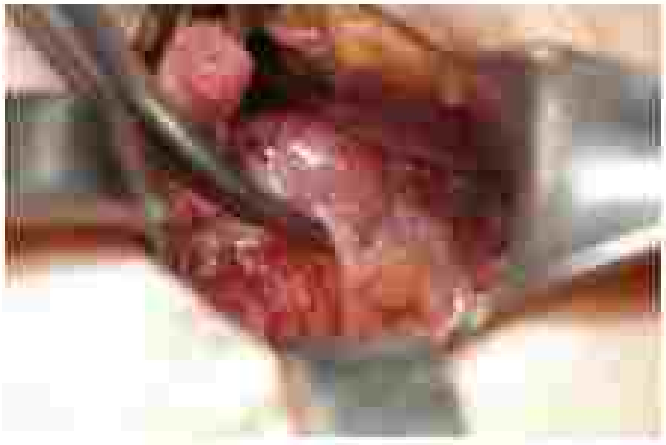

FIG. 3. Blood supply to the inferior parathyroid gland may often arise from a superior vector and can be inadvertently sacrificed if not anticipated.

Once this has been completed, the RLN proper is identified. This can be completed either at the insertion or more proximally and inferior to the gland. We believe it most appropriate to then dissect the nerve off of the thyroid and to the laryngeal insertion to remove the maximum amount of thyroid tissue. In the process of this dissection, parathyroid glands must be reflected off the thyroid if not completed previously. It is our experience that the blood supply to the inferior parathyroid may come from a superior vector and may thus be inadvertently sacrificed without appropriate caution (Fig. 3). Both parathyroid glands will generally draw their blood supply from the inferior thyroid artery.

Once the RLN and parathyroid glands have been reflected away from the thyroid, the thyroid may be cautiously removed from the trachea with any number of techniques. We prefer some combination of electrocautery, thermal cautery, vessel sealants, or bipolar energy delivery. Functionality of the RLN is confirmed throughout with the intermittent application of a stimulus via a monopolar probe. Whereas hemostatic agents such as fibrin glue may be placed after confirming hemostasis, we generally do not find a surgical drain to be necessary. Lobectomy patients are generally discharged the same day, whereas total thyroidectomy patients generally merit monitoring of postoperative calcium levels, which may necessitate overnight observation. It has been demonstrated that, in the appropriately selected patient, same day discharge may be safe for both groups.

REMOTE ACCESS APPROACHES

One of the primary concerns for some patients is the position of a cervical incision in the mid neck, often the neck of a young female patient. Although not all patients find this problematic, it is clear that at least some patients prefer other alternatives. Kocher himself first adjusted the position of his incision to improve cosmesis by using a transverse rather than a vertical incision. Beginning near the early 2000s, there was a concerted interest in improving cosmesis further. Incisions shrank and various sites for remote access were used, including the breast, axilla, and retroauricular positions. Surgical robotics were likewise used. Although all of these were found to be effective in Asian populations, they have not garnered broad acceptance in the Western Hemisphere.

More recently, however, we have demonstrated the safety and efficacy of the transoral endoscopic vestibular approach in a North American population. First demonstrated to be clinically effective by Anuwong, the technique is gaining popularity in rapid fashion because of the relatively small area of dissection required for the approach, bilateral access to the central necks, and a familiar vantage point. Briefly, the technique requires placement of 3 surgical ports via the lower oral vestibule (Fig. 4). Insufflation (CO_2) assists with flap elevation, and the case is then completed with standard laparoscopic instrumentation. With a safety profile and operative times similar to that of the traditional approach, we have found this technique to be ideal for selected patients without advanced thyroid cancer who are motivated to avoid a cervical incision (Fig. 5).

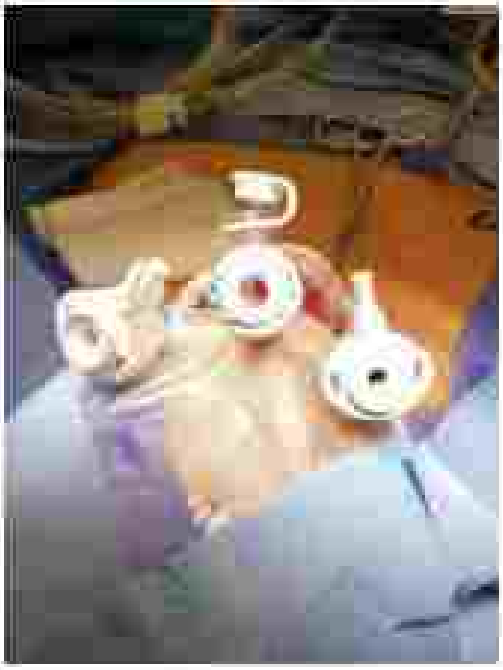

FIG. 4. Port placement during the transoral endoscopic vestibular approach to the thyroid.

FUTURE DIRECTIONS

Molecular testing has already decreased the need for diagnostic surgery in patients with behavior indeterminate nodules. Future efforts will become even more effective and may add prognostic information as well. This will ensure that only patients who will benefit from treatment receive treatment.

Additional approaches to treat thyroid nodules may also decrease the need for surgery. Image guided ablation techniques (such as radiofrequency ablation or ethanol injection) effectively reduce nodule size and symptoms in benign goiter. Others in the Far East are already using these approaches to manage small cancers primarily. Although such approaches remain to be validated in a Western population, the indolent behavior of these tumors and the ability to successfully manage these cancers in a delayed fashion make such techniques theoretically appealing. Furthermore and in the future, such approaches may appeal to patients who do not feel comfortable with watchful waiting for small thyroid cancers.

FIG 3 (A) Preoperative and (B) 1 week postoperative appearance of a male after removal of a 4-cm benign thyroid goiter.

CONCLUSION

Thyroid nodules and differentiated thyroid cancer are extremely common but rarely cause death. A simple diagnostic algorithm with thyroid function testing followed by ultrasound scanning and FNA is appropriate in most situations. Treatment should add personal value by minimizing morbidity and improving long-term outcomes. Novel technologies, approaches, and techniques all promise to redefine our approach to thyroid nodules in the immediate future.

SUGGESTED READINGS

Angelos A, Schwarz K, Bjorndahl P, et al. Safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach. JAMA Surg. 2017;152(1):23–27.

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NONTOXIC GOITER

Matthew A. Nobis, MD, and Gerard M. Doherty, MD

Goiter is a nonspecific term referring to any enlargement of the thyroid gland. However, in common use, it mainly denotes benign causes of thyroid enlargement, such as toxic multinodular goiter, diffuse toxic goiter (Graves disease), or nontoxic multinodular goiter. Although malignant enlargement of the thyroid gland can technically be considered a goiter, it is usually referred to as a mass or nodule.

Nontoxic goiter is a benign condition even though some specimens may contain small incidental cancers (up to 20% contain microcarcinomas). The predominant process and the decision making are based on the benign enlargement and resulting symptoms (e.g., dysphagia, dyspnea, or neck pressure). In some areas of the world, nontoxic goiters are endemic because of iodine deficiency, although public health efforts have reduced this somewhat.

PATHOGENESIS

A nontoxic multinodular goiter is defined as an enlargement of the thyroid gland containing follicles that are morphologically and functionally altered. The pathogenesis is multifactorial and can include iodine deficiency, goitrogens such as bamboo shoots, maize, and sweet potatoes, growth factors, and dyshormonogenesis. A family history of nontoxic goiter could implicate the environment, diet, or dyshormonogenesis as causes. Aside from severe iodine deficiency, the cause in an individual is typically not evident, nor does it often influence management.

CLINICAL FEATURES

Nontoxic goiters may remain asymptomatic, or they may give rise to compressive features such as dyspnea, dysphagia, or venous congestion/discomfort with certain movements. A change in the voice can occur from direct pressure on the larynx, or from stretching of the laryngeal nerves. Direct effects on the nerve causing paresis of the ipsilateral vocal fold are uncommon from benign goiter because nerve paresis is much more commonly associated with malignant infiltration of the nerve. Sudden changes in the goiter, as from hemorrhage into a nodule, can cause transient, intermittent, or permanent hoarseness. Thyroidectomy can often assuage voice changes due to direct pressure on the larynx, but the benefits for overt uncommon changes due to effects on the nerve are less consistent.

On physical examination, the size of the gland, the features of diffuse enlargement or nodularity, tracheal deviation, extension of the gland below the sternum or clavicular heads, or high up into the neck near the angle of the mandible are all important for treatment planning. Many large goiters are not palpable by physical examination, particularly if they have a predominant substernal or posterior component (Fig. 1). Associated lymphadenopathy should raise suspicion of malignancy.

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SUGGESTED READINGS

Amawong A, Amawong K, Bhimakorn P, et al. Safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach. JAMA Surg 2017;152(1):23–27.

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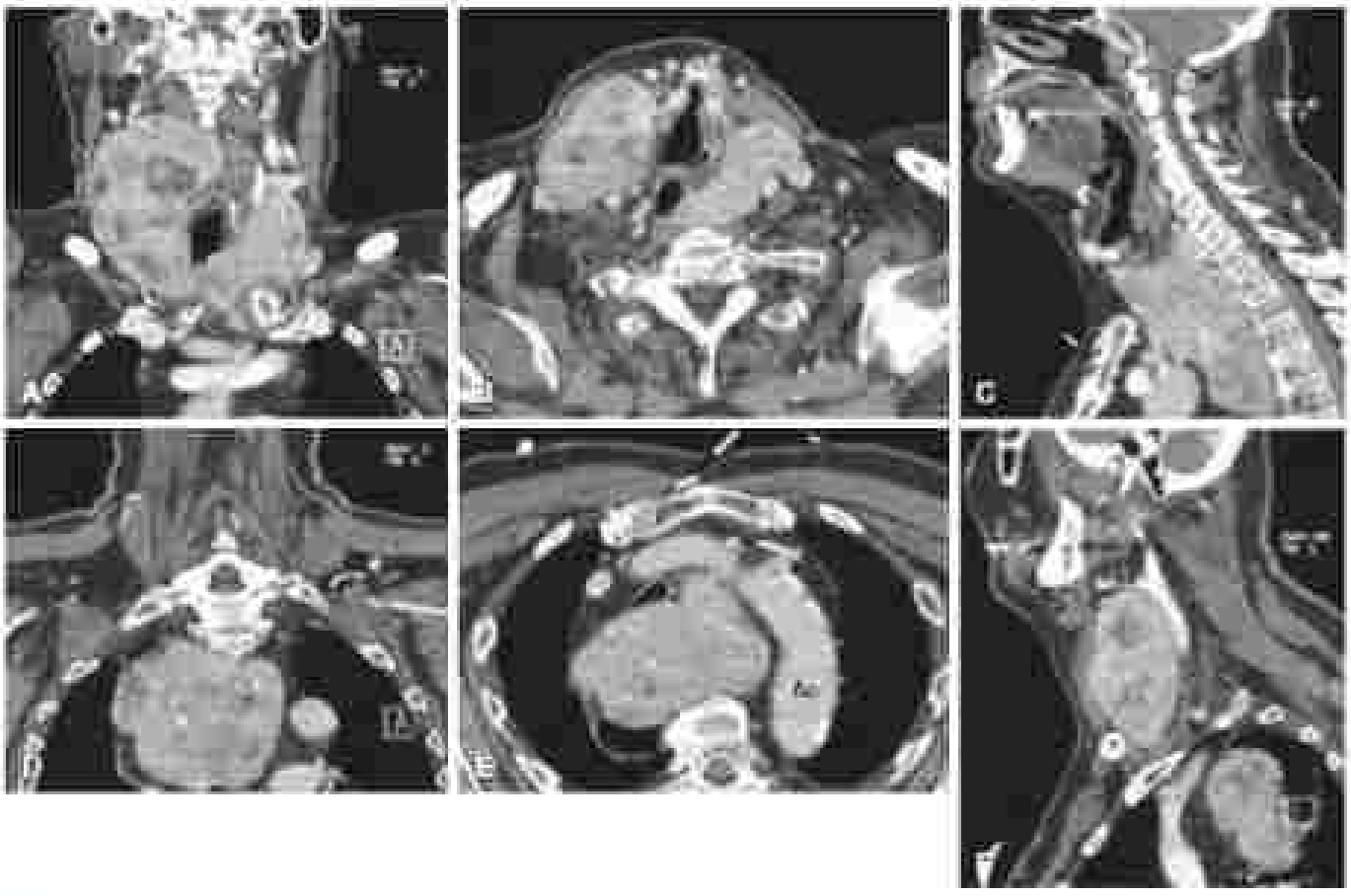

FIG. 1 An 82-year-old man with a palpable right thyroid mass. The patient presented with a large palpable right neck mass. Cross-sectional imaging revealed a heterogeneous infiltrating multinodular goiter (A–B) with a thalassemia left thyroid lobe (C–D). Note that the retrosternal component is below the arch of the aorta (*), and has grown along the prevertebral fascia (C). The right upper pole has displaced the course of the right common carotid artery (*). This patient required thoracotomy to deliver the mediastinal component of the gland safely.

EVALUATION

Thyroid-stimulating hormone (TSH), free T_4, and T_3 levels should be assessed to identify subclinical or overt thyrotoxicosis, hypothyroidism, or a euthyroid state. Fine needle aspiration should be performed with ultrasound guidance for any suspicious thyroid nodule. Ultrasound features that raise the risk of malignancy include hypoechogenicity, microcalcifications, hypervascularity, and solid components of complex (cystic and solid) nodules, as well as regional lymphadenopathy.

Plain chest films can demonstrate tracheal deviation, mediastinal and intrathoracic extension, airway compression, and gross calcifications. However, cross-sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MR) is more informative for these findings. In particular, evaluating the extent of airway compression, the precise geometry of goiter position in the chest, and any associated lymphadenopathy that might indicate a clinically significant malignant component, is much more effective with CT or MR.

Radioiodine scans, pulmonary function tests, flow volume loops and barium swallow studies may each be useful in specific situations but are not typically necessary in the era of accurate cross-sectional imaging.

Preoperative assessment of vocal fold movement should be considered for each patient. Deliberate voice assessment is mandatory, and fiberoptic laryngoscopy should be considered for patients with any voice alteration or any prior neck or chest operation that places the vagus or recurrent laryngeal nerves at risk. We find that it is useful to assess for respiratory stridor, which can be associated with severe narrowing of the tracheal lumen (Fig. 2).

INDICATIONS FOR TREATMENT

Nontoxic goiter that causes local discomfort, such as tightness, or a choking sensation especially with certain movements, or that has caused mechanical partial obstruction of the upper aerodigestive tract should be considered for treatment. Substernal extension of the goiter into the chest, even in the absence of symptoms, should be considered a relative indication for treatment, as further enlargement of this intrathoracic component can lead to the need for a more disruptive operation to resect it in the future. Cosmetic issues rarely are isolated concerns or indications for therapy, as most patients with goiter of sufficient size to be bothersome are also associated with other symptoms.

TREATMENT MODALITIES

TSH suppression therapy with thyroxine has little role in the management of an established goiter. Prospective trials have failed to demonstrate a benefit for management of multinodular goiter. The side effects of TSH suppression, including bone density loss and atrial arrhythmias, negate the theoretical value, particularly in the elderly patients for whom nonoperative therapy might be most attractive.

Radioactive ablamentation can cause goiter size reduction of 40% to 60% within 2 years, decreasing compressive symptoms. Complications include radiation thyroiditis and hypothyroidism, as well

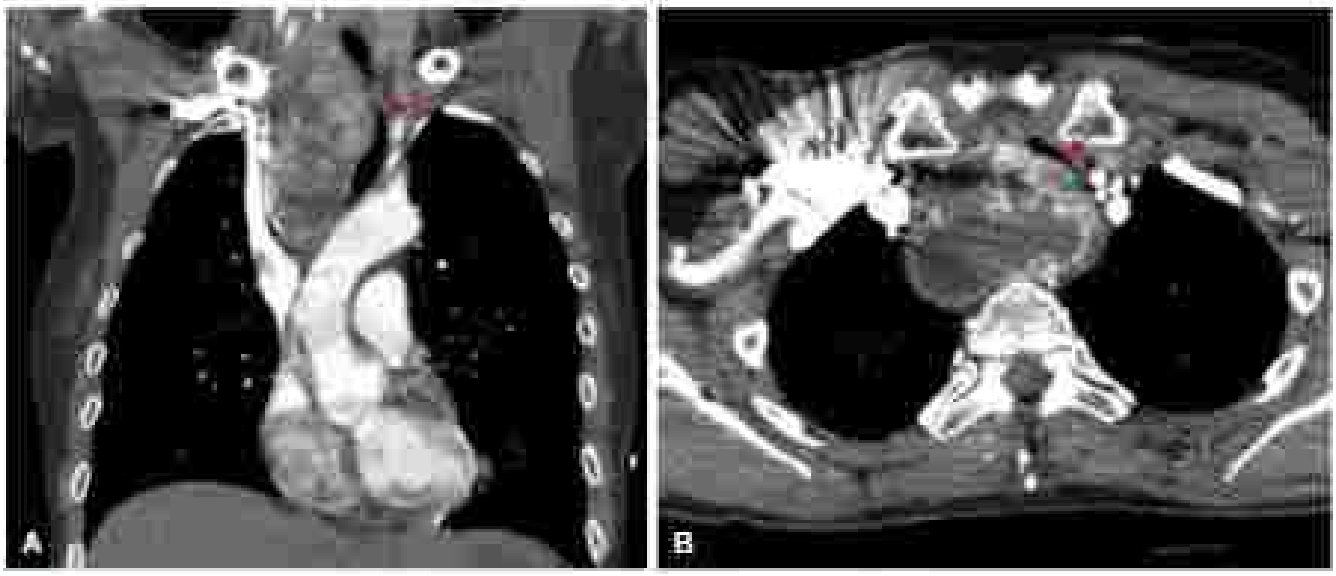

FIG. 2. A 68-year-old woman with an incidental goiter found during workup for dyspnea. On physical examination, the patient had an obvious, at a palpable thyroid mass, but she had little respiratory symptom. A, computed tomography scan revealed a large, right-sided substernal thyroid with tracheal deviation to the left (A), as well as severe narrowing at the lumen of the tracheal (B).

as a temporary enlargement of the gland, which may be important in some clinical situations. Recent experience with the use of exogenous TSH administration to increase the efficiency of radioiodine administration to patients with limited iodine uptake shows some improvement over radioiodine alone. These approaches may be useful for patients who have comorbidities that affect the safety of operative management, but these same comorbidities must be considered if the patient becomes temporarily hyperthyroid from treatment or as the time course of correction of the local pressure symptoms of the goiter is extended.

Surgical management is the mainstay of treatment for symptomatic, nontoxic goiter and is generally well tolerated, even in patients with limited physiologic reserve. The operation should typically be a bilateral procedure, removing all, or nearly all, of both thyroid lobes, in addition to any substernal extension. The operation is nearly always limited to a cervical incision, with median sternotomy or posterolateral thoracotomy being necessary only very rarely in previously unoperated patients. In experienced centers, complication rates are low (<2%) with techniques that include careful hemostasis and liberal parathyroid autotransplantation. For patients with significant airway compression or deviation, securing the airway can be the most critical part of the operation and may require conscious fiberoptic intubation under topical anesthesia to begin the procedure.

The thyroid gland should be exposed by a sufficient incision, although many thyroid operations can be done through very limited incisions, the geometry of the large multinodular goiter often requires long incisions to expose and remove the gland safely. Suprasternal flaps improve the exposure of the limits of the gland, especially superiorly for glands with upper poles that extend high in the neck. The strap muscles can be separated in the midline, or divided, near the upper pole, as necessary to expose the thyroid gland. In almost all cases, division of the sternothyroid muscle at the thyroid cartilage is sufficient for this exposure, but the sternohyoid can be divided as well if necessary. The larger the cervical portion of the gland, especially the upper poles, the more likely it is that transverse division of the sternothyroid and sternohyoid muscles will be helpful.

We find it helpful to divide the isthmus early in the case, as this provides a useful anterior landmark, particularly in cases where tracheal deviation distorts the typical course of the trachea and larynx. We then begin the dissection on the side of the larger lobe if the goiter is asymmetric. This ensures that the patient will have the most benefit in case the procedure has to be confined to a unilateral procedure (e.g., intraoperative recurrent laryngeal nerve [RLN] injury).

The upper pole of the gland is isolated by first separating the lateral aspect of the upper portion of the thyroid gland from the carotid sheath. If recurrent nerve monitoring is used, then the sheath is opened and the vagus nerve stimulated to establish baseline electromyography (EMG) function. The plane between the larynx and the upper pole of the thyroid gland is then opened, exposing the superior thyroid artery. The external branch of the superior laryngeal nerve (EBSLN) can be identified during some operations by direct inspection or by nerve monitor stimulation, keeping in mind that many EBSLNs run in an intramuscular course. Positive confirmation of the nerve can be determined by seeing a symmetric wave in both the anterior and posterior segments of the ipsilateral cricothyroid muscle in response to nerve stimulation. However, in any case, the delicate fascia over the cricothyroid muscle should be kept intact because the nerve is deep to this. Because the plane is followed superiorly, the EBSLN should stay medial and superior to the upper pole of the thyroid and its vessels. The upper pole vessels can then be divided safely using any number of hemostatic strategies, including ligatures, clips, and powered dissection tools. The branches of the superior thyroid artery should be individually controlled immediately adjacent to the thyroid parenchyma to minimize the risk to the EBSLN.

Once the upper pole is fully mobilized, the thyroid is partially rotated anteriorly and medially to continue dissecting the lateral portion of the thyroid gland. The middle thyroid vein, if present, is divided, and the thyroid separated from the carotid sheath along its entire extent. The dissection can then be carried posteriorly into the paratracheal space. The ability to rotate the thyroid gland may be limited by a large substernal component. The decision of whether to proceed with the dissection of the tracheoesophageal groove, recurrent laryngeal nerve and parathyroid glands first preferred, or whether to dissect the substernal portion of the goiter in order to create the necessary mobility, is dictated by the geometry of the particular patient and goiter. A large substernal component with a narrow thoracic inlet can create severe compression of the goiter and significant hemorrhage from the capsular veins of the gland. Delivery of the substernal component (either transcervically or by sternotomy) will often relieve this compression and allow a more hemostatic dissection.

The tracheoesophageal groove is dissected to identify the RLN. We try to identify the RLN as low in the neck as possible, because

this is the area where the nerve is least tethered to surrounding structures, and least likely to be stretched during dissection and identification. The nerve is identified by its appearance, anatomic course, and by stimulation if nerve monitoring is used; however, stimulation alone is not sufficient to identify the RLN. In particular, the absence of an EMG signal does not prove that a stimulated structure is not the RLN. Although intraoperative nerve monitoring is used by many experienced thyroid surgeons as an intraoperative adjunct, large trials have failed to show a benefit to patients as measured by RLN injury rates. The use of intraoperative nerve monitoring is a reasonable adjunct at the discretion of the surgeon but is not a standard of care.

Once the recurrent nerve is identified, it can be separated from the posterior aspect of the thyroid gland, and the intrathoracic portion can be safely delivered into the wound. The arterial supply to the thyroid gutter comes entirely from branches in the neck; there is no intrathoracic arterial supply to be concerned with (with the exception of the rare thyroid ima, which can arise from the innominate artery or the aorta). The main risk, then, is traction on the RLN as the substernal or paraesophageal intrathoracic portion of the goiter is delivered into the cervical wound by blunt dissection and gentle traction.

An important note of caution: in posteriorly displaced goiters with a component that extends inferiorly along the esophagus, especially on the right, the RLN may pass anterior to some portion of the goiter and may appear to be buried within the thyroid parenchyma because it has been trapped between nodules. This configuration makes the RLN especially vulnerable to stretch injury if this possibility is not recognized and anticipated early in the dissection.

Once the nerve is identified and the inferior portion of the thyroid gland mobilized, the RLN is traced up to its insertion into the larynx under the inferior border of the cricopharyngeus muscle. The small branches of the inferior thyroid artery are divided along the parenchymal surface of the gland, with the RLN always in view and protected. The parathyroid glands typically become evident during this portion of the dissection. Their blood supply from the inferior thyroid artery should be preserved if possible. If not, then the glands should be removed and grafted into the sternocleidomastoid muscle. As the dissection approaches the insertion of the RLN into the larynx, the RLN becomes progressively more fixed by surrounding tissues, including branches of the inferior thyroid artery, the fascial attachments of the thyroid gland to the trachea, and the insertion itself. Great care is necessary to dissect the thyroid gland safely away from the RLN without directly injuring or stretching the RLN. Once the RLN is fully separated from the thyroid gland, then the final attachments of the thyroid gland to the trachea can be divided. If intraoperative nerve monitoring was used, then the EMG signal with vagus nerve stimulation should be assessed at the completion of the dissection.

The process is then repeated on the opposite side. If there has been difficulty with the dissection on the initial side, then the contralateral procedure may be modified to reduce the risk of complications. For example, if the RLN lost function as documented by intraoperative nerve monitoring, then the contralateral RLN dissection may be modified to leave the RLN segment near the laryngeal insertion undisturbed by leaving a portion of the thyroid lobe in place in that position.

Devitalized parathyroid tissue should be cut into small (1–2 mm) pieces and grafted into small pockets in the sternocleidomastoid muscle. It is best to close each pocket with a suture to hold the graft in place while it develops a blood supply over the ensuing 6–12 weeks. It is not necessary to attempt to mark the site with permanent sutures or clips as subsequent exploration to remove these remnants is extremely rare, and best guided by ultrasound if necessary.

Meticulous hemostasis is important, because bleeding in the confined space of the neck can compress the airway. The strap muscles are reapproximated in some fashion, depending on how they were opened or divided, but the closure should not be occlusive. We routinely leave a large gap at the inferior aspect of the strap muscles to allow decompression if a postoperative hematoma should occur. The platysma muscle is reapproximated to align the skin edges and remove tension from the wound. The skin is closed according to the preference of the surgeon; one popular preference is to approximate the skin edges with a running 3-0 polypropylene pullout subcuticular suture, followed by skin glue. The suture is removed after the glue is dry (about 2 minutes). This provides a cosmetic closure that requires no further attention until after the glue peels away at about postoperative day 14.

POSTOPERATIVE CARE

In our practice, patients remain hospitalized overnight after removal of a nontoxic goiter to manage their limited pain and to monitor them for neck hematoma or hypocalcemia. All patients are managed with oral calcium supplement: Calcium citrate 950 mg by mouth four times daily) and escalcitol 0.25 μg by mouth daily beginning immediately after the operation. If they are symptomatic with numbness or tingling or if their calcium on the morning after surgery is below 8 mg/dL, then the dose is doubled. If their symptoms persist, either before or after discharge, or if there is special concern about the immediate parathyroid function, for example if two or more parathyroid glands were grafted, then we will consider keeping the patient for further observation or facilitating calcium laboratory draws within a few days of discharge.

Postoperative voice assessment is mandatory in all patients. Most patients have some immediate voice changes, but these nearly all resolve within 2 weeks of operation. Laryngoscopy to document vocal cord motion should be performed for all patients with significant voice changes that persist beyond 2 weeks, and for all patients who have a change in their intraoperative nerve monitoring findings during the procedure, if that adjunct has been used. Although some have advocated for more broad use of laryngoscopy before and after surgery, there is no evidence that this changes patient outcomes, and we most experienced surgeons focus this effort in a more selective way.

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MANAGEMENT OF THYROIDITIS

Mustapha El Lakis, MD, Douglas Wiseman, MD, and Elac von Kobadow, MD

Thyroiditis is an inflammatory process of the thyroid gland that may manifest with or without goiter formation and with gradual loss of thyroid function and episodes of hyperthyroidism. It includes a diverse group of disorders that can be clinically categorized as painful or painless thyroiditis (Table 1). Thyroiditis is most commonly asymptomatic but may be associated with a wide range of symptoms related to mass effect, hypothyroidism, or hyperthyroidism (Box 1). The inflammatory processes that cause acute illness with severe pain are (1) subacute thyroiditis, (2) acute suppurative thyroiditis, (3) radiation-induced thyroiditis, and (4) trauma-induced thyroiditis. On the other hand, thyroiditis in which there is usually no pain or tenderness includes (1) Hashimoto's thyroiditis, (2) postpartum thyroiditis, (3) drug-induced thyroiditis, and (4) Riedel's thyroiditis. Medical therapy remains the mainstay of the management of thyroiditis, but surgical treatment is warranted in certain circumstances (Table 2).

PAINLESS THYROIDITIS

Hashimoto's Thyroiditis

Hashimoto's thyroiditis, or chronic autoimmune thyroiditis, is the most common type of thyroiditis and cause of hypothyroidism in iodine sufficient areas of the world. The condition is named from a 1912 pathology report by Hakaru Hashimoto, who described four female patients with goiter and intense lymphocytic infiltration of the thyroid by stroma lymphomatosa. The prevalence of Hashimoto's thyroiditis varies depending on the criteria used for diagnosis. Autopsy studies demonstrate that 40% to 45% of women and 20% of men in the United States and the United Kingdom have focal thyroiditis.

Hashimoto's thyroiditis results from autoimmune-mediated destruction of the thyroid gland, which can manifest with different phenotypes, including hypothyroidism, however, many patients can have normal thyroid function. It can present with or without a goiter or, sometimes, with atrophic autoimmune thyroiditis. The cause of Hashimoto's disease is poorly understood, although a combination of environmental and genetic factors has been attributed to its development. The amount of iodine intake parallels the prevalence of Hashimoto's thyroiditis. Similarly, drugs containing high amounts of iodine, such as amiodarone, often precipitate autoimmune thyroiditis, although a variety of mechanisms has been suggested. In recent years, genetic susceptibility has been established for this disorder based on several observations: it clusters in families, the concordance rate in monozygotic twins is 30% to 40%, it is more common in patients with Down syndrome and Turner syndrome, and it has an association with human leukocyte antigen allele DR3.

Hashimoto's thyroiditis, like other autoimmune disorders, is more common in women (a male to female ratio of 1:7) between the ages of 30 and 50 years. Most patients are symptom free and present with a relatively small and firm granular thyroid. Some patients present with an enlarging diffuse goiter that causes compressive symptoms such as fullness, neck pressure, dysphagia, dyspnea, hoarseness, cough, or a choking sensation. Hypothyroidism is the characteristic functional abnormality; however, the inflammatory process that occurs early in the course may cause thyroid follicular disruption and thyroid hormone release, leading to transient hyperthyroidism referred to as Hashitoxicosis. Ophthalmopathy may occur rarely in patients with Hashimoto's thyroiditis. Furthermore, thyroid lymphoma has been associated with Hashimoto's thyroiditis, with up to 80% of patients with thyroid lymphoma having Hashimoto's thyroiditis. Most thyroid lymphomas are of the non-Hodgkin B cell type and tend to occur in older female patients.

On physical examination, patients with Hashimoto's thyroiditis have a nontender, diffusely firm, or lumpy thyroid gland. Associated thyroid nodules are usually benign Hürthle cell nodules. When Hashimoto's thyroiditis is suspected clinically, thyroid ultrasound scanning is indicated. Ultrasound features can vary depending on the severity and the phase of disease. The classical finding is a diffusely enlarged gland with heterogeneous echotexture (Fig. 1). The biochemical workup should include measurement of antimicrosomal antibody, antithyroglobulin antibody titers, thyroid peroxidase antibodies, and serum thyroid stimulating hormone (TSH) levels. Almost all patients have elevated antimicrosomal antibodies (>90%) and less often, antithyroglobulin antibodies (20% to 30%) and TSH receptor blocking antibodies (10%). All thyroid nodules should be evaluated according to their ultrasound features (see the chapter on management of thyroid nodules). Enlarged lymph nodes may be present, but they are usually benign and reactive. A rapidly enlarging goiter should raise suspicion of lymphoma and warrants a fine-needle aspiration (FNA) biopsy with flow cytometry analysis.

In patients with hypothyroidism, treatment consists of thyroid hormone replacement—which may result in a decrease in goiter size—with a goal of normal TSH levels. The management of patients with subclinical hypothyroidism (normal T_4 and elevated TSH) is controversial. All patients are followed up long term for the potential development of hypothyroidism, thyroid enlargement, compressive symptoms, or lymphoma. Surgery is indicated in patients with a dominant nodule that is or may be malignant, goiters causing compressive symptoms, or cosmetic concerns. Thyroidectomy for thyroiditis may be challenging because of the obliteration of tissue planes from inflammation/fibrosis, and a stiff thyroid gland may result in excessive traction on the recurrent laryngeal nerves when mobilizing the gland. Some series for thyroidectomy in patients with Hashimoto's thyroiditis have higher complication rates than thyroidectomy for differentiated thyroid carcinoma.

Histologically, the thyroid gland can be atrophic, or it can be diffusely enlarged (25–250 g) with an intact capsule and a potentially observable prominent pyramidal lobe. Grossly, the cut surface shows a pale, grayish tan nodular gland, and histologic examination reveals an extensive lymphocytic infiltrate with germinal center formation (Fig. 2). Thyroid follicles are smaller than normal and contain reduced amounts of colloid. The follicles are lined by Hürthle or Askanazy cells, which are characterized by abundant eosinophilic and granular cytoplasm. In addition, fibrosis may be increased but does not extend beyond the capsule.

Postpartum Thyroiditis

Postpartum thyroiditis is considered a variant of Hashimoto's thyroiditis; it is a destructive thyroiditis induced by an autoimmune mechanism within 1 year of parturition. Postpartum thyroiditis can also occur after spontaneous or induced abortion. It usually presents in one of three ways: transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by hypothyroidism and recovery. Its prevalence ranges from 1% to 17%, and its incidence is increased in women with type 1 diabetes mellitus, women with a prior history of postpartum thyroiditis, and women with positive antithyroid peroxidase antibodies. Postpartum thyroiditis is self-limited, and most women recover within 1 year postpartum; however, it increases the risk for development of permanent hypothyroidism within 5 to 12 years in up to 45% of patients.

TABLE 1 Types of Thyroiditis

Disorder	Cause
PAINLESS THYROIDITIS	
Hashimoto's thyroiditis	Autoimmune thyroiditis
Postpartum thyroiditis	Postpartum exacerbation
Riedel's thyroiditis	Fibrous thyroiditis
Drug-induced thyroiditis	Amiodarone, tyrosine kinase inhibitors, interferon α, checkpoint inhibitor immunotherapy, lithium
PAINFUL THYROIDITIS	
Subacute thyroiditis	Viral infection
Acute suppurative thyroiditis	Bacterial infection (*Staphylococcus aureus*, *Streptococcus pyogenes*)
Radioiodine-induced thyroiditis	Iodine-131 treatment
Trauma-induced thyroiditis	Vigorous palpation or trauma

BOX 1 Symptoms Associated with Thyroiditis

Mass Effect
- Neck pressure
- Dysphagia
- Dyspnea
- Hoarseness
- Cough

Hypothyroidism
- Fatigue
- Constipation
- Depression, mood swings
- Cold intolerance
- Weight gain

Hyperthyroidism
- Hair loss
- Palpitations
- Tremors
- Heat intolerance
- Weight loss
- Sweating
- Anxiety, nervousness
- Depression, mood swings

Patients are usually seen with the acute onset of the thyrotoxic phase, which typically occurs 2 to 8 weeks after delivery and lasts for a few months until the thyroid hormone stores have been depleted. This phase is characterized by moderate thyroid enlargement and is followed by a euthyroid phase, which can last for a few months, then by a hypothyroid phase with symptomatic hypothyroidism, which can last for up to 1 year. Unlike in Graves' disease, patients' thyroid stimulating immunoglobulin levels are within the normal range. However, patients have elevated antimicrosomal and antithyroglobulin antibody titers. Ultrasound examination of the thyroid gland reveals diffuse hypoechogenicity, which resolves with resolution of the thyroiditis.

Patients are monitored with serial thyroid function tests to determine their clinical progression through the various phases. Antithyroid drugs and radioiodine therapy are not effective for treatment of thyrotoxicosis, because the thyrotoxicosis occurs as a result of increased release of thyroid hormone stores, not as a result of increased synthesis of thyroid hormones. However, β-blocker therapy may be used for symptoms of thyrotoxicosis. Thyroid hormone replacement is initiated in the hypothyroid phase, but it should eventually be discontinued to determine a patient's transition to the recovery phase.

TABLE 2 Indications for Thyroid Surgery

Condition	Indication
Hashimoto's thyroiditis	Suspicion of malignancy or malignant thyroid nodule Local compressive symptoms Cosmetic concern
Postpartum thyroiditis	Not indicated
Drug-induced thyroiditis	Thyrotoxicosis refractory to medical treatment
Riedel's thyroiditis	Tracheostomy for decompression and diagnosis
Subacute thyroiditis	Thyrotoxicosis refractory to medical treatment
Acute suppurative thyroiditis	Refractory to percutaneous drainage and antibiotics
Radioiodine-induced thyroiditis	Not indicated
Trauma-induced thyroiditis	Not indicated

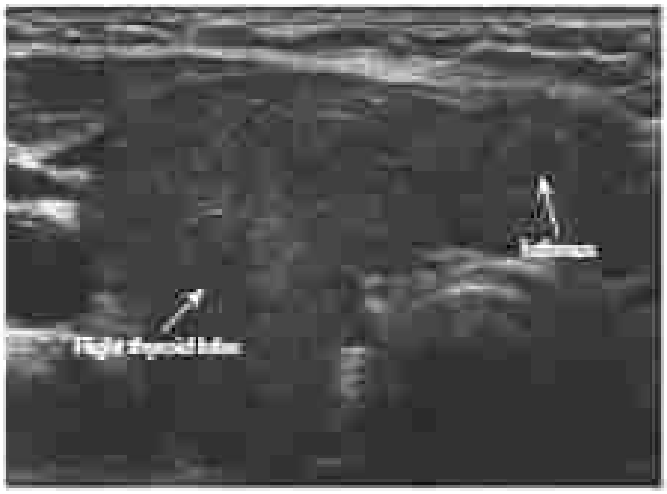

FIG. 1 Transverse ultrasound image showing right thyroid lobe and isthmus in a patient with chronic lymphocytic thyroiditis. The thyroid gland has diffuse and heterogeneous hypoechogenicity.

Drug-Induced Thyroiditis

Patients receiving interferon alpha, amiodarone, interleukin 2, lithium, tyrosine kinase inhibitors, or checkpoint inhibitor immunotherapy may develop painless thyroiditis. Hypothyroidism and hyperthyroidism are potential toxicities of interferon α therapy. Up to 10% of patients may develop either Hashimoto's thyroiditis or Graves' disease. The risk for development of a thyroid abnormality increases when serum antithyroid antibody concentrations are elevated before initiation of the drug. Patients with hepatitis C infection are also at an increased risk. When symptoms are severe, interferon α is discontinued.

FIG. 1. Left thyroid lobe in a patient with chronic lymphocytic thyroiditis that required a left thyroid lobectomy and isthmusectomy for an inconclusive fine-needle aspiration biopsy that on cytologic examination showed a Hürthle cell neoplasm. Grossly the thyroid lobe was pale and firm.

Amiodarone, a class III antiarrhythmic drug, is associated with both hypothyroidism and hyperthyroidism due to its high iodine content and its direct toxic effect on the thyroid. With every 200 mg of amiodarone, 9 mg of inorganic iodine is released into the systemic circulation, which significantly exceeds the recommended amount of 0.3 mg/day. Amiodarone-induced thyrotoxicosis (AIT) occurs in 2% to 5% of patients on chronic amiodarone therapy and is more common in patients with underlying Hashimoto's thyroiditis. AIT is classified into two types. Type I occurs as a result of an iodine-induced increase in thyroid hormone synthesis, especially in patients with a preexisting multinodular goiter. Type II is secondary to a direct toxic effect on the thyroid gland, causing thyroiditis and inflammatory-induced destruction of follicular epithelial cells. It is often followed by transient hypothyroidism. In the absence of life-threatening arrhythmias, amiodarone may be discontinued. However, because of its high lipid solubility and half-life of about 100 days, plasma levels of amiodarone decrease very slowly. The management of AIT consists of high-dose prednisone (40–60 mg/d). β-Blockers may be used for thyrotoxic symptoms, but they must be used with caution because, in combination with amiodarone, they may cause bradycardia and chest arrest. Potassium perchlorate, which inhibits iodine uptake and release by the thyroid gland, has also been used to treat AIT, often in combination with a thionamide agent. Patients with type II AIT who respond to medical therapy, including discontinuation of amiodarone, may develop transient or less commonly, permanent hypothyroidism requiring thyroid hormone replacement. Rarely in patients with persistent AIT despite medical therapy, near total or total thyroidectomy is indicated.

Tyrosine kinase inhibitors (most frequently sunitinib) sometimes include hypothyroidism—which can occur in up to 39% of patients—and to a lesser extent, thyrotoxicosis, possibly from destructive thyroiditis. TSH should be determined before initiation of the drug and at least every three months thereafter. Hypothyroidism is managed by thyroid hormone replacement; however, drug discontinuation or dosage reduction is typically unnecessary.

Riedel's Thyroiditis

Riedel's thyroiditis, also known as *Riedel struma* or *invasive fibrous thyroiditis*, is an extremely rare condition with a prevalence of 0.05% or less of surgical thyroid diseases. It was originally described in 1896 by Bernhard Riedel as a "specific inflammation of mysterious solitary producing an iron hard tumefaction of the thyroid." It is characterized by a replacement of the thyroid gland with dense fibrous tissue that extends beyond its capsule and involves the perithyroidal soft tissue. In contrast to other inflammatory conditions, extrathyroidal extension of the fibrosis may result in hypoparathyroidism, hoarseness, and compression of the trachea. Riedel's thyroiditis can occur with other fibrotic conditions affecting the retroperitoneum, mediastinum, lungs, lacrimal and parotid glands, bile ducts, and orbits, suggesting that it may be a primary fibrotic disorder. No etiologic relationship to drugs or other autoimmune diseases has been identified.

Patients present with slowly growing, painless goiters manifesting with neck pressure, dysphagia, or hoarseness from mass effect and the involvement of the esophagus and recurrent laryngeal nerves, respectively. Patients can also have symptoms related to hypothyroidism and hypoparathyroidism. On physical examination, one or both of their lobes are enlarged. Furthermore, the gland is "stony" hard, nontender, and adherent to the adjacent soft tissue and muscles.

Like other thyroid conditions, the diagnostic armamentarium should include screening thyroid function tests, and an ultrasound of the neck. Serum calcium, phosphorus, and parathyroid hormone levels help identify hypoparathyroidism. Ultrasound examination typically demonstrates diffuse hypoechogenicity, reduced vascularity throughout the entire thyroid gland, and the absence of demarcation between the thyroid gland and other surrounding structures. The extent of the fibrosis is best defined by computed tomography or magnetic resonance imaging. FNA biopsy is often inadequate, but when successful, it demonstrates a paucity of follicular epithelial cells and extensive fibrotic change. Sometimes these cytologic findings cannot be distinguished from the fibrotic change that occurs in patients with poorly differentiated or anaplastic thyroid cancer; consequently, the definitive diagnosis is confirmed by open thyroid biopsy, which also helps to exclude carcinoma.

Untreated, Riedel's thyroiditis usually progresses slowly and may stabilize or even regress spontaneously. Surgery may be indicated. The aim is to decompress the trachea by an isthmusectomy and to make a tissue diagnosis. More extensive surgery can be dangerous because of the loss of normal tissue planes, which is associated with a higher risk of injury to important structures (recurrent laryngeal nerves, parathyroid glands, and carotid arteries). Hypothyroidism is managed by thyroid hormone replacement, and hypoparathyroidism by calcium and calcitriol. High-dose corticosteroids reduce goiter size and are important in relieving compressive symptoms. Tamoxifen has also been shown to reduce goiter size and relieve compressive symptoms. More recently, some success has been reported with combined prednisone and mycophenolate mofetil therapy in a patient with disease that was resistant to prednisone and tamoxifen.

PAINFUL THYROIDITIS

Subacute Thyroiditis

Subacute thyroiditis is also known as subacute granulomatous thyroiditis, de Quervain's thyroiditis, subacute nonsuppurative thyroiditis, giant cell thyroiditis, and painful thyroiditis. It is a self-limited inflammatory condition of the thyroid gland presumed to be caused by a viral infection. It affects women between 30 and 40 years of age more often than males (a ratio of 3 to 5:1). The condition is characterized by a sudden or gradual onset of unilateral or bilateral neck pain that may radiate to the jaw, ear, and upper chest. In some cases, the pain is so severe that the patient cannot tolerate palpation of the neck or tight-fitting clothing. Pain can be exacerbated by coughing or turning the head. Fever, fatigue, malaise, anorexia, and myalgia are common. On physical examination, patients have an enlarged, firm, and tender thyroid gland, particularly in the acute phase. The overlying skin may be erythematous if the inflammation is severe.

Patients usually present with thyrotoxicosis followed by euthyroidism, hypothyroidism, and, ultimately, restoration of normal thyroid function. Fifteen percent of patients may develop permanent hypothyroidism. The thyrotoxic phase pathophysiology is similar to

other destruction-induced thyroiditis. Hyperthyroidism symptoms are usually mild and transient and last until the thyroid hormones are depleted. Each phase typically lasts 2 to 8 weeks. Some patients may progress directly from the hyperthyroid phase to the recovery phase, without the intervening hypothyroid phase. Up to 4% of patients develop recurrent disease. This condition is typically diagnosed clinically. In the early stages of the illness, TSH is suppressed (typically <0.1 mIU/L), whereas free T_4 and free T_3 levels are elevated. Thyroid antibody titers (antithyroglobulin, antimicrosomal, and TSH receptor antibody) are also elevated in 10% to 20% of patients. Inflammatory serum markers, such as erythrocyte sedimentation rate (ESR), are typically elevated (ESR >100 mm/h), and a normal ESR rules out active subacute thyroiditis. Leukocytosis and elevated C-reactive protein may also be present. Radioiodine imaging shows low uptake (typically <1%–3%), which helps to confirm the diagnosis. Ultrasound examination and FNA or core needle biopsy are rarely necessary, especially in patients with a tender thyroid. The sonographic features in a patient with subacute thyroiditis are a heterogeneous hypoechoic gland with a diffuse decrease in vascularity, unlike Graves' disease, which manifests with an enhanced flow on Doppler scanning. However, fine-needle biopsy may be useful to differentiate subacute thyroiditis from suppurative thyroiditis. Typical cytologic features include neutrophils, lymphocytes, histiocytes, and giant cells.

The condition is self-limited. Patients complaining of severe pain will benefit from nonsteroidal antiinflammatory drugs. For refractory severe neck pain or persistent pain after 2 to 3 days of nonsteroidal antiinflammatory therapy, prednisone (40 mg/d) is indicated. Hyperadrenergic symptoms may require short-term β-blocker therapy; however, thionamides are not indicated. Thyroid hormone replacement may be needed in the hypothyroid phase if patients are symptomatic. Therapy should be withdrawn and the patient reevaluated after a months. Iodine-131 therapy is not indicated, nor is it effective because radioiodine uptake in patients with subacute thyroiditis is suppressed. Thyroidectomy is reserved for the rare patient who has a prolonged course that is unresponsive to medical treatment.

Acute Suppurative Thyroiditis

Acute suppurative thyroiditis is a rare condition that manifests with a neck abscess, sudden onset of neck pain, and tenderness. Pain is usually unilateral and is accompanied by fever, chills, and other systemic symptoms and signs of infection. Most patients have a unilateral fluctuant neck mass. The condition is caused by gram-positive or gram-negative organisms, with Staphylococcus and Streptococcus species being the most commonly reported bacterial agents. Fungal, mycobacterial, and parasitic agents have been reported in immunocompromised patients. The thyroid gland is very well vascularized and has a capsule and extensive lymphatic drainage, which makes it resistant to infections. Therefore acute suppurative thyroiditis often occurs in immunocompromised or elderly frail patients. Infectious agents most commonly reach the thyroid gland via hematogenous spread, but they can also do so through lymphatic spread, direct extension, such as via esophageal perforation, or neck trauma. Acute suppurative thyroiditis in children is usually secondary to direct extension from a pyriform sinus fistula.

Thyroid function in patients with acute suppurative thyroiditis is usually normal, but thyrotoxicosis may be present. Thyroid ultrasound scans can differentiate between subacute thyroiditis (diffuse heterogeneity and low intensity vascular flow) and suppurative thyroiditis (abscess), as can FNA biopsy (multinucleated giant cell granulomas in subacute thyroiditis versus purulent collection in suppurative thyroiditis).

Acute suppurative thyroiditis is treated by empiric intravenous antibiotics and abscess drainage, the latter of which can be achieved via ultrasound guidance. Infrequently, surgical drainage or removal of the thyroid gland is required in patients who do not respond to percutaneous drainage and systemic antibiotic therapy.

Radioiodine-Induced Thyroiditis

Less than 1% of patients treated with radioactive iodine develop thyroiditis. It typically manifests with thyroid pain and tenderness 5 to 10 days after therapy, which can be due to radiation-induced injury and necrosis of thyroid follicular cells and associated inflammation. The neck pain and tenderness are usually mild and spontaneously subside in a few days to 1 week. There also may be transient exacerbation of hyperthyroidism, unless hormone stores were first depleted with thionamide therapy in cases of Graves' disease. Nonsteroidal antiinflammatory drugs are usually sufficient for analgesia, but prednisone may be required in severe cases.

Trauma-Induced Thyroiditis

Thyroiditis has been reported secondary to vigorous physical examination, thyroid biopsy, neck surgery (parathyroid surgery), or trauma (seat belt). Similar to other causes, it manifests by transient neck pain and tenderness, as well as transient hyperthyroidism. It usually requires no intervention and is self-limited.

Suggested Readings

Hiddal N, Nielsen ..., (20..) Environment [illegible] recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polygenic autoimmunity. [illegible] 2015;6:1276.

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Management of Hyperthyroidism

Tracy S. Wang, MD, MPH, FACS, and Julie Ann Sosa, MD, MBA, FACS

Hyperthyroidism is a common condition, with an estimated prevalence of 1% to 3% in the United States. It is diagnosed more frequently in women and represents a form of thyrotoxicosis, a term that refers to the clinical state of having excess thyroid hormone, which can have multiple causes. The thyroid is regulated by production of thyroid-stimulating hormone (TSH) by the pituitary gland, which in turn stimulates secretion of thyroxine (T_4) and triiodothyronine (T_3), the active form of thyroid hormone). T_3 and T_4 secretion prompts a negative feedback loop to the pituitary to regulate TSH secretion. Hyperthyroidism is specifically defined as a disorder in which excess thyroid hormone is produced and secreted by the thyroid gland. The most common cause of hyperthyroidism is Graves' disease, followed by a toxic multinodular goiter or a toxic thyroid nodule (toxic adenoma).

Management of hyperthyroidism includes medical management with antithyroid medications, radioactive iodine (RAI) therapy, or thyroidectomy (thyroid lobectomy or total thyroidectomy based on underlying disease). The choice of therapy is dependent on the cause of the hyperthyroidism, clinical features, patient values, and preferences with respect to logistics of each treatment option, risks and benefits, potential side effects, and costs. If surgery is chosen, consideration should be given to availability of a high-volume thyroid surgeon to minimize risks of recurrent laryngeal nerve injury, hypoparathyroidism, or both.

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TABLE 1 Signs and Symptoms Associated with Thyrotoxicosis

	Signs	Symptoms
General		Weight loss despite increased appetite, heat intolerance, sweating
Cardiovascular	Tachycardia, hypertension, arrhythmia (atrial fibrillation)	Palpitations
Pulmonary	Tachypnea	Dyspnea
Gastrointestinal		Diarrhea, nausea, vomiting
Reproductive	Changes in menstrual cycle	
Ocular	Proptosis, eyelid retraction, periorbital edema	Diplopia, blurry vision, retro-orbital pain, irritated eyes
Dermatologic	Warm and moist ("clammy") skin	
Neuromuscular	Tremor, hyperactivity, hyperreflexia	Tremor, nervousness, anxiety, fatigue, weakness, disturbed sleep, poor concentration

INITIAL EVALUATION AND MANAGEMENT

Hyperthyroidism may be overt or subclinical; overt hyperthyroidism is characterized by low serum TSH levels and high levels of both T3 and T4; in contrast, subclinical hyperthyroidism is defined by the presence of low serum TSH levels and normal T3 and T4 levels. Patients with subclinical hyperthyroidism are often symptom free, in contrast to those with overt hyperthyroidism, in which symptoms may manifest across a spectrum of target organs, including the cardiovascular, pulmonary, gastrointestinal, reproductive, ocular, dermatologic, and neuromuscular systems (Table 1).

In patients with suspected hyperthyroidism, serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid dysfunction. If the TSH is low, serum T3 and T4 levels (free or total) should be obtained to differentiate between subclinical and overt hyperthyroidism. Once the diagnosis is established, the cause should be determined; current American Thyroid Association (ATA) guidelines recommend the following diagnostic strategies, depending on available expertise and resources: (1) measurement of thyroid receptor antibodies (TRAb), (2) determination of RAI uptake (RAIU), or (3) measurement of thyroidal blood flow on ultrasonography (Fig. 1). TRAb levels above the normal range are diagnostic for Graves' disease. The ratio of total T3 to total T4 can be useful in determining the cause of thyrotoxicosis, because T3 will be more elevated in hyperthyroidism, whereas T4 is more elevated in thyrotoxicosis caused by thyroiditis.

In patients with hyperthyroidism, thyroid ultrasonography should be performed in patients who have nonfunctioning or hypofunctioning nodules identified on RAIU scans (if performed) or on physical examination; routine ultrasonography is otherwise not recommended. The evaluation of a thyroid nodule with fine needle aspiration (FNA) biopsy should be guided by existing guidelines for the management of thyroid nodules in euthyroid individuals; thyroid nodules that are functional on radioiodine uptake scans need not undergo FNA.

Although the long-term management of hyperthyroidism can take many routes, initial treatment should be focused on controlling the signs and symptoms of hyperthyroidism. The initial management of all patients with symptomatic thyrotoxicosis should include β-adrenergic blockade, particularly in elderly patients and patients with resting heart rates greater than 90 beats/min or coexistent cardiovascular disease. These include a nonselective β-adrenergic receptor blocker such as propranolol (10–40 mg, 3–4 times a day) or those with relative β-1 selectivity, such as atenolol (25–100 mg, 1–2 times daily) or metoprolol (25–50 mg, 2–3 times daily). β-Adrenergic drugs are generally contraindicated in patients with asthma, given that there is insufficient β-1 selectivity at the recommended doses; they also should be used cautiously in patients with congestive heart failure, bradyarrhythmias, and Raynaud's disease. For patients who do not tolerate β-adrenergic agents, calcium channel blockers have been shown to affect rate control.

Thyroid storm (thyrotoxic crisis) is a rare condition that occurs in 1% to 5% of patients admitted to a hospital for thyrotoxicosis and is associated with a high (up to 25%) risk of death. Development of thyroid storm is not dependent on serum TSH levels, and the pathogenesis is not well understood; it can be triggered by cessation of antithyroid medications, acute illness, trauma, or stress. The diagnosis is clinical, and a scoring system to assess the severity of the crisis has been proposed; based on temperature, central nervous system manifestations (none, mild agitation, delirium/psychosis, or progression to seizures/coma), gastrointestinal-hepatic dysfunction (none, diarrhea or nausea/vomiting, or unexplained jaundice), cardiovascular dysfunction (presence of tachycardia, congestive heart failure, and atrial fibrillation), and any precipitating factors. Treatment is supportive and a multidisciplinary approach to management, including definitive therapy with RAI or thyroidectomy, is recommended. Thyroid storm also can be precipitated by manipulation of the thyroid during surgery, particularly in patients who are not biochemically euthyroid before surgery.

MANAGEMENT OF GRAVES' DISEASE

Graves' disease is an autoimmune disease caused by antibodies to the TSH receptor on thyroid follicular cells, resulting in excess production of thyroid hormone. Treatment options for Graves' disease include antithyroid medications, RAI therapy, or thyroidectomy; choice of therapy should incorporate the patient's specific clinical scenario and preference (Table 2). In the United States, RAI has been a preferred modality of treatment by physicians, although the trend has been to reduce use of RAI in favor of antithyroid medications; in a 2011 survey of clinical endocrinologists, 60% selected RAI as their primary therapy for uncomplicated Graves' disease, compared with 20% 30 years earlier. However, in Europe, Latin America, and Japan, there has been greater physician preference for antithyroid medications as first-line therapy.

Antithyroid Medications

Antithyroid medications include the thionamides, which include methimazole (MMI) and propylthiouracil (PTU), both inhibit thyroid hormone synthesis, with PTU having the additional benefit of blocking peripheral conversion of T4 to T3. MMI is favored as first-line therapy in nearly all patients, except during the first trimester of pregnancy and for the treatment of thyroid storm, given the association of PTU with fulminant hepatic failure and death. Use of PTU is reserved for specific indications, such as during the first trimester

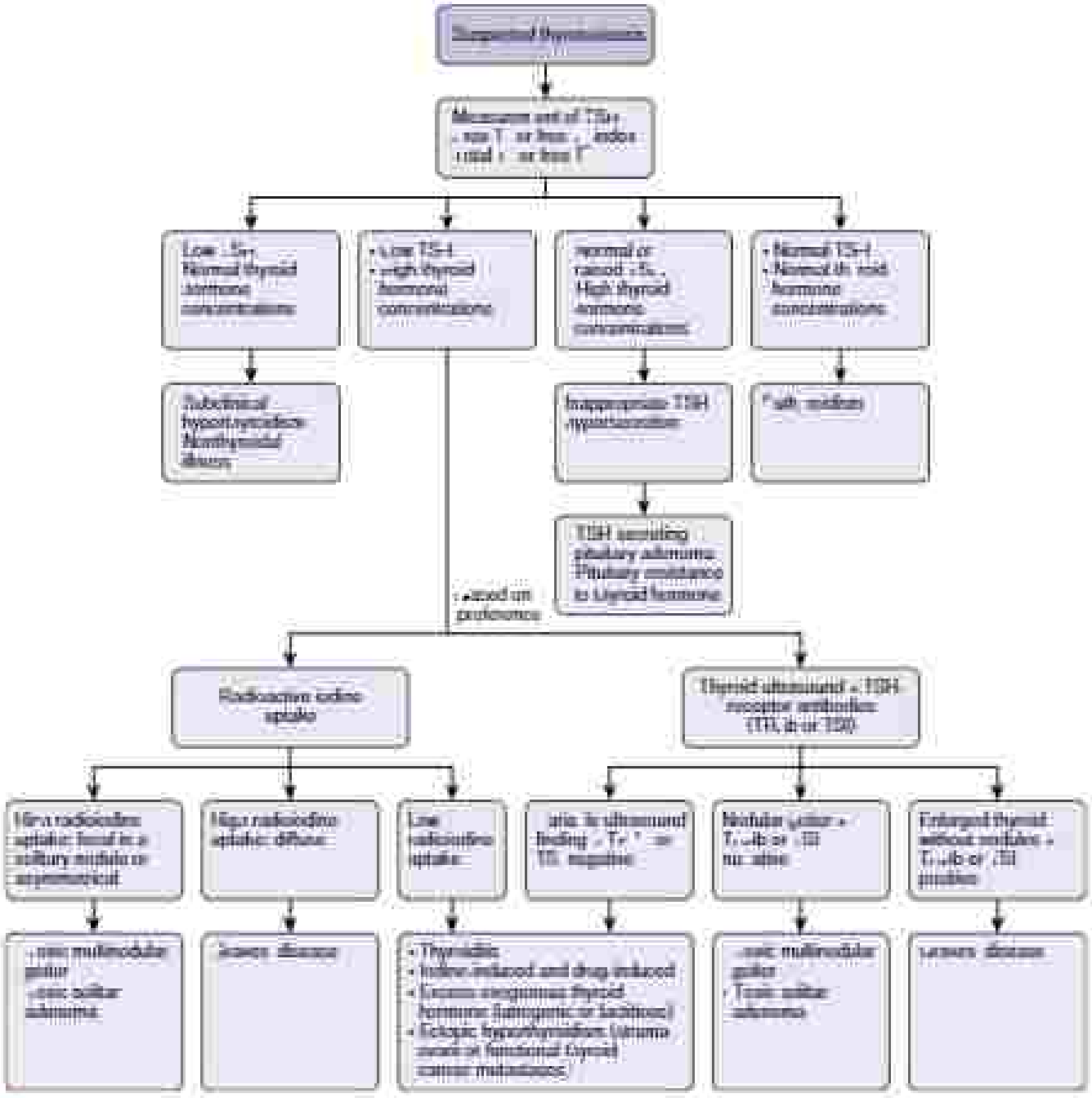

FIG. 1. Algorithm for assessment of thyroid acute. ... ...ethoxythyroxine. ... types are bot... T... H-receptor antibodies. ...SH thyroid stimulating hormone. ...T thyroid stimulating immunoglobulins. (From ... [illegible])

of pregnancy, given the potential teratogenic effects of MMI. Antithyroid medications can be used either as the primary treatment for Graves' disease or as pretreatment for patients undergoing RAI or thyroidectomy. If being used as primary treatment, patients should be treated for 12 to 18 months, because results of a randomized clinical trial found that remission rates are not improved after more than 18 months of treatment.

After completion of initial therapy, the medications can be tapered or discontinued among patients where TRAb levels have normalized, based on the clinical symptoms. Remission is defined as biochemical euthyroidism more than 12 months after discontinuation of therapy; relapse rates are 20% to 30% over 3 to 5 years of follow-up. In patients who relapse, definitive therapy with RAI or thyroidectomy should be considered. Side effects of antithyroid medications include the risk of agranulocytosis, which is dose related with methimazole and almost always occurs within the first 90 days of treatment. MMI-induced hepatotoxicity is usually cholestatic, in contrast to the hepatocellular injury associated with PTU, which can lead to fulminant hepatic failure. Milder side effects of antithyroid medications include development of a pruritic rash, arthralgias, abdominal pain, nausea, fatigue, and pharyngitis.

RAI Therapy

The goal of RAI therapy is to render the patient hypothyroid. RAI is incorporated into thyroid hormone, causing ionizing damage to thyroid follicular cells and destruction of the gland. RAI treatment can cause a transient exacerbation of hyperthyroidism, therefore

TABLE 2 Clinical Situations that Favor a Particular Modality as Treatment for Graves' Hyperthyroidism

Clinical Situations	RAI	ATD	Surgery
Pregnancy[a]		Preferred, use caution	Acceptable, use caution
Comorbidities with increased surgical risk and/or limited life expectancy	Preferred	Acceptable	Contraindicated
Smoker (+)	Acceptable	Acceptable	Acceptable
Active GO		Preferred	Preferred
Liver disease	Preferred	Use caution	Acceptable
Major adverse reactions to ATDs	Preferred	Contraindicated	Acceptable
Patients with previously operated or externally irradiated necks	Preferred	Acceptable	Use caution
Lack of access to a high-volume thyroid surgeon	Preferred	Acceptable	Use caution
Patients with high likelihood of remission (especially women with mild disease, small goiters, and negative or low titer TRAB)	Acceptable	Preferred	Acceptable
Patients with periodic paralysis	Preferred	Acceptable	Preferred
Patients with right pulmonary hypertension, or congestive heart failure	Preferred	Acceptable	Use caution
Elderly with comorbidities	Acceptable	Acceptable	Use caution
Thyroid malignancy confirmed or suspected	Contraindicated	*	Preferred
One or more large thyroid nodules	*	Acceptable	Preferred
Coexisting primary hyperparathyroidism requiring surgery	*	*	Preferred

[a]For women considering a pregnancy within 6 months.
*Not first-line therapy but may be acceptable depending on the clinical circumstances.
ATD, antithyroid drugs; GO, Graves' ophthalopathy; RAI, radioactive iodine.
Source: from Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(1):1343–1421.

consideration should be given to initiation of antithyroid medications and/or β-adrenergic blockade in symptom-free patients who may be at risk of complications from worsening thyrotoxicosis (the elderly or patients with cardiovascular or pulmonary disease). Antithyroid medications should be stopped 2 to 3 days before RAI therapy and restarted 3 days later, to allow for RAI incorporation into the thyroid. Most patients will develop hypothyroidism 2 to 3 months after a single dose of 12 to 15 mCi of RAI. Patients should have initial assessment of TSH, total T3, and free T4 1 to 2 months after therapy; biochemical monitoring should occur every 4 to 6 weeks for 6 months or until the patient is hypothyroid and stable on thyroid hormone replacement. Consideration for repeat therapy should not be considered for at least 6 months after initial treatment.

RAI is contraindicated during pregnancy, lactation, for coexisting thyroid cancer/suspicion of thyroid cancer, and among individuals unable to comply with radiation safety guidelines. Assuming a dose of 10 to 15 mCi, these precautions include that the patient sleep alone for 3 to 6 days (15–18 days in the case of a pregnant partner), and to keep a distance of 3 feet from adults and 6 feet from pregnant women and children during the day. RAI also should be used with caution among women planning a pregnancy within the first 4 to 6 months after treatment.

The presence of mild Graves' orbitopathy is also a relative contraindication to use of RAI, because RAI can worsen orbitopathy, compared with antithyroid medications or thyroidectomy, particularly in patients with other risk factors for worsening disease, such as use of tobacco. If patients have no risk factors for worsening of eye disease, RAI therapy is considered equally acceptable. Patients with mild orbitopathy may benefit from corticosteroid prophylaxis, but RAI should not be used in patients with active and moderate to severe Graves' orbitopathy. Other side effects of RAI include transient worsening of thyrotoxicosis, risks of secondary malignancy, and potential anterior neck pain from radiation thyroiditis, sialadenitis, and dry mouth.

Surgery

Indications for Surgery

Despite the safety and effectiveness of antithyroid medications and RAI for the long-term treatment of hyperthyroidism secondary to Graves' disease, there may be circumstances that warrant a patient preference for surgery. Indications for surgery include women planning a pregnancy in less than 6 months; patients with other indications for cervical surgery (presence of large thyroid nodules ≥4 cm, or large goiters with compressive symptoms of dysphagia, dysphagia, or voice changes, suspicion of or documented thyroid malignancy, or concurrent primary hyperparathyroidism requiring parathyroidectomy); relatively low uptake of RAI, persistent disease despite previous treatment with antithyroid medications or RAI, and patients with moderate to severe Graves' orbitopathy. Contraindications to surgery include severe patient comorbidities such as cardiopulmonary disease, end-stage cancer, or other disorders that may shorten the patient's life expectancy or place the patient at an increased risk for operative morbidity and death.

Surgery as First-Line Treatment for Graves' Disease

Several studies have compared the different treatment options for Graves' disease with respect to rates of recurrent hyperthyroidism. A recent systematic review and meta-analysis of eight studies (one

randomized controlled trial and seven comparative cohort studies) included 1402 patients (667 on antithyroid medications, 214 RAI patients, and 419 surgical patients) with Graves' hyperthyroidism. There was a higher relapse rate with antithyroid medications compared with RAI (odds ratio [OR], 4.25; 95% confidence interval [CI], 2.48 to 6.67; $P < .01$) and surgery (OR, 9.09; 95% CI, 4.65 to 19.23; $P < .01$). There was no difference in relapse rates between RAI and surgery (OR, 1.53; 95% CI, 0.61 to 3.65; $P = .34$), although patients in the surgical arm underwent both subtotal and total thyroidectomy.

A separate systematic review of the published literature between 2001 and 2011 included 14,246 patients who underwent either surgery (subtotal [3158, 22%] or total [1308, 10%] thyroidectomy) or RAI (9690, 68%). Overall, any thyroid surgery was favored over any dose of RAI for definitive treatment of Graves' disease, and total thyroidectomy was favored over subtotal thyroidectomy (OR, 40.37; 95% CI, 15.0 to 108.44; $P < .001$). Persistent or recurrent hyperthyroidism was present in 2080 (21%) patients who received a single dose of RAI, 330 (10%) patients after subtotal thyroidectomy, and 4 (0.3%) patients after total thyroidectomy.

A cost effectiveness analysis has suggested that (total) thyroidectomy also may be more cost effective than RAI or lifelong use of antithyroid medications in patients who have previously been treated with 18 months of antithyroid medications and have failed to achieve a euthyroid state. In this study, the decision model assumed that 52% of patients would fail initial therapy; these patients were then assigned to either additional treatment with antithyroid medications, RAI, or total thyroidectomy. In the base case of a 36 year old patient with uncomplicated Graves' disease, total thyroidectomy was the most effective (associated with highest quality of life, measured by quality-adjusted life years) and most cost effective. RAI was less costly, but also was associated with the lowest quality of life. These findings were robust as long as the cost of total thyroidectomy remained less than $19,300 (2007 USD), after which antithyroid medications became more cost effective.

Other studies have focused on the outcomes after thyroidectomy. A recent study of 99 patients with hyperthyroidism has suggested that earlier intervention may allow for faster biochemical recovery and improved postoperative management of thyroid function levels and therefore patient quality of life. In this study, patients were divided into two groups: the early therapy group did not undergo previous therapy except for use of antithyroid medications to achieve euthyroidism before surgery, and the delayed therapy group had at least one trial of antithyroid medications, previous RAI, or previous thyroidectomy. Patients in the early therapy group had a quicker biochemical recovery, as measured by the mean duration to reach a normal TSH (121 vs 240 days; $P = .007$) and free T4 (91 vs 183 days; $P = .015$). There may also be long term benefits of thyroidectomy with respect to extrathyroidal manifestations of Graves' disease. A recent study of patients younger than 40 years with hyperthyroidism studied patients who underwent surgery (n = 122) or treatment with antithyroid medications (n = 42) and found that 96% of surgical patients had significant improvement in cardiovascular dysfunction, compared with 79% of patients treated with medications alone, suggesting that total thyroidectomy was a preferred choice of treatment for patients with hyperthyroid cardiac dysfunction. A study of 10,992 hyperthyroid patients in the Swedish national registry compared 10,250 patients treated with RAI and 742 patients treated with surgery between 1986 and 2000. The hazard ratio (HR) for all cause mortality was 0.82 (95% CI, 0.71 to 0.96) for patients who underwent surgery versus RAI; this was in large part secondary to the decrease in cardiovascular related deaths: (HR, 1.70; 95% CI, 0.53 to 0.91), as compared with cancer-related death (HR, 1.04; 95% CI, 0.80 to 1.36) or death from other causes (HR, 0.78; 95% CI, 0.59 to 1.04).

Extent of Surgery

Current recommendations from the American Thyroid Association for the management of hyperthyroidism state that "If surgery is chosen as the primary therapy for Graves' disease, near total or total thyroidectomy is the procedure of choice." In contrast to near total/total thyroidectomy, subtotal thyroidectomy involves preservation of remnant of the thyroid (typically the tubercle of Zuckerkandl), which can extend posteriorly behind the recurrent laryngeal nerve and encircles the anterolateral portion of the trachea) to preserve both the integrity of the recurrent laryngeal nerve as it enters the cricothyroid muscle and the blood supply to the superior parathyroid gland. However, leaving a remnant of thyroid increases the risk of persistent or recurrent hyperthyroidism, and near total/total thyroidectomy has been shown to have acceptably low rates of morbidity when performed by high volume thyroid surgeons. Total thyroidectomy remains the favored surgical option for patients with Graves' disease.

Multiple studies have supported recommending total thyroidectomy as the procedure of choice. In a randomized clinical trial of 288 patients who underwent subtotal or total thyroidectomy for Graves' disease, 191 had 5 years of follow-up: 85 underwent subtotal thyroidectomy, and 56 underwent total thyroidectomy. Overall, recurrent hyperthyroidism occurred in nine (9%) patients after subtotal thyroidectomy and no patients after total thyroidectomy ($P = .002$). There was no difference in rates of transient or permanent hypoparathyroidism or recurrent laryngeal nerve injury. Feinet al performed a meta analysis of total thyroidectomy versus subtotal thyroidectomy including 23 studies (14 randomized controlled trials and 9 nonrandomized comparative studies) and 3242 patients. Overall, recurrent hyperthyroidism was less frequent in the total thyroidectomy group (2 of 1665; 0.1%) than in the subtotal thyroidectomy group (127 of 1577; 8.0%; OR, 0.16; 95% CI, 0.06 to 0.38; $P < .0001$); these findings remained true for both the randomized controlled trials (OR, 0.15; 95% CI, 0.05 to 0.43; $P = .0005$) and the comparative studies (OR, 0.09; 95% CI, 0.02 to 0.38; $P = .0006$). There was no difference in rates of permanent recurrent laryngeal nerve injury between the two groups (OR, 0.91; 95% CI, 0.41 to 2.02; $P = .82$), although rates of both temporary (OR = 2.78; 95% CI, 2.04 to 3.5e; $P < .00001$) and permanent (OR, 2.01; 95% CI, 1.38 to 3.35; $P = .005$) hypoparathyroidism were higher in the total thyroidectomy group. However, when only the randomized controlled trials were included in the analysis, there was no longer a difference in rates of permanent hypoparathyroidism (OR, 2.32; 95% CI, 0.73 to 7.38; $P = .15$).

Preoperative Management:

Patients should be euthyroid before undergoing thyroidectomy for Graves' disease. In addition to antithyroid medications and use of β-adrenergic blockade, use of potassium iodide in the immediate preoperative period has been advocated, to use originated from the observation by Plummer that its use decreased the risk of thyroid storm during thyroidectomy in an era in which thionamides and β-blockers were not available. Studies have shown a reduction in gland vascularity after administration of potassium iodide, and since surgical studies have demonstrated that this reduction in gland vascularity allows for an easier technical procedure. Attie et al. randomly assigned 56 patients to preoperative treatment with Lugol's solution or to no treatment. They found that patients who took Lugol's solution had lower mean blood flow (74.7 vs 128.62 mL/min; $P = .0001$) and blood loss (54.6 vs 108.5; $P = .0001$) than patients who did not, although other clinical variables were not studied.

However, other studies have shown that use of potassium iodide does not influence surgical outcomes in all settings. Single institution retrospective studies have suggested that use of preoperative potassium iodide did not affect outcomes from thyroidectomy (blood loss, operative time, or rates of transient/permanent hypoparathyroidism or recurrent laryngeal nerve injury). However, these studies examined outcomes by high volume thyroid surgeons, and it remains unclear whether these data are applicable if surgery is performed by low-volume thyroid surgeons, given the established relationship between surgeon volume and patient outcomes. Current ATA guidelines state that "a potassium iodide containing preparation should be given in the immediate preoperative period", although this is a "strong recommendation," it is based on "low quality evidence." If given, it can

TABLE 3 Clinical Situations That Favor a Particular Modality as Treatment for Toxic Multinodular Goiter or Toxic Adenoma

Clinical Situations	RAI	ATD	Surgery
TMNG			
Pregnancy*	Contraindicated	Preferred, use caution	Acceptable, use caution
Advanced age, comorbidities with increased surgical risk and/or limited life expectancy	Preferred	Acceptable	Contraindicated
Patients with previously operated or externally irradiated necks	Preferred	Acceptable	Use caution
Lack of access to a high-volume thyroid surgeon	Preferred	Acceptable	Use caution
Symptoms or signs of compression within the neck	Acceptable	†	Preferred
Thyroid malignancy confirmed or suspected	Contraindicated	†	Preferred
Large goiter/nodule	Acceptable	†	Preferred
Goiter/nodule with substernal or retrosternal extension	Acceptable	†	Preferred
Coexisting hyperparathyroidism requiring surgery	†	–	Preferred

*Not women considering a pregnancy within 6 months.
†Not first-line therapy but may be acceptable depending on the clinical circumstances.
ATD, antithyroid drugs; RAI, radioactive iodine; TMNG, toxic multinodular goiter.
From Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26:1343–1421.

be given as either potassium iodide (SSKI 50 mg iodide/drop; 1 to 2 drops three times daily) or Lugol's solution (5% elemental iodine and 10% potassium iodide; 8 mg iodide/drop; 5 to 7 drops three times daily) for 7 to 10 days before surgery. Potassium iodine should not be given to patients with thyroid nodular disease.

MANAGEMENT OF TOXIC THYROID NODULES/TOXIC MULTINODULAR GOITER

Hyperthyroidism secondary to the presence of a toxic multinodular goiter or toxic thyroid nodule/adenoma can be differentiated from Graves' disease by the pattern of uptake on radioactive iodine imaging (if performed; Fig. 1) or by the presence of normal levels of TRAb or thyroid stimulating immunoglobulins. The primary modalities of treatment are RAI therapy and thyroidectomy, with a goal of rapid and durable elimination of hyperthyroidism. Treatment with antithyroid medications would require long-term (possibly lifelong) treatment and should be considered only in select instances, such as for patients with advanced age, limited life expectancy, and/or comorbidities that would increase the risk of morbidity at the time of surgery. Considerations with respect to choice of RAI or thyroidectomy are not dissimilar to those influencing the decision in patients with Graves' disease (Table 3).

In contrast to patients with hyperthyroidism secondary to Graves' disease, not all patients with a toxic thyroid nodule/multinodular goiter will require pretreatment with antithyroid medications (preferentially methimazole, unless there is a contraindication). Current ATA guidelines recommend that any patient who would be at increased risk for the potential complications of a persistent hyperthyroid state (e.g., the elderly, patients with cardiovascular disease) be pretreated with antithyroid medications, with consideration of β-blockade for symptom-free patients at risk for complications due to hyperthyroidism. However, younger/middle-aged patients may only require β-blockade for symptomatic hyperthyroidism.

It is critically important that patients with a toxic thyroid nodule/goiter undergo cervical ultrasonography before surgery. Nonfunctioning nodules on radionuclide scintigraphy or nodules with suspicious characteristics on ultrasonography should be managed with FNA biopsy, according to current evidence-based guidelines. For patients with a toxic multinodular goiter, near-total/total thyroidectomy is recommended; for patients with a toxic thyroid nodule/adenoma, ipsilateral thyroid lobectomy may be performed for single nodules if the contralateral thyroid lobe is unremarkable on ultrasonography.

In certain patients, alternative therapies may be considered for patients with a toxic thyroid nodule/goiter for whom the standard treatment options are not appropriate, contraindicated, refused by the patient, or for whom expertise in other procedures is available. These alternative therapies may include ethanol ablation, radiofrequency ablation, or high-intensity focused ultrasonography (HIFU). HIFU is a type of thermal ablation that delivers energy in the form of ultrasound waves extracorporeally to a targeted area beneath the skin; the effects on benign tissues occurs via a thermal effect and by acoustic cavitation. Recent studies have examined the efficacy and safety of HIFU in patients with benign thyroid nodules, toxic thyroid nodules, and persistent Graves' disease. Although initial studies are promising in select patients and when performed by experienced clinicians, there remain questions with respect to patient pain, risk of recurrent laryngeal nerve injury, and long-term outcomes of this technique.

TECHNICAL CONSIDERATIONS OF THYROIDECTOMY

Thyroidectomy for hyperthyroidism can be challenging because of the hypervascularity of the gland; from a technical perspective, this can make identification of the parathyroid glands and recurrent laryngeal nerves more difficult, although a standard approach to thyroidectomy can be useful. A few technical aspects that should be considered during thyroidectomy include the following:

- Although extensive is important, particularly for patients with benign disease, the emphasis should be on safe visualization of key structures. Therefore the incision length should be made with careful consideration of gland size and the likely hypervascularity of the gland.
- It is often helpful to ligate the superior thyroid vessels first; there are often engorged in patients with hyperthyroidism, and early ligation can facilitate mobilization of the superior pole of the thyroid. This can be done with silk ties or with vessel-sealing devices, but one should be mindful that the maximum vessel size for many devices is 7 mm.

- The recurrent laryngeal nerve typically lies within the tracheoesophageal groove. Its course can be more variable on the right, and it can lie anterior or posterior to the inferior thyroid artery. In rare cases, a nonrecurrent laryngeal nerve can be present (typically on the right side); surgeons can be alerted to this by aberrant vascular anatomy if a computed tomography scan of the neck was obtained.
- The blood supply to both the superior and inferior parathyroid glands are derived from the inferior thyroid artery. The inferior gland can be more variable in location, and dissection close to the thyroid gland provides the safest plane to avoid inadvertent devascularization of the parathyroid glands.

Intraoperative recurrent laryngeal nerve monitoring is increasingly used during thyroidectomy, although visualization of the nerve remains the gold standard. During surgery, the vocal fold response to nerve stimulation can be measured by an electrode system incorporated in the endotracheal tube, which is positioned at the level of the vocal cords. Auditory or visual electromyographic signals can be obtained from the vagus or recurrent laryngeal nerve by intermittent stimulation using a handheld probe during thyroidectomy and at the time of visualization of the nerve or when dissection is occurring close to the nerve, depending on the system used. Changes in the pattern of the signals may hint at possible nerve irritation and dysfunction. Routine use of intraoperative nerve monitoring has not been shown to decrease rates of recurrent laryngeal nerve injury, and, if a surgeon chooses to incorporate it into his/her practice, routine use allows for familiarity with the system and ability to troubleshoot the technology by all who are involved in the surgical procedure, including the surgeons, anesthesiologists, and nurses.

POSTOPERATIVE MANAGEMENT

Management of Thyroid Function

After total thyroidectomy for either Graves' disease or a toxic multinodular goiter, potassium iodide–containing preparations should be discontinued, and β-blockade can be tapered in patients for whom they are used solely for management of symptoms of hyperthyroidism (rather than preexisting hypertension). Thyroid hormone replacement should be initiated at a dose appropriate to the patient's weight (typically 0.8 μg/lb or 1.5–1.7 μg/kg) and age (typically lower doses in the elderly). TSH levels should be measured 6 to 8 weeks after surgery and then every 1 to 2 months until levels are stable, followed by annual assessment. After lobectomy for a toxic thyroid nodule, TSH and free T4 levels should be obtained 4 to 6 weeks after surgery; thyroid hormone supplementation should be started if there is a persistent rise in TSH levels. Long-term thyroid hormone supplementation may be required in 15% to 30% of patients after thyroid lobectomy.

Complications of Thyroidectomy

The most common complications of thyroidectomy include transient or permanent recurrent laryngeal nerve injury and postoperative hypocalcemia/hypoparathyroidism. Both are uncommon (1% to 2% in the hands of experienced thyroid surgeons) but can have a significant effect on the patient's quality of life. Patients who elect to undergo thyroidectomy should have a preoperative voice evaluation, based on any subjective voice changes perceived by the patient and the surgeon's objective assessment of voice quality. Formal vocal cord evaluation should be obtained for any patient with subjective findings of voice change and any patient with previous anterior neck surgery (e.g., parathyroidectomy, thyroidectomy, carotid endarterectomy, or cervical fusion via the anterior approach) or mediastinal/thoracic surgery that places the vagus nerve at risk. Evaluation can include indirect or direct laryngoscopy, videostroboscopy, or transcutaneous vocal cord ultrasonography. Recurrent laryngeal nerve injury can be transient or permanent; subjective changes in voice quality should prompt referral to a voice specialist for evaluation and management.

During thyroidectomy, manipulation, devascularization, or unintentional resection of the parathyroid glands can result in transient or permanent hypoparathyroidism and associated hypocalcemia. Following total thyroidectomy, the goal is to prevent the development of symptomatic hypocalcemia in patients at risk for hypoparathyroidism, although the optimal algorithm remains unclear; options include routine oral calcium supplementation or selective supplementation, based on serum calcium or parathyroid hormone (PTH) levels. Evaluation of calcium/PTH levels and supplementation is not required for patients after thyroid lobectomy.

SPECIAL CONSIDERATIONS

Graves' Disease in Children

Graves' disease is the most common cause of hyperthyroidism in children. Although antithyroid medications, RAI, and thyroidectomy remain treatment options, the choice of initial treatment may vary based on the patient' age, clinical status, and patient/parent values and preferences; particularly for pediatric patients, the availability of a high-volume thyroid or pediatric surgeon is critical, given the possibility of life-long hypoparathyroidism or recurrent laryngeal nerve injury. If antithyroid medications are chosen, MMI therapy for 1 to 2 years is considered appropriate initial management, although it is important to recognize that most pediatric patients will not have durable remission on medication alone. MMI should be used and use of PTU avoided because of the risk of hepatotoxicity.

In patients who are not in remission after initial MMI therapy, consideration for RAI or surgery should be given. The goal of RAI therapy is to reduce hyperthyroidism to a single treatment, either as an estimated or fixed dose; smaller doses aimed at euthyroidism result in higher rates of persistent/recurrent hyperthyroidism and exposure of residual thyroid tissue to multiple doses of radiation that may lead to increased risk to the development of thyroid neoplasms. Long-term studies have not yet shown definitively there to be an increased risk of thyroid or nonthyroid malignancies; however, given the theoretical risk, RAI therapy is generally avoided in children younger than 5 years.

For patients younger than 5 years, surgery is the preferred treatment when definitive therapy is required and surgery can be performed by a high-volume surgeon. Surgery is also preferred in patients with large thyroid glands (>80 g), when response to RAI may be poor, and for those who are nonadherent or nonresponsive to antithyroid medications. If chosen, total or near-total thyroidectomy should be performed. Particularly in pediatric patients, access to a high-volume thyroid surgeon is critically important; current ATA guidelines on the management of pediatric thyroid nodular disease recommend that pediatric thyroid surgery be performed in a hospital with the full spectrum of pediatric specialty care.

Graves' Disease in Pregnancy

The diagnosis of hyperthyroidism in pregnancy can be challenging, because normal pregnancy leads to changes in thyroid physiology that results in altered thyroid function testing that mimics biochemical hyperthyroidism but does not require treatment. The diagnosis is made with serum TSH values and either total T3 and T4 levels, but reference ranges should increase to 1.5 times above that of the nonpregnant range by the second/third trimester or be trimester specific. If overt hyperthyroidism is diagnosed during pregnancy, treatment with antithyroid medications should be initiated. PTU should be used during the first trimester, given the teratogenic effects associated with MMI, including aplasia cutis, choanal/esophageal and other intestinal atresia, abdominal wall abnormalities (e.g., omphalocele), and eye, heart, and urinary tract malformations. PTU associated birth defects have been reported but appear to be less severe than those related to use of MMI. MMI can be used after the first trimester. RAI therapy is contraindicated during pregnancy.

Surgery as definitive therapy should be considered by patients considering starting families and who require high doses of antithyroid medications for euthyroidism, making spontaneous remission less likely. Surgery for patients diagnosed during pregnancy should be reserved only for those patients for whom medical management is not successful or those who have a contraindication to antithyroid medications. If performed, surgery during the first and third trimesters should be avoided, given the risks for fetal development and premature labor, respectively.

Amiodarone-Induced Thyrotoxicosis

Amiodarone is an iodine-rich antiarrhythmic drug that can result in amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism in 15% to 20% of patients. AIT may develop at any point during amiodarone treatment, even several months after cessation, secondary to its long half-life (up to 100 days) and storage in fat tissues within the body. There are two forms of AIT, although both forms may occur in a single patient: type 1 develops in patients with underlying thyroid disease (iodine-induced hyperthyroidism), and type 2 develops in patients without underlying thyroid disease (destructive thyroiditis). Thyroid ultrasonography is helpful because it identifies the presence of thyroid nodules and the vascularity of the gland; type 2 AIT is characterized by hypervascularity, whereas type 1 AIT is associated with increased vascularity and blood flow velocity. Thyroid 131I uptake scans can also be useful, as uptake is very low in patients with type 2 AIT but may be normal or high in type 1 AIT.

For patients with type 1 AIT, the preferred treatment strategy is medical (thionamides), although spontaneous remission is unlikely because of the high levels of iodine present. Therefore higher doses of thionamides may be needed, and definitive therapy with surgery may be required, particularly given the risks of ongoing thyrotoxicosis in patients with underlying cardiac disease. Type 2 AIT may be self-limited, given that the destructive thyroiditis is caused by the amiodarone. It is best treated with glucocorticoids, at an initial dose of 0.5 to 0.7 mg/kg per day, with an initial course of 3 months. ILAI is not feasible in patients with either type of AIT because of the high iodine levels in the thyroid.

Suggested Readings

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Surgical Management of Thyroid Cancer

Jessica B. Shonk, MD, and James D. Perrier, MD, PhD

Surgery is the standard of care for management of most thyroid malignancies, and oncologic thyroid surgery, including resection of thyroid nodules suspicious for primary malignancy, is an important area of surgical expertise. The American Cancer Society estimated diagnosis of 56,870 new thyroid cancer cases in the United States in 2017, with 2010 thyroid cancer–related deaths expected that year. Most thyroid cancers occur in women (42,470 expected cases in 2017), with approximately equal mortality rates between the sexes. Thyroid cancer incidence in the United States has increased dramatically over the last four decades, rising from 4.9 per 100,000 individuals in 1975 to 14.3 per 100,000 in 2009. This increase is primarily due to rising incidence of the papillary thyroid cancer (PTC) subtype, and in particular, the fraction of newly diagnosed PTCs represented by small tumors (e.g., less than 1 cm in maximum dimension) has increased significantly. In light of this latter finding, previous expert consensus opinion attributed increasing thyroid cancer rates to expanded surveillance and improved diagnostic sensitivity. However, in the more than 30 years since introduction of ultrasonography into clinical practice (the most sensitive tool for thyroid structural assessment), thyroid cancer rates have continued to rise, suggesting that the increasing thyroid cancer incidence rate is not fully explained by a corresponding increase in the use and sensitivity of diagnostic technology. Finally, although PTC incidence has risen dramatically, as have corresponding rates of thyroid surgery, the overall thyroid cancer–related mortality rate in the United States over the last 4 decades has remained stable at 0.5 deaths per 100,000 individuals. This finding implies that many thyroid cancers will not ultimately result in death, regardless of whether such cancers are resected or otherwise treated. The role of this finding on surgical decision-making for thyroid cancer is under active investigation.

Preoperative Workup

Optimal thyroid cancer management is multidisciplinary, involving endocrinologists, radiologists, pathologists, and surgeons. Thyroid cancer diagnosis begins with discovery of a thyroid nodule, defined as an intraparenchymal lesion that is radiologically discrete from surrounding thyroid tissue. Palpable thyroid nodule incidence in euthyroid postprandial areas is approximately 4.8% in women and 1.5% in men between the ages of 30 and 60 years. This translates into an annual incidence of 0.09% and a lifetime risk for thyroid nodule development of 10%. Not all thyroid nodules are palpable, however, and incidental thyroid nodule discovery (so-called incidentalomas) during unrelated imaging is common. A thyroid incidentaloma will be identified in roughly one of every six neck computed tomography (CT) scans and 19% to 68% of neck ultrasound examinations results will reveal a thyroid nodule. Seven percent to 15% of thyroid nodules will be malignant. Indications for oncologic thyroid surgery are classified into three general categories: (1) diagnosis and treatment of thyroid nodules for which primary malignancy is suspected, (2) treatment of a known or recurrent thyroid cancer, and (3) prophylactic surgery for patients harboring gene mutations associated with high risk of thyroid cancer development. Thyroid cancer subtypes for which surgery is indicated include differentiated thyroid cancer (DTC, which includes the PTC and follicular subtypes), poorly differentiated thyroid cancer (PDTC), medullary thyroid cancer (MTC), and, in some cases, anaplastic thyroid cancer (ATC).

Malignancy workup for a thyroid nodule begins with a detailed history and physical examination. This includes assessment for familial thyroid cancer history, history of ionizing radiation exposure (especially during childhood), and signs/symptoms of hypothyroidism or hyperthyroidism. In addition, evaluation for evidence of rapidly progressive disease, including rapid nodule growth or rapid development of compressive/invasive symptoms (including hoarseness, dysphagia, or neck pain), is critical to early recognition of ATC, whereas careful physical examination of the bilateral central and lateral neck fields is crucial for nodal metastasis disease detection (Fig. 1). Familial thyroid cancer accounts for 5% to 10% of cases, and

Surgery as definitive therapy should be considered by patients considering starting families and who require high doses of antithyroid medications for euthyroidism, making spontaneous remission less likely. Surgery for patients diagnosed during pregnancy should be reserved only for those patients for whom medical management is not successful or those who have a contraindication to antithyroid medications. If performed, surgery during the first and third trimesters should be avoided, given the risks for fetal development and premature labor, respectively.

Amiodarone-Induced Thyrotoxicosis

Amiodarone is an iodine-rich antiarrhythmic drug that can result in amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism in 15% to 20% of patients. AIT may develop at any point during amiodarone treatment, even several months after cessation, secondary to its long half-life (up to 100 days) and storage in fat tissues within the body. There are two forms of AIT, although both forms may occur in a single patient: type 1 develops in patients with underlying thyroid disease (iodine-induced hyperthyroidism), and type 2 develops in patients without underlying thyroid disease (destructive thyroiditis). Thyroid ultrasonography is helpful because it identifies the presence of thyroid nodules and the vascularity of the gland; type 2 AIT is characterized by hypervascularity, whereas type 1 AIT is associated with increased vascularity and blood flow velocity. Thyroid ^{123}I uptake scans can also be useful, as uptake is very low in patients with type 2 AIT but may be normal or high in type 1 AIT.

For patients with type 1 AIT, the preferred treatment strategy is medical (thionamides), although spontaneous remission is unlikely because of the high levels of iodine present. Therefore higher doses of thionamides may be needed, and definitive therapy with surgery may be required, particularly given the risks of ongoing thyrotoxicosis in patients with underlying cardiac disease. Type 2 AIT may be self-limited, given that the destructive thyroiditis is caused by the amiodarone. It is best treated with glucocorticoids, at an initial dose of 0.5 to 0.7 mg/kg per day, with an initial course of 3 months. ILAI is not feasible in patients with either type of AIT because of the high iodine levels in the thyroid.

Suggested Readings

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Surgical Management of Thyroid Cancer

Jessica B. Shonk, MD, and James D. Prescott, MD, PhD

Surgery is the standard of care for management of most thyroid malignancies, and oncologic thyroid surgery, including resection of thyroid nodules suspicious for primary malignancy, is an important area of surgical expertise. The American Cancer Society estimated diagnosis of 56,870 new thyroid cancer cases in the United States in 2017, with 2010 thyroid cancer–related deaths expected that year. Most thyroid cancers occur in women (42,670 expected cases in 2017), with approximately equal mortality rates between the sexes. Thyroid cancer incidence in the United States has increased dramatically over the last four decades, rising from 4.9 per 100,000 individuals in 1975 to 14.3 per 100,000 in 2009. This increase is primarily due to rising incidence of the papillary thyroid cancer (PTC) subtype, and in particular, the fraction of newly diagnosed PTCs represented by small tumors (e.g., less than 1 cm in maximum dimension) has increased significantly. In light of this latter finding, previous expert consensus opinion attributed increasing thyroid cancer rates to expanded surveillance and improved diagnostic sensitivity. However, in the more than 30 years since introduction of ultrasonography into clinical practice (the most sensitive tool for thyroid structural assessment), thyroid cancer rates have continued to rise, suggesting that the increasing thyroid cancer incidence rate is not fully explained by a corresponding increase in the use and sensitivity of diagnostic technology. Finally, although PTC incidence has risen dramatically, as have corresponding rates of thyroid surgery, the overall thyroid cancer–related mortality rate in the United States over the last 4 decades has remained stable at 0.5 deaths per 100,000 individuals. This finding implies that many thyroid cancers will not ultimately result in death, regardless of whether such cancers are resected or otherwise treated. The role of this finding on surgical decision-making for thyroid cancer is under active investigation.

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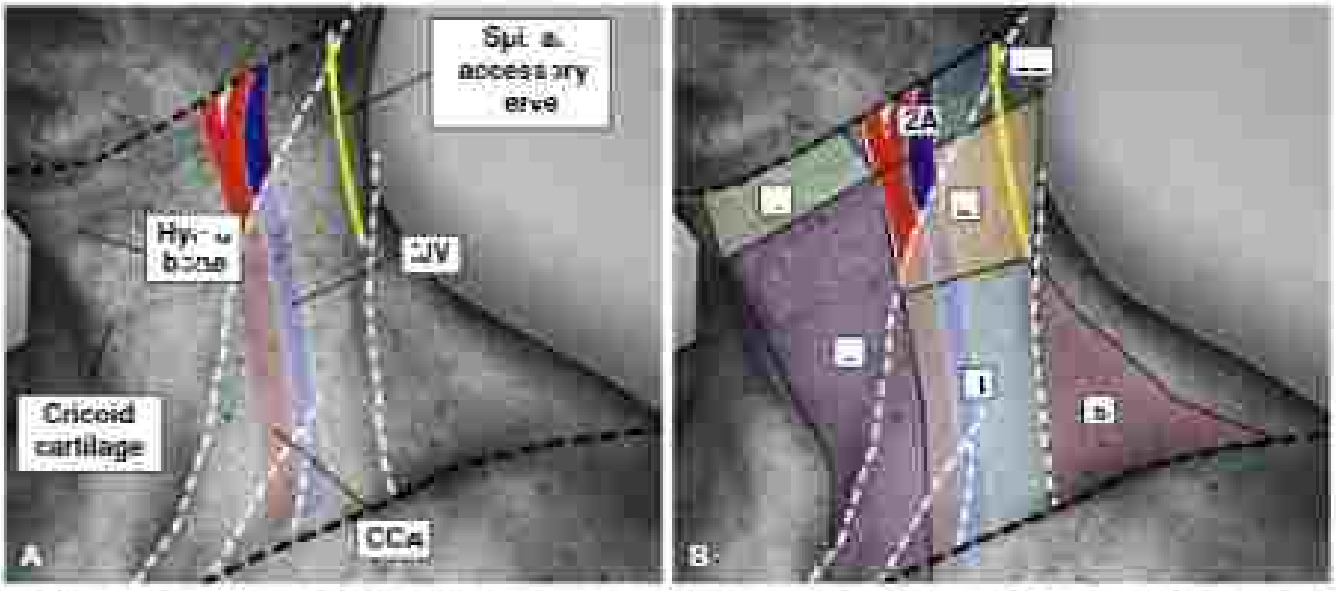

FIG. 1. Neck level team organization. (A) The left neck is shown. Important landmarks include the sternocleidomastoid muscle (SCM, white dashed line), the clavicle and lower border of the mandible (*not labeled*). (B) The common carotid artery (CCA), the internal jugular vein (IJV), the hyoid bone, the thyroid cartilage, and the spinal accessory nerve. (B) Nodal compartments. The boundary of the central (*level 6*) and lateral (*level 2–5*) nodal compartments, in which thyroid cancer may metastasize, are shown. Level 6: superior: hyoid bone, inferior: innominate artery, medial: tracheal midline, lateral: CCA. Level 2A: superior: inferior mandibular border/inferior hyoid bone, medial: spinal accessory nerve, lateral: posterior SCM border. Level 2B: superior: hyoid bone, inferior: cricoid cartilage, medial: CCA, lateral: posterior SCM border. Level 4: superior: cricoid cartilage, inferior: clavicle, medial: CCA, lateral: posterior SCM border. Level 5: superior: skull base, inferior: clavicle, medial: posterior SCM border, lateral: trapezius muscle.

patients with a first-degree relative diagnosed with DTC or MTC are at increased risk of thyroid cancer development. In addition, patients having known or suspected family history of gene mutations associated with thyroid malignancy will have increased thyroid cancer risk. These include mutations in the *PTEN* gene (Cowden's/*PTEN* syndrome), the *TSHR*-*ARMS* gene (Carney complex), the *APC* gene (familial adenomatous polyposis), and the *RET* gene (multiple endocrine neoplasia 2A and 2B). Exposure to ionizing radiation, especially during childhood, is also an important thyroid cancer risk factor. The risk of PTC development among children chronically exposed to fallout after the Chernobyl nuclear disaster, for example, is approximately nineteenfold higher than that of comparable unexposed populations. Thyroid function also influences thyroid cancer risk. Hypothyroidism not only confers an increased risk of disease development but is also associated with a more advanced cancer stage at the time of diagnosis. Hyperfunctional/hot thyroid nodules, in contrast, are associated with very low thyroid cancer risk (e.g., <2%). Physical examination findings suggestive of thyroid malignancy include hard nodule characteristics, fixed nodules, and palpable cervical adenopathy.

Thyroid Nodule Malignancy Assessment: Thyroid Function and Imaging

All thyroid nodule patients should undergo thyroid function assessment, which, for most patients, requires only serum thyroid-stimulating hormone (TSH) level testing. A suppressed serum TSH level indicates hyperthyroidism and should prompt radioiodine uptake scanning. Radioiodine avid (hyperfunctional/hot) nodules are associated with very low malignancy risk and do not merit additional workup for cancer. Otherwise, all thyroid nodules should undergo high-resolution Doppler ultrasonography (US), which is the most sensitive method for assessing thyroid malignancy risk. Other imaging modalities, including positron emission tomography (PET) scanning, CT, and magnetic resonance imaging, generally do not play a role in the initial workup for thyroid malignancy. Thyroid nodule US features concerning for malignancy have been well described, and high-risk findings (>90% specificity) include microcalcifications, hypervascularity, taller than wide shape, irregular nodule borders, and extrathyroidal nodule extension. Similarly, nodule US features reassuring for benign disease have also been defined, including spongiform character and purely cystic composition.

The cervical nodal basins in which thyroid cancer may preferentially metastasize (including levels 2A, 2B, 3, 4, 5 and 6, Fig. 1) should also be assessed by US when a potentially malignant thyroid nodule is discovered. Lymph node US features suggestive of metastasis include microcalcifications, loss of the normal nodal fatty hilum, cortical thickening, cystic composition, rounded shape, associated hypervascularity and hyperechogenicity. One or more of these US features will be identified in 20% to 30% of DTC patients, for example, and may change the associated operative strategy in approximately 20% of such cases.

Thyroid Nodule Malignancy Assessment: Aspiration Biopsy

A formal diagnosis of (thyroid) cancer requires tissue analysis, and suspicious thyroid nodules should undergo US guided fine needle aspiration (FNA) biopsy. Specific guidelines informing which thyroid nodules warrant FNA have been published by several different professional organizations, including the American Thyroid Association and the American College of Radiology. In general, all solid thyroid nodules greater than 1 cm in maximum diameter having US findings suspicious for malignancy should undergo FNA, as should most solid nodules greater than 1.5 cm in maximum diameter lacking suspicious US features. In addition, any cervical lymph node demonstrating US features suspicious for metastasis should undergo US guided FNA.

Interpretation of thyroid FNA samples (cytology) can be challenging in cases of DTC because the cytologic diagnosis of DTC depends on the aggregate presence of individual cellular features associated with malignancy, some of which are, in themselves, pathognomonic

TABLE 1 Bethesda Criteria for Categorization of Indeterminate Thyroid Nodule Cytology, with Associated Predicted Malignancy Risk in Each Case

Bethesda Category	Thyroid Malignancy Risk
1. Nondiagnostic/unsatisfactory	Up to 20%
2. Benign	1%–3%
3. Atypia of undetermined significance	5%–15%
4. Follicular/Hürthle cell neoplasm	15%–30%
5. Suspicious for papillary thyroid cancer	60%–75%
6. Malignant	97%–99%

For this reason, thyroid FNA findings are stratified into one of six possible categories (known as the *Bethesda categories*) according to the associated relative malignancy risk (Table 1). The Bethesda 1 category represents nondiagnostic findings, whereas benign cytology falls into the Bethesda 2 group. Cells having malignant features, but for which definitive evidence of malignancy is absent, are classified as indeterminate and represent the Bethesda categories 3 to 5, atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda 3), follicular neoplasm/suspicious for follicular neoplasm/suspicious for Hürthle cell neoplasm (Bethesda 4), and suspicious for papillary cancer (Bethesda 5), where each numerical increase in category designation is associated with an incremental increase in malignancy risk. The Bethesda 6 category is reserved for frankly malignant cytology. In contrast to DTC, cytologic identification of MTC, poorly differentiated thyroid cancer, and ATC tends to be more straightforward for the interpreting pathologist.

Approximately 25% of thyroid FNAs will be designated as Bethesda 3, 4, or 5. The risk of malignancy for these indeterminate cases may be further informed by aspirate genetic testing. In particular, mutations in the *BRAF* oncogene (most commonly the *BRAF*V600E mutation) confer 99% specificity for PTC, and the presence of this mutation should prompt thyroid surgery. Additional oncogenic driver mutations potentially characterizing DTC have also been described, and commercially available assays for these mutations have been developed. Other testing platforms comparing the genetic profile of aspirated thyroid samples against panels of mutations associated with thyroid cancer are also now commercially available. In general, the predictive values afforded by currently available genetic testing for the presence or absence of thyroid malignancy are imperfect. Most experts thus agree that the current value of such testing for clinical decision making in these cases is limited; cytologic assessment remains the gold standard in this regard. Nonetheless, the development of new genetic testing platforms, and the refinement of existing tests, for greater diagnostic accuracy among cytologically indeterminate thyroid nodules remains an area of intense interest and improved testing options are forthcoming.

Aspirate from suspicious cervical lymph nodes are, in general, readily assessed for metastasis because identification of thyroid epithelial cells in a lymph node represents metastatic disease. The sensitivity of nodal FNA may be increased by determining the associated level of the thyroid-specific protein, thyroglobulin (Tg), in the aspirate, and this testing should thus be routine. A nodal aspirate Tg value exceeding 33 ng/mL in a patient who has not undergone thyroidectomy is suggestive of metastasis and should prompt compartment-oriented neck dissection.

Thyroid Malignancy: Preoperative Testing and Preparation

Additional testing and optimization may be required before proceeding with surgery in cases of thyroid malignancy or suspected malignancy. Coexisting hyperthyroidism, if present, should be managed medically, and biochemical euthyroidism should be achieved using thionamide treatment before surgery (to minimize risk of intraoperative hyperthyroid crisis/thyroid storm). Serum calcium levels should also be assessed before surgery, and the presence of hypercalcemia should prompt blood parathyroid hormone level testing. Coexisting primary hyperparathyroidism should be assessed with parathyroidectomy concomitantly during thyroid surgery. Fine-cut CT scanning of the neck and upper chest, with intravenous (IV) contrast, should be performed in selected cases for which high-resolution anatomic imaging may direct operative planning. This includes cases for which locally invasive disease is suspected, including all suspected or confirmed cases of poorly differentiated and anaplastic cancer, cases for which nodal metastatic disease has been identified or is suspected (particularly when lateral neck nodal basins are involved), in reoperative/recurrent cases, and when substernal mediastinal disease extension is suspected. Preoperative voice change/hoarseness, evidence of thin liquid aspiration, or hemoptysis is suggestive of locally invasive disease and should prompt endoscopic assessment, including direct laryngoscopy, esophagoscopy, or both.

Blood calcitonin and carcinoembryonic antigen are biomarkers for MTC, and baseline levels for each should be established before surgery for patients diagnosed with MTC. In particular, marked elevation in blood calcitonin levels are suggestive of distant metastatic disease, and levels exceeding 400 pg/mL should prompt preoperative whole-body imaging, most commonly CT scanning with IV contrast and triple phase liver imaging. *RET* proto-oncogene assessment for mutations associated with MTC should be performed in the postnatal period for all children having family history of multiple endocrine neoplasia (MEN) type 2. Specific *RET* gene mutations correlate with MTC onset age, as well as relative disease aggressiveness, and thus direct the relative urgency of thyroid surgery. All patients diagnosed with MTC should be assessed for concomitant pheochromocytoma, either with plasma metanephrine and normetanephrine level testing or with 24 hour urine fractionated catecholamine level testing because these adrenal tumors may coexist in cases of MEN2. Pheochromocytomas are associated with potentially life-threatening intraoperative hypertensive crisis and should be resected, following appropriate perioperative α-blocker treatment, before proceeding with any invasive procedure (e.g., thyroidectomy). Finally, although the blood Tg level is an important marker for DTC recurrence after total thyroidectomy, this testing is neither sensitive nor specific preoperatively for thyroid cancer and thus should not be assessed before thyroidectomy.

THYROID SURGERY FOR MALIGNANCY OR SUSPECTED MALIGNANCY

Differentiated Thyroid Cancer

Thyroid surgery is indicated for most patients diagnosed with DTC. For symptom-free patients having unilateral DTC, the extent of thyroid surgery chosen depends primarily on the speculated need for postoperative radioactive iodine (RAI) treatment. Iodine is a primary component of thyroid hormone and the thyroid epithelium (including DTC, which is epithelium derived) is thus iodine avid. This thyroid-specific feature allows therapeutic targeting of DTC with radioiodine, and adjuvant RAI has been shown to improve disease outcomes under specific circumstances. These include DTC cases for which tumor diameter exceeds 4 cm, local invasion is identified, aggressive histologic findings are present (e.g., tall cell, columnar cell, and hobnail PTC variants), distant metastatic disease is identified, and, potentially, when cervical nodal metastasis is present. Under these circumstances, total thyroidectomy is required, as the presence of normal iodine and thyroid tissue (e.g., the contralateral thyroid lobe) likely decreases adjuvant RAI treatment efficacy. RAI treatment after total thyroidectomy for DTC may also facilitate disease recurrence monitoring because blood Tg levels in such cases should remain very low in the absence of recurrence.

The extent of thyroid surgery for unilateral DTC when adjuvant RAI is not indicated appears to play little, if any, role in long-term outcome. Limiting surgery to these cases to unilateral thyroid lobectomy affords several advantages. First, most of the patients who are euthyroid before surgery will remain euthyroid (up to 90%) if the contralateral thyroid lobe is left in situ, thus obviating need for obligate life long thyroid hormone replacement in most cases. Second, the risks of permanent postoperative hypoparathyroidism and of intraoperative bilateral recurrent laryngeal nerve (RLN) injury among patients undergoing thyroid lobectomy, relative to total thyroidectomy, are extremely low, if not completely obviated. The potential need for emergency management of life threatening postoperative expanding cervical hematoma after thyroid surgery is the primary reason for hospital admission after thyroidectomy. This risk is lower when surgery is limited to thyroid lobectomy and, as a result, some patients who undergo lobectomy are discharged on the day of surgery. In contrast, total thyroidectomy is frequently associated with overnight observation for hematoma development.

It is important to note that PTC is multifocal in approximately 20% to 30% of cases and that microscopic disease involving the lobe contralateral to an identified PTC may not be detectable by preoperative ultrasound. Thus patients undergoing thyroid lobectomy for identified unilateral PTC will require postoperative ultrasound surveillance of their remaining thyroid tissue. Associated development of new nodularity may require aspiration biopsy, and, if concern for malignancy is identified, completion thyroidectomy will be required. In addition, several DTC tumor features informing adjuvant RAI treatment decision making are only identifiable during formal postoperative surgical specimen analysis (e.g., aggressive histologic subtype, lymphatic invasion, and vascular invasion). Identification of such tumor features after thyroid lobectomy necessitates subsequent completion thyroidectomy, most commonly performed approximately 4 weeks after the index operation. Similarly, identification of new cervical nodal metastatic disease during surveillance after thyroid lobectomy for DTC necessitates completion thyroidectomy, as well as compartment-oriented neck dissection, followed by RAI administration. Total thyroidectomy is also generally recommended in cases of unilateral DTC when (1) benign contralateral thyroid nodularity is present, (2) concomitant Graves' disease or hyperthyroidism has been diagnosed, (3) preexisting comorbidities would preclude possible future completion thyroidectomy, (4) significant ionizing radiation exposure history is identified, especially during childhood, (5) a significant family history of thyroid cancer is identified, and (6) when the patient prefers total thyroidectomy.

Finally, recent prospective data have called into question the need for thyroidectomy among average risk patients diagnosed with isolated, small (≤1 cm) PTCs for which clinical and radiographic evidence of invasive or metastatic features are absent. Ongoing prospective serial monitoring studies involving such patients indicate that most of these cases will not progress, especially with increasing age at diagnosis (e.g., >40 years). Close serial observation for such PTCs by an experienced endocrinologist is thus a management option, especially among patients identified as high risk surgical candidates. Evidence for disease progression during follow up, namely primary tumor growth, development of multifocal disease or evidence of new metastatic nodal involvement, however should prompt surgery.

Identification of metastatic DTC involving cervical lymph nodes requires compartment oriented neck dissection at the time of total thyroidectomy (Fig. 1). It is important to note that metastatic disease involving the lateral neck (levels 2 to 5), without concomitant involvement of the ipsilateral central neck (level 6), is rare. Thus all DTC cases for which lateral neck nodal metastatic disease has been identified will require both ipsilateral lateral and central neck dissections, even when no clinical or radiographic evidence of central neck involvement is identified. In contrast, isolated metastatic DTC nodal involvement of the central neck, without concomitant lateral neck nodal disease, is common, and lateral neck dissection should be limited to cases for which associated metastatic disease is confirmed.

Occult nodal metastatic disease involving the ipsilateral central neck is common, and some experts thus recommend ipsilateral central neck dissection at the time of thyroidectomy for all cases of DTC, even when radiographic and clinical evidence of nodal metastasis absence is absent (prophylactic central neck dissection). Nonetheless, the impact of occult nodal metastatic central neck disease on DTC recurrence and disease specific survival, if any, appears to be minimal, and many surgeons therefore do not routinely perform prophylactic central neck dissection in these cases.

Nondiagnostic and Indeterminate FNA Biopsy Findings

Thyroid nodules for which aspiration biopsy findings are nondiagnostic (Bethesda I category) should undergo repeat biopsy. If this repeat testing remains nondiagnostic, thyroid surgery should be considered because thyroid malignancy may be present in up to 20% of such cases (Table 1). Indeterminate biopsy findings (Bethesda 2–5 categories) should also prompt referral for surgery, given associated malignancy rates between 5% and 75%, depending on the specific Bethesda category. The accuracy of intraoperative frozen section analysis for identification of thyroid malignancy in these cases is generally poor, and the extent of thyroid surgery selected (ipsilateral thyroid lobectomy versus total thyroidectomy) will thus depend on factors specific to the individual patient. Because at least some fraction of these nodules will be benign for each category, a lower threshold for limiting the extent of thyroid surgery (e.g., thyroid lobectomy only) should be used. Patients having indeterminate biopsy findings should be counseled carefully regarding the potential need for subsequent completion thyroidectomy should thyroid cancer requiring adjuvant RAI be identified during formal postoperative surgical specimen analysis. In general, thyroid lobectomy is recommended for average risk patients having indeterminate thyroid biopsy findings when the index nodule is less than 1 cm in maximal diameter and remains an option for nodules up to 4 cm in maximal diameter.

Medullary Thyroid Cancer

MTC is derived from the parafollicular C cells of the thyroid, which are neuroendocrine in origin and thus do not absorb iodine. RAI therefore plays no role in MTC management. All cases of MTC should be managed with total thyroidectomy. In addition, local nodal metastatic disease is relatively common for this tumor type, and bilateral central neck dissection (levels 6, Fig. 1) is indicated in all cases of MTC, even when preoperative workup is negative for suspicious adenopathy. Lateral neck dissection (levels 2 to 5) is formally indicated whenever associated nodal metastatic disease is discovered, generally by FNA of suspicious adenopathy identified before surgery. Prophylactic ipsilateral lateral neck dissection may be considered, especially when blood calcitonin levels are significantly elevated (e.g., >400 pg/mL), although the potential morbidity of this procedure must be carefully weighed against an unproven associated benefit. Finally, preoperative identification of distant metastatic disease in cases of MTC does not obviate need for total thyroidectomy and compartment oriented neck dissection. Although surgical cure is not possible in such cases, total thyroidectomy will prevent local disease progression, including development and progression of direct invasion into adjacent structures, including the RLN(s), the larynx, the esophagus and the trachea. Elevated calcitonin levels may also produce significant symptoms, including flushing, weight loss, and intractable diarrhea. Disease debulking by primary tumor resection and resection of cervical metastatic disease may thus produce significant symptomatic improvement (or prevent/delay symptom development) in some patients.

RET proto-oncogene mutations associated with familial MTC syndromes, most commonly MEN2A and MEN2B, have been

classified by the American Thyroid Association according to disease penetrance and relative aggressiveness: moderate risk mutations, high risk mutations, and highest risk mutations. Children carrying moderate risk mutations should be screened regularly for blood calcitonin elevation that, when present, should prompt total thyroidectomy. The presence of a high risk RET mutation is an indication for total thyroidectomy within the first 5 years of life, whereas prophylactic total thyroidectomy should be performed within the first year of life for the highest risk mutation category. Adults found to be RET gene mutation carriers but for whom both blood calcitonin level testing and thyroid ultrasonography results are normal should undergo annual blood calcitonin level reassessment, with total thyroidectomy and bilateral central neck dissection reserved for cases in which this level becomes elevated.

Anaplastic and Poorly Differentiated Thyroid Cancers

Thyroidectomy plays a limited role in the management of anaplastic thyroid cancer because surgery does not generally improve survival for this rare malignancy. Most anaplastic thyroid cancers are metastatic or unresectable at the time of diagnosis, and it is these two features that drive the very poor prognosis associated with this cancer. Surgery for anaplastic thyroid cancer should thus be limited to (1) patients for whom high-resolution CT, US, or PET scanning is negative for local and distant metastatic disease, as well as for locally invasive disease (and for whom surgical cure may thus be possible) and (2) patients requiring symptomatic palliation related to locally invasive disease. Anaplastic thyroid cancer is rapidly progressive, and surgery for the former group should be performed as soon as possible. The appropriate extent of surgery among these patients, however, remains an area of controversy. Anaplastic thyroid cancer cells are undifferentiated and do not absorb iodine. Thus radioiodine plays no management or adjuvant treatment role in these patients. In the absence of contralateral nodularity, ipsilateral thyroid lobectomy is therefore usually recommended to minimize potential operative risk. That being said, one or more concomitant foci of PTC will be identified in up to 20% of ATC cases and some experts thus recommend total thyroidectomy. All patients who undergo thyroid surgery for anaplastic cancer should be referred promptly for adjuvant oncologic care, including chemoradiation and long-term disease recurrence follow-up (during which clinically significant PTC among long-term survivors managed initially with thyroid lobectomy can be identified and appropriately treated). Palliative surgery for locally invasive anaplastic thyroid cancer should be limited to cases of anticipated impending airway compromise and generally involves placement of a tracheostomy tube. Debulking plays no significant role in treatment, as residual unresected tumor will rapidly regrow, often fungating from the surgical wound, and generally involves significant blood loss. Even in the context of tracheostomy, anaplastic tumors may still produce airway compromise because rapid tumor growth may occlude the tracheostomy tube.

The considerations informing surgical decision making for PDTC are similar to those arising when managing DTC. Relative to DTC, PDTC is more likely to present with distant metastatic disease and, although this malignancy is by definition less responsive to radioiodine therapy, most patients will undergo adjuvant radioiodine therapy. Total thyroidectomy is thus indicated for known or suspected cases of PDTC. PDTC is also more likely to be locally invasive at the time of diagnosis and en bloc resection of involved structures is indicated in such cases. As in the case for DTC, central neck dissection, with or without lateral neck dissection, should be performed when clinical or radiologic evidence of cervical nodal metastatic disease is identified. Such disease is more common in PDTC (up to 45%) relative to DTC. Routine prophylactic compartment-oriented neck dissection in for PDTC remains controversial because data linking this practice to improved disease outcomes remain scant.

Rare Thyroid Tumors

Rare tumor types involving the thyroid include primary thyroid lymphomas, teratomas, and metastatic disease of extrathyroidal origin. Biochemical studies and thyroid imaging will not distinguish these tumors from benign or malignant primary thyroid nodules, and diagnosis thus depends on tissue assessment. Aspiration biopsy in cases of thyroid lymphoma is frequently nondiagnostic, although specimens characterized by high lymphocyte content are suggestive of this pathology. Core needle biopsy, with immunohistochemical or flow cytometric analysis, is generally required for diagnosis confirmation. Aspiration biopsy in cases of thyroid teratoma is also generally nondiagnostic, although the morphologically unusual cells identified by cytologic assessment may prompt core needle biopsy, which may be diagnostic. Nonetheless, the diagnosis of thyroid teratoma is frequently made during formal surgical specimen analysis after thyroidectomy. Finally, metastatic disease involving the thyroid, most commonly renal cell carcinoma or melanoma, generally occurs in the context of established primary tumor history and is usually readily diagnosed through FNA.

Indications for resection of unusual thyroid tumors depends on the specific diagnosis suspected. Surgery does not play a role in the management of thyroid lymphoma, and these patients should be referred for chemotherapy. Thyroid lobectomy with en bloc resection of involved structures and ipsilateral central neck dissection is likely to afford the best long-term outcome among patients diagnosed with a thyroid teratoma, although the data informing surgical decision-making for these rare tumors are extremely limited. These patients should also be referred for postoperative adjuvant therapy, generally involving both external beam radiation and chemotherapy. Finally, the utility of thyroidectomy for metastatic disease involving the thyroid will be informed by (1) the prognosis associated with the originating primary malignancy and (2) local associated symptoms for which palliation may be considered. When indicated, thyroid surgery in these cases is generally limited to en bloc resection of the involved lobe only.

THYROIDECTOMY: TECHNICAL CONSIDERATIONS

Disease recurrence and survival rates for resectable thyroid cancers are directly related to completeness of resection and an R0 resection should thus be attempted whenever possible. The surgeon should therefore be prepared for possible en bloc resection of involved structures, most commonly the strap musculature, followed by the ipsilateral RLN, the trachea, the esophagus, the larynx and the ipsilateral internal jugular vein. Residual tumor should not be left in situ under the assumption that this tissue will be destroyed by adjuvant RAI therapy, which may not clear such disease. Careful intraoperative inspection and palpation of the central neck is also critical because this may identify metastatic nodal disease missed during preoperative ultrasound scanning. When resected, the RLN should be reconstructed by primary anastomosis of its unresected ends to minimize ipsilateral laryngeal muscle atrophy. An ansa cervicalis nerve graft may be used for this purpose if the RLN cannot be primarily reconstructed in a tension-free manner. Complete initial disease resection also minimizes risk of local/regional cervical recurrence, which often requires reoperative surgery. Reoperative neck surgery is often technically challenging because wound bed scarring after the index operation may obliterate local tissue planes and distort normal anatomic organization. Risk of injury to associated structures, including the ipsilateral RLN and parathyroid glands, is thus higher in reoperative cases.

As is the case for all thyroid surgery, meticulous intraoperative hemostasis must be maintained because even low volume postoperative bleeding may produce life-threatening airway compromise, requiring emergency evacuation. Intraoperative hemostatic control may be facilitated by use of commercially available vessel sealing energy devices, in addition to traditional electrocautery, suture tie,

and titanium clips. Identification of the ipsilateral RLN is required during thyroid surgery and, although nerve identification and functional assessment may be facilitated by use of nerve monitoring technology, this technology is not a surrogate for manual nerve exposure and dissection. Nonetheless, intraoperative nerve monitor signal loss from an otherwise intact RLN indicates nerve dysfunction and may prompt deferment of planned contralateral thyroid lobe resection. Comorbid oral RLN injury in this context results in bilateral vocal cord paralysis, with possible associated airway compromise. Last, the thyroid surface should be carefully scrutinized during dissection for adherent parathyroid glands, and, assuming no direct tumor involvement, such glands should be carefully mobilized away from the thyroid, with their native blood supplies preserved. Inadvertent intraoperative devascularization or resection of all four parathyroid glands will produce permanent hypoparathyroidism, with significant morbidity stemming from resultant hypocalcemia. Even when the parathyroid glands are carefully preserved, temporary postoperative hypocalcemia is common, and liberal calcium supplementation may be required temporarily in the immediate postoperative period after total thyroidectomy. Devascularized parathyroid glands should be autotransplanted, most commonly into the ipsilateral sternocleidomastoid muscle.

A number of alternative surgical approaches intended to avoid or minimize a cervical incision, and thus development of a potentially unsightly cervical scar, have been developed for thyroidectomy. These include endoscopic/robotic axillo-breast, facelift, and transoral approaches. Such approaches are intended to maximize postoperative cosmesis and may not afford equivalent oncologic outcomes relative to the traditional open approach, especially in cases of invasive or locally metastatic disease. Such alternative surgical approaches should thus be used with caution and, in general, only by surgeons with significant expertise in their use.

Suggested Readings

1. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid. 2017;27(11):1341–1346.
2. Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS Committee. J Am Coll Radiol. 2017;14(5):587–595.
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1–133.
4. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association Guidelines for the management of medullary thyroid carcinoma. American Thyroid Association Guidelines task force on medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610.

Primary Hyperparathyroidism

Kathryn E. Cosa, MD, and Tracy S. Wang, MD, MPH, FACS

Parathyroid glands are responsible for the synthesis and secretion of parathyroid hormone (PTH), which acts to increase serum calcium levels to achieve calcium homeostasis. PTH synthesis is tightly controlled by feedback mechanisms involving serum calcium and vitamin D levels. Primary hyperparathyroidism (PHPT) is the result of inappropriate PTH production by one or more abnormal parathyroid glands, leading to elevated serum calcium levels (Fig. 1).

Epidemiology

The prevalence of PHPT has increased over the last 30 years but remains underdiagnosed and undertreated. Currently, the prevalence of PHPT is estimated to be 0.86% of the general population, increasing to 1% in postmenopausal women. The incidence of PHPT appears to increase with age and is estimated to be two to three times higher in women. Autonomous parathyroid function may be secondary to adenoma(s), hyperplasia, or, rarely, parathyroid carcinoma. Approximately 80% of cases of PHPT results from a single gland adenoma, 10% to 15% of cases are secondary to four gland hyperplasia, and 4% are attributed to adenomatous expansion to two or three glands. Parathyroid carcinoma is responsible for approximately 1% of PHPT cases and generally is characterized by very high serum calcium and PTH levels.

Diagnosis and Evaluation

The diagnosis of PHPT is biochemical and is characterized by hypercalcemia with a high or inappropriately normal PTH level. The biochemical evaluation should include serum levels of total calcium, concurrent PTH, creatinine, and 25-hydroxyvitamin D. Elevated total calcium levels, representing biologically active calcium, are not required for the diagnosis of PHPT but may aid in the diagnosis of patients with normal serum calcium levels and suspected PHPT. A 24-hour urinary calcium level should be obtained to rule out familial hypocalciuric hypercalcemia (FHH), an autosomal dominant syndrome resulting from loss-of-function mutation in the calcium sensing receptor gene. A value less than 100 mg/24 h should raise suspicion for FHH, and a calcium/creatinine clearance ratio should be calculated [(24-hour Ca urine/Ca serum) divided by (24-hour creatinine urine/creatinine serum)]. A value of less than 0.01 is diagnostic for FHH whereas a ratio greater than 0.02 is diagnostic of PHPT. In patients with values in between 0.01 and 0.02, other causes of hypocalciuria should be evaluated, such as chronic kidney disease, increased age, and use of thiazide diuretics. Genetic testing may also be considered in these patients.

The clinical presentation of PHPT is heterogeneous and continues to evolve. A thorough preoperative evaluation should address objective manifestations of PHPT, including nephrolithiasis, osteoporosis, and fragility fractures. If not previously obtained, a bone mineral density test is recommended and should include the lumbar spine, hip, and distal one third of the radius. A complete history should address subjective symptoms of PHPT, which can range from mild to severe. These include neurocognitive complaints such as irritability, anxiety, depression, short-term memory deficits, and difficulty concentrating; constitutional symptoms, including fatigue and insomnia; gastrointestinal complaints such as dyspepsia, abdominal pain, and constipation; musculoskeletal symptoms, including muscle, bone, and joint pain; and genitourinary complaints such as polydipsia/polyuria. A careful family history is critical to the workup of PHPT because several familial syndromes are associated with this disease. These include multiple endocrine neoplasia (MEN) type 1, MEN type 2A, and hyperparathyroidism–jaw tumor syndrome. In patients in whom an inherited syndrome is suspected (patients <40 years and those with multigland hyperplasia), genetic counseling is recommended because the specific disease and mutation may impact timing and extent of surgery.

Indications for Surgery

Parathyroidectomy remains the only curative intervention for PHPT and should be considered in all symptomatic patients. In

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Suggested Readings

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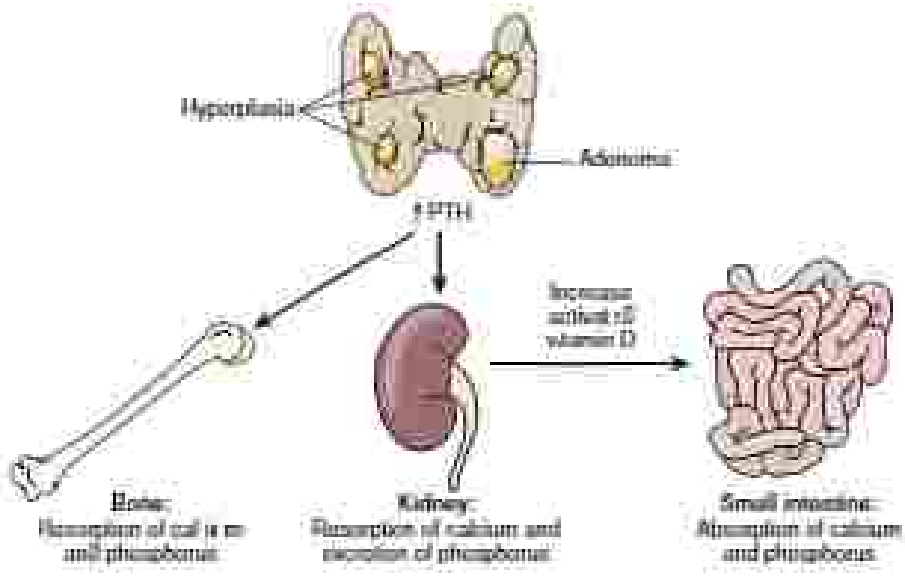


FIG. 1 Pathophysiology of primary hyperparathyroidism.

symptom free patients, both the American Association of Clinical Endocrinologists and the National Institutes of Health recommend parathyroidectomy when

- Serum calcium level is greater than 1 mg/dL above the normal laboratory range
- Presence of renal insufficiency, hypercalciuria, nephrolithiasis, or creatinine clearance less than 60 mL/min
- Presence of osteoporosis, vertebral compression fracture, or bone mineral density T-score of −2.5 or lower
- Patient younger than 50 years

Surgery in these patients should be considered even for patients without symptoms who are many asymptomatic patients may have mild symptoms that are difficult to identify. Patients with mild symptoms may benefit from surgery. Surgery is also recommended for patients who are unable to undergo regular follow-up. Surgery may be more cost-effective than medical management for some patients, especially those who are not operative candidates.

Localization

The majority of cases of PHPT are secondary to a solitary adenoma, which may be seen on single-dose imaging. Currently, the extent of our knowledge may not confirm a unilateral or bilateral disease, although it is usually possible to localize the lesion. The most common imaging modalities used to localize parathyroid adenomas are ultrasound (US), sestamibi scan, and four-dimensional computed tomography (4D-CT). Choice of imaging depends on availability and multidisciplinary skills, in addition to the clinical presentation by the patient and the surgeon.

Cervical Ultrasonography

Cervical US is often considered for all patients with PHPT, primarily to detect thyroid nodules, which are found in 40% of patients, and to identify concomitant thyroid pathology that can be addressed at the time of surgery. However, it is also a very operator-dependent study. However, it can still show parathyroid adenomas, which may be missed by clinical palpation. Patients with a thyroid ultrasound experience has a sensitivity of 76% to 94% and a specificity of 94% to 96%. Parathyroid adenomas appear as oval or round masses that are usually near the thyroid gland (Fig. 2).

Sestamibi Scanning

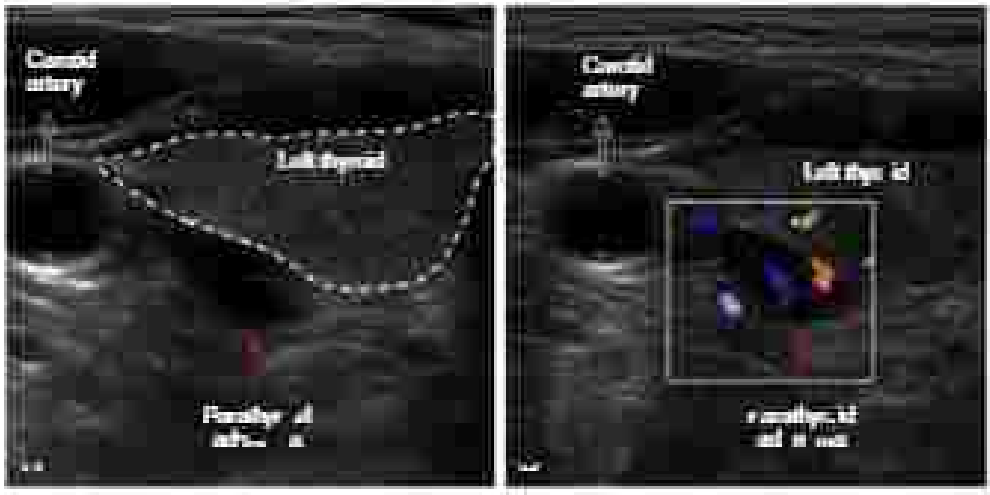
Sestamibi imaging is the most commonly performed nuclear medicine test used to localize parathyroid adenomas. There are multiple protocols available, such as dual-phase or subtraction techniques with single-photon emission CT (sestamibi SPECT) or dual-tracer subtraction (Fig. 3). The sensitivity and specificity of sestamibi SPECT are 80% to 90% and 97% to 98%, respectively. These localization studies are highly necessary for reoperative parathyroidectomy, minimally invasive surgery, and for patients who are unable to undergo neck exploration. Sestamibi scans may have a higher false-negative rate than US, but it may have further accuracy.

Four-Dimensional Computed Tomography

Four-dimensional CT is similar to traditional CT. The technique involves thin slices (0.5 mm) multiphasic CT scanning, with a fourth dimension consisting of contrast administration over time. Comparison between images obtained with three different phases allows differentiation of enlarged parathyroid glands from adjacent structures, including thyroid tissue and cervical lymph nodes (Fig. 4). Four-dimensional CT has a reported sensitivity and specificity of 85% and 99% for localization of disease and 66% and 89% for specific localization. Overall, the use of either 4D-CT or sestamibi SPECT improves accuracy and surgical success compared with US alone. The sensitivity of imaging studies is partially determined and all are operator variables by region and performance, per case. In general, more experienced providers achieve the best localization accuracy. The above-mentioned studies should be performed at high-volume centers when possible.

Preoperative Management

Most patients with PHPT should be maintained on 1000 to 1200 mg of calcium per day because low calcium intake can stimulate PTH secretion, resulting in worsening bone demineralization. Vitamin D deficiency is also common in PHPT, and patients with vitamin D deficiency (<20 ng/mL) should be supplemented. Multiple studies have shown it is not only safe but beneficial to supplement vitamin D to levels greater than 30 ng/mL to prevent increased bone loss.



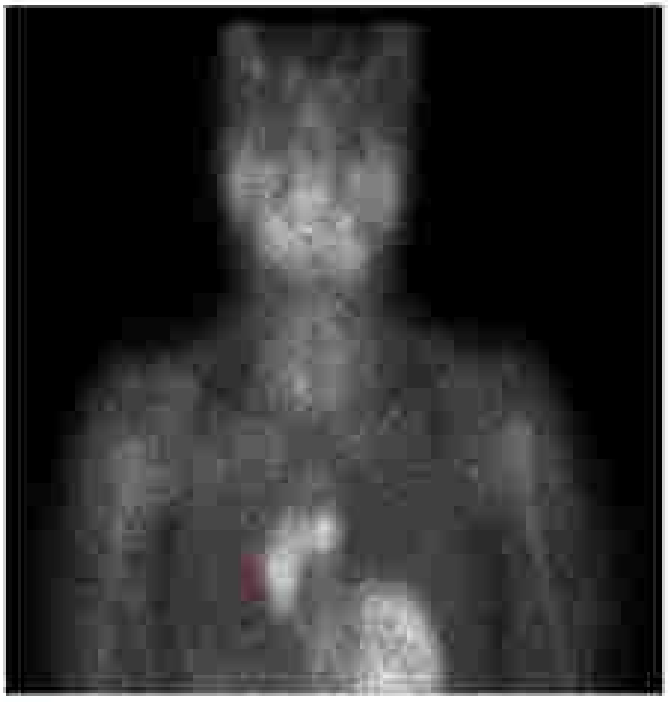


FIG. 3. Single-photon emission computed tomography acquisition obtained at 2 hours demonstrating increased uptake in a nodule of mass in the anterior upper mediastinum.

Severe hypercalcemia (>14 mg/dL) is rare in PHPT. However, patients who present to hypercalcemic crisis should be stabilized before surgery, and the possibility of parathyroid carcinoma should be considered. Stabilization begins with volume repletion using isotonic saline. Once adequately rehydrated, loop diuretics may be used to blunt calcium absorptive and proximal calciuresis. In refractory cases, calcitonin and bisphosphonates that inhibit bone resorption may be used. Once stabilized these patients should undergo parathyroidectomy.

Subjective assessment of vocal quality should be addressed before surgery. Patients with a history of prior operations involving either the vagus or recurrent laryngeal nerve should undergo preoperative vocal cord evaluation. Patients with subjective voice complaints should also be thoroughly evaluated for vocal cord function. Vocal cord evaluation can include direct or indirect laryngoscopy, videostroboscopy, or transcutaneous vocal cord ultrasonography.

INTRAOPERATIVE ADJUNCTS

Intraoperative Parathyroid Hormone Monitoring

Intraoperative PTH (IOPTH) monitoring allows for real time evaluation of parathyroid function. PTH has a short half life of 2 to 4 minutes, and therefore PTH levels should drop rapidly after successful excision of hyperfunctioning parathyroid tissue. Failure of the IOPTH level to decrease appropriately after excision of an enlarged parathyroid gland indicates the presence of additional disease and should prompt conversion to bilateral neck exploration.

Various IOPTH criteria exist to ensure cure. The Miami criterion protocol uses a greater than >50% IOPTH drop from the highest preexcision or postexcision measurement of IOPTH in a blood sample taken 10 minutes after resection of hyperfunctioning glands to confirm successful parathyroidectomy. Cure rates of 95% to 99% have been reported with this criterion. However, some studies have suggested that the Miami criteria are more likely to miss multigland disease with a sensitivity of only 80% for this pathology. This has led to the investigation of more stringent protocols, one of the most widely used is the [illegible] protocol. This protocol requires a greater than 60%-drop from the preexcision value at 10 minutes after resection of hyperfunctional glands and the 10 minute value should to be close to or within normal range to ensure successful parathyroidectomy. This protocol also has reported cure rates of 97% to 99%, with an improved sensitivity of 95% for multigland disease. However, surgeons should be aware that this protocol has been associated with an increased incidence of negative bilateral explorations ranging from 1% to 2%.

Surgeons should be aware of factors that can influence IOPTH results. Blood drawn from an ipsilateral central neck vein may have higher PTH levels than a peripheral sample and may take longer to decrease. It is also important to ensure samples are not diluted with intravenous fluids. Intravenous anesthetics (particularly propofol), or hemolysed, as these may lead to falsely low IOPTH levels.

Bilateral Internal Jugular Sampling or Localization

In patients with results showing preoperative imaging, or during a parathyroidectomy in which the abnormal parathyroid gland cannot be identified, IOPTH levels obtained from each internal jugular vein may help localize the location of an adenoma. Bilateral internal jugular vein IOPTH levels and a peripheral IOPTH level should be obtained in a close time proximity, a gradient of 5% to 10% is suggestive of lateralization to the side of the higher IOPTH level. This method was found to be more accurate for superior parathyroid glands, believed to be secondary to drainage patterns, because of this, samples should be obtained as low as possible on the internal jugular vein to ensure that the sample is obtained inferior to the site of venous drainage.

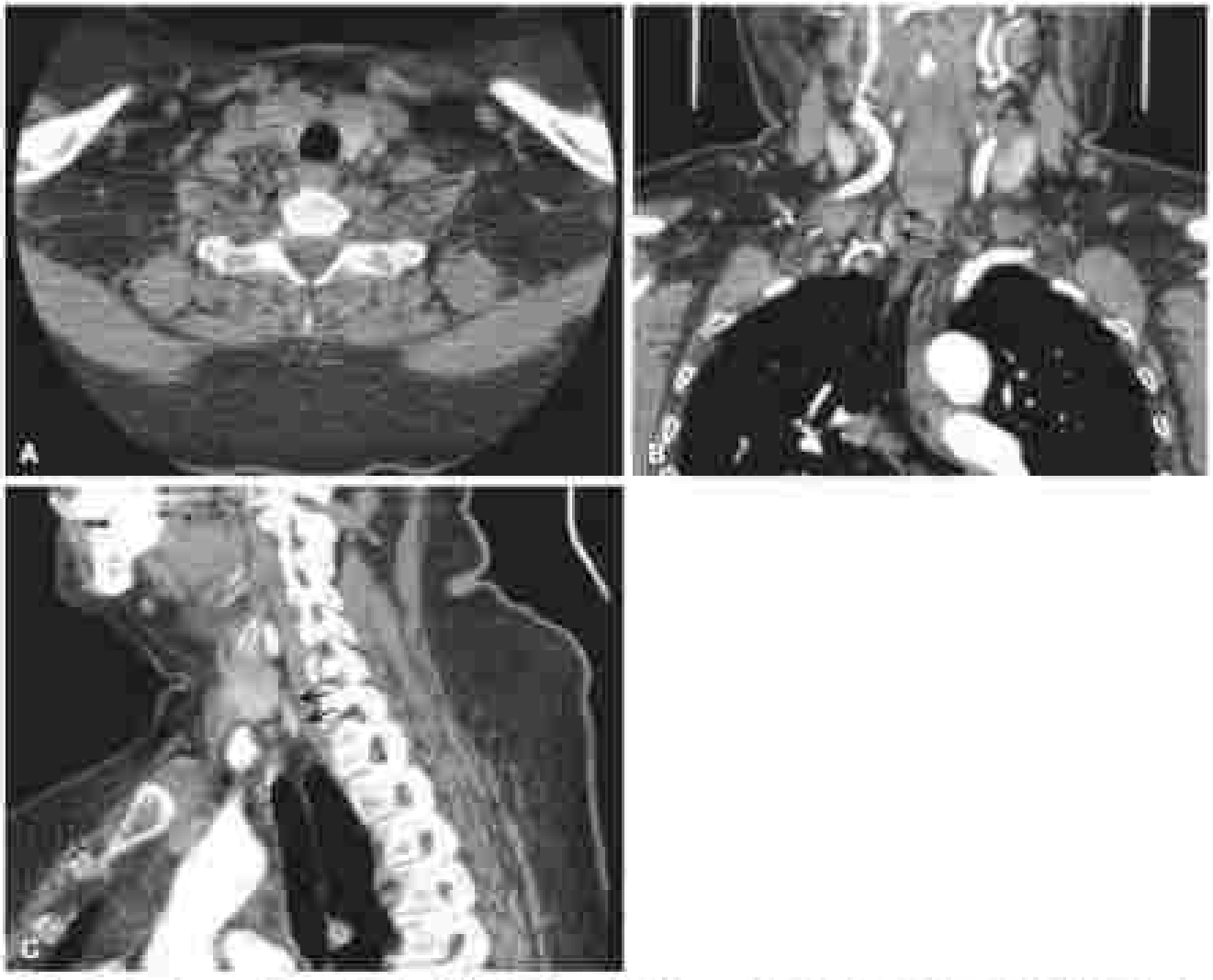


FIG. 4 Four-dimensional computed tomography scan with (A) axial, (B) coronal, and (C) sagittal multiplanar views during the arterial phase of an enlarged right inferior parathyroid adenoma.

Gamma Probe–Mediated Intraoperative Parathyroid Adenoma Localization

This technique is performed using technetium 99 m, the nuclear tracer used for metabolic scanning. Technetium 99 m is injected 1 to 2 hours before the operation. A handheld gamma probe is used to help guide the dissection. Once the gland is excised, ex vivo counts are obtained. This value is compared with the counts of the resection field, with a 20% drop in gamma emission indicating resection of an abnormal gland. This can be used as an adjunct with IOPTH monitoring or bilateral exploration. It has not been validated as an independent utility to identify or exclude multigland disease.

Gland Confirmation

Excision of abnormal parathyroid tissue is critical for successful parathyroidectomy. However, thyroid nodules or lymph nodes may be misidentified as parathyroid tissue during surgery. Traditionally, parathyroid tissue has been confirmed with intraoperative frozen section. However, at some institutions this may increase operative time and cost. In vivo aspiration using IOPTH is an accurate and inexpensive option to distinguish parathyroid tissue. In vivo aspiration of the gland is performed using a 25-gauge needle to aspirate the abnormal parathyroid (Fig. 5). The aspirate is then run with the serum IOPTH samples. An ex vivo aspirate IOPTH level of more than 1.5 times that of the baseline serum IOPTH level is consistent with parathyroid tissue with a 100% specificity and 98.3% accuracy.

PARATHYROIDECTOMY

Parathyroid Embryology and Anatomy

Surgeons' familiarity with parathyroid anatomy is critical to identify eutopic and ectopic parathyroid glands. Most patients have four parathyroid glands. However, up to 13% may have additional parathyroid tissue. Embryologically, the inferior and superior parathyroid glands are derived from the third and fourth pharyngeal pouch, respectively, secondary to embryologic descent, parathyroid gland location can be variable (Fig. 6). However, superior and inferior glands are symmetric 70% to 85% of the time. The superior parathyroid glands descend with the thyroid and are posterior to the recurrent laryngeal nerve. They can commonly be found near the cricothyroid junction and are associated with the posterolateral aspect of superior thyroid. The inferior parathyroid glands descend with the thymus and tend to be located in a more anterior plane. They are usually close to the inferior pole of the thyroid gland or within the thymofalyx ligament. Ectopic parathyroid glands can be found in a variety of locations related to their descent. The most common location is the thymus, but other locations include the tracheoesophageal groove, retroesophageal space, intrathyroidal, mediastinal or undescended in the carotid sheath (Fig. 7).

FIG. 5 Ex vivo parathyroid adenoma.

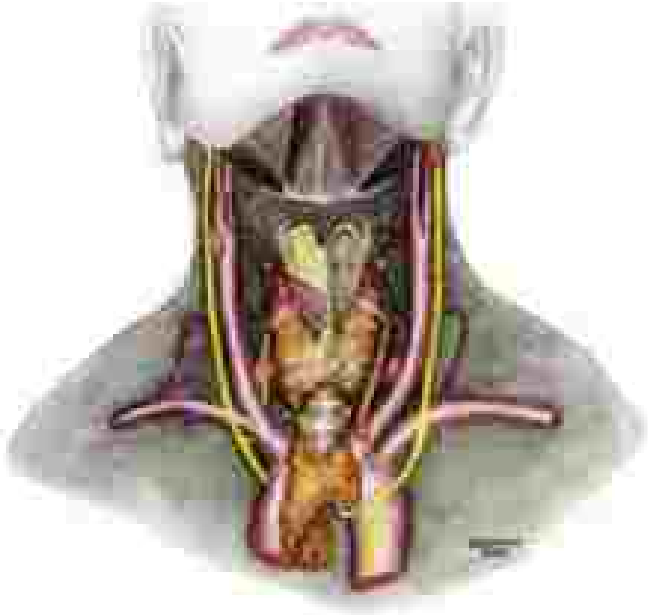


FIG. 6 Ectopic and complex parathyroid locations. (From White ML, [illegible] Radiographics. 1998;18(4):937–957.)

Minimally Invasive Parathyroidectomy

Minimally invasive, or "focused," parathyroidectomy (MIP) should be performed in patients when preoperative localization is successful and IOPTH monitoring is available because this improves the rate of cure, compared with relying on preoperative imaging alone. MIP is not recommended for patients when there is evidence of bilateral disease on preoperative imaging or evidence of familial hyperparathyroidism. MIP can be performed with the patient under general anesthesia or with superficial cervical plexus nerve blockade and local anesthesia. However, the latter requires a compliant patient and coordination between the surgical and anesthesia teams.

Before MIP, the surgeon should review the preoperative imaging and, if possible, have these available in the OR. Before intubation, a baseline serum PTH level is obtained to avoid a potential spike in the PTH level from manipulation of the neck with intubation or surgical prep. The patient is then positioned with the neck slightly extended, using a shoulder roll or inflatable cuff. A 2- to 4-cm transverse incision is made approximately one or two fingerbreadths above the sternal notch, in a preexisting skin crease, if possible. The platysma is divided with electrocautery, and subplatysmal flaps are raised. The midline raphe between the strap muscles is opened. The strap muscles are then taken off the thyroid and retracted laterally. At this point the thyroid is retracted medially to expose the targeted parathyroid gland.

If there is difficulty finding a suspected parathyroid adenoma, it is important to refer to the embryology and anatomy described above. When looking for a superior gland, it is important to evaluate the thyroid is elevated and medially rotated. This allows for adequate posterolateral exposure of the superior aspect of the gland. When looking for an inferior parathyroid gland, it is important to evaluate the preoperative imaging to determine inferior extent of the gland in relation to the inferior pole of the thyroid because this gland may be adherent to the pole or more inferiorly to the thymus ligament or thymus. Identification of the recurrent laryngeal nerve may also be beneficial because superior parathyroid glands are located posteriorly relative to the recurrent laryngeal nerve and superior to the inferior thyroid artery, whereas the inferior glands are generally anterior to the nerve and inferior to the inferior thyroid artery. It is also necessary to fully evaluate the thyroid capsule as the parathyroid gland may be located underneath.

Once the abnormal parathyroid gland is identified, it should be carefully dissected, taking care to avoid rupture of the capsule because this may lead to spillage and implantation, resulting in parathyromatosis. Once the gland is excised, it should be confirmed to be parathyroid tissue. This can be done with visual inspection accompanied by an appropriate decrease in IOPTH levels, intraoperative frozen section, or ex vivo operation with IOPTH level, as described above. Serum IOPTH levels are assessed immediately after excision of the

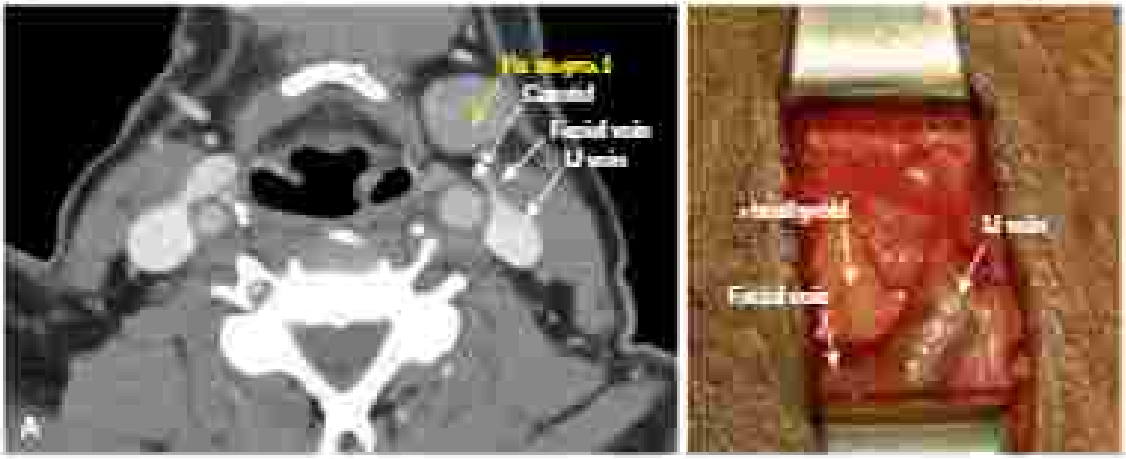


FIG. 7 Ectopic parathyroid adenoma located in the carotid sheath adjacent to the facial vein. (A) Four-dimensional computed tomography scan demonstrating an ectopic parathyroid adenoma located in the carotid sheath adjacent to the facial vein (F). (B) Operative view of the same patient with the ectopic parathyroid identified between the internal jugular and facial veins. J, Internal jugular.

abnormal gland (three now) and again 5 and 10 minutes after excision. The probability of cure is estimated using the protocol the surgeon is most familiar with as discussed above. Once the gland is excised and while awaiting IOPTH results, hemostasis is ensured. Any normal parathyroid glands identified during exploration are inspected for viability, and the anatomic integrity of the recurrent laryngeal nerve, if exposed, is verified. Hemostatic agents may be placed in the wound bed. The operation concludes with reapproximating the strap muscles and platysma using absorbable 3-0 suture. The skin is closed using a cosmetic technique the surgeon is most comfortable with.

Conversion from MIP to bilateral exploration is recommended when evidence of multigland disease is found, when an abnormal parathyroid cannot be found, or if there is failure of the IOPTH levels to drop appropriately per the surgeon's designated protocol, as discussed previously.

Bilateral Neck Exploration

Bilateral neck exploration may be the initial operative intervention planned when preoperative studies are discordant or nondiagnostic, if IOPTH monitoring is unavailable, when there is a high suspicion of multigland disease such as familial hyperparathyroidism, or by surgeon preference. As discussed previously, surgeon familiarity with parathyroid embryology and anatomy is critical for successful surgery. If bilateral exploration is performed for localized disease, it is recommended to identify this gland first. If performed for nonlocalized disease, initial dissection can be started on either side. During bilateral neck exploration, all four parathyroid glands should be identified before resection of any tissue. Normal parathyroid glands are typically 20 to 40 mg. They are soft and often associated with fat. These glands should be carefully preserved. If a single parathyroid adenoma is identified, it is resected, and the remaining normal parathyroid glands left in situ. If IOPTH is available, it can be used for confirmation of visual findings but is not mandatory when all glands are identified. If multiple abnormal parathyroid glands are identified subtotal parathyroidectomy is performed. Again only abnormal parathyroid glands should be excised, such as in the case of a double adenoma. In this situation IOPTH can be especially useful to confirm visual findings of this less frequently encountered pathology.

When tissue gland hyperplasia is present, a subtotal (3.5-gland) parathyroidectomy is generally the preferred approach. Leaving the remaining parathyroid tissue in situ improves parathyroid viability, decreases the risk of permanent hypoparathyroidism and avoids the need to wait for autotransplanted parathyroid tissue to function, as this may take 6 to 8 weeks or longer. The choice of which parathyroid to leave should be decided early to ensure remnant viability. The gland to be divided should be the most normal appearing and, ideally, be easily accessible in case reoperation is needed for recurrent disease. The volume of parathyroid gland being left in situ should approximate one to two times the volume of a normal parathyroid gland. Division can be performed by placing a large titanium hemoclip across the gland and then dividing distally. A permanent suture may be left on the remnant with long tails to facilitate easy identification if recurrent disease or reoperative neck surgery is necessary in the future.

In rare cases when a total parathyroidectomy is performed, autotransplantation of parathyroid tissue is required to avoid leaving the patient with permanent hypoparathyroidism. When performing a total parathyroidectomy with autotransplantation, the parathyroid tissue to be transplanted may be placed into the nondominant brachioradialis muscle rather than the sternocleidomastoid muscle. This avoids complications of reoperative neck surgery in the case of recurrent disease. Autotransplantation is performed by harvesting a volume of parathyroid tissue approximately equivalent to that of a normal parathyroid gland from the most normal-appearing gland resected. This tissue then is minced sharply into 1 mm fragments. The nondominant brachioradialis muscle then is exposed, and three or four pockets are made in the muscle bluntly using blunt dissection. Equal volumes of the prepared parathyroid are placed into each respective muscle pocket. The pockets are closed with nonabsorbable suture with the ends left long to facilitate future operative localization, if necessary. A hemoclip may be placed on each suture to allow subsequent radiographic localization.

If available, use of IOPTH monitoring should be considered during bilateral exploration because this may help confirm visualized findings, as well as aid in recognition of supernumerary parathyroid glands. It can also help with the decision for autotransplantation. If the IOPTH drops to values below normal range after a 3.5-gland subtotal parathyroidectomy, autotransplantation may be a consideration to avoid permanent hypoparathyroidism. Similarly, if IOPTH levels remain marginally elevated after subtotal parathyroidectomy, consideration can be given to additional resection of the remnant gland.

When no abnormal parathyroid glands are identified during bilateral exploration, thorough evaluation of ectopic locations should be performed. This includes thorough evaluation of the tracheoesophageal groove and retroesophageal space, opening the carotid sheath, and consideration of a cervical thymectomy or rarely ipsilateral thyroid lobectomy. Bilateral internal jugular sampling, as described above, may be helpful. If an abnormal parathyroid is not identified, normal parathyroid glands should be left in situ. Terminating at the time of initial surgery without preoperative consent is not recommended. We highly recommend calling in a colleague to take a look because two pairs of eyes are better than one.

Parathyroid Carcinoma

Parathyroid carcinoma is a rare cause of PHPT (approximately 1% of cases), and surgical resection remains the only curative option. This is best accomplished at the index operation. Before surgery, parathyroid carcinoma may be suggested by very high PTH and calcium levels. During surgery, parathyroid carcinoma should be suspected if the parathyroid appears white or gray and is firm, hypervascular, and densely adherent to surrounding structures.

These findings should prompt en bloc resection of surrounding structures to avoid damaging the tumor capsule because this can result in implantation of spilled tumor cells and incurable parathyromatosis. Resection may need to include thyroid tissue, muscle, strap, or the recurrent laryngeal nerve. However, radical resection of uninvolved tissue is unnecessary and results in increased morbidity and mortality rates. Prophylactic lymph node dissection is not recommended. In a recent study, only 6.9% of patients had lymph node metastases, and a second study demonstrated that lymph node status was not associated with disease-specific survival.

Immediate Postoperative Care

Patients should be monitored for postoperative complications, including hematoma and hypocalcemia. Postoperative supplementation with calcium or vitamin D should be considered. We use the following algorithm (Fig. 9). Signs and symptoms of hypocalcemia are paresthesias (usually perioral or involving the distal extremities), as well as muscle spasms. These symptoms can usually be managed with oral calcium and calcitriol. Severe hypocalcemia may present with tetany and seizures and require intravenous calcium gluconate supplementation. Outpatient parathyroidectomy may be performed in specific circumstances. However, an overnight stay may be appropriate in the setting of extensive dissection, subtotal parathyroidectomy, patients with social issues, or significant vitamin D deficiency.

Operative Complications Postoperative Outcomes

The primary complications associated with parathyroidectomy are recurrent laryngeal nerve injury and hypoparathyroidism. The overall complication rate is approximately 4% for bilateral neck exploration and between 1% and 3% for MIP. If transection of the recurrent laryngeal nerve is identified during surgery, a reinnervation

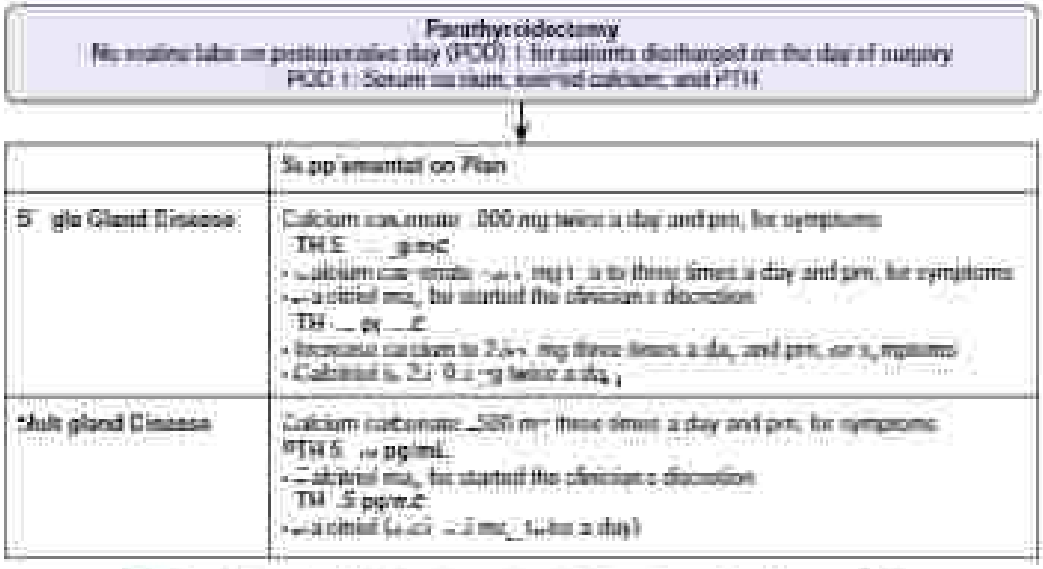


FIG. [illegible] serum and calcium supplementation algorithm after parathyroidectomy (PTX).

procedure should be attempted at that time. Temporary hypoparathyroidism is common after parathyroidectomy because the function of the remaining normal parathyroid tissue has been suppressed and often requires several days to regain function. Permanent hypoparathyroidism is rare and occurs when all parathyroid tissue is resected, inadvertently damaged, or if autotransplantation is unsuccessful.

After surgery, serum calcium and PTH levels should be checked 1 to 2 weeks after surgery to establish postoperative baseline levels and allow for weaning of any supplemental calcium, if appropriate. If serum calcium levels are normal after surgery but PTH levels are elevated, this is likely due to secondary hyperparathyroidism from vitamin D deficiency and will normalize with oral vitamin D supplementation. Prior studies have demonstrated that elevated PTH levels with normal calcium levels after parathyroidectomy are not associated with an increased risk of recurrence.

Surgical cure, defined as normal calcium homeostasis 6 months after parathyroidectomy, is achieved in greater than 95% of cases when bilateral exploration is required, with comparable results among patients undergoing MEP (cure rates as high as 98%). Approximately 2% of patients develop recurrent PHPT after initially curative surgery. Therefore blood testing should be repeated 6 months after surgery and then yearly. Long-term follow up by a multidisciplinary team including the surgeon is critical after parathyroidectomy. This ensures that surgeons are aware of their postoperative outcomes including rate of cure, permanent hypoparathyroidism, or persistent recurrent laryngeal nerve paralysis.

Suggested Readings

[illegible]

[illegible] Guidelines for the definitive management of PHPT. JAMA Surg. 2014;149(10):1013–1020.

Evaluation and Management of Persistent or Recurrent Primary Hyperparathyroidism

[illegible]

Remedial (revision, redo, reoperative) surgery for primary hyperparathyroidism (PHPT) has posed significant challenges that can be traced to the first cases in Austria and the United States. The earlier successful operation was performed by Felix Mandl in Vienna in 1925 for the street car conductor, Albert Ishmo, whose initial surgical cure was followed by recurrent disease, failed remedial surgery, and disease related death. In the United States, the merchant seaman Captain Charles Mansell underwent six unsuccessful explorations until his ectopic mediastinal parathyroid adenoma was resected at the Massachusetts General Hospital. In spite of a well performed operation, he died after surgery due to profound hypocalcemia and osteopenia resulting from retained nephrolithiasis. These tales cautionary illustrate the conundrums and dangers associated with remedial parathyroid surgery. Fig. 1 demonstrates the locations of ectopic and the most common ectopic sites of abnormal parathyroid glands in remedial cases and their relationship to the recurrent laryngeal nerves.

In this chapter I have summarized more than 30 years of experience based on the largest series of remedial parathyroid explorations. Persistent PHPT is defined by either (1) the absence of cure after an operation for PHPT or (2) apparent cure, followed by biochemical recurrence within 6 months. Recurrent PHPT is defined by an initial biochemical cure for at least 6 months, followed by recurrence

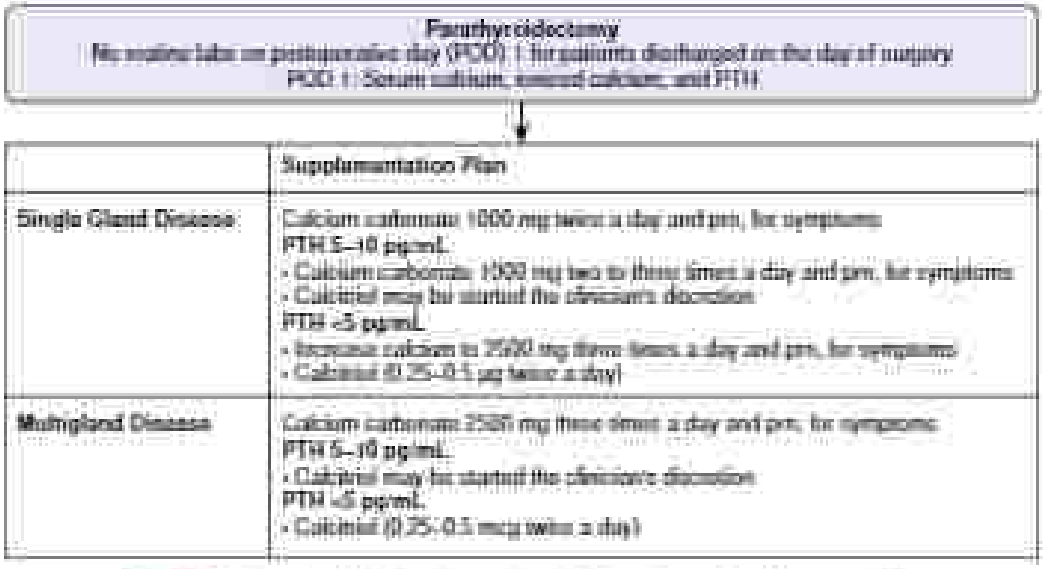


FIG. 4 Calcium and calcitriol supplementation algorithm after parathyroidectomy (PTH).

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Suggested Readings

Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic PHPT: summary statement from the Fourth International workshop. J Clin Endocrinol Metab. 2014;99:3561–3569.

Chen H, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. Arch Surg. 2009;144(12):1165–1168.

Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. J Clin Endocrinol Metab. 2014;99:3595–3606.

Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for definitive management of primary hyperparathyroidism. JAMA Surg. 2016;151(10):959–968.

Evaluation and Management of Persistent or Recurrent Primary Hyperparathyroidism

Robert Udelsman, MD, MBA, FACS, FACE

Remedial operation, redo, reoperative surgery for primary hyperparathyroidism (PHPT) has posed significant challenges that can be traced to the first cases in Austria and the United States. The earliest successful operation was performed by Felix Mandl in Vienna in 1925 for the renal calculi disorder, Albers-Schönberg disease. Mandl's initial surgical cure was followed by recurrent disease, failed remedial surgery, and disease-related death. In the United States, the merchant seaman Captain Charles Mansell underwent six unsuccessful explorations until his ectopic mediastinal parathyroid adenoma was resected at the Massachusetts General Hospital. In spite of a well performed operation, he died after surgery due to profound hypocalcemia and osteopenia resulting from retained nephrolithiasis. These twelve cases illustrate the conundrums and dangers associated with remedial parathyroid surgery. Fig. 1 demonstrates the locations of ectopic and the most common ectopic sites of abnormal parathyroid glands in remedial cases and their relationship to the recurrent laryngeal nerves.

In this chapter I have summarized more than 30 years of experience based on the largest series of remedial parathyroid explorations. *Persistent PHPT* is defined by either (1) the absence of cure after an operation for PHPT or (2) apparent cure, followed by biochemical recurrence within 6 months. *Recurrent PHPT* is defined by an initial biochemical cure for at least 6 months, followed by recurrence.

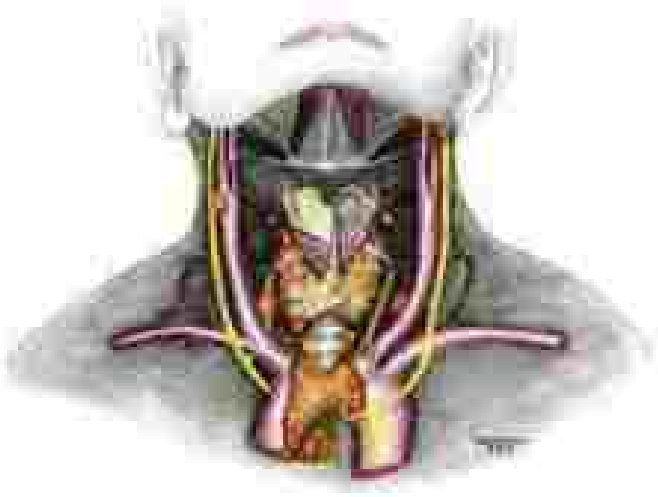


FIG. 1 Location of ectopic (yellow) and ectopic (red) parathyroid tissue and their relationship to the recurrent laryngeal nerves (yellow). (From Wilhelmi SJ, Lee AK, Rosenthal RJ, et al. Evaluation and management of persistent and recurrent primary hyperparathyroidism: a practical approach to optimizing success and minimizing complications. *Ann Surg Oncol*. 2010;17:1–11.)

Although this interval is arbitrary, it distinguishes what in most cases is either an inadequate initial operation (persistent PHPT) from an adequate operation followed by progression of the underlying disease (recurrent PHPT).

DIFFICULTY OF REMEDIAL EXPLORATION

Reoperative parathyroid surgery is inherently more difficult for the following three reasons: (1) Reoperative neck and mediastinal anatomy is often distorted and fibrotic, resulting in disruption of normal tissue planes making identification and protection of critical structures including the recurrent laryngeal nerves and normal parathyroid glands difficult. (2) Critical information gleaned from previous operative and pathology reports is often insufficient, inaccurate, and occasionally misleading. (3) Alleged visualization of a normal parathyroid gland cannot be assumed to be accurate in the absence of histologic confirmation. (4) Even an experienced surgeon can inadvertently compromise the end artery blood supply to a normal parathyroid gland left in situ. (5) An inexperienced surgeon may misidentify upper and lower parathyroid glands, thereby contributing subsequent exploration. (6) Mislabeling of specimens, especially during prolonged exploration, is not infrequent. (7) Although pathologists can distinguish an enlarged from a normal parathyroid gland, they cannot accurately discriminate between a hyperplastic and an adenomatous parathyroid gland. (8) Preoperative localization in remedial cases is compromised due to scarring, altered revascularization, and anatomic distortion. (9) Underlying thyroid disease, such as nodular goiter or Hashimoto's thyroiditis, undermines imaging and exploration. The cumulative effects of these compromises result in decreased cure and increased complication rates in the remedial neck.

REMEDIAL NECK/MEDIASTINUM

Patients who have undergone previous parathyroid or thyroid surgery are defined as remedial cases. However, nonendocrine cervical or mediastinal procedures also pose similar challenges. These include patients who have undergone anterior cervical spinal procedures, carotid endarterectomy, transcervical thymectomy, and, in select cases, median sternotomy.

TEAM APPROACH

Patients with persistent or recurrent PHPT should be managed by an experienced team in an institution with sophisticated resources. The team includes endocrinologists, parathyroid surgeons, imaging experts, and pathologists. Furthermore, every patient with persistent or recurrent PHPT does not require exploration. Patients with mild asymptomatic disease, especially those with a limited lifespan, can be managed without surgery with or without a calcimimetic agent. Although there are no published guidelines defining indications for remedial parathyroid exploration, it is logical that the threshold for remedial surgery should be higher than for de novo cases. Accordingly, it is strongly recommended that all remedial cases be referred to an experienced team for evaluation and treatment recommendations.

CONFIRM THE DIAGNOSIS

It is critical to confirm the diagnosis in every patient who presents with persistent or recurrent PHPT. A subset may not have PHPT or have familial hypocalciuric hypercalcemia (FHH) and may not require intervention. Other causes of elevations of both serum parathyroid hormone (PTH) and calcium levels must be considered. These include mild secondary hyperparathyroidism due to renal insufficiency, gastrointestinal malabsorption, or vitamin D deficiency. In addition, a variety of medications, including lithium and thiazide diuretics, alter calcium metabolism and may either interfere with establishing a diagnosis of PHPT (thiazides) or contribute to or cause the disease (lithium).

FAMILY HISTORY

It is critical to obtain and consider the family history in all patients. Table 1 summarizes familial hyperparathyroid disorders, genetic characteristics, presentation, and associated features. Patients with FHH are generally symptom free and rarely benefit from surgical intervention. Patients with MEN1 usually present with PHPT before age 30 and are likely to develop recurrent disease. Patients with MEN2A generally present with medullary carcinoma of the thyroid. Their parathyroid disease, when present, is usually mild and managed by removing only enlarged parathyroid glands during resection of their thyroid cancer. However, it is critical to rule out pheochromocytoma before surgical exploration. Explorations for PHPT in patients with MEN1 are guided by the concept that every parathyroid cell is genetically abnormal and therefore prone to recurrence. In effect, the surgeon should debulk the parathyroid disease and either leave a single remnant or transplant viable parathyroid tissue to ease management of recurrent disease. The other genetic conditions listed in Table 1 are rare; however, the autosomal dominant inheritance pattern results in 50% of male and female patients inheriting the syndrome. It is also important to obtain genetic counseling for these individuals.

REVIEW ALL AVAILABLE DATA AND EXAMINE THE PATIENT

Planning intervention for remedial parathyroid exploration is an exercise in investigation, imaging, and hypothesis generation. The initial step requires a carefully performed history and physical examination, including detailed review of previous operative notes, illustrations, pathology reports, and imaging studies. The physical examination will confirm the site of previous exploration and include a general assessment of the patient. Laryngoscopy by either indirect mirror examination or with a flexible nasopharyngoscope is essential to rule out or evaluate the extent of vocal cord dysfunction due to previous laryngeal nerve injury. This is critical because patients with complete unilateral vocal cord paralysis can have a normal voice, and subsequent injury to the contralateral recurrent laryngeal nerve would be devastating.

TABLE 1 Familial Hyperparathyroid Disorders, Genetic Characteristics, Presentation of Primary Hyperparathyroidism (PHPT), and Associated Features

Disorder	Inheritance	Responsible Gene	Chromosomal Location	PHPT	Associated Tumors
MEN1	AD	*MEN1*	11q13	High penetrance (approximately 90%); multiglandular	Pituitary, EPT
MEN2A	AD	*RET*	10q21	Low penetrance (approximately 20%); multiglandular/adenoma	MTC, pheochromocytoma
HPT-JT	AD	*HRPT2*	1q21-q32	Cystic parathyroid tumors; 15% risk of carcinoma	ossifying fibroma, renal lesions
FIHPT	AD	*HRPT2*	1q21-q32	Adenoma/multiglandular	
	AD	*MEN1*	11q13	Adenoma/multiglandular	
	AD			Adenoma/multiglandular	
ADMH	AD	*CDC73*	1q13.2-21	Multiglandular/adenoma	
FIHH	AD	*CASR*	3q13.3-21	Mildly hypercalcemic	
NSHPT	AR/AD	*CASR*	3q13.3-21	Markedly hypercalcemic	

AD, autosomal dominant; AHH, autosomal dominant mild (FHH); AR, autosomal recessive; ATJ, multiglandular parathyroid tumors; FHH, familial hypocalciuric hypercalcemia; FIHPT, familial isolated PHPT; HPT-JT, hyperparathyroidism-jaw tumor; MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; NSHPT, neonatal severe PHPT.
From Carling T, Udelsman R. Parathyroid surgery in familial hyperparathyroid disorders. *J Int Surg*. 2009;23(1):27–37.

IS REMEDIAL INTERVENTION APPROPIATE?

Patients present with a wide range of symptoms and signs, including those who are symptom free, with minimal elevations of serum PTH and calcium levels or those with life-threatening hypercalcemic crisis. In addition, the anticipated difficulty of remedial exploration for what is likely a single missed parathyroid adenoma varies widely from patients who present for a first or six time reexploration for parathyroid remnants or parathyroid carcinoma. Critical judgment is required to balance the probability of success and morbidity with the probable benefit and lifespan. Once the decision has been made for surgical intervention, imaging is always indicated and critical for operative planning.

PREOPERATIVE LOCALIZATION

Several localization studies are available; however, their quality is highly dependent on the equipment used and the commitment and skills of the imaging team. In general, normal parathyroid glands cannot be visualized on imaging studies. Furthermore, all imaging is more sensitive in patients with single versus multigland disease. Ultrasound examination of the neck is often the first study obtained because it is readily available, avoids ionizing radiation and is relatively inexpensive. It is highly dependent on the skills of the imager. It can provide exquisite detail and demonstrate a hypoechoic nodule in the neck in both eutopic and ectopic locations (Fig. 2). Because ultrasonography cannot penetrate the sternum or clavicles and is compromised in patients with multinodular goiters, Hashimoto's thyroiditis, obesity, or retroesophageal parathyroid glands, its limitations must be recognized.

Technetium-99m sestamibi scanning using single photon emission computed tomography is also a first-line imaging study. Unlike ultrasonography, enhanced sestamibi uptake is due to the increased mitochondrial content seen in adenomatous or hyperplastic parathyroid glands. The scans can detect ectopic parathyroid glands in the neck and mediastinum (Fig. 3). The quality of the scans is extraordinarily variable depending on the institution where they are performed.

Four-dimensional CT scans (4D CT) have emerged as a sensitive and at times invaluable study. The fourth dimension is time and is obtained by multiple runs with intravenous (IV) contrast (Fig. 4). This

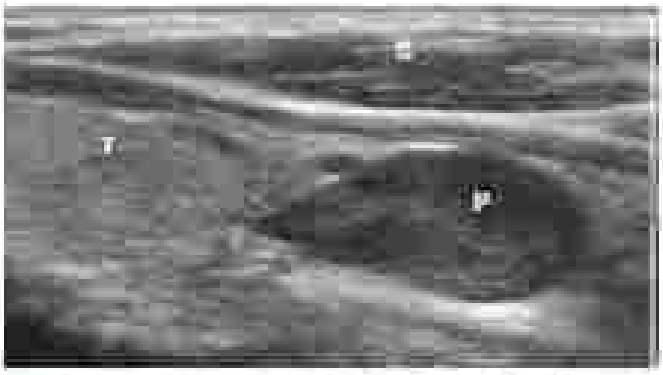


FIG. 2 Ultrasound demonstration of a left lower parathyroid adenoma as a hypoechoic ovoid mass (*P*) lateral to the thyroid lobe (T) and posterior to the overlying strap muscles (S).

FIG. 3 Technetium-99m sestamibi scan demonstrating a mediastinal parathyroid adenoma in a patient who had undergone previous coronary artery bypass grafting. In this case, the left internal mammary artery graft to the left anterior descending coronary artery draped over the parathyroid adenoma. Physiologic sestamibi uptake is seen in the salivary glands.

study is often positive when ultrasonography and sestamibi fail but exposes the patient to moderate amounts of ionizing radiation and IV contrast. In several institutions 4-D CT scanning has emerged as a first-line imaging study. Although MRI scans have been reported to be useful, they are inferior compared to 4D CT scans and rarely used except in pregnant patients who cannot be exposed to ionizing radiation.

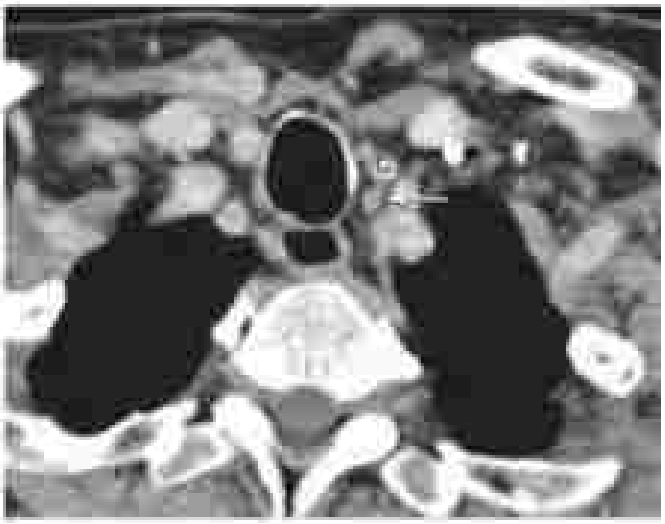


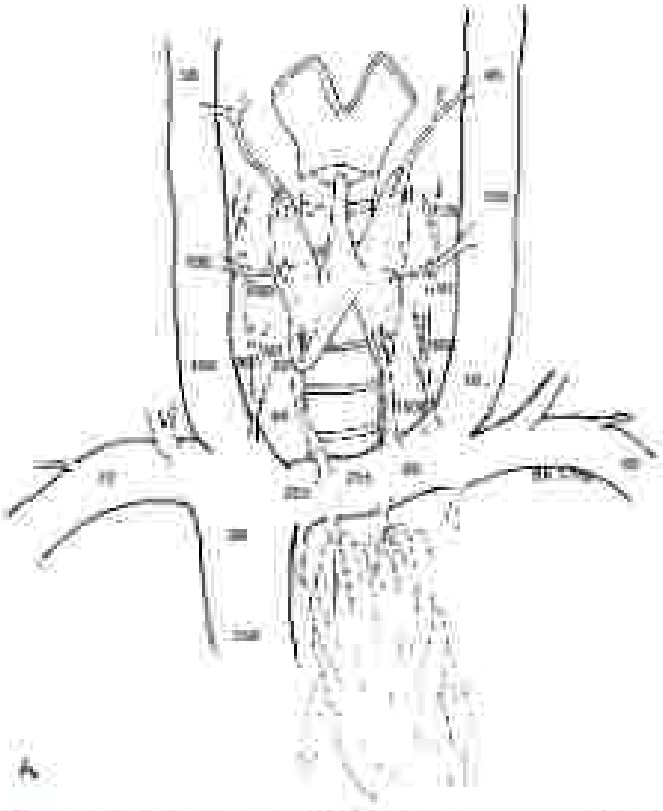
FIG. 4 Four-dimensional CT scan demonstrating a persistent parathyroid adenoma (arrow) in the left carotid sheath directly posterior to the common carotid artery (C).

If the results of the above noninvasive imaging studies are negative, discordant, or noncontributing, invasive imaging should be considered. Invasive imaging procedures are never indicated to de novo (unexplored) patients due to their risks and expense. The easiest is ultrasound-guided aspiration of a putative enlarged parathyroid gland. This is a relatively simple outpatient procedure. It is essential to aspirate the ultrasound-identified lesion and measure PTH levels because cytology alone may fail to discriminate a parathyroid gland from a thyroid nodule. This procedure must be organized with the clinical pathologists who analyze PTH to be certain that the collection conditions are optimized.

Parathyroid localization with arteriography and venous localization is the most sensitive and expensive of the localization studies. It should only be performed by experienced angiographers, and multiple venous samples are required from the neck and mediastinum. Access is usually obtained via the femoral vessels. The utility of this study is enhanced by on-site PTH analyses because data obtained in near real time informs the radiologists whether they have a subtle but not diagnostic PTH gradient, thereby directing them to obtain superselective samples from small blood vessels as shown in Fig. 5A. The corresponding operative photograph demonstrated a carotid sheath parathyroid adenoma (Fig. 5B). In addition, demonstration of an inappropriately positive gradient allows termination of the study. In the rare patient in whom imaging fails to identify a candidate lesion, it is better to delay surgery if possible until imaging is positive.

FORMULATE A WORKING HYPOTHESIS

Based on the cumulative information, the surgeon should formulate a literally working hypothesis. (1) Is it likely that the patient has single-site recurrence? (2) Are both recurrent nerves functional? (3) Is the



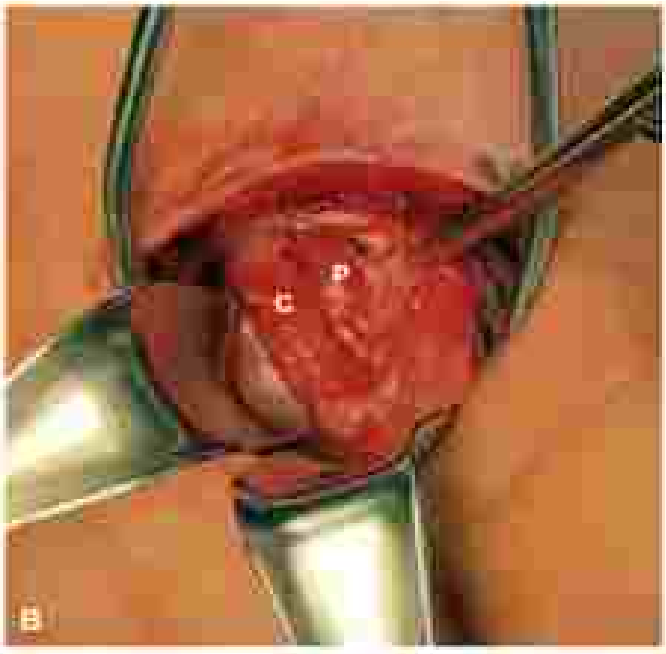


FIG. 5 (A) Selective venous sampling with on-site PTH measurement in a patient with multiple failed parathyroid explorations. The two samples obtained in the left inferior posterior neck (1,649 pg/mL and 1,276 pg/mL) are 12 times greater than the other samples, demonstrating near lateralization. (B) Operative image from the patient demonstrating an ectopic parathyroid adenoma (P) medial and posterior to the common carotid artery (C).

TABLE 2 Differential Diagnosis of Persistent or Recurrent Primary Hyperparathyroidism

Missed adenoma	40%
Inadequate resection for parathyroid hyperplasia	20%
Recurrent disease in a subtotal resection site	18%
Parathromatosis	12%
Parathyroid carcinoma	5%

FIG. 6 Video-assisted anterolateral operative finding in a patient with metastatic parathyroid carcinoma implanted on the parietal pleura next to the lung. Innumerable metastatic implants precluded curative resection.

imaging reasonably convincing? (4) Does the site of recurrence likely represent the only residual parathyroid tissue? (5) If all the imaging is noncontributing, should the surgeon proceed with exploration?

DIFFERENTIAL DIAGNOSIS OF PERSISTENT OR RECURRENT PHPT

The differential diagnosis of persistent or recurrent PHPT and their relative frequencies are listed in Table 2. Most are due to inadequate initial surgery where the surgeon was unable to identify a single parathyroid adenoma. However, it is not uncommon for a surgeon to fail to appreciate subtle asymmetric parathyroid hyperplasia and perform an inadequate resection.

In patients who have recurrent disease after undergoing a successful subtotal resection, the most likely site of recurrence is at the subtotal site because the residual abnormal parathyroid tissue has grown to the point that it causes recurrent disease. Other rare causes of recurrent disease are parathromatosis where an abnormal parathyroid gland had been ruptured during resection and multiple recurrent nodules of benign implanted parathyroid tissue have grown in soft tissues. Finally, parathyroid carcinoma recurrence usually presents at the site of previous resection. However, distant sites of metastasis can also occur as shown in Fig. 6.

LOCATIONS OF PATHOLOGIC PARATHYROID GLANDS IN THE REOPERATIVE NECK AND MEDIASTINUM

Surgeons who undertake parathyroid surgery must have a clear understanding of the anatomy and embryology of the parathyroid glands. The anatomic locations of persistent or recurrent PHPT are demonstrated in Fig. 7. The vast majority are in the neck and can be resected by cervical exploration. Most mediastinal sites can also be

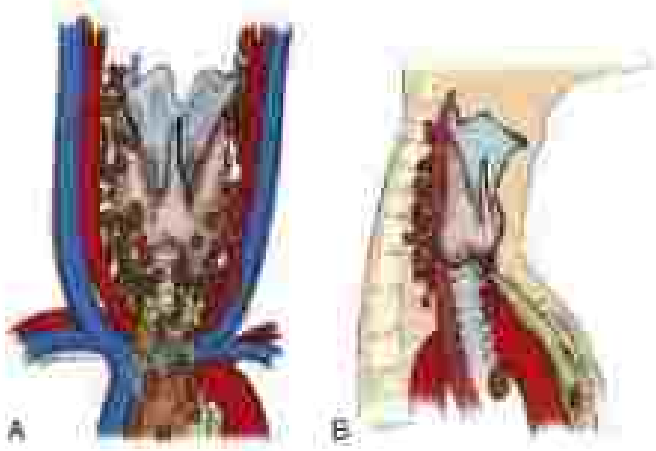


FIG. 7 Sites of persistent or recurrent parathyroid glands in the neck and mediastinum seen on anteroposterior (A) and lateral (B) views. The vast majority are located in the neck, and the retroesophageal space is a frequent site of disease. (From Udelsman R, Donovan PI. Essentials of parathyroid surgery: imaging and localization. In: Cameron JL, ed. Current Surgical Therapy. 10th ed. Philadelphia: Elsevier Saunders; 2011:722–726.)

approached by a cervical approach. However, a rare ectopic mediastinal parathyroid, such as those in the aortopulmonary window may require a partial sternotomy, a complete sternotomy, a Chamberlain procedure, or a transthoracic endoscopic approach. Other ectopic sites include retroesophageal, intrathymic, intrathyroidal, carotid sheath, retromandibular, and intravascular locations.

SURGICAL EXPLORATION

Once the surgeon has verified the diagnosis and the team has agreed to proceed to exploration, a preoperative working hypothesis should be generated, and, in the best of circumstances, a single enlarged parathyroid gland has been localized. A fundamental concept in remedial cases is to do as little exploration as required, but as much as necessary to achieve a durable cure. Ideally a unilateral cervical approach will be successful; however, bilateral exploration may be necessary, and supplementary techniques and adjuncts are essential.

OPERATIVE AJUNCTS

Intraoperative PTH Assay

Intraoperative PTH analysis requires a rapid PTH assay in proximity to the operating room and is a critical adjunct for initial and especially reoperative parathyroid surgery. The assay will demonstrate a physiologic clearance curve of elevated circulating PTH once all hypersecreting parathyroid tissue has been removed. By confirming cure with a high degree of confidence, the surgeon can terminate the operation and obviate unnecessary exploration, thereby protecting critical structures. The assay can also be used to analyze excised tissue by an ex vivo aspiration and prove whether it is of parathyroid origin, thereby rendering intraoperative frozen section analysis obsolete. Finally, in rare cases, the assay can analyze intraoperative bilateral internal jugular vein samples obtained in the inferior neck, which may demonstrate an ipsilateral gradient suggesting a pathologic hypersecreting parathyroid gland upstream.

Other Adjuncts

A variety of other adjuncts have been proposed and abandoned by most experienced parathyroid surgeons. These include the following: (1) Intraoperative ultrasonography because it adds little incremental information compared to a well performed preoperative study. (2) Intraoperative neural monitoring of recurrent nerve function,

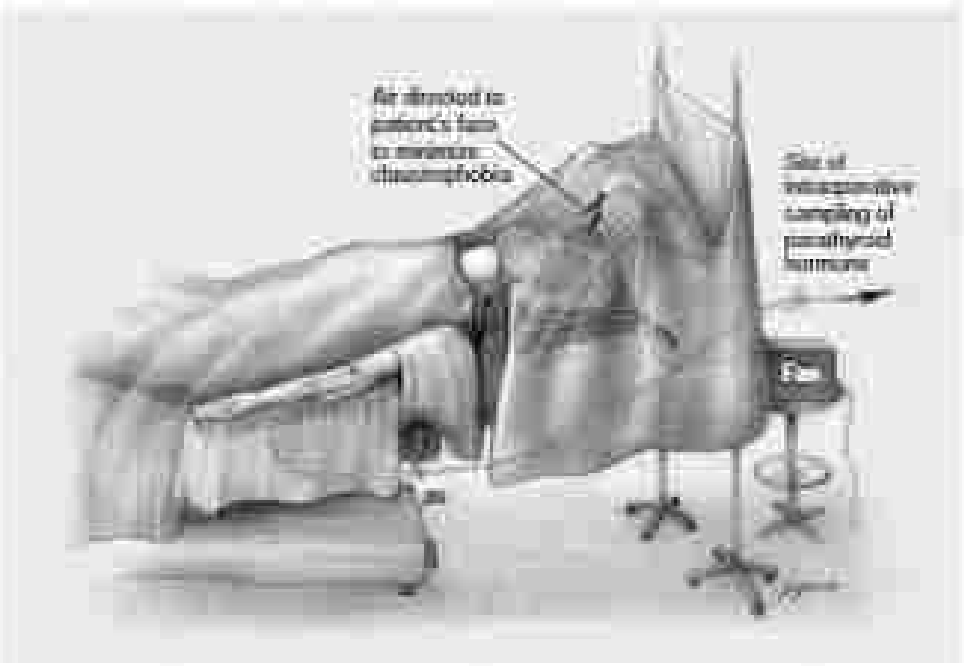


FIG. 8 Operative setup for an awake minimally invasive parathyroidectomy including peripheral intravenous sampling of parathyroid hormone. [illegible] (Adapted from [illegible] Surgery [illegible] Wilkins, 2012.)

because well performed prospective studies, mainly in thyroid surgery, failed to demonstrate improved outcomes with regard to postoperative recurrent nerve function. (3) Use of an intraoperative gamma probe after IV administration of technetium labeled sestamibi because it yields little incremental information compared to a well performed preoperative study. In addition, it does not replace the utility of intraoperative PTH analysis.

OPERATIVE APPROACHES

Many operative approaches are available, ranging from an awake minimally invasive neck parathyroidectomy to bilateral cervical exploration under general anesthesia with or without mediastinal exploration. The selection of approach is highly dependent on the location of the index lesion(s) and the experience of the surgeon. In general, the least invasive approach is preferred guided by preoperative imaging.

Minimally Invasive Approach

A minimally invasive neck parathyroidectomy is appropriate in patients with persistent or recurrent PHPT who appear to have single site disease demonstrated on preoperative imaging studies. This procedure can be performed with the patient under local or superficial cervical block anesthesia in combination with monitored anesthesia with supplemental IV sedation as shown in Fig. 8. An advantage of operating on an awake patient is the opportunity to serially examine the patient's voice during exploration to confirm functional integrity of the recurrent laryngeal nerves. The intraoperative rapid PTH assay is required to optimize this procedure. The approach can be extended to include bilateral exploration and, if necessary, converted to general anesthesia.

Lateral Approach

The lateral approach can be accomplished during a minimally invasive parathyroidectomy because a superficial cervical block results in excellent analgesia. The lateral approach, demonstrated in Fig. 9, is particularly attractive for intraesophageal or other posterior parathyroid glands because it allows for early exposure into the carotid sheath and avoids adhesions associated with the more common anterior approach. It expedites early recurrent laryngeal nerve identification and can also be performed with the patient under general anesthesia.

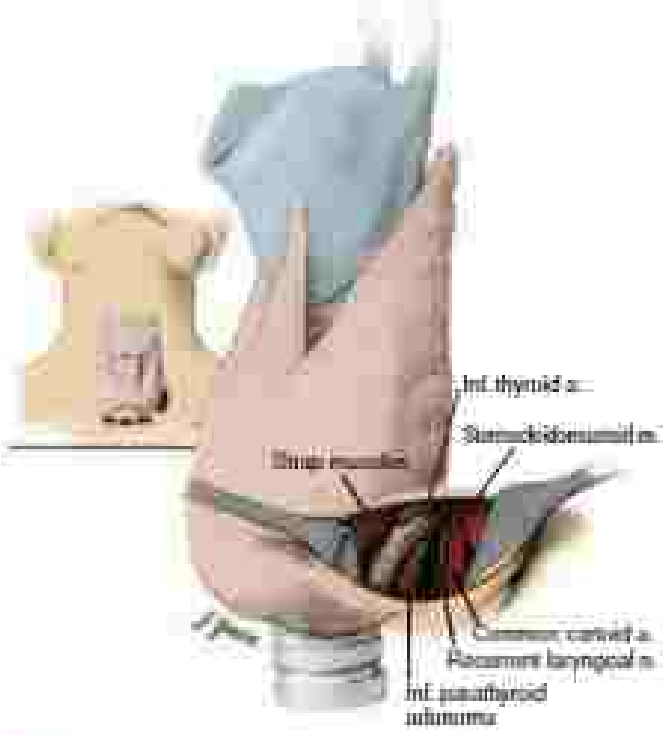


FIG. 9 Lateral approach for cervical exploration in primary hyperparathyroidism. The plane between the strap and sternocleidomastoid muscles is opened using the previous Kocher incision. This facilitates posterior access and avoidance of scar tissue. (Adapted from [illegible] Surgery of primary hyperparathyroidism. In: [illegible] 2012.)

Difficult Exploration

Remedial parathyroid surgery requires flexibility. Imaging is often inaccurate or misleading because it is common to encounter lymph nodes or thyroid nodules that appear consistent with enlarged parathyroid glands on one or more imaging studies. At times, remedial

FIG. 18 Parathyroid autografting technique to the brachioradialis muscle. (From Udelsman R. Secondary hyperparathyroidism. Operative techniques in General Surgery. 1999;1:68.)

exploration becomes an exercise in exploration of autopsy and exhaustion. The most important concept is to avoid creating a lifelong complication by resecting the only residual parathyroid tissue because it is far better to live with mild chronic PHPT than to render a patient aparathyroid. Accordingly, the surgeon must know how to perform a subtotal resection of parathyroid tissue, leaving a well-vascularized remnant of viable parathyroid tissue weighing 20 to 40 mg. In some cases, heterotopic autotransplantation of parathyroid tissue, preferably in the nondominant brachioradialis muscle, will be required (Fig. 18).

An array of other techniques is occasionally required for difficult cases. These include bilateral internal jugular vein sampling for a unilateral PTH gradient, thymic lobectomy based on the presumed location of a missing parathyroid gland, carotid sheath exploration, cervical thymectomy, and extensive retroesophageal explorations. In rare cases, ipsilateral ligation of the inferior thyroid artery can result in infarction of the culprit occult parathyroid adenoma. However, this is only done when the ipsilateral thyroid lobe has been excised.

Mediastinal Exploration

The vast majority of mediastinal parathyroid gland excisions can be performed by a well-trained parathyroid surgeon via a transcervical approach. There are typically performed for intrathymic and intrathoracic retroesophageal parathyroid adenomas. A rare patient will require a transthoracic approach and a variety of options including video-assisted thoracoscopic, transsternal, or anterior mediastinotomy (Chamberlain procedure) are usually performed by a thoracic surgeon. A blind median sternotomy in the absence of a positive imaging study is not recommended.

COMPLICATIONS OF SURGERY

Complications associated with redo parathyroid surgery are rare but higher than those associated with de novo cases. These include recurrent or superior laryngeal nerve injury, pneumothorax, bleeding, infection, internal jugular vein injury and esophageal injury. The overall complication rates in the best series range from 1% to 3%. Neurological complications such as urinary bladder distention, deep venous thrombosis, and cardiac complications are also uncommon.

The risks of permanent hypoparathyroidism should always be considered during remedial cervical exploration. Patients who have undergone previous explorations, especially when one or more parathyroid glands were excised, are at higher risk. Furthermore, any patient who has had a previous cervical exploration may have had the blood supply to one or more parathyroid glands compromised. Accordingly, it is possible that, by removing a single abnormal gland in the redo setting, the surgeon is excising the only residual functional parathyroid tissue. This can have devastating long-term consequences because patients who are aparathyroid are difficult to manage. Therefore during remedial exploration the surgeon should use an intraoperative PTH assay because the clearance of PTH can help the surgeon determine whether there appears to be sufficient residual postresection parathyroid function. It may be necessary to autotransplant parathyroid tissue to a heterotopic site, preferably the nondominant brachioradialis muscle. It is also important to recognize that, if parathyroid autotransplantation is anticipated, the parathyroid tissue must be maintained viable and harvested as long as possible because warm ischemia time should be minimized, and excised parathyroid tissue should be held in a saline solution in a container immersed in an ice slurry. Parathyroid autotransplantation is demonstrated in Fig. 18.

NONOPERATIVE APPROACHES

Nonoperative techniques have been described to ablate hypersecreting parathyroid tissue. They require the ability to localize an abnormal parathyroid gland in the neck or mediastinum and employ image-directed ethanol injection or angiolysis with catheter-based injection of hypervascular contrast agents. Both techniques are inferior to surgical resection and are associated with recurrent laryngeal nerve injury, as well as high recurrence rates.

Medical treatment for patients with persistent or recurrent PHPT is routinely used before surgical intervention and in some cases in lieu of surgical treatment. The most important aspect of medical management is to treat severe hypercalcemia with hydration to improve renal, cardiac, and cognitive function. A variety of medications can then be used including bisphosphonates and the calcimimetic agent cinacalcet.

POSTOPERATIVE MANAGEMENT

Postoperative management of redo parathyroidectomy patients is similar to, but more intense than, de novo cases because the risks are higher. Recurrent nerve injury and postoperative bleeding resulting in acute airway compromise are of paramount concern. In addition, postoperative hypocalcemia is exacerbated because these patients often have a reduced mass of normal parathyroid tissue and are also likely to have hungry bone syndrome. Serial measurement of postoperative serum calcium levels will confirm cure and enable early oral calcium treatment and selective use of the active vitamin D analog, calcitriol (Rocaltrol). At times, IV calcium replenishment with a solution of calcium gluconate can be life-saving.

RESULTS

The cure and complication rates associated with remedial surgery for PHPT can approach those obtained for de novo cases when performed by experienced teams. Cure rates above 95% and complication rates between 1% and 3% have been reported in large series. High success rates are also associated with reductions of hospital-based and outpatient expenses.

CONCLUSION

Remedial surgery for PHPT is challenging and rewarding because dramatic improvements occur for the vast majority of patients. However, disastrous consequences, including bilateral recurrent laryngeal nerve injuries and lifelong refractory hypocalcemia, can be devastating. Surgeons who are interested in performing these procedures are urged to obtain the requisite skills and judgment by training with experienced endocrine surgeons.

Acknowledgment

I thank Katherine Estrada for assisting with manuscript preparation.

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Surgical Management of Secondary and Tertiary Hyperparathyroidism

Zeya T. Sahli, MD, and Martha A. Zeiger, MD, FACS

Hyperparathyroidism (HPT) is a product of autonomous secretion of parathyroid hormone (PTH) from one or more parathyroid glands. Secondary HPT develops after chronic parathyroid gland stimulation from hypocalcemia, hyperphosphatemia, or vitamin D deficiency and, results in increased PTH synthesis and parathyroid cell proliferation among all four glands. This occurs most commonly "secondary" to chronic kidney disease (CKD), with up to 90% of patients with renal failure developing the disease by the time hemodialysis is required. Secondary HPT can also be caused by vitamin D deficiency or gastrointestinal malabsorption due to chronic pancreatitis, small bowel disease, or malabsorption-dependent bariatric surgery. When left untreated, changes such as decreased extracellular calcium sensing, vitamin D, and klotho and fibroblast growth factor 1 receptors may cause further derangement in calcium metabolism, leading to tertiary HPT. Up to 30% of renal transplant recipients with secondary HPT are at risk for development of tertiary HPT. Unlike secondary HPT that is associated with hypocalcemia, patients with tertiary HPT exhibit normal to elevated calcium levels and hypophosphatemia.

The prevalence of secondary or tertiary HPT is difficult to determine because of the variability in diagnostic criteria. A consistent indicator of their prevalence is the rate of parathyroidectomy (PTX). Data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample database showed 52,971 PTX admissions for secondary HPT performed in the United States between 2002 and 2011, a rate of 1.4 PTX per 1000 patients.

Physicians should have a high level of suspicion for the diagnosis of HPT when evaluating patients with renal failure (Box 1). Symptoms can include bone pain due to renal osteodystrophy, hyperphosphatemia, and hypercalcemia. More severe symptoms due to HPT occur at PTH levels greater than 1000 pg/mL. Calciphylaxis or calcific uremic arteriolopathy, a disease in which calcium accumulates in small vessels of fat and skin, can be found in patients with renal failure involving subcutaneous vascular calcification and calcium necrosis (Fig. 1). This sign is indicative of severe HPT and its often fatal sequelae, and PTX should be offered because it can enhance wound healing.

Medical Management

Secondary HPT can initially be managed medically, whereas tertiary HPT is treated surgically. Primarily, calcium and calcitriol supplementation can be used to slow the progression of secondary HPT until the patient can undergo renal transplantation. Other treatment options include calcimimetics, phosphate binders, and vitamin D analogues. Approved by the Food and Drug Administration in March 2004, Cinacalcet is a calcimimetic that functions by allosteric activation of the calcium sensing surface receptor expressed by parathyroid gland chief cells to reduce PTH production. It is commonly used among patients with end stage renal disease who are not transplant candidates because its use before renal transplantation has been associated with rebound hypercalcemia and hypophosphatemia if discontinued at the time of transplantation. Moreover, its long-term effect on patients or allograft survival has not been studied.

Investigations into Cinacalcet's effect on disease progression and PTX rates have been ongoing. The randomized trial Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) found that CKD patients treated with Cinacalcet were less likely to develop secondary HPT (relative hazard ratio, 0.31; 95% confidence interval [CI], 0.26–0.37). Another randomized, double-blind, placebo-controlled clinical trial study reported a significant reduction in the risk of needing PTX (HR, 0.07; 95% CI, 0.03–0.22), fracture (HR, 0.46; 95% CI, 0.27–0.97), and cardiovascular hospitalization (HR, 0.63; 95% CI, 0.43–0.86) among the Cinacalcet group compared with placebo. The PTX rate has decreased from 2.9 per 1000 patients in 2003 to 2.3 per 1000 patients in 2011, likely due to increased medical management. However, the rate increased to 5.4 per 1000 patients in 2006 and has remained relatively stable despite the increased clinical use of Cinacalcet. This may be due to higher treatment doses used in clinical trials than those used in clinical practice, thus the overestimation of its benefits.

Parathyroidectomy

Despite the initial medical management of secondary HPT, PTX is required in approximately 30% of patients after 5 to 10 years of dialysis and up to 40% after 20 years (see Box 2). The goals of parathyroid surgery include the immediate reduction in PTH levels, long-term symptomatic relief, and end-stage organ improvement. Due to the paucity of randomized clinical trial data, indications for and timing of PTX vary

Acknowledgment

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Parathyroidectomy

Despite the initial medical management of secondary HPT, PTX is required in approximately 20% of patients after 5 to 10 years of dialysis and up to 40% after 20 years (Box 2). The goals of parathyroid surgery include the immediate reduction in PTH levels, long-term symptomatic relief, and end-stage organ improvement. Due to the paucity of randomized clinical trial data, indications for and timing of PTX vary

greatly among experts. Because there is no consensus on the required percentage reduction of PTH to account for cure, the presence or absence of symptoms among HPT patients should be considered.

INDICATIONS FOR SURGERY

Symptomatic Patients

All patients with symptomatic HPT should be considered a surgical candidate. There is no clear consensus regarding PTH cutoff levels as clear indications for surgery. The National Kidney Foundation recommends PTX in patients with a PTH greater than 800 pg/mL associated with hypercalcemia or hyperphosphatemia refractory to medical therapy as an indication for surgery. Among children, the authors recommend PTX for a PTH level greater than 1000 pg/mL or doubling associated bone disease. However, the Kidney Disease: Improving Global Outcomes Group recommends a PTH target threshold for treatment nine times above the upper limit of normal for the PTH assay (e.g., 585 pg/mL).

Symptom-Free Patients and Patients Waiting for Transplantation

Among symptom-free patients, consensus among experts regarding indications for PTX is also lacking. HHD patients with a PTH greater than 1000 pg/mL that is refractory to medical therapies should undergo PTX. However, PTX patient selection must be individualized on the basis of age, comorbidities, and risk-benefit evaluations. Younger patients (<65 years) with little comorbidity are more likely to tolerate surgery and benefit over the long term. Moreover, observational studies have documented the benefits of PTX, including a reduction of 10% to 37% in mortality, 33% to 41% in cardiovascular risk, 32% in fracture risk, as well as improvements in erythropoietin resistant anemia, nutritional status, and humoral and cellular immunity. All transplant candidates, with or without symptoms, with a PTH greater than 800 pg/mL and despite optimal medical therapy should be referred for subtotal PTX.

Renal Transplant Recipients

Despite the potentially high incidence of tertiary HPT, PTX is only performed in less than 10% of renal transplant recipients who harbor this disorder at 1 year after surgery but should be considered the standard of care and recommended to all.

BOX 1 Symptoms of Hyperparathyroidism

- Fatigue/mood status changes
- Renal calculi
- Proximal muscle pain
- Bone pain due to osteitis fibrosa cystica, mainly affecting weight-bearing joints including hips, knees, ankles, and lower back
- Joint pain, joint inflammation due to periarticular calcium deposits
- Bone fracture, nontraumatic fractures or nonhealing of fractures
- Pruritus
- Calciphylaxis, resulting in expanding, painful, cutaneous, purpuric lesions that cause tissue calcifications and ischemic necrosis that lead to dry gangrene if untreated

PREOPERATIVE MANAGEMENT

Preoperative evaluation includes patient risk assessment and counseling. Risk assessment of HHD patients is important for the selection of appropriate surgical candidates because patients who have HHD may have chronic comorbidities that prevent safe surgery. These comorbidities include coronary artery disease, heart failure, myocardial infarction, hypertension, stroke, anemia, uremic coagulopathy, pulmonary disease, and general debility. Moreover, patients with calciphylaxis may develop unique complications, including peripheral vascular disease and wound sepsis, potentially requiring vascular/interventional procedures or wound debridement, respectively. Although renal transplant patients are commonly healthier, their immune system is medically suppressed, which may increase the risk of postoperative complications. Coordination with the patient's nephrologist or dialysis center should be done when scheduling surgery to have the patient undergo dialysis 1 day before surgery and to avoid unnecessary delay caused by conditions such as hyperkalemia.

Preoperative localization studies should be performed to localize ectopic glands among patients with secondary or tertiary HPT. Either 99mTc Sestamibi scans or four-dimensional computed tomography

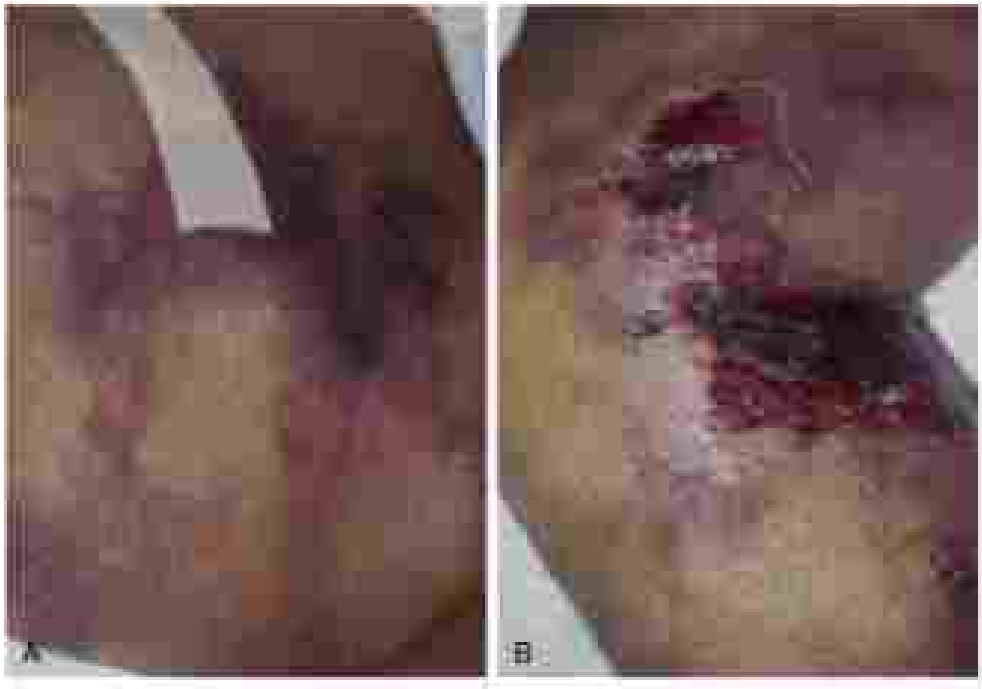

FIG. 1 Calciphylaxis showing cutaneous purpuric lesions and ischemic necrosis on the nares (*A*) and medial leg (*B*) of a patient with secondary hyperparathyroidism. (From Ali SI, Appel RG, Chen J: Secondary and tertiary hyperparathyroidism: state of the art surgical management. Surg Clin North Am. 2009;89:1277–1293.)

BOX 1 Adult Parathyroidectomy Indications for Secondary vs Tertiary HPT

Secondary HPT

- Calciphylaxis
- Patient preference
- Medical observation not possible
- Symptoms due to hyperparathyroidism
- Failure of maximal medical management with:
  - Hypercalcemia
  - Hypercalciuria
  - PTH >800 pg/mL
  - Hyperphosphatemia (with calcium × phosphorus >70)

Tertiary HPT

- Severe hypercalcemia (serum calcium >12.5 mg/dL)
- Persistent hypercalcemia (serum calcium >10.2 mg/dL >3 months after surgery)
- Osteoporosis
- Symptomatic hyperparathyroidism

scans should be used. The importance of preoperative imaging among patients with secondary/tertiary HPT is highlighted by that 32% of recurrent or persistent cases are due to supernumerary glands. In cases of reoperation, including previous thyroidectomy, parathyroidectomy, carotid endarterectomy, or cervical spine surgery, vocal cord visualization by laryngoscopy should be performed to exclude prior recurrent laryngeal nerve injury. Preoperative ultrasound examination may identify abnormal parathyroid glands or abnormalities in the thyroid gland that may require further evaluation or simultaneous surgical management.

EXTENT OF SURGERY

The extent of parathyroid surgery ranges from targeted PTX to subtotal or near-total PTX, or total PTX with or without heterotopic autotransplantation. A total PTX with a heterotopic autotransplantation removes all cervical parathyroid glands, including supernumerary, that can be identified and autotransplants a small portion of a gland to a new, nonpulsatile site such as the neck, chest, or forearm. Subtotal parathyroidectomy is the resection of three (or more, if supernumerary glands are present) glands and subtotal resection of a fourth gland, with preservation of a viable, histologically confirmed remnant approximately the size of a normal gland.

Published literature regarding the recommended extent of surgery in both secondary and tertiary HPT is inconsistent. For this reason, the decision regarding extent of surgery is largely dependent on surgeon preference in addition to several other factors, including whether the surgery is primary or reoperative and whether the patient has an existing or planned renal transplant. In contradistinction to total PTX and autotransplantation, a parathyroid gland remnant left during subtotal PTX mitigates against postoperative permanent hypocalcemia because of the maintenance of its original blood supply congruent with that of an autograft. However, the risk of recurrent HPT has been shown to be greater among patients undergoing subtotal rather than total PTX with autotransplantation. Moreover, total PTX without autotransplantation has been reported to prevent recurrence more effectively than with autotransplantation. Patients presenting with calciphylaxis are associated with more than 50% mortality within the first year, and thus it is recommended that they undergo total parathyroidectomy without autotransplantation.

Targeted PTX is not commonly performed among patients with secondary or tertiary HPT but can be considered in patients with recurrent HPT or in post-renal transplant patients with single or double adenomas, reported in up to 29% among patients who have undergone renal transplantation. However, this may be associated with an increased risk of recurrence. Patients with a relative contraindication for future neck surgery because of prior history of repeated neck surgery, known recurrent laryngeal nerve injury, or significant medical comorbidities, should undergo a total PTX with autotransplantation to facilitate access to the gland in case of recurrent HPT. Currently, debate exists regarding the need for a prophylactic thymectomy. Thymectomy should be performed, however, during the search for a missing inferior parathyroid gland or supernumerary glands.

SURGICAL TECHNIQUE

The patient should be placed in a supine position with the neck hyperextended. Potential sites of autotransplantation should be exposed and prepped. General anesthesia is required for most patients undergoing PTX with bilateral neck exploration. However, local anesthesia has been also been described in patients deemed to be at too high a risk for general anesthesia. A standard Kocher incision measuring 3 to 5 cm should be made through skin and platysma. Superior and inferior flaps should be created in usual fashion to thyroid cartilage superiorly and sternal notch inferiorly. Strap muscles are divided longitudinally in the midline and retracted (Fig. 1). Throughout the procedure the recurrent laryngeal nerves should be noted and carefully preserved. First, all four parathyroid glands should be exposed after a thorough bilateral neck exploration. Biopsy, capsular rupture, or fragmentation of the glands should be avoided to prevent parathyromatosis.

Identification of fewer than four parathyroid glands should prompt a search for the missing gland. The surgeon should have an intimate familiarity with parathyroid embryology and be aware of the following ectopic locations: the tracheoesophageal groove, retroesophageal, ectopic/mid-parathyroid, carotid sheath, intrathyroidal, mediastinal, and thymus (Fig. 2). Parathyroid tissue should be confirmed on frozen section.

Intraoperative PTH Monitoring

Unlike in the case of primary HPT, an established intraoperative PTH monitoring protocol, such as the Miami criteria, to confirm treatment has not been established to confirm cure of patients with secondary or tertiary HPT. The reason for this is due to the change in PTH half-life from 2.2 minutes in patients with normal renal function to 4.8 minutes in ESRD patients as a result of the decreased renal clearance. Despite this, recommendations regarding PTH level decline during surgery compared with baseline value are commonly used. These include a recommended range of decline of 50% to 80% at anywhere between 10 and 20 minutes after PTX as a reliable predictor of postoperative cure.

Creating A Parathyroid Remnant

During subtotal PTX, the parathyroid remnant should be created first before resection of other glands to monitor its viability throughout the operation. The parathyroid remnant should be approximately 50 to 100 mg and, preferably, an inferior parathyroid gland remnant. Choosing an inferior gland leaves the remnant in a safe position, away from the recurrent laryngeal nerve should the patient require reoperation and resection. Marking the remnant with a titanium clip or nonabsorbable suture facilitates its localization in the event of a reoperation.

Creating an Autograft

Autotransplantation entails mincing a portion of the excised gland into a total of 10 to 15 pieces approximately 1 to 2 mm that are then inserted into one or several pockets subcutaneously or intramuscularly in the neck, chest, or forearm. Before autotransplantation, a frozen section should confirm parathyroid tissue. There is no consensus

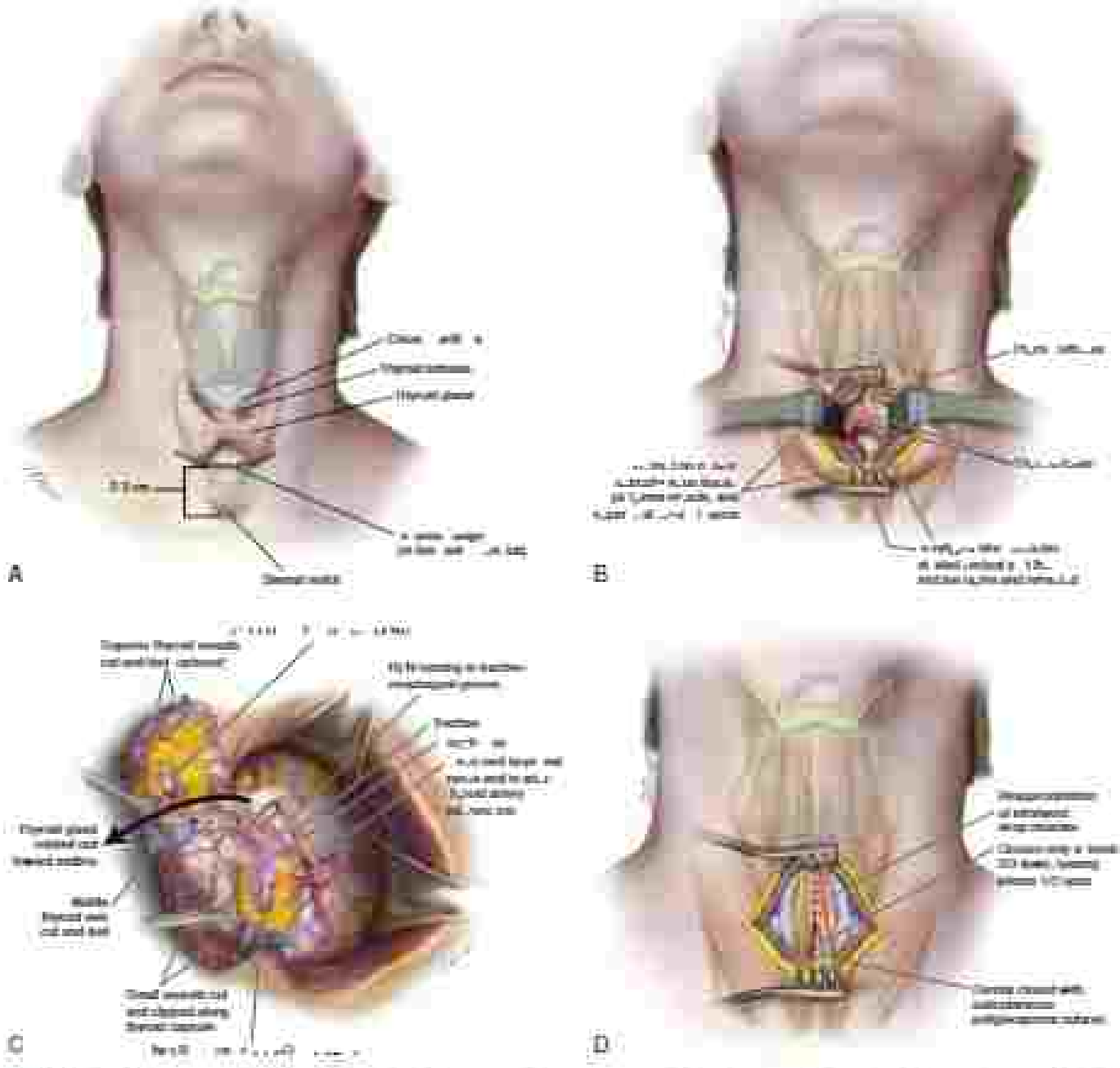

FIG. 2 Parathyroidectomy steps highlighted. (A) A 2- to 3-cm incision will allow access to a majority of parathyroid glands. (B) Middle raphe of the infrahyoid strap musculature has been identified and retracted to reveal the thyroid isthmus. (C) Parathyroid glands are identified with careful dissection; the recurrent laryngeal nerve may be confirmed if necessary. Conservative ligation of the superior vascular pedicle may be required for adequate visualization. (D) Wound closure includes shallow subcutaneous and platysmal suture approximation to prevent the overlying soft tissue from adhering to the trachea and resulting in poor cosmesis. (From Kuhnigk E, Hauss FR. Atlas of oral and maxillofacial surgery. Philadelphia: Elsevier; 2014.)

regarding the optimal site for grafting. Implantation and resection of subcutaneous parathyroid autografts is simpler to perform than intramuscular procedures. Regardless of implantation sites, parathyroid fragments often infiltrate surrounding tissues, which may make resection of all foci challenging. Furthermore, one must always be circumspect about an additional cervical gland complicating the picture of recurrent HPT.

We recommend implanting the autograft in the nondominant forearm brachioradialis muscle or subcutaneously because of its relatively easy access under local anesthesia for reexplorations. Furthermore, determination of autograft function can be performed by comparing PTH levels of blood samples drawn from the antecubital vein of the implanted arm versus the contralateral arm. Patients with a forearm autograft may require several reoperations to completely remove autografts from the forearm because of regrowth causing recurrent HPT. For this reason, during reexploration procedures, it may be appropriate to excise all viable autograft tissue.

The sternocleidomastoid muscle is another convenient location for autotransplantation as it is within the operative field. A third possible location for autotransplantation is in the middle to lower third

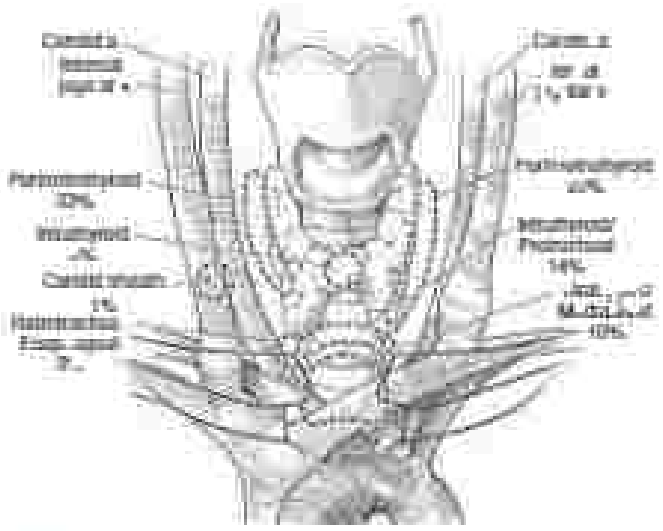

FIG. 3 Locations and frequencies of parathyroid glands removed at reoperation. (From Akerström G, Grimelius L, Heath H. Review: parathyroid surgery. Operative Techniques. 2010;21:72–81.)

of the proximal area subcutaneously. The autograft can be easily located and excised under local anesthesia in the event of a recurrence. Autografts are rarely placed intramuscularly in the chest due to technical difficulties.

Cryopreservation

When possible, we recommend cryopreservation of parathyroid tissue in patients undergoing subtotal or total PTX that are at high risk of hypoparathyroidism. The preserved tissue can be used for delayed autotransplantation in case of parathyroid remnant ischemic necrosis or autograft failure. However, cryopreservation of parathyroid tissue is available in less than 20% of centers. Variable success rates have been reported ranging from 17% to 83%.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Among ESRD patients, parathyroid surgery has a similar operative complication rate despite an increased risk for uremia-related bleeding diathesis among ESRD patients. However, patients with ESRD are up to five times more likely to be readmitted when compared with surgery for patients with primary HPT. The shared risks include bleeding and hematoma, wound infection, superior laryngeal nerve or recurrent laryngeal nerve injury, or hypoparathyroidism. Moreover, 5% to 20% of patients experience persistent disease, which is defined as hypercalcemia or PTH level above the recommended target range according to CKD stage after PTX. Compared with patients with primary HPT, patients with ESRD are more likely to develop postoperative transient hypocalcemia or hungry bone syndrome—the hyperdynamic, osteoblastic uptake of calcium into bones. Severe postoperative hypocalcemia may occur in up to 97% of ESRD patients and, for this reason, protocols must be in place to administer perioperative calcitriol, intravenous calcium gluconate during the immediate postoperative period, dialysis or readmission, along with oral calcium, magnesium, and calcitriol when discharged home. Patients with hypocalcemia should also be considered for continuous cardiac monitoring due to potential QT prolongation.

Patients typically do not require pain medications stronger than acetaminophen. Patients may resume dialysis after surgery in the hospital, however, the minimum amount of heparin should be used during the first few dialysis sessions to minimize the risk of neck hematoma.

After hospital discharge, patients should be followed up with a baseline laboratory profile of serum and ionized calcium, magnesium, and serum PTH at 1 to 8 weeks after surgery, and vitamin D levels at 3 and 6 months. Long-term follow-up, with serum calcium measurements, at least annually, is important because the time for ESRD patients to achieve new homeostasis can vary significantly, and, for this reason, laboratory results should be interpreted with caution and be monitored for potential persistent or recurrent HPT.

SUMMARY

Surgical management of secondary and tertiary hyperparathyroidism is a complex surgical issue due to the lack of specific guideline consensus. Despite a 1.1% increase in the incidence of ESRD in 2016, the prevalence of secondary/tertiary HPT increased approximately 3.5%, likely because of a decline in mortality rate among these patients according to the United States Renal Data System. These statistics highlight the importance of knowing how to effectively manage these patients. Ongoing research and discussion regarding the surgical management of secondary and tertiary HPT is needed. A well-developed prospective multiinstitutional randomized controlled clinical trial comparing the three procedures (subtotal versus total with autotransplantation versus total without autotransplantation) is needed.

Subtotal parathyroidectomy is the preferred surgical approach. However, all three procedures are safe and effective at treating HPT and its associated metabolic disturbances. Future advances in our understanding regarding the ideal surgical management of these patients will aid in the creation of consensus guidelines.

SUGGESTED READINGS

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Metabolic Changes Following Bariatric Surgery

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METABOLIC CONSEQUENCES OF OBESITY

The accumulation of excess body fat results in obesity, which is commonly defined as a body mass index (BMI) greater than 30. The BMI uses the ratio of weight to height (kg/m^2) to estimate adiposity. Although BMI is easy to calculate, it has several limitations. For example, athletic individuals may have an elevated BMI due to increased muscle mass (vs excess fat). Although obesity can be defined as percentage body fat greater than 32% in women and 25% in men, these calculations are difficult. More importantly, neither BMI nor percent body fat provide information regarding the distribution of excess body fat, which is critical because the metabolic consequences of obesity are determined by both the amount and distribution of body fat. Abdominal or visceral obesity leads to a chronic inflammatory state caused in part by the release of free fatty acids and cytokines from adipose tissue. Visceral obesity is associated with increased risk of insulin resistance, hyperlipidemia, hypertension, cardiovascular disease (CVD), and stroke. This pattern is also referred to as *android* obesity and is more commonly seen in men. The gynoid pattern of obesity is characterized by an excess accumulation of subcutaneous fat in the gluteal and hip thigh areas, is more commonly seen in women, and is less frequently associated with adverse metabolic effects. The importance of central obesity is highlighted in populations who, despite relatively low BMIs, have high levels of abdominal adiposity (visceral obesity). Such groups (e.g., Asians) are prone to adverse effect of obesity at a lower BMI. A simple measurement of waist circumference or waist to hip ratio can address central adiposity but does not accurately address height and fat content. A waist circumference of more than 35 inches in women or 40 inches in men indicates higher risk of metabolic syndrome and obesity related comorbidities, and a waist to hip ratio above 0.85 for females or 0.90 for males can be used to classify obesity.

Although the obesity epidemic in the United State is well documented, affecting 40% of women, 35% of men, and 17% of children and adolescents, the problem is an international one, with many Western countries reporting similar rates. Some of the highest rates of obesity in adults are observed in some of the South Pacific Islands such as Samoa. The global epidemic of obesity is multifactorial and has genetic, environmental, and epigenetic roots. Although recent exposure of humans to an environment with excess cheap food leads to an imbalance between caloric intake and energy expenditure results in increased risk of obesity, this risk is modulated by genetic risk factors, lifestyle, culture, and economic factors.

Although adipose tissue was originally thought to be a relatively quiescent accumulation of stored calories, more recent studies indicate adipose tissue to be metabolically and hormonally active. In severe obesity, excess lipid accumulates in these metabolically active adipocytes, as well as hepatocytes and muscle cells. Excess accumulation of nutrients and fat within these cells leads to increased secretion of adipocyte derived peptides (e.g., leptin, adiponectin, resistin) and cytokines (e.g., tumor necrosis factor α, interleukin 6) collectively referred to as adipokines. The paracrine and endocrine actions of these adipokines contribute to a state of chronic low grade inflammation, which in turn interferes with many physiologic cellular processes (such as insulin signaling) and leads to the metabolic derangements seen in obesity (such as insulin resistance and diabetes).

The obesity induced inflammatory state adversely affects most organ systems in the body and contributes to a shortened life expectancy. Each 5 unit increase in BMI is associated with a 30% increase in all cause mortality, with BMIs greater than 40 associated with a reduced life expectancy of 8 to 10 years. Obese individuals have a poor quality of life with increased risk of many life threatening conditions, including cancers, heart disease, type 2 diabetes, hypertension, stroke, hyperlipidemia, and sleep apnea. The prevalence of these comorbidities often increases with the severity of obesity (Table 1). This is most evident when looking at type 2 diabetes. At age 18, women with a BMI of 30 to 35 have a 51.6% lifetime risk of developing diabetes, which is increased to 71.4% for those with a BMI greater than 35.

Although modest weight loss (5%–10% excess weight) can lead to reductions in the risk of these chronic diseases, nonsurgical weight loss is often unsuccessful or short lived in 90% to 95% of patients. Thus bariatric surgery has become the standard of care in the treatment of medically complicated or morbid obesity.

METABOLIC IMPROVEMENTS AFTER WEIGHT LOSS SURGERY

Weight Loss

The term excess body weight loss (EBWL), calculated using the actual and ideal body weight, has traditionally been used by surgeons to describe degree of weight loss, although there is a general move away from this metric, with total body weight loss or BMI reduction being increasingly used. Not surprisingly, the degree of weight loss varies between procedures. The mean EBWL is 70% to 80% for biliopancreatic diversion with or without duodenal switch (BPD), 60% to 70% for Roux-en-Y gastric bypass (RYGB), 50% to 60% for sleeve gastrectomy (SG), and 40% to 45% for laparoscopic adjustable gastric banding (LAGB) at 2 years. In general, procedures with higher weight loss are also associated with increased short and long term complications. The balance between the desired weight loss and surgical risk influences the patients when choosing an operation and the surgeons when offering the procedure.

The mechanisms underlying the weight loss are multifactorial and vary by procedure. The proposed mechanisms for postsurgical weight loss are summarized in Table 2. Of critical importance are long term reductions to appetite and hunger after surgery. In contrast, nonsurgical weight loss leads to increased hunger and reduced energy expenditure, which presumably contributes to the ultimate failure of dieting to achieving long term weight reduction. Weight loss surgery prevents such physiologic responses and maintains hunger control despite limited caloric intake.

Long term, follow up studies such as the Swedish Obesity Study demonstrate significant long term weight loss in surgical patients compared with control subjects, with up to 20 years of follow up. The durability of postsurgical weight loss is a concern for patients and clinicians. Definition of successful weight loss in bariatric surgery patients varies depending on the procedure but for gastric bypass is described as losing and maintaining 50% or more EBWL. Most patients regain some weight after reaching their nadir weight, with pathological weight regain (>20% of the maximal weight loss) reported in 15% to 20% of patients. This observation highlights the fact that bariatric surgery is not a replacement for long term lifestyle changes that are needed to help maintain weight loss. A commitment to changes to diet and exercise are critical for long term success. The importance of such changes and the need for regular postoperative follow up with the bariatric team should be emphasized to patients before surgery.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease is present in more than 70% of individuals with a BMI greater than 35 and represents a spectrum of

TABLE 1 Risks of Cardiovascular and Metabolic Disorders With Obesity

Life expectancy	• 30% increase in mortality rate for each 5 unit increase in BMI • In patients with BMI >40, life expectancy is reduced by 8 years
Hypertension	• 5 fold risk of hypertension in obese individuals • 85% of hypertensive patients have a BMI >25
Cardiovascular disease	• A 9% increase in cardiovascular mortality rate with each unit increase in BMI
Type 2 diabetes	• Men with BMI >35 have a 42 fold increase in risk of diabetes compared with men with BMI <23 • 74% lifetime risk of type 2 diabetes if BMI>35

BMI, body mass index.

disease characterized initially by the accumulation of liver fat (steatosis), which, if severe, causes inflammation and nonalcoholic hepatosteatitis (NASH) and later fibrosis or cirrhosis. Hepatic steatosis and NASH, markers of central adiposity, are believed to be important in the pathogenesis of obesity related metabolic disorders often referred to as metabolic syndrome (visceral adiposity, insulin resistance and hyperinsulinemia, hyperuricemia, hyperlipidemia). NASH is now a leading cause of cirrhosis in the United States and one of the main indications for liver transplantation. Therefore resolution of NASH related hepatic injury is an important endpoint in bariatric and metabolic surgery. Studies have shown that weight loss operations lead to a near universal improvement in the severity of hepatic steatosis, inflammation, and fibrosis. Imaging studies using magnetic resonance imaging have shown that liver volume is reduced within 1 month after surgery and liver steatosis is resolved in about 80% of patients by 6 months. Overall RYGB leads to greater improvement in liver disease compared with restrictive only procedures (SG and LAGB) because of better weight loss.

Lipid Profiles

Dyslipidemia is seen in up to 50% of patients undergoing bariatric surgery, with over 80% experiencing an improvement or resolution of this comorbidity within 2 years of surgery. Surgery leads to significant reductions in triglyceride with a more modest decrease in total cholesterol. High density lipoprotein (HDL) levels are also significantly increased. There is variation in the remission rate of dyslipidemia between the common bariatric procedures, and better results are achieved by the more malabsorptive operations. Comparing SG and RYGB, gastric bypass leads to a reduction in cholesterol, low density lipoprotein (LDL) and an increase in HDL, whereas the SG only increased HDL without altering LDL levels. Both operations lead to a significant decrease in triglycerides. The 5-year remission rates for dyslipidemia are about 40% after SG and 60% after RYGB.

Hypertension

Hypertension is common in obesity and rises in prevalence with increasing weight. The odds ratio for hypertension is 1.7 for overweight compared with normal-weight individuals, 2.6 for BMI 30 to 34.9, 3.7 for BMI 35 to 39.9, and 4.8 for BMI of 40 or more. In the normal weight population (BMI <25), hypertension is present in 15% to 20% of population, rising to 30% to 40% in those with BMI greater than 30. Elevated blood pressure is seen in up to 50% of patients undergoing bariatric surgery, with 60% to 70% documenting an improvement or remission after weight loss surgery. Improvements in blood pressure are also linked to weight loss, and the remission rates vary between the bariatric procedures.

A European study of patients undergoing RYGB or intensive medical therapy showed the rate of hypertension remission was 89% for the surgical group versus 23% for the control group. In randomized studies comparing RYGB to SG, hypertension remission rates at 5 years were reported at 50% to 70% for RYGB and 30% to 40% for SG. Remission rates are generally lower for LAGB (around 20%) and higher for BPD (40%–80%).

TABLE 2 Proposed Mechanisms for Weight Loss After Bariatric Procedures

Physical restriction of food intake	Unlikely. Although a common belief especially in case of LAGB, there is little data to support this. Food transit through the stomach is only minimally altered after LAGB and the upper pouch compartment is empty of food within 1–2 minutes after ingestion. BPD has a large gastric reservoir and yet leads to the best weight loss results.
Malabsorption	Unlikely. Although a degree of this occurs after BPD, little malabsorption is seen after LAGB, SG or RYGB.
Decreased hunger signals and reduced food intake	This is true for all bariatric procedures, and secondary to neuro hormonal changes seen after surgery.
Increased energy expenditure and diet induced thermogenesis	Although this has been documented in rodents, there is little data to support this in humans.
Changes in food preference	Changes in food preference have been documented and are related to pain in alterations in reward and taste, as well as concerns about physiologic implications of ingestion of certain foods that may lead to dysphagia or dumping syndrome.
Changes in gut microbiota	Animal studies demonstrate a role for intestinal microbacteria in obesity and diabetes. Definitive human data are presently lacking, but this is an area of significant scientific interest.

BPD, biliopancreatic diversion + duodenal switch; LAGB, laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Cardiovascular Risk and Mortality

CVD remains the leading cause of death in the United States. Several risk scores have been developed to calculate an individual's risk of having a cardiovascular (CV) event and used to help guide strategies for primary prevention. Of these risk scores, the Framingham Risk Score (FRS) is widely used. This risk score is calculated based on age, sex, smoking status, as well as cholesterol, HDL, and systolic blood pressure. These parameters are all improved after bariatric surgery, and it is therefore not surprising that weight loss procedures have

TABLE 3 Weight Changes and Metabolic Improvements After Bariatric Procedures

	TBWL (%)	Hypertriglyceridemia Remission	Hypertension Remission	Type 2 Diabetes Remission
RYGB	30%–35%	60%–65%	60%–70%	75%–80%
SG	30%–25%	50%–60%	30%–60%	50%–70%
LAGB	10%–15%	40%–70%	20%–30%	30%–60%

LA, L laparoscopic adjustable gastric banding; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; TBWL, total body weight loss.

been shown to reduce CHD and the 10-year risk of a cardiac event by 40%. Serum and laboratory risk predictors, such as C-reactive protein, have also been shown to decline after surgery by about 60%.

Several large cohort studies have shown that the reductions in risk factors also translate to reductions in overall mortality rate. In a large cohort study from Utah, at a mean follow up of 7.1 years, the overall mortality rate was reduced by 40%. Specifically, the cause-specific mortality rate decreased by 56% for coronary artery disease, by 92% for diabetes, and by 60% for cancer. Similar improvements in mortality rates have also been reported in the Swedish Obesity Study, which showed at 10 years a 23.7% unadjusted (30.2% adjusted) reduction in overall mortality.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of unknown cause characterized by menstrual abnormalities with hyperandrogenism and is a common cause of infertility, especially in severe obesity. Up to 50% of those with PCOS are overweight or obese, and phenotypic severity of PCOS is reported to correlate with severity of insulin resistance and to worsen with increased weight. In a meta-analysis of available data, incidence of PCOS before surgery was 45.6%, which significantly decreased to 6.8 % at 12-month follow up. Surgery has been reported to normalize menstruation in majority of cases, with improvements in infertile PCOS patients seeking pregnancy.

Reproductive Function and Pregnancy after Bariatric Surgery

Reproductive function and pregnancy are important topics to consider because 80% of individuals having bariatric surgery are women, and many of them are of reproductive age. Obesity is commonly associated with infertility, which is multifactorial in nature. Increased adipose tissue results in overproduction of the hormones leptin, estrogen, and testosterone. Impaired leptin signaling and increased levels of estrogen interfere with the hypothalamic, pituitary ovarian axis, resulting in dysfunctional uterine bleeding, anovulatory cycles, and reduced fertility. Insulin resistance is commonly observed with visceral adiposity, resulting in increased ovarian production of testosterone and decreased production of sex hormone binding globulin by the liver. In aggregate, these changes result in an increase in free androgen index, libido, and PCOS. Obesity also impacts body image and sexual health, which can also adversely impact reproductive function.

Women who are planning to have bariatric surgery are advised to avoid pregnancy and use reliable forms of birth control for 1 to 2 years after surgery. The rapid weight loss that occurs after bariatric surgery poses risks for both mother and baby. Many young women undergoing bariatric surgery have been unable to get pregnant for years despite being active sexually and do not routinely use contraception. However, rapid changes in hormonal function and fertility after bariatric surgery mandate education regarding the need for contraception to prevent pregnancy in the early postoperative period. Although oral contraceptives are normally very effective, after RYGB and other malabsorptive surgeries, oral contraceptives may be less effective due to impaired absorption. Other types of birth control, including transdermal and vaginal systems and barrier methods, should be considered. Once weight loss has stabilized, women interested in becoming pregnant should consider antepartum consultations with a dietitian, bariatric specialist, and obstetrician. Obesity is also associated with multiple complications related to pregnancy including gestational diabetes, hypertension, preeclampsia, congenital malformations, and stillbirth.

Several studies have examined the effects of bariatric surgery on outcomes of pregnancy with matched control subjects. Collectively they suggest that risk of gestational diabetes and large for gestational age infants during pregnancy are decreased after bariatric surgery. Although preterm birth, stillbirth, and congenital malformations were not impacted, the risk of small for gestational age babies appears to be increased after bariatric surgery. Several recent studies suggest that surgical weight loss before pregnancy has the potential to reduce the risk of obesity and metabolic risk factors by epigenetic mechanisms involving DNA methylation. These data raise potentially important questions regarding the benefits of bariatric surgery in future offspring. However, additional data are needed to further understand the long-term risk and benefits of maternal bariatric surgery on future offspring.

Type 2 Diabetes

Of all metabolic changes after bariatric surgery, none have been as impressive as the improvements in glucose homeostasis. Type 2 diabetes has reached epidemic proportions in the United States, and, despite significant investments in preventive measures, the rate is set to continue to climb. The diabetes epidemic is worldwide, significantly impacting countries such as China and Southeast Asia, including India, where about half of the world population of diabetic patients live. The number of patients with diabetes is expected to climb to more than 600 million worldwide by 2040. New pharmacological therapies (glucagon-like peptide 1 [GLP-1] analogues and dipeptidyl peptidase IV inhibitors) have been disappointing, and many diabetics fail to reach the therapeutic goals set by the American Diabetic Association and other endocrine societies (HbA_{1c} <7%). These trends and the remarkably rapid improvement in diabetes seen after bariatric interventions have pushed surgery to the forefront of diabetes treatment and created the field of Metabolic Surgery, defined for this purpose as "manipulation of the gastrointestinal tract with the goal of treating diabetes."

The observation that alterations in gastrointestinal anatomy can lead to diabetes resolution was first noted in the 1960s, and improvements in glycemic control after weight loss operations have been well documented since the early reports in 1995. Several large studies and meta-analyses have confirmed that all bariatric procedures lead to significant improvements in glucose control and diabetes remission, although success rates vary among the different operations, with RYGB and BPD offering the best chance of disease remission (Table 3). Although improvements in glycemic control are expected after any form of weight loss (surgical or diet induced), studies have confirmed weight independent effects on diabetes after RYGB and BPD.

There have now been at least 11 randomized studies confirming that bariatric surgery leads to better diabetes control than intensive

medial therapy. In the study comparing LAGB to medical therapy, surgery led to a diabetes remission (defined by fasting glucose <126 mg/dL and HbA_{1c} <6.5% in the absence of pharmacologic therapy) rate of 73% versus 13% for the medical arm at 2 years. The improved outcomes in surgical arm were linked to improved weight loss. Mingrone et al compared medical therapy to RYGB or BPD and showed that, at 5 years, diabetes remission (defined by fasting glucose <100 mg/dL and HbA_{1c} <6.5% in the absence of pharmacologic therapy) was seen in 0% in the medical arm compared with 37% in RYGB and 63% for BPD. The 5-year results of the Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently Trial, which compared medical therapy to RYGB or SG, and reported the remission rate (defined as HbA_{1c} <6% with or without medications) was 5% in the medical group versus 20% in the RYGB and 23% in the SG arms. In a large cohort study of more than 800 patients who had RYGB, with a 98% long term follow up rate, the 12 year diabetes remission rate was 51%.

These data have prompted many of the diabetes societies to alter their treatment guidelines for management of type 2 diabetes and recommend surgery in patients with poorly controlled diabetes and BMI less than 35 (see below section on surgery in low BMI patients). Although the antidiabetic effects of LAGB are directly linked to weight loss, the studies point to a weight independent effect for RYGB and BPD. This topic has received significant scientific attention over the last several years with many proposed mechanisms (Table 4). Although many hormones have been investigated to help elucidate the mechanisms of weight independent effect of RYGB on glucose homeostasis, there has been limited progress. GLP-1, an incretin hormone that leads to enhanced insulin secretion and satiety, has been shown to increase after many bariatric procedures. It is, however, likely that this is not the only contributing factor, and it appears that isolation of the proximal bowel from nutrient exposure also plays a critical role by altering nutrient sensing. Alterations in signaling represent another potential mechanism contributing to the metabolic benefit of surgery.

Cases of post RYGB hyperinsulinemic hypoglycemia have been reported, the cause of which remains unclear. Although initially the symptoms were thought to be related to pancreatic β cell hyperemia (nesidioblastosis), this theory is now questioned, with alternative hypotheses proposed and under study, including those related to changes in intestinal hormone secretion and rate of intestinal glucose absorption. These symptoms can often be managed with careful dietary modifications.

METABOLIC SURGERY AND FUTURE DIRECTIONS

The slow progress in finding effective new medical therapy for type 2 diabetes, the increasing prevalence of the disease, and increasing data confirming effectiveness of bariatric surgery to diabetes remission have been the impetus behind recommendations to lower the BMI threshold for surgical intervention in diabetic patients to 30. There is also an intense interest in understanding the scientific mechanisms underlying the antidiabetic effects of these procedures to help develop less invasive alternatives that can replicate their metabolic benefits. Alternative surgical procedures have been tested, and there has been significant investment in developing endoluminal devices for treatment of diabetes, heralding with it the emerging field of "interventional diabetology."

Surgery in Diabetic Patients with Low BMI

The 1991 NIH Consensus statement recommends bariatric surgery in patients with BMI greater than 35 and type 2 diabetes. Although most patients with type 2 diabetes are overweight or obese, around 20% have BMI below 35 and fail to qualify for surgical intervention based on their BMI. They struggle with their chronic disease, which is often poorly controlled by medications alone. Considering the impressive results of bariatric surgery, there is great interest in lowering the BMI threshold for diabetic patients who desire surgical intervention. It has been suggested to lower the surgical threshold BMI to 30, with a reduction to 27 for those of Asian ethnic origin where adverse metabolic effects are seen at a lower BMI.

A meta analysis of all randomized surgical studies looked at the outcomes of surgery in low BMI patients and showed that surgery can be effective in this group. The Diabetes Surgery Summit II in 2015 gathered the leading international diabetes organizations and surgical societies together and recommended that patients with BMI greater than 30 and diabetes that is poorly controlled with medications should also be considered for surgery. There is no consensus, however, about the best surgical procedure for these patients. In a randomized study from Taiwan involving diabetic patients with BMI of 25 to 34, RYGB was shown to be more effective than SG in achieving diabetes remission (95% vs 47%). The mean postoperative BMI was 22.8 for RYGB and 24.4 for SG, confirming that the patients do not experience excessive weight loss and their postoperative weight remains within normal range. The Diabetes Surgery Summit II's recommendations, which was endorsed by more than 40 international societies, was that patients with BMI greater than 30 and poorly controlled diabetes on

TABLE 4 Proposed Mechanisms for Antidiabetic Effects of RYGB and Other Similar Procedures

Restriction and acute decrease in food intake after surgery	Unlikely. Food intake is reduced after many GI surgeries where patients are kept off by mouth. Most these surgeries however lead to a state of insulin resistance rather than sensitivity.
Malabsorption	Unlikely. No evidence that RYGB leads to enough nutrient malabsorption to account for the rapid improvement in diabetes.
Changes in post-prandial incretin response	Post-prandial GLP-1 levels are increased after these surgeries leading to enhanced insulin release. This is likely due to earlier delivery of food to the distal small bowel where GLP-1 is primarily secreted.
Isolation of proximal bowel from nutrient flow	Evidence points to a role for proximal bowel in sensing nutrient availability and quality. Isolation of this region of the intestine from nutrient exposure can lead to alterations in nutrient absorption and glucose homeostasis. This idea is behind some of the metabolic devices in development.
Intestinal gluconeogenesis	Rodent studies have suggested that ability of proximal bowel to generate glucose and release it to the portal circulation leads to changes in hepatic insulin sensitivity and glucose homeostasis. Human studies are lacking.
Changes in circulating bile acids	Human and animal studies have shown increased circulating bile acid levels in patients after RYGB, and linked this to improved glucose homeostasis.

GI, Gastrointestinal; GLP-1, glucagon-like peptide-1; RYGB, Roux-en-Y gastric bypass.

medication should also be considered for surgery. However, despite this recommendation, surgery is rarely used in this patient group, and bariatric surgical procedures are not covered in low BMI patients by most insurance providers in the United States.

Adolescent Bariatric and Metabolic Surgery

Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years. Studies have also shown that childhood obesity is strongly linked to adult obesity and that obese youth are more likely to have risk factors for cardiovascular disease, such as high cholesterol or hypertension. In a population-based sample of 5- to 17-year-olds, 70% of obese youth had at least one risk factor for cardiovascular disease. Current estimates predict a decrease in life expectancy in obese adolescents of 5 to 20 years depending on additional risk factors such as race and sex. Although studies are limited, current data suggest bariatric surgery is as safe in adolescents as it is in adults, having similar success in both weight reduction and resolution of metabolic derangement. Because of the paucity of long-term outcome data, the role of bariatric surgery in the pediatric patient remains controversial. When pediatricians were polled, even for adolescents with life-threatening comorbidities, half of the respondents would not refer their patients who are under 18 years of age for bariatric surgery.

In a study of 541 adolescent (12–19 years) patients undergoing bariatric surgery, mean age was 17 years, with a BMI of around 50. The most common procedure was LSG, followed by RYGB and LAGB, with mean BMI changes of −28%, −31%, and −18%, respectively, at 1 year. For RYGB and SG, BMI changes of −29% and −25% were maintained at 3 years. In a prospective study of 242 adolescent patients in the United States (Teen Label) similar weight loss rates were reported at 3 years, along with improvements to cardiometabolic health and weight-related quality of life.

Alternative Surgical Procedures

The surgical rearrangement of gastrointestinal anatomy is thought to be critical to the metabolic success of most bariatric procedures. This includes (1) isolation of duodenum and proximal bowel from nutrient exposure and (2) earlier exposure of distal bowel and ileum to undigested food (Table 1). Some surgical groups have worked on developing alternative novel procedures that achieve one or both of these goals and could have therapeutic value to diabetic patients with low BMI. Of these procedures, duodenal-jejunal bypass and ileal interposition with or without sleeve gastrectomy have received the most attention and been tested in human subjects with good early results. These procedures are, however, complex, and it is not clear whether they offer any advantages in terms of effectiveness, durability, or safety over the more standard procedures such as RYGB.

Endoluminal Devices

With the recognition that gastrointestinal manipulation can lead to improvements in glycemic control, several endoluminal devices are in development with the goal of replicating the metabolic success of bariatric procedures without the need for an invasive procedure. There are many such devices in various stages of development, and a few have received regulatory approval. This reduction will herald an era when diabetes management will not be only handled by endocrinologists, but also by surgeons who will help manage the obese diabetics by means of surgery, as well as advanced interventional endoscopists who will deploy the endoluminal devices to manage the patients with poorly controlled diabetes who do not qualify for surgery or wish to avoid it.

Suggested Readings

Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study. JAMA Surg. 2018;153(5):427–434.

Inge TH, Courcoulas AP, Jenkins TM, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med. 2016;374(2):113–123.

Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–1585.

Peterli R, Wölnerhanssen BK, Peters T, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss in patients with morbid obesity: the SM-BOSS randomized clinical trial. JAMA. 2018;319(3):255–265.

Rubino F, Nathan DM, Eckel RH, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care. 2016;39(6):861–877.

Schauer PR, Bhatt DL, Kirwan JP, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic Roux-en-Y gastric bypass on weight loss at 5 years among patients with morbid obesity: the SLEEVEPASS randomized clinical trial. JAMA. 2014;312(11):1351–1363.

Cardiovascular Disease Risk Reduction After Bariatric Surgery

Essa M. Aleassa, MD, Ali Aminian, MD, and Philip R. Schauer, MD

Cardiovascular disease (CVD) is a summative term that relates to diseases of the heart and blood vessels. Examples of these diseases include coronary artery disease, heart failure, stroke, hypertension, and cardiomyopathy. The Centers for Disease Control and Prevention data, through the National Health and Nutrition Examination Survey 2013 to 2016, estimated that 48% of adults older than 20 years were affected by CVD. The prevalence of CVD excluding hypertension is 9%. The prevalence is elevated with increasing age. Although the mortality rate owing to the different CVD entities vary, collectively they are responsible for more deaths than cancer and trauma. Coronary heart disease is the most common (43.2%) cause of CVD related death followed by stroke (16.9%), hypertension (9.8%), and heart failure (9.8%).

The health care and economic burden of CVD on the community are major. The Healthcare Cost and Utilization Project tallied more than 8 million admissions in 2014 and 88 million outpatient visits, and 4.7 million emergency department encounters in 2015 related to a primary diagnosis of CVD. CVD is among the leading conditions filed for disability in the United States. The American Heart Association projected that by the year 2035, CVD will affect 45% of the United States population in some form, with total medical cost cost to be around $1.1 trillion.

Risk factors leading to CVD are well established, among which is obesity. It is considered an independent risk factor, especially when the obesity is most pronounced in the trunk, otherwise known as central obesity. This chapter will shed light on the relationship between central obesity and CVD. Furthermore, it will discuss the effect of bariatric and metabolic surgery on CVD risk factors and actual reduction of cardiovascular events such as myocardial infarction, stroke, and death.

medication should also be considered for surgery. However, despite this recommendation, surgery is rarely used in this patient group, and bariatric surgical procedures are not covered in low BMI patients by most insurance providers in the United States.

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Risk factors leading to CVD are well established, among which is obesity. It is considered an independent risk factor, especially when the obesity is most pronounced in the trunk, otherwise known as central obesity. This chapter will shed light on the relationship between central obesity and CVD. Furthermore, it will discuss the effect of bariatric and metabolic surgery on CVD risk factors and actual reduction of cardiovascular events such as myocardial infarction, stroke, and death.

BOX 1 Cardiovascular Disease Risk Factors, Including Major Independent Factors Accounted for in the Framingham Risk Score*

Traditional Nonmodifiable

- Age (men >45 years; women >55 years)†
- Family history of premature CHD (CHD in male first-degree relative age <55 years; CHD in female first-degree relative age <65 years)
- Sex
- Race

Traditional Modifiable

- Smoking‡
- High blood pressure (blood pressure >140/90 mm Hg or on antihypertensive medication)‡
- High cholesterol (low HDL cholesterol [<40 mg/dL])‡
- Diabetes
- Prediabetes

Emerging Nontraditional Cardiovascular Disease Risk Factors (Associated With Visceral Obesity)

- Insulin resistance/hyperinsulinemia
- Dyslipidemia with elevated triglycerides, low HDL cholesterol, and increased apolipoprotein B serum concentrations
- Procoagulation and abnormal fibrinolysis with increased serum fibrinogen concentrations and increased production of plasminogen activator inhibitor
- Inflammation with increased serum levels of C-reactive protein, tumor necrosis factor, interleukin-6
- Endothelial dysfunction
- Premature atherosclerosis
- Microalbuminuria

*The current version of the Framingham Risk Score (FRS) was published in 2008. The score is used to estimate the 10-year cardiovascular risk of an individual based on data obtained from the Framingham Heart Study. The score is sex specific. Individuals with low risk have 10% or less CHD risk at 10 years, those with intermediate risk have 10% to 20% CHD risk, and those with high risk have >20% CHD risk. In the current version of the FRS, diabetes was removed from the score, if a person has type 2 diabetes, he or she is classified as having a CHD risk equivalent.

†Black race is a risk factor for CVD, but it is not included in the FRS.

‡Smoking, high blood pressure, and low HDL cholesterol are modifiable risk factors that are included in the FRS.

CHD, Coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL, high-density lipoprotein.

TABLE 1 International Diabetes Federation Criteria for Metabolic Syndrome

International Diabetes Federation defines metabolic syndrome as the presence of central obesity* (defined as waist circumference by ethnicity plus two of the following four factors)	
Raised triglycerides	>150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality
Raised BP	Systolic BP >130 or diastolic BP >85 mm Hg
Raised fasting plasma glucose	>100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes If >5.6 mmol/L or 100 mg/dL, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome

*If body mass index is >30 kg/m², central obesity can be assumed and waist circumference does not need to be measured.

BP, Blood pressure; HDL, high-density lipoprotein cholesterol.

BOX 2 Diagnostic Criteria for Metabolic Syndrome as Defined by the National Cholesterol Education Program Adult Treatment Panel III

Three or more of the following five cardiovascular risk factors:

1. Central obesity (waist circumference >102 cm in men; >88 cm in women)
2. Hypertriglyceridemia: triglycerides >1.7 mmol/L (>150 mg/dL)
3. Low high-density lipoprotein: <1.03 mmol/L (<40 mg/dL) in men; <1.29 mmol/L (<50 mg/dL) in women
4. Systemic hypertension: blood pressure >130/85 mm Hg or medication
5. Elevated fasting plasma glucose: glucose >5.5 mmol/L (>100 mg/dL)

CARDIOVASCULAR DISEASE RISK FACTORS

Overview

CVD risk factors have been extensively studied and can be divided into traditional and nontraditional risk factors. Furthermore, the traditional risk factors can be subclassified into modifiable and nonmodifiable (Box 1). Population-based studies have revealed that most CVD is due to lifestyle-related risk factors such as dietary risks, low level of physical activity, and tobacco smoking. Other risk factors are high systolic blood pressure, triglyceride cholesterol levels, fasting plasma glucose (FPG) levels, and body mass index (BMI). In 2012, Fryar and colleagues had estimated that approximately 47% of the United States population already had one of three risk factors for CVD, that is high blood pressure, tobacco smoking, and high cholesterol levels.

Traditional nonmodifiable risk factors for CVD are increasing age, sex, race, and family history of premature coronary heart disease. Men are at higher risk of CVD. Patient sex also dictates the age cut-off as to when the risk for CVD increases (>45 years for men and >55 years for women). Patients of black race are at a higher risk for CVD than their white race counterparts. Having a family history of CVD in a first-degree family member increases the risk for CVD. This appears to be more pronounced in certain ethnicities.

Metabolic Syndrome

Metabolic syndrome, previously known as syndrome X, is a cluster of conditions that lead to CVD and type 2 diabetes. The International Diabetes Federation (IDF) revised the term to metabolic syndrome. Metabolic syndrome is diagnosed by the presence of central obesity and two or more metabolic risk factors. These risk factors are high systolic blood pressure, triglyceride cholesterol levels and FPG, and low high-density lipoprotein (HDL) cholesterol (Table 1). National Cholesterol Education Project Adult Treatment Panel uses similar clinical criteria to define metabolic syndrome (Box 2). The prevalence of metabolic syndrome in the United States is estimated to be 34.2%. The prevalence increases with age affecting >43% of patients aged 65 years or older. It has been shown that metabolic syndrome substantially increases risk for CVD (relative risk [RR], 1.78; 95% confidence interval [CI], 1.58 to 2.00). Furthermore, all-cause mortality was higher in patients with CVD in the presence of metabolic syndrome (RR, 1.58; 95% CI, 1.38 to 1.78).

Diabetes Mellitus

Diabetes mellitus is an endocrine disorder in which blood glucose level is dysregulated. It is further subclassified by the pathogenesis of the dysregulation. More than 98% of diabetes mellitus is of type 2. In type 2 diabetes, insulin is produced by the pancreas but is inadequate to maintain normal glucose levels due to insulin resistance in body tissue. Type 2 diabetes is a major risk factor for CVD. The prevalence of type 2 diabetes has been increasing with an upward annual trend by 30.5%. Of note, approximately 80% of youth with type 2 diabetes have obesity. The prevalence of type 2 diabetes has been up trending among adults as well, regardless of the sex and ethnicity. Diabetes is associated with microvascular and macrovascular complications that can eventually lead to CVD. Furthermore, a longitudinal study conducted by the National Health Interview Surveys enrolled patients with and without diabetes between 2000 and 2009 and followed them through 2011. It concluded that patients with diabetes had a higher overall and CVD-related mortality as compared to patients without diabetes.

Obesity

Central obesity is determined by the measurement of the waist circumference. The waist circumference is sex and ethnic group–specific. However, based on the IDF definition, patients with a BMI of 30 kg/m^2 or greater are assumed to have central obesity and do not require waist circumference measurement. Obesity has been recently declared as a chronic disease, not merely a risk factor. The prevalence of obesity has been increasing over the past decades. Its prevalence in 2016 was 18.5% and 39.6% of the youth and adult population in the United States, respectively. Obesity is classified by the severity of the BMI calculated as kilograms per square meter. Normal BMI is less than 25 kg/m^2, whereas overweight and obesity are diagnosed with BMIs of 25 to 29.9 kg/m^2 and 30 kg/m^2 or greater, respectively.

BOX 3 Cardiovascular Conditions Associated With Obesity

- Early and accelerated atherosclerosis
- Hypertension
- Myocardial infarction or acute coronary syndrome
- Structural heart changes and congestive heart failure
- Atrial fibrillation
- Sudden cardiac death
- Stroke

Obesity is associated with many other comorbidities (Box 3). Its presence specifically increases the lifetime risk for CVD, type 2 diabetes, hypertension, sleep apnea, and venous thromboembolism. Overall obesity has been linked to increased all cause mortality (hazard ratio [HR], 1.18; 95% CI, 1.12 to 1.25). This might be explained by the increased risk for other comorbidities that accompany weight gain. When the different ranges of weight were compared side by side in young adults, the higher the weight class the higher the HR was for mortality. Moreover, patients with overweight, obesity, and extreme obesity had HR of 1.07 (95% CI, 0.94 to 1.2x), 1.41 (95% CI, 1.16 to 1.73), and 2.46 (95% CI, 1.91 to 3.16), respectively.

Effect of Weight Loss on Cardiovascular Disease Risk

Lifestyle-Induced Weight Loss

Obesity has been established as an independent risk factor for CVD. Furthermore, weight loss has been linked to improvement of the CVD risk factors individually; that is decrease in BMI, systolic blood pressure, triglyceride levels, and fasting blood glucose. Weight loss strategies are numerous. Weight loss of any degree is encouraged as every pound lost may potentially decrease the risk for CVD. This notion stems from lifestyle intervention studies such as the Look AHEAD (Action for Health in Diabetes) trial. The Look AHEAD trial is the largest trial of its kind. It aimed to assess the benefit of lifestyle induced weight loss on CVD risk factors. The study enrolled 3165 patients with type 2 diabetes and overweight and obesity. The participants were randomly assigned to either intensive lifestyle intervention or to diabetes support and education. The patients were followed up for 4 years. The initial results of the study published in 2013 showed that patients who lost at least 5% to 10% of their excess body weight had an improved CVD risk factors profile. This was reflected in decrease in BMI, systolic blood pressure, diastolic blood pressure, and triglycerides. An increase in HDL cholesterol was also noted (Table 2). However, an improved CVD risk profile does not necessarily equate with absolute risk reduction. The 10 year Look AHEAD follow up study in 2014 showed that weight loss by lifestyle intervention compared with the control group (6% vs 5.5%) did not reduce the rate of cardiovascular events in patients with obesity and type 2 diabetes.

Drug-Induced Weight Loss

Medical weight loss using drugs has been on the rise. Their use has been limited due to cardiovascular and central nervous system adverse effects. However, a few drugs have been recently investigated

TABLE 2 Mean Changes in Weight and Cardiovascular Disease Risk Factors in Intensive Lifestyle Intervention and Diabetes Support and Education Groups, and the Difference Between Groups Averaged Over 4 Years as Reported in 2010 by the Look AHEAD Group

Measure	Diabetes Support and Education	Intensive Lifestyle Intervention	Between-Group Mean Difference	P value
Weight, % initial weight	−0.68	−6.15	−5.7	<.001
HbA$_{1c}$ level	0.29	−0.36	−0.27	<.001
Systolic blood pressure	−2.97	−5.33	−2.56	<.001
Diastolic blood pressure	−2.48	−2.82	−0.63	.01
High density lipoprotein cholesterol	1.87	3.67	1.78	<.001
Triglycerides	−10.75	−25.56	−6.81	<.001
Low density lipoprotein cholesterol (adjusted for medication use)	−4.22	−8.35	−0.47	.02

Abbr: hemoglobin A1c.

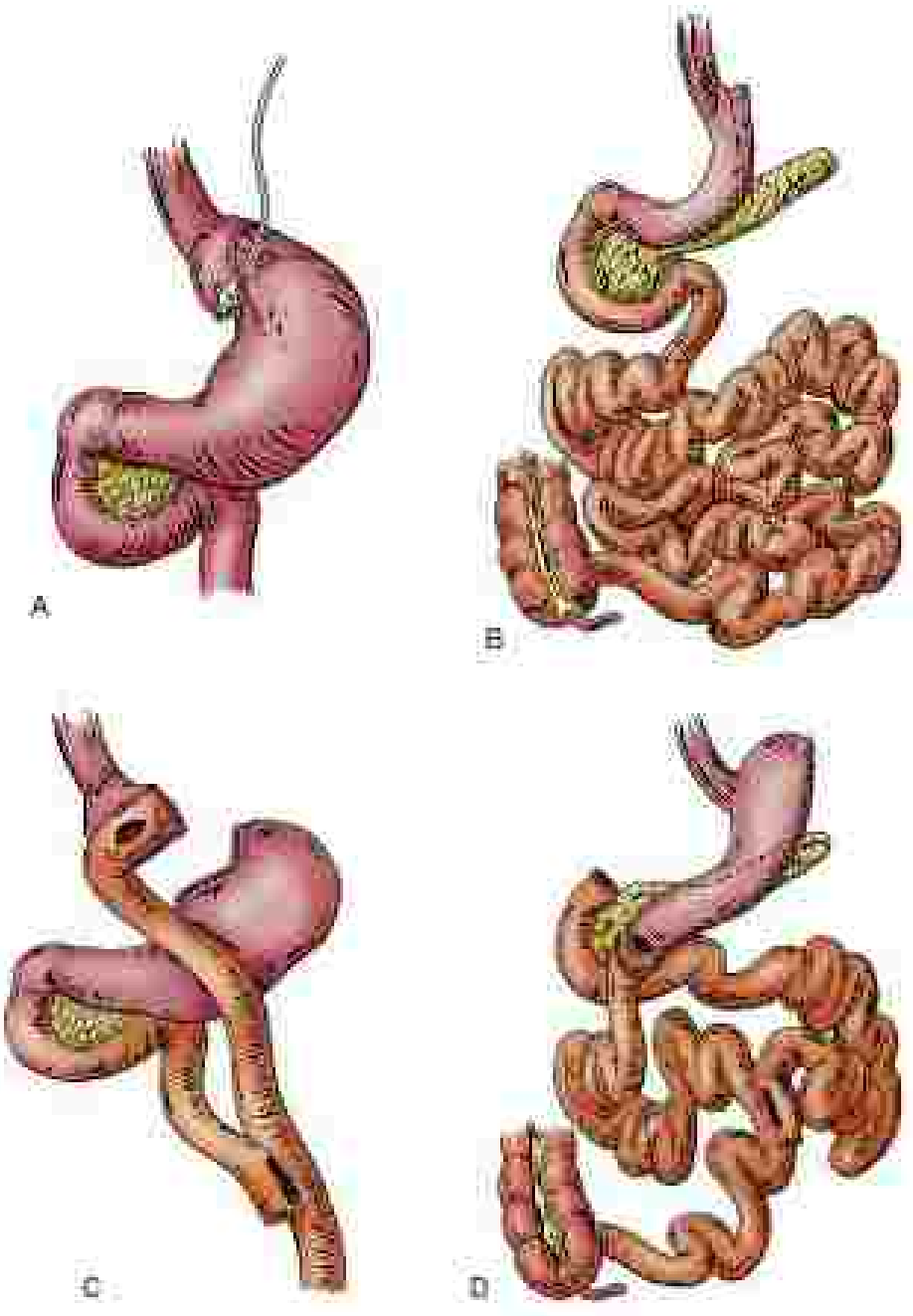


FIG. 1 Commonly performed bariatric procedures. (A) Adjustable gastric banding. (B) Sleeve gastrectomy. (C) Roux-en-Y gastric bypass. (D) Biliopancreatic diversion (shown with duodenal switch).

for cardiovascular safety such as lorcaserin, orlistat, and liraglutide. These medications have been Food and Drug Administration approved for patients with CVD. Use of orlistat has been associated with improvement of systolic and diastolic blood pressure and lipid profile. This is believed to be secondary to weight loss. Liraglutide was found to decrease cardiovascular events in a population with type 2 diabetes. The study concluded that the reduction in cardiovascular events was not exclusive for patients with obesity, therefore weight loss alone may not necessarily be the only driver of CVD risk reduction with this agent. Although lorcaserin has been established to be safe in patients with CVD, it is unknown if it has a positive effect on CVD.

Metabolic and Bariatric Surgery: Overview of Common Procedures (Fig. 1)

Metabolic and bariatric surgery, unlike lifestyle intervention and weight loss medications, have been shown to decrease weight substantially. Ample evidence exists on the benefit of metabolic and bariatric surgery in improving the cardiovascular risk profile and metabolic diseases. This benefit has also been translated to improved quality of life and overall survival, although randomized controlled cardiovascular outcome trials have yet to be conducted. Bariatric and metabolic surgery are believed to improve cardiovascular risk profile through weight loss and perhaps other mechanisms such as reduced inflammation. The operative safety

TABLE 3 Weight Loss and Resolution Rates of Obesity-Associated Comorbidities after Weight Loss Surgery According to Procedure Performed as Summarized by a 2004 Systematic Review of 22,094 Patients

	Gastric Banding	Gastric Bypass	BPD or DS	Total
Excess weight loss	47%	62%	70%	61%
Resolution of type 2 diabetes	48%	84%	99%	77%
Resolution of hyperlipidemia	38%	67%	91%	79%
Resolution of hypertension	47%	68%	83%	62%
Resolution of sleep apnea	95%	80%	97%	86%

BPD, biliopancreatic diversion; DS, biliopancreatic diversion with duodenal switch.
From Buchwald H, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724-1737.

of metabolic and bariatric procedures has been established. Moreover, most procedures can be performed laparoscopically. These procedures differ in their effect magnitude and durability of weight loss and the degree of metabolic disease resolution (Table 3). They also have different risk profiles that needs to be included in the informed consent (Table 4).

Effect of Bariatric Surgery on Cardiovascular Disease Risk Factors

Improving glucose and lipid metabolism and systemic inflammation are among the principal biochemical mechanisms by which bariatric surgery reduces CVD risk. The surgically induced weight loss and associated blood pressure improvement also contribute independently to decreasing CVD risk.

Glycemic Control

Insulin resistance and type 2 diabetes mellitus are remarkably improved after bariatric surgery. In 1995, a landmark article by Pories and colleagues described the durable effect of bariatric surgery in controlling type 2 diabetes mellitus. Since then, many reports have emerged confirming the therapeutic effect of the various bariatric procedures in patients with prediabetes (with impaired fasting glucose) and type 2 diabetes.

In fact, bariatric surgery has been shown to improve insulin sensitivity and play a role in prevention by halting the development of diabetes in patients with prediabetes. Currently, the mechanisms for such postoperative improvement in glucose metabolism as a function of time remain an active area of research. Clinically, however, improved glycemic control occurs within days after surgery, even when the amount of weight loss is insufficient to explain the observed improvement. In one series, Schauer and colleagues reported immediate postoperative independence from oral hypoglycemic agents on discharge from hospital after Roux-en-Y gastric bypass (RYGB) in 30% of patients who were on such medication preoperatively. What is more remarkable than the ability of bariatric surgery to completely reverse established diabetes is the ability to put the condition into remission for prolonged periods of time. In a study published by Pories and colleagues, 83% of 146 patients with diabetes experienced remission on a mean follow-up of 9.6 years after RYGB.

The best evidence for the durability of remission over time comes from a large scale controlled observational study, the Swedish Obese Subjects (SOS) project. This study showed reversal of diabetes in 72.3% of the surgical group as compared with just 16.8% of the control group at 2 years of follow-up (odds ratio [OR], 48.5; 95% CI, 21.9 to 78.2; $P < .001$). The durability of this remission was related to maintenance of weight loss. At 15 years, as weight regain was observed, diabetes remission rates remained impressive but were decreased to 30% in the surgical group and 6.3% in the controls (OR, 6.3; 95% CI, 2.1 to 18.9; $P < .0012$).

Meta-analyses of smaller scale studies also demonstrate the durability of diabetes remission after bariatric surgery. A 2009 meta-analysis by Buchwald and colleagues reviewed the results of 621 studies and observed an overall 78.1% resolution of clinical manifestations of diabetes after surgery, noting that the proportion of patients with diabetes resolution or improvement was similar before or after 2 years of follow-up. Diabetes resolution was reported to be the greatest for patients undergoing biliopancreatic diversion (BPD) with duodenal switch (95.1%), followed by RYGB (80.7%), and adjustable gastric banding (AGB) (54.7%). A limitation of this study rests in the use of clinical reports of diabetes remission rather than hard biochemical markers of glucose control.

The American Society for Metabolic and Bariatric Surgery (ASMBS) recently published a position statement that systematically reviewed medium- and long-term durability of weight loss and diabetic outcomes after bariatric surgery. The position statement concluded that more than 50% of patients with RYGB had sustained remission on 15 year follow-up.

Strong evidence for the superiority of bariatric surgery to conventional medical therapy in achieving improved glycemic control in diabetic patients is accumulating. We now have evidence from many well-designed randomized controlled trials (RCTs) that address this question using hard biochemical markers of glucose metabolism, such as FPG and hemoglobin A_{1c} (HbA_{1c}) as endpoints. In 2008, Dixon and colleagues found that remission of diabetes was significantly higher in patients who underwent laparoscopic adjustable gastric banding (LAGB) than in those who received standard treatment (73% vs 13%) when comparing a surgical group of 30 patients with diabetes to a matched control group of 30 patients over 2 years based on achieving an HbA_{1c} less than 6.2%, an FPG less than 7 mmol/L, and no antidiabetic medications. In 2012, Schauer and colleagues released the first report from the Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently randomized clinical trial. This study randomly assigned 150 patients with type 2 diabetes mellitus (mean age, 49 years; 48% women; mean preoperative HbA_{1c} 9.2%), with equal duration of diabetes before surgery, between intensive medical therapy alone versus medical therapy plus RYGB, or sleeve gastrectomy (SG), placing 50 patients in each of the three groups. After 1 year, weight loss was greatest in the RYGB group, and an HbA_{1c} less than 6% (primary endpoint) was achieved in 42% of patients after RYGB, in 37% after SG, and in only 12% after medical therapy. Two year follow-up results, published in 2017, showed weight loss of −23%, −19%, and −5% for RYGB, SG, and medical therapy, respectively. With that, HbA_{1c} less than 6% was achieved in 22.4%, 16.9%, and 0 patients after RYGB, SG, and medical therapy, respectively. Also in 2012, Mingrone and colleagues published results of their study on bariatric surgery versus conventional medical therapy for type 2 diabetes mellitus. Their primary endpoint was diabetes remission at 2 years as measured by an FPG less than 5.6 mmol/L and an HbA_{1c} less than 6.5% in the absence of diabetic drug therapy. Patients (mean age 45.4 years; 47% women; mean preoperative HbA_{1c} 8.65%) were randomly assigned between RYGB, BPD, and medical therapy. Better glycemic control was observed in the surgical groups after 2 years, and although diabetes remission rates were 95% and 75% after BPD and RYGB, respectively, no remission was seen in the medical therapy group. An important post hoc analysis also showed that, unlike previously seen with the LAGB in the Dixon and colleagues trial, initial BMI and postoperative weight loss were not predictive of the improvement in hyperglycemia seen after surgery. Furthermore, the 5 year follow-up of Mingrone and colleagues' RCT showed 43%

TABLE 4 Bariatric Procedure-Related Postoperative Complications

Procedure	Complications	
	Early Postoperative Period (< 30-day)	Late
LRYGB	Anastomotic leak with peritonitis Abdominal abscess Pulmonary embolism Bleeding Pulmonary complications Acute distal gastric dilatation Roux limb obstruction Wound infection	Stomal stenosis Marginal ulcer Dumping syndrome Intestinal obstruction Internal hernia Incisional hernia Cholecystitis Vitamin and mineral deficiencies Weight regain Hypoglycemia
LBPD ± DS	Same as LRYGB	Same as LRYGB with the following being more common in the BPD procedure than in RYGB if aggressive prophylactic measures are not followed postoperatively: Anemia Protein calorie malnutrition Vitamin B_{12} deficiency Hypocalcemia Osteoporosis Fat soluble vitamin deficiency Night blindness
LSG	Staple line leak Abscess Hemorrhage Sleeve stricture Wound infection	Intractable nausea ± vomiting Reflux symptoms Gastric dilation Weight loss failure Weight regain
LAGB	Hemorrhage Wound infection Food intolerance Reflux Nausea ± vomiting Slippage Wound infection	Reflux symptoms Erosive esophagitis Esophageal dilation Pouch enlargement Band slippage Gastric prolapse Vomiting Tubing-related problems Leakage of the reservoir Band erosion Weight loss failure Lower average weight loss

BPD, biliopancreatic diversion; LAGB, laparoscopic adjustable gastric banding; LBPD ± __, laparoscopic biliopancreatic diversion with or without duodenal switch; LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass.

and 17% of the BPD and RYGB patients, respectively, achieved diabetes remission compared with none of the medical therapy patients. Another prominent long-term RCT was reported by Schauer and colleagues in 2018, that compared intensive medical and lifestyle intervention with and without the addition of RYGB in achieving durable weight loss and improvement of type 2 diabetes. At 5-year follow-up, 95% and 88% of the RYGB and medical therapy patients achieved an HbA_{1c} level of less than 7.0%.

Although bariatric surgery for patients with poorly controlled type 2 diabetes mellitus and BMI 35 kg/m^2 or greater is commonly considered an acceptable therapy, such treatment remains controversial for patients with class I obesity, or BMI between 30 and 35 kg/m^2. In 2011, the IDF released a position statement recognizing the role of bariatric surgery as a treatment option alternative for patients with class I obesity whose diabetes cannot be adequately controlled by optimal medical regimens, especially in the presence of other major CVD risk factors. The American Diabetes Association recommendations with regard to bariatric and metabolic surgery have been evolving over the years to favor surgical management of type 2 diabetes in patients with obesity. Their recently released standard of care guidelines (2019) indicate that surgery for class I obesity and diabetes should be considered in patients who fail to achieve weight loss and resolution of comorbidities with nonsurgical management. In 2018, the ASMBS also reviewed the currently available clinical evidence and released a position statement highlighting the emerging role of bariatric surgery in class I obesity and type 2 diabetes mellitus. The ASMBS summarizes that AGB, SG, and RYGB have all been shown to be safe in randomized trials and are effective in patients with BMI of 30 to 35 kg/m^2 in the short and medium term. It also states that patients with class I obesity who are unable to achieve substantial and durable weight and comorbidity control with nonsurgical therapeutic methods should be considered eligible for surgery.

Lipid Metabolism

As visceral adiposity diminishes and insulin resistance improves after bariatric surgery, so does the metabolic syndrome with its associated components, including dyslipidemia, thereby decreasing CVD risk. In 2008, Ikeda and colleagues performed a population-based retrospective study and showed the prevalence of metabolic syndrome to decrease from 87% to 29% of 100 patients who were surgically treated, whereas the risk reduction was only 10% in the nonsurgical group over a mean follow-up period of 3.8 years. Postoperative improvements in serum lipid profiles have now been documented in numerous reports, and include reductions in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and increases in HDL cholesterol. These changes are seen in the majority of patients and are more frequent after procedures with a malabsorptive component. One study by Nguyen and colleagues in 2006, for example, found that 82% of patients on lipid-lowering therapy were off such drugs 1 year after RYGB. A much larger retrospective study performed in 900 patients showed that plasma concentrations of triglycerides, HDL cholesterol, and LDL cholesterol all significantly improved over a similar 1-year time frame after RYGB. Heneghan and colleagues, a smaller study, demonstrated improvement in apolipoprotein B levels as early as 3 months postoperatively. After BPD, long-term 5- to 10-year improvements in dyslipidemia is particularly impressive with resolution rates of 91% to 100% having been reported.

Inflammatory State

Many investigators have now described the favorable modulation of a number of obesity-associated inflammatory markers after bariatric surgery. Adipose tissue is no longer viewed as inert energy storage tissue; it is now appreciated as an endocrine organ, which produces a spectrum of adipokines that have important inflammatory and immune functions. Obesity, particularly the central or abdominal type, is seen as a state of chronic systemic inflammation contributing to various aspects of CVD risk, including accelerated atherosclerosis and endothelial dysfunction. Surgically induced weight loss and the resultant improvement in visceral adiposity, insulin resistance, dyslipidemia, and reduction in inflammatory molecules all contribute to improving the inflammatory state. High-sensitivity C-reactive protein (CRP) levels, for example, show consistent decreases after bariatric procedures by up to 80%. In one study in which over 450 patients were followed for about 1 year, CRP levels were above the 3 mg/dL cut-off level in only 10% of patients postoperatively compared with 50% before RYGB.

Although interleukin (IL)-6 levels have been shown to decrease by up to 41% after bariatric surgery, Brethauer and colleagues observed no such decrease in IL-6 or IL-10 after RYGB in a prospective study of inflammatory markers. Leptin, plasminogen activator inhibitor 1, and CRP levels decreased significantly; however, at 3 and 6 months of follow-up. Fibrinogen and IL-1Ra levels also decreased, and adiponectin significantly increased at 6 months in our study. Adiponectin is an important adipose tissue–derived cytokine, which is decreased in obesity and increased with weight loss surgery anywhere from 30% to 140% in some reports. The function of adiponectin is not fully understood at this time, but it correlates positively with improved insulin sensitivity. It can also cause vasodilation by stimulating nitric oxide in endothelial cells and contribute to decreased atherogenesis and CVD risk.

Effect of Bariatric Surgery on Cardiovascular Disease and Mortality

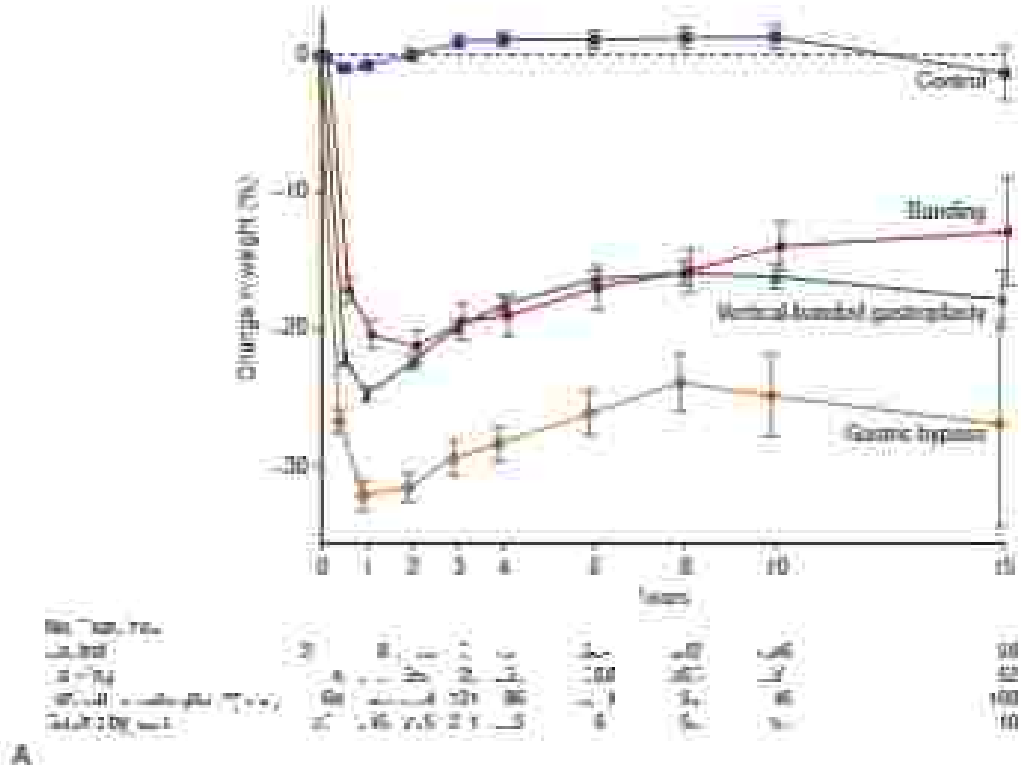
It is now recognized through multiple observational studies that surgically induced weight loss is associated with a reduction in overall mortality (Table 2). The strength of available evidence varies and is limited by study design, surgical procedure, and patient selection. In 2004, the McGill Bariatric Cohort Study was among the first to report that a 67% excess weight loss at 5 years was associated with an HR reduction for mortality of 89% in a retrospective case-control analysis comparing over 1000 patients surgically treated to over 7000 controls with normal BMI. A retrospective study from the University of Utah also showed a survival advantage to their surgical group after RYGB with a mean follow-up of 7.3 years: the adjusted long-term mortality in the surgical cohort of 7925 patients decreased by 60% compared with the same size matched control group (HR, 0.4; $P < .001$). Coronary artery disease–related mortality decreased by 56% in the surgical cohort in this retrospective case-control matched study. Survival benefits were even demonstrated by others in higher-risk Medicare patients with 2-year follow-up data; specifically, a survival advantage was seen as early as 6 months postoperatively in the younger than 65 years age group and as early as 11 months in the older than 65 years age group.

Despite the evidence from observational studies for improved CVD risk profile and survival in general after bariatric surgery, what remains to be established is whether this risk reduction translates into decreased incidence of CVD and related mortality. The best evidence to address this question at present comes from the SOS project. The SOS study is a nonrandomized, matched, prospective observational study in which more than 4000 patients were enrolled and followed over time in Sweden. Reports on the primary endpoint (overall mortality) of the SOS project were published in 2007 (Fig. 2). A 23.7% overall unadjusted (20.7% adjusted) mortality decrease was observed in patients with bariatric surgery at 10 years compared with a well-matched nonsurgical control population. This improvement in overall mortality after bariatric surgery, along with the repeated observations of the beneficial effect of such surgery on diabetes, dyslipidemia, and hypertension, suggests that bariatric surgery directly influences CVD. In fact, the most recent report from the SOS project described the impact of obesity surgery on the predefined endpoints of myocardial infarction and stroke, reported as fatal and total (fatal and nonfatal) cardiovascular event incidence rates (Fig. 3). The study groups included 2010 patients with bariatric surgery (BMI: >34 kg/m^2 in men; BMI >38 kg/m^2 in women) receiving gastric bypass (15.2%), gastric banding (16.2%), or vertical banded gastroplasty (68.1%), and 2037 contemporaneously matched controls with obesity receiving usual medical care. Over a median follow-up of 14.7 years (range 0 to 20 years), bariatric surgery was associated with a reduction in the number of cardiovascular deaths and first time cardiovascular events (fatal or nonfatal), after controlling for the cardiometabolic risk profile at baseline. Compared with controls, the adjusted HR of bariatric surgery for fatal cardiovascular events was 0.47 (95% CI, 0.24 to 0.83; $P < .001$); for fatal cardiovascular events, the adjusted HR of 0.47 (95% CI, 0.29 to 0.76; $P = .02$). It is noteworthy that weight loss was only approximately 16% at 15 years in the treatment group, whereas over time the control group showed weight changes around a maximum of 7%. Interestingly, secondary subgroup analyses of the SOS data failed to demonstrate an association between initial BMI and postoperative health benefits of bariatric surgery. Even the magnitude of surgery-induced weight loss did not predict cardiovascular events in this cohort. This puts into question the current clinical practice of using BMI as a main indication and eligibility criteria for bariatric surgery, when cardiovascular benefits are realized independent of differences and changes in body weight. Further post hoc analysis of the SOS data revealed that, unlike baseline BMI or the magnitude of postoperative weight loss, a high baseline insulin level was in fact a predictor of cardiovascular events in the study. This suggests that weight-independent mechanisms rather than the magnitude of weight loss alone may explain part of the cardiometabolic benefits of surgery. Moreover, Carlsson and colleagues have shown in a recent meta-analysis published in 2017, that patients postbariatric surgery were at a lower risk of dying from CVD compared with patients who did not have bariatric surgery (HR, 0.42; 95% CI, 0.25 to 0.72; $P < .001$).

Very recently, Aminian and colleagues, in a cohort study of 13,722 patients with obesity and diabetes (including 2287 patients who underwent metabolic surgery and 11,435 matched controls), showed that metabolic surgery compared with usual care was associated with a significantly lower risk of major cardiovascular events, including coronary events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, and all-cause mortality (HR, 0.61; 95% CI, 0.55 to 0.68; $P < .001$).

TABLE 5 Observational Studies Reflecting the Mortality Risk Reduction with Bariatric Surgery Compared With Control Groups

Study	Publication Year	Sample Size		Mortality Risk Reduction (%)	Procedures
		Control (n)	Surgery (n)		
MacDonald RC, et al (J Gastrointest Surg)	1997	78	154	68	100% open RYGB
Christou NV, et al (Ann Surg)	2004	1746	1035	89	79.2% open RYGB 2.2% laparoscopic RYGB 18.7% VBG
Pham TH, et al (J Am Coll Surg)	2009	42,701	3528	33	100% RYGB
Adams TD, et al (N Engl J Med)	2007	3925	3925	40	100% RYGB
Buchwald C, et al (Surg Obes Relat Dis)	2007	871	871	68	100% AGB
Pontiroli A, et al (Ann Surg)	2007	3519	866	72	100% AGB
Sjostrom L, et al (N Engl J Med)	2007	2037	4047	29	18.3% ABG; 15.2% RYGB 48.1% VBG
Sowemimo OA, et al (Surg Obes Relat Dis)	2007	112	908	82	>99.9% BPDD
Perry CD, et al (Ann Surg)	2008	11,301	11,903	50	0.3% AGB 4.7% open RYGB 28.5% laparoscopic SG or RYGB 1.8% VBG 2.4% revision
Mutrik R, et al (Br J Surg)	2010	3322	2765	30	25.5% AGB 51.7% RYGB 4.3% jejunoileal bypass 16.5% VBG
Maciejewski ML, et al (JAMA)	2011	43,348	849	56	AGB VBG RYGB SG
Johnson BL, et al (Ann Surg)	2012	903	348	40	AGB RYGB
Scott JD, et al (Surg Obes Relat Dis)	2013	1327	4707	25-50	AGB RYGB SG
Arterburn DE, et al (JAMA)	2015	7462	2752	53	10% AGB 74% RYGB 13% SG 1% other
Ohwovoriole E, et al (Lancet Diabetes Endocrinol)	2015	4132	4131	58	100% RYGB
Gadiby GA, et al (Ann J Surg)	2015	802	802	52	100% RYGB
Pontiroli AE, et al (Gastroenterol Diabetol)	2016	681	386	59	100% AGB
Lent MR, et al (Diabetes Care)	2017	2428	3243	56	100% RYGB
Rogers O, et al (JAMA)	2018	25,155	8386	50	43.3% AGB 16.6% RYGB 40.1% SG
Fisher DP, et al (JAMA)	2018	18,838	5301	47	7% AGB 76% RYGB 17% SG
Mitsuma OM, et al (Ann Surg)	2019	178,577	3845	51	100% bariatric surgery
Aminian A, et al (JAMA)	2019	11,435	2287	41	100% bariatric surgery



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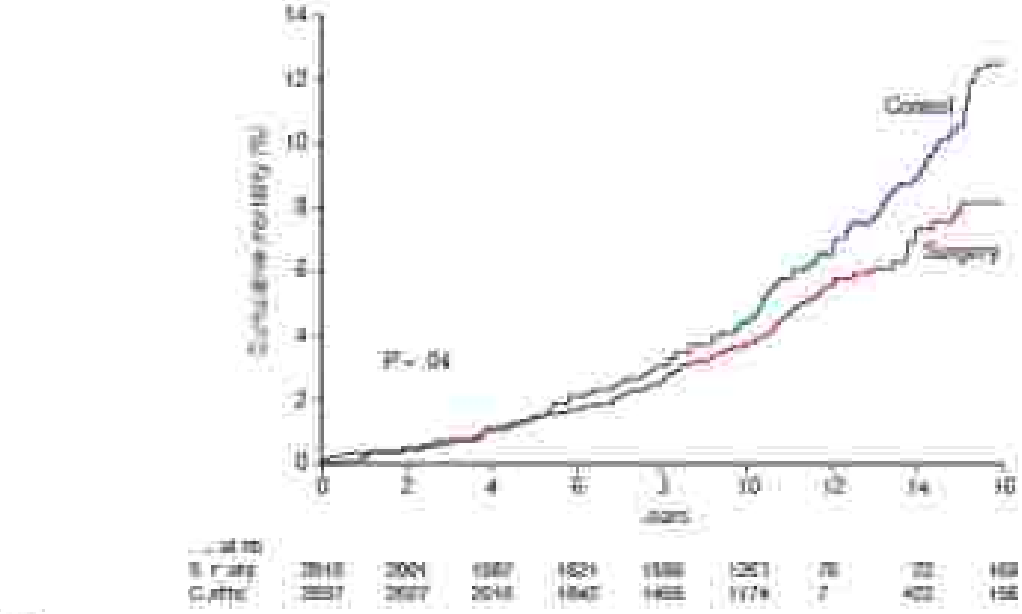

B

FIG. 2 (A) Overall mortality reported in the Swedish Obese Study comparing persons who underwent surgical intervention versus controls. (B) Univariate mortality. The hazard ratio for subjects who underwent bariatric surgery as compared with control subjects was 0.76 (95% confidence interval, 0.59 to 0.99; P = .04) with 129 deaths in the control group and 101 deaths in the surgery group.

To gain further insight into the role of bariatric surgery in reducing CVD risk and improve cardiac structure and function, Yeat and colleagues performed and published a systematic review of over 19,500 patients with bariatric surgery in 33 clinical studies. Although diagnostic criteria, cardiovascular risk factor reporting, and cardiac imaging parameters varied across published reports evaluated by the review, useful results were summarized: baseline preoperative prevalence of hypertension, diabetes, and hyperlipidemia were 44%, 19%, and 44%, respectively. On mean follow up of 38 months (3 to 156 month range), an average of 34% excess weight loss was reported, and this was associated with a postoperative resolution/improvement of hypertension, diabetes, and hyperlipidemia in 63%, 73%, and 62% of patients, respectively. What is most remarkable about the review is that echocardiographic data from 715 patients were summarized and evidence for significant improvements in left ventricular function, with regression in hypertrophy after surgery and improved diastolic function, was observed. This adds to current evidence that bariatric surgery enhances future

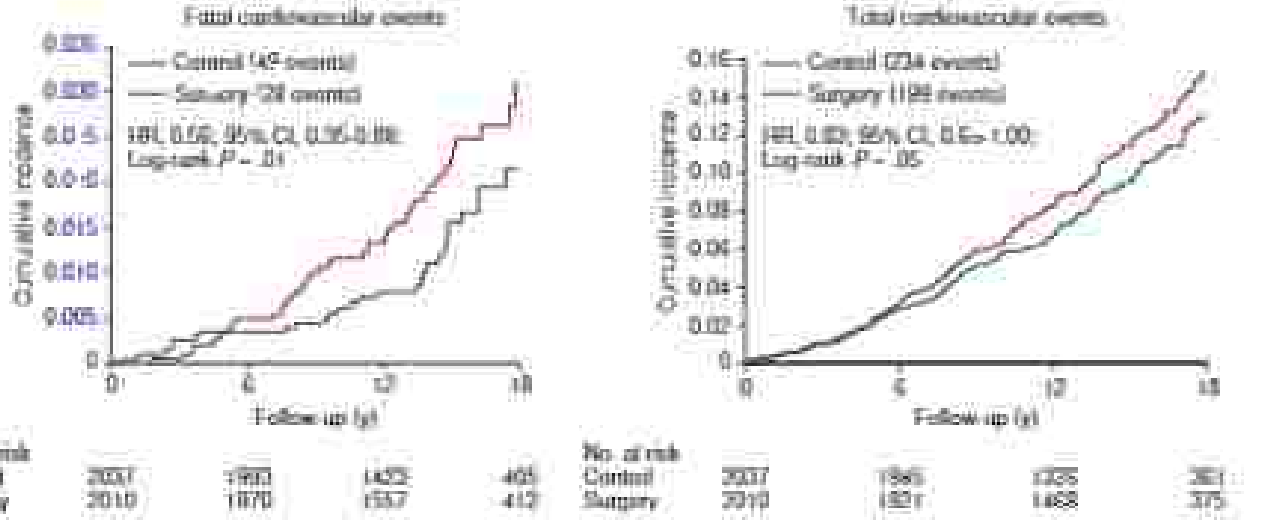

FIG. 2 Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. Cumulative incidence of fatal and total cardiovascular events (myocardial infarction + stroke) in the control and surgery groups of the SOS study (*left*). Fatal cardiovascular events (myocardial infarction + stroke) in control subjects and patients undergoing surgery during follow-up for up to 18 years. *Right*, Total cardiovascular events, that is fatal or nonfatal events, in control and surgery patients for up to 18 years. Calculations are based on data available on July 1, 2011. (*From* Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307[1]:56-65.)

cardiovascular health and may in fact be doing so by having direct physiologic and organ effects on the heart.

A recent nationwide study by Ahmed and colleagues assessed the effect of having a history of bariatric surgery on the length of stay and mortality in patients admitted with a primary diagnosis of heart failure exacerbation. The study showed that patients with a history of bariatric surgery had a significantly lower mortality rate and length of hospital stay compared with patients with no history of bariatric surgery (0.96% vs 1.86%; OR, 0.52; 95% CI, 0.35 to 0.77; $P = .001$). Moreover, these favorable outcomes persisted when matching patients by propensity score (0.86% vs 1.86%; OR, 0.52; 95% CI, 0.35 to 0.77; $P = .001$).

CONCLUSIONS

The pandemics of obesity, diabetes, and CVD have multifactorial impact on individuals and societies. The surgeon's current role in addressing this pandemic cannot be underrated as research into improving therapeutic interventions, understanding mechanisms of bariatric procedures, and developing preventive strategies continue. Beyond weight loss, bariatric surgery is proving to have remarkable metabolic and cardiovascular effects in the short and long term and its safety profile continues to improve. Recently, national and international societies have started to advocate a role for bariatric surgery even in patients with class I obesity with poorly controlled type 2 diabetes mellitus, especially in the presence of other CVD risk factors. Results of large-scale systematic reviews and important long-term prospective studies, like the SOS study, all point to the important role of bariatric surgery in improving cardiovascular risk profile and decreasing the overall incidence of cardiovascular events in patients with severe obesity over long follow-up. However, many clinicians and investigators alike argue that clear and convincing evidence of cardiovascular risk reduction after bariatric surgery remains elusive until such time that a well-conducted RCT provides definitive supporting evidence. Regardless of the reality of conducting such a definitive trial, surgeons and scientists will continue to find innovative ways to study and serve patients with severe obesity and CVD.

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NONMELANOMA SKIN CANCERS

Paul N. Manson, MD, and Michael P. Grant, M[illegible] CS

[illegible]

RISK FACTORS AND PRECURSER LESIONS

Risk factors for BCC and SCC include a number of carcinogens. The most agreed on is sunlight. Cumulative exposure to sun, especially [illegible] tropical sun without protection, in fair skinned individuals who burn rather than tan, is the most generally discussed and accepted risk. Although there is a clear relationship between sun exposure and the incidence of nonmelanoma skin cancers, clinicians debate the exact relationship, and most agree that the relationship to the development of SCC is linked more closely than is BCC. Patients who have had sun lamp treatment for psoriasis are especially prone to skin SCC. Some individuals believe that microtrauma to the skin contributes to the etiology of skin BCC. We know that tumors are more common on sun-exposed surfaces such as the face, scalp, and neck; we also know that radiation exposure, such as that commonly delivered at one time for acne in teenagers, also predisposes to the development of cases of skin cancer and thyroid cancer.

Certain lesions are assumed to be precancerous. Actinic keratoses (AKs) are red, crusty lesions that erupt and sometimes develop cutaneous horn proliferation or thick layers of scaly skin. They have an incidence of in situ and invasive squamous cell skin cancer development of at least 1.0%. Treatment of these lesions with destructive treatments such as liquid nitrogen, curettage, or excision seems reasonable in appropriate patients. Others believe that topical chemotherapy such as 5-fluorouracil can eliminate superficial lesions.

Because sun exposure has been implicated in the predisposition to these lesions, there has been considerable attention to programs aimed toward preventing excess exposure, especially sunburns. Two guides to this prevention are "Safe Sun Guidelines" and "Skin protection from Ultra Violet Light exposure." The exact effectiveness of this prophylaxis is not known but under study.

We also know that genetics may contribute to the development of these lesions. There are hereditary conditions such as basal cell nevus syndrome that predispose to the development of hundreds of multiple cutaneous basal cell skin cancers. Northern Europeans, such as those of Irish and English heritage, also seem more prone to the development of skin cancer. Mutations in oncogenes (RAS and p53) have been implicated with the sonic hedgehog signaling pathway for BCC. The *PTCH* (patched) gene on chromosome 9Q has been suggested in the genesis of these lesions as well.

Recent literature has emphasized higher risk lesions in the BCC and SCC groups that predisposed to incomplete resection, and therefore lesion persistence, recurrence, and metastasis. These are described later in this chapter so that they may be treated with more gentle evaluation with greater attention to complete clearance.

Finally, we know that immune suppression, such as that used for organ transplantation, leads to a greatly increased frequency of cutaneous skin cancer after a period of 10 to 15 years. It is not unusual for these individuals to finally suffer lethal aggressive skin cancers as a result of this immunosuppression. Those who are immunosuppressed

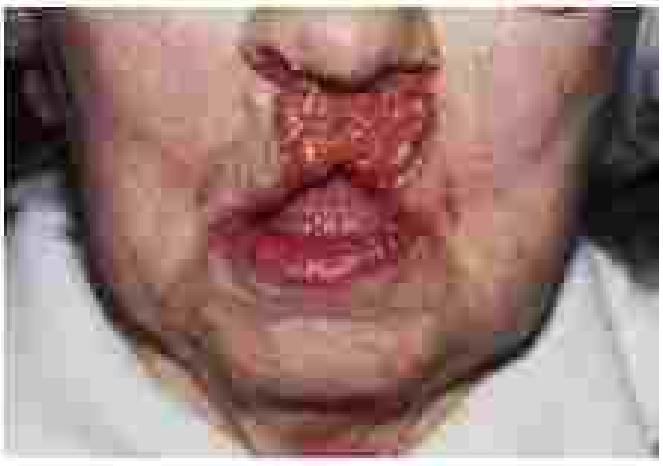

FIG. 1 Neglected basal cell skin cancer originating in the ... ear lip, invading the anterior ... ia, nasal base, and floor of orbit.

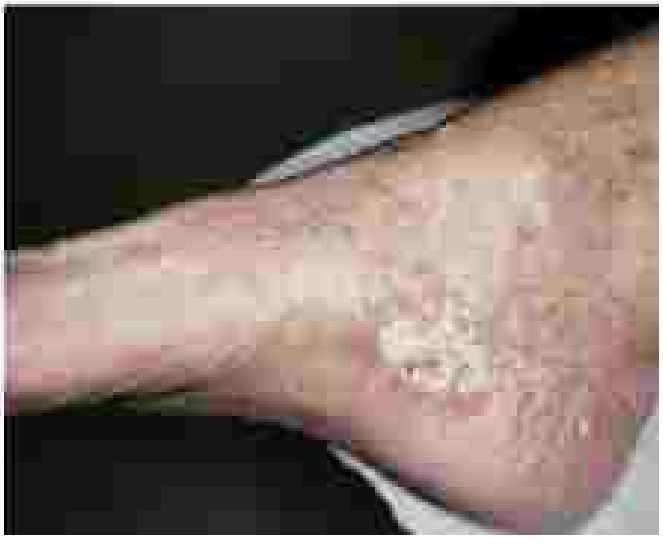

FIG. 2 Actinic keratoses are flaky, crusty, ... ish-red, often ... ish a red border. They are characterized by slight ... lowering to ... e skin, evident and ... ning c... flaking ... hey ma... be ... quite a... r lesions, e.g. ... ...ation. They are clinically diffic... to di...tinguish fro... ... her ... kin diseases and ... a... e a risk ... cinoma to de... ...ney are pre... alignant le... ...ns, ...ay be considered to represent a ...ve ...ge ... e risk ... carcinoma ... lesion.

also tend to experience more aggressive lesions, which are less differentiated, have a higher recurrence rate, and a lower cure rate.

Ultraviolet light exposure, such as that used in psoriasis treatment, frequent sunburns (which impair local skin immunity), and certain medications can predispose to skin cancers. Although occurrence at a young age has been implicated by some to have an adverse effect on prognosis, there is not general agreement that this is a significant risk factor for a poorer outcome.

CLINICAL EVALUATION OF BCC AND SCC

The physical examination and evaluation of BCC (Fig. 3) and SCC (Fig. 4) first includes an analysis of tumor location and size. The tumor should be characterized by its apparent appearance as a probable skin cancer type. The evaluation should evaluate the borders of the tumor and the entire local and regional area and examine local lymph nodes. A generalized skin examination and a complete history and physical would indicate whether the lesion is primary, recurrent, or has less common features. The general health of the patient dictates treatment considerations. Certain locations have been known to predispose to recurrence (such as fusion planes, which are areas where the primitive parts of the face come together in the fetus) or head and neck BCC, the areas of the nasal labial fold, and the groove between the nose and the cheeks. Certain areas such as the ear, mucosal surfaces, genitalia, and lip tend to produce SCC that possesses a greater capacity for metastasis. The mask area of the face has been known to have deeper skin cancers that are more likely incompletely resected and therefore have a higher risk for recurrence or persistence. These lesions, which are greater than 1 cm in diameter or more than ... mm in thickness, present more risk of persistence and recurrence than do smaller lesions. In general, all lesions that have higher risk should have surgical complete margin determination.

Although curettage and desiccation were formally appropriate for small, ... to 10 mm or less, low risk lesions, a higher recurrence rate must be accepted; the practice is becoming distinctly less common in academic medical centers as an acceptable treatment. We know that tumors that have occurred in areas of prior radiation treatment, those that occur in areas of prior scar (i.e. "arsenic ulcer"), persistent ulcers such as pressure sores, and BCC or skin SCC that has perineural involvement all have a lower cure rate, lower overall survival, and higher recurrence rates. Lesions where large nerve perineural involvement is confirmed should have magnetic resonance imaging evaluation with gadolinium to rule out perineural spread. We have rarely had patients with facial poorly differentiated squamous cell carcinomas who present with sensory symptoms (numbness) and on magnetic resonance imaging have perineural spread proximally along the cranial nerves up to the skull base. In these lesions, and for those with higher risk of infiltrative spread, the peripheral and deep margins may be increased to accommodate these unfavorable histologic characteristics. With regard to skin SCC, moderate and poorly differentiated lesions have a higher recurrence rate and a greater potential for infiltrative local spread and local or regional lymphatic and or systemic metastasis.

Originally, skin SCC was divided into several grades, however, most pathologists believe that two general groups of behavior can be identified for squamous cell cancers: (1) well differentiated and (2) a group consisting of moderately differentiated, poorly differentiated, and undifferentiated lesions. Although the prognosis within the latter groups becomes dramatically worse in the poor and undifferentiated categories (which, like melanomas, are capable of to transit metastasis) the tendency is to treat these as high risk lesions with wider and deeper resection margins, perhaps sentinel lymph node biopsies if the lesion is greater than " cm area or 2 mm deep, and histologic confirmation of negative peripheral and deep margins before defect closure or "ap reconstruction is accomplished.

...ost as SCC has higher risk types characterized by less differentiated lesions, BCC has been characterized into various histologic subtypes, some of which carry a higher risk of more infiltrative spread, and in particular spread frequently exists beyond the apparent clinical margins. Skin BCC can be divided into two broad groups based on their activity and tendency for subtle infiltrative spread. It is very unusual for BCC to exhibit lymph node or systemic metastasis, and these lesions are frequently neglected, previously radiated, and/or multiply recurrent lesions. Nonaggressive subtypes (A) of BCC are (1) keratotic, (2) infundibulocystic, (3) nodular type, and (4) superficial. These are the less aggressive types of BCC, and primary lesions in this group may generally be managed with 5 mm resection margins.

The subtypes (B) possessing more risk include those with more aggressive growth patterns and include (1) micronodular, (2) infiltrative, (3) sclerosing, (4) morpheaform, (5) desmoplastic, and (6) basosquamous. These tumors in group B.6 include areas that have the histologic appearance of both BCC and SCC in some parts of the lesion, and this process likely represents a "collision" type lesion that should be treated according to the differentiation of the squamous cell type component.

Some basal cells are pigmented (Fig. 5) and are easily confused with melanoma by appearance. The difference is established pathologically only.

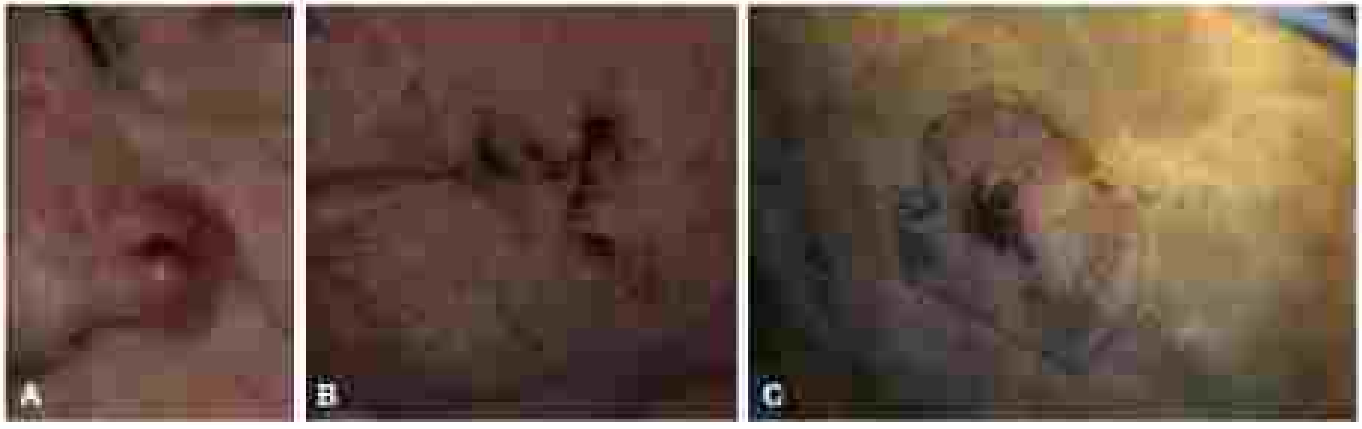

FIG. 3 (A) Nodular basal cell carcinoma presents as a surface of pink, firm, translucent, gravelly well-circumscribed tissue in the skin. It may be accompanied by telangiectasia and some redness of surrounding skin. The tumor shown is in the nasal alar. (B) Morphoeiform basal cell skin cancer has a flat, red, crusty appearance with poorly defined borders. (C) Intermediate basal cell skin cancer has diffuse, irregular, infiltrative characteristics and is red with areas of crusting and ulceration. Thickening and vascularity are variably present.

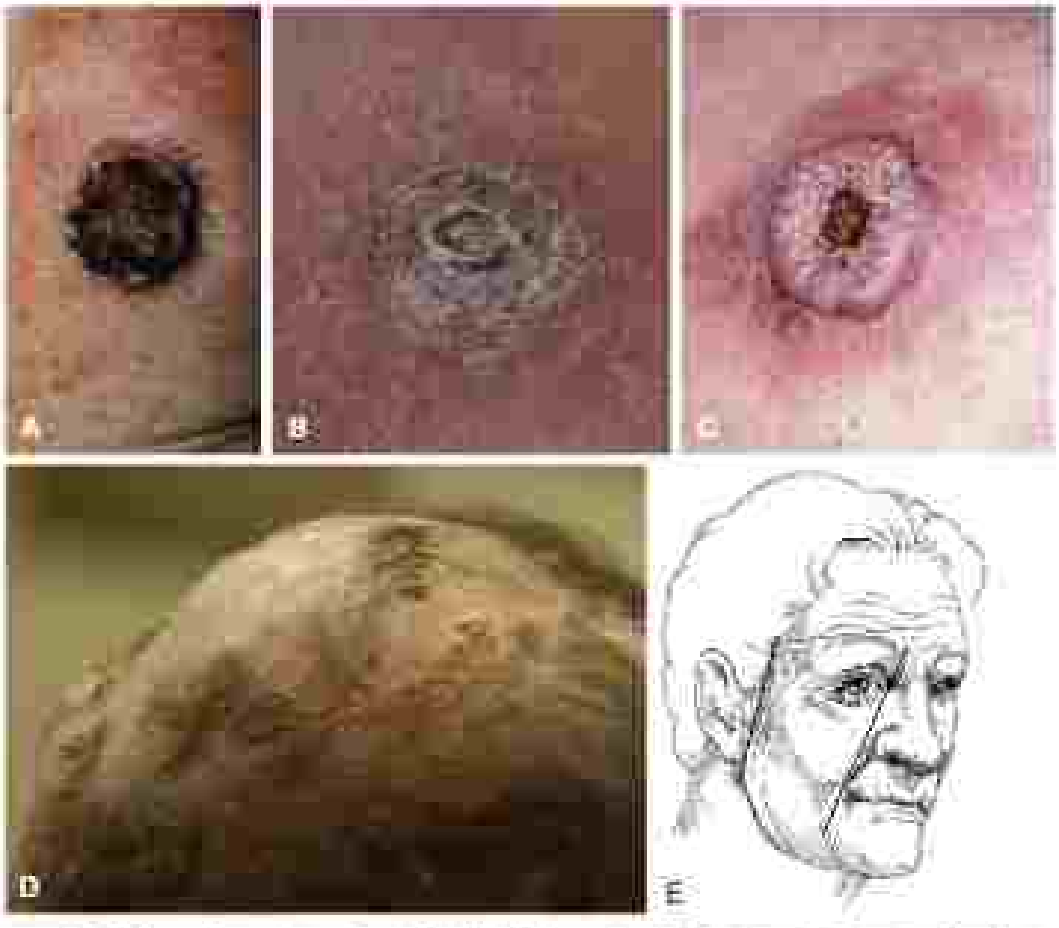

FIG. 4 (A–C) Squamous cell skin cancer, keratoacanthoma variant, has a nodular appearance with rolled, translucent margins and some surrounding erythema. It grows rapidly, often from week to week, and frequently is ulcerated in the center. (D) Squamous cell skin cancer may have a flat, red, scaly appearance with considered cutaneous horn formation. The overlying thin is bleeding. Loss of thickening of the skin in the area of cancer is seen. Well differentiated tumor are often flat and diffusely infiltrative. (E) The "mask" area of the face represents where total tumor ablation occurs. In these areas basal cells may invade more deeply, following the planes of fascia.

BCCs or SCCs that develop in an area of chronic ulceration or chronic scarring (so-called Marjolin's ulcers) such as burn scars and pressure sores have a worse prognosis, perhaps related partly to the difficulty of making the diagnosis and therefore to late detection and the larger size of these lesions.

The rapidity of growth according to the history provided by the patient is important because some lesions will double in size quite rapidly, such as the keratoacanthoma (Fig. 4A–C) variant of SCC. These lesions should be completely excised because the more rapidly growing lesions should be removed for diagnosis as soon as feasible as

FIG. 1. (A) Pigmented basal cell skin cancer resembles melanoma in appearance, with the difference being distinct histologically only. They frequently demonstrate redness, bleeding, and brown-black pigmentation. (B) Author technique for marking margins of resection: (1) lesion border is traced, (2) surgical margin is added to the lesion border, and (3) further margin or orientation of the resection is considered to accomplish a direct closure without "dog ears," and perhaps oriented parallel to the relaxed lines of skin tension.

most of these lesions are malignant, and it is impossible to differentiate the benign keratoacanthoma lesions clinically.

Nerve symptoms are especially concerning such as numbness, pain, burning, paresthesias, and, in the case of motor nerves, paralysis, or muscular symptoms such as weakness or double vision. These symptoms immediately place treatment of the tumor in a high-risk category.

Subtypes of squamous cell, such as the adenoid cystic type or adenosquamous carcinoma, and those producing squamous cell variants are tumors whose characteristics increase the risk of incomplete resection, recurrence, and metastasis. Desmoplastic cutaneous SCC similarly has a high risk of recurrence resulting from incomplete resection because of deeper extensions along fascial planes with failure to achieve clear margins. Although some have suggested that invasion of a tumor into the fat or invasion deep enough to penetrate lymphatics constitutes (as is known with melanoma) more potential for recurrence and metastasis resulting from invasion of blood and lymph vessels, confirmation of this opinion is as yet incomplete. These characteristics certainly should be noted by the treating physician, and more extensive treatment/evaluation locally, regionally, and systemically should be contemplated.

SCC IN SITU

SCC in situ represents full thickness atypia of the upper skin layer (epidermis) but the lesions are still noninvasive and may be treated by simple complete excision. Because dermal invasion is not seen in these lesions, metastasis is not possible, so complete excision is all that is necessary. Although some believe that topical chemotherapy agents such as fluorouracil can be used for SCC in situ, excision is the treatment of choice and especially with margin pathology for tissue demonstrating any evidence of recurrence, persistence, or previous failure of treatment. Superficial therapies for actinic keratosis or very superficial basal cells or in situ SCC include 5-fluorouracil, or Imiquimod. It is difficult to predict the cure rate of these treatments because they are not predicated on complete biopsies and follow-up is generally incomplete and lacking biopsy proof of eradication.

Clinical Appearance and Patient Examination

The clinical appearance of lesions such as SCC and BCC is characteristic. They include color change, nodularity and ulceration (Figs. 3, 4, and 5). Scaling and telangiectasia are frequent. Generally, the skin is reddened and thickened. Hairing or keratosis may be present, and both types of lesions frequently demonstrate surrounding premalignant lesions, such as keratosis. Frequently squamous cells arise in areas of actinic keratoses, which are known to be precursor lesions.

Once the diagnosis is suspected, a complete regional examination of the skin and lymph nodes should be completed. A complete, careful skin examination is always recommended because of the frequency of additional lesions. Attention should particularly be directed to sun-exposed skin sites. Patients with SCC and BCC are at increased risk for developing melanoma as well as additional nonmelanoma skin cancers.

To determine the best treatment for a particular skin cancer, it is often necessary to obtain a full-thickness lesion biopsy. This information is usually able to establish lesion type, differentiation, and histologic type. Although these biopsies are commonly used, they may not reveal the full extent of tumor penetration and may miss areas that provide more accurate classification of the tumor. Biopsies that include the deep reticular dermis are more accurate in identifying deeper processes and in characterizing the lesion. Infiltrative histology or deeper penetration will be missed by more superficial biopsies, in particular. higher risk lesions may be incompletely diagnosed by these biopsies. , or instance, a shave biopsy of an SCC will frequently be read as SCC in situ and not confirm the invasive component of the lesion. We know that SCCs with poorly or undifferentiated histologic characteristics and those greater than 2 cm in area or more than 2 mm thick (tumor can invade lymph vessels in the dermis) are at more risk for infiltrative spread and lymph node involvement. Some practitioners, based on the histologic confirmation of aggressive characteristics, will do a sentinel lymph node examination for these lesions. Although clinically enlarged nodes can have a needle aspiration biopsy, a negative result by needle aspiration does not eliminate the need for an excisional biopsy of an enlarged lymph node if the initial needle biopsy is benign.

The most recent two decades have resulted in improved treatment of both BCC and SCC. This is related primarily to accurate pathologic characterization of the tumor and to tailoring the treatment to the aggressiveness of the lesion. Although either surgery or radiation can be used for early lesions, surgery is generally preferred because of its confirmation of diagnosis and complete margin evaluation, and (usually) one step definitive, efficient treatment. In some cases, age, cosmesis, or functional considerations of the part affected may cause the patient to choose radiation in certain cases. In general, treatment by surgery should include a complete excision of the lesion with an additional margin where margin size relates to the differentiation or subtype and thus the behavior of the tumor. The margins and accuracy of pathologic confirmation of complete resection become much more important in more serious lesions.

Although in the past, curettage or desiccation was used for many skin cancers, today this treatment is becoming less common because of the desire to achieve a complete histologic examination. Most skin lesions should be excised with confirmation of the diagnosis and the excision margins, especially for more aggressive cancers. These

cancers of higher risk need complete excision, confirmed with standard pathologic peripheral and deep margin evaluation (either Mohs micrographic or standard pathology in which frozen section and permanent sections confirm negative deep and peripheral margins).

When curettage and/or electrodessication is used, if the subcutaneous tissue is reached, surgical excision should be performed. The effectiveness of treatment for superficial lesions by curettage depends on the clinicians' perception of reaching appropriate normal dermis tissue. Fat, being less dense than dermis, is not able to be used to detect entry the characteristics of normal skin tissue. In addition, if some of the tumor curettaged is sent for biopsy identification of a higher risk lesion should prompt a secondary surgical excision. Curettage does not provide pathologic confirmation of negative margins nor a more thorough complete evaluation of the tissue.

Complete Excision and Peripheral Margin Evaluation

Low risk tumors, BCCs (less than 2 cm) with well differentiated and nonaggressive characteristics, can generally have a greater than 95% to 99% cure rate with 4- to 5-mm clinical margins. The perception of a negative margin depends on identification of the edge of clinically normal skin without erythema, telangiectasia, or any characteristics of the tumor. A nodular lesion with a surrounding rim of erythema must be treated beyond the erythema, which could represent invasion of skin by cancer. With regard to SCC, margins of 5 to 6 mm are considered more appropriate. Recurrent lesions generally deserve more margin, such as 1 cm. Lesions that are capable of in transit metastasis, such as poorly differentiated and multidifferentiated skin SCC, need an additional margin of tissue, perhaps 1 to 2.5 cm to account for the possibility of in transit and intralymphatic spread beyond clinically evident boundaries. These lesions behave like melanoma in that they are capable of intralymphatic spread, which can appear adjacent to the lesion or to regional lymphatics or lymph node drainage areas.

MARKING FOR RESECTIONS

Careful tracing of the exact clinical edges of the tumor with marking ink under good illumination is required. The proper peripheral margin for cure is then added to the exact lesion border of the tumor, with a second line of marking ink indicating the true resection margin. Excision of large lesions, or those representing scars in tension planes, may require 10 mm margins, with clear deep and peripheral margins confirmed.

Reconstruction of the Defect

In most cases, elliptical excision with the long axis oriented parallel to the relaxed lines of skin tension, and layered primary closure, with careful side to side approximation, is appropriate. In some areas, secondary intention healing can be used. The scar from such healing may be more depressed, shiny, and obvious than that occurring from primary layered wound closure. Skin grafting, either partial or full thickness, is a simple method of closure of larger defects where side to side approximation cannot be obtained. In the face, cosmetic considerations of appearance may lead to closure of defects with local flaps, and more extensive lesions need distant flap reconstruction with secondary procedures for cosmetic improvement. In all cases, we believe that absolute confirmation of negative surgical margins is always necessary before any complex closure, such as a flap, is accomplished.

Confirmation of negative Margins

Techniques for rapid or intraoperative evaluation of margins include intraoperative frozen section assessment and Mohs surgery. In the Mohs technique, an immediate determination of the full length of each margin is performed. Either of these techniques may have the immediate margin evaluation supplemented by a further determination of permanent margins in cases where more confirmation is desired. Finally, in higher risk lesions, and especially in those where a more complex reconstruction is required, good confirmation of margins can be obtained by intraoperative (and then should be confirmed by permanent) analysis techniques before reconstruction is undertaken. The wound may be left open or dressed with an allograft while awaiting the final pathologic opinion. Another technique that has been suggested, in which the size of the lesion would produce a large open defect to manage wound, is that of resection of a small strip of tissue at each of the four peripheral margins anticipated for the lesion, with immediate closure of the thin strip defect edge to the remaining central specimen, leaving the major portion of the lesion intact as the four peripheral strip margins biopsies are evaluated. The margins can then be altered appropriately and the remainder of the lesion resected at the definitive resection and reconstruction.

A complete assessment of the deep and all peripheral margins, being careful to label these so that they are clearly able to be analyzed by the pathologist in proper sequence and in proper orientation, is desired for most lesions. We have learned to resect each margin separately and place it separately labeled in a separate bottle for clarity, which eliminates the confusion generated by having the specimens serially examined and labeled by three to four separate individuals, which is the usual pathologic sequence of specimen processing. For all high risk lesions, a complete determination of all peripheral and deep margins is necessary; this should be completed before any reconstruction is accomplished. If the margins are equivocal in such lesions, a repeat assessment is performed awaiting the results before any reconstruction is initiated. An allograft can be placed over the defect until the permanent complete margin evaluation is available. We prefer at least consideration of sentinel node evaluation in poorly differentiated or undifferentiated high risk SCC, although the benefit of this technique in the minority in less differentiated SCC has yet to be proven.

Enlarged Regional Nodes

Positive needle or excisional biopsies of an enlarged regional lymph node or positive sentinel node biopsies predict the need for removal of regional lymph nodes. This sentinel node biopsy technique, in high risk lesions, has minimized the use of elective regional node dissection, limiting morbidity to those with proven lymph node spread. A negative needle lymph node biopsy is suggestive but not absolutely confirmatory of a lymph node's benign status because it does not involve complete histological evaluation.

Radiation as Primary or Adjunctive Treatment

Radiation therapy in cases of primary straightforward nonmelanoma skin cancer of the head or squamous type can produce good cure rates and excellent cosmetic results. Multiple treatments are required over a period of weeks, and there is no confirmation of negative margins nor is there complete examination of the histology of the lesion to absolutely confirm its histologic characteristics. Of course, as in surgery, proper techniques must be applied. Radiation therapy is often offered to older patients or to areas where the cosmetic sensitivity of the area makes reconstruction difficult. Some physicians prefer it for thin, widespread lesions such as Bowen's disease and for patients who have widespread lesions who refuse surgery. We have found many elderly patients with lesions of the lower extremities do not do well either in terms of care or symptoms following radiation treatment.

Radiation is not generally used alone for lymph node treatment or for treatment of high risk lesions that frequently occur in the absence of initial surgical clearance, but may be added as adjunctive treatment (e.g., to poorly differentiated squamous cell lesions with the possibility of in transit spread). Sometimes, radiation with or without concurrent chemotherapy will be used following lymph node dissection in high risk cases. Radiation therapy has also been used as adjunctive treatment to patients to whom the margins are histologically but not clinically positive and for perineural involvement or where the danger of intralymphatic spread into adjacent skin is high. Patients who have extensive local penetration of tumor are also candidates for postoperative radiation, for instance, in extracapsular spread of tumor beyond lymph nodes.

Patients with disease remaining following radiation and chemotherapy may be candidates for Vismodegib, a hedgehog pathway inhibitor, when further surgery and radiation are contraindicated.

Long-Term Follow-Up of BCC and SCC

All patients with BCC and SCC, especially those with high risk lesions, should have a complete skin examination periodically, with special attention to the area where recurrence, either locally or regionally, is likely. Although most recurrences of lesions develop within a 2 year period, rarely a tumor will recur after 5 to 10 years. One third to one half of patients having BCC or SCC will develop a separate lesion within the next 5 to 10 years. Although most recurrences of lesions develop within a 2 year period, a tumor can recur in the next 5 to 10 year period. Follow up schedules should be tailored to the particular severity and extent of disease of the patient, and to the risk of recurrence and to the severity of the original lesion.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a fibrotic skin lesion that is uncommon. It is a tumor rising in the dermis with a low incidence. The most frequent age range of affected individuals is between 20 and 50 years. Most lesions are located on the trunk or proximal extremities, with the head and neck area affected less commonly (Fig. 6). Some patients provide a causal history of trauma; however, the relationship has not been proven. The lesion is slow growing as a rule, and for practical purposes does not metastasize; however, it has a strong tendency for local fascial extension along tissue planes to small, thin fingers that defy clinical perception. Conservative surgical excisions have (because of this) yielded up to a 60% recurrence rate, generating the recommendation that 3- to 4 cm clinical margins in Mohs surgery be used.

Dermatofibrosarcoma protuberans presents clinically as a painless, firm, red to brown or purple plaque. It can demonstrate soft areas or protrusions. This indolent presentation is often enough to prevent early diagnosis because of its benign nature. The diagnosis can prove difficult, and differentiating it from other fibrotic skin processes can require special stains. Negative biopsies in one area should not be reassuring but should prompt more biopsies and/or complete excision of a suspicious lesion. Immunostaining with CD-34 factor, XIIIA metalloproteinases, vimentin, and stromelysin-3 are helpful in making the diagnosis. The lesion is frequently misdiagnosed, both clinically and pathologically, and frequently underrecognized unless Mohs techniques are used.

Treatment

Treatment for dermatofibrosarcoma protuberans is surgical excision with wide margins. Up to 3 to 4 cm have been recommended. Currently, Mohs micrographic surgery is the surgical method of choice, which has reduced recurrence rates to about 2%. Regional lymph node biopsies are not indicated because the incidence of metastatic spread is so low, probably 1%. Although adjuvant radiation has been recommended following standard surgical treatment, it is highly recommended to achieve widely negative margins surgically, and Mohs surgery is strongly recommended. The value of supplemental radiation in patients who have widely negative Mohs surgical margins has yet to be established.

Cutaneous T Cell Lymphoma

Lymphomas may present as cutaneous lesions and include mycosis fungoides and Sézary's syndrome, which are cancers originating from T4 helper cells. These are rarer tumors that appear a reddish patch, plaque, or lump. They sometimes come or have a "psoriatic" appearance. Itching is a prominent clinical symptom. Because of its benign appearance, diagnosis is commonly delayed because it overlaps in appearance with many other cutaneous dermatologic conditions. Some patients progress to frank systemic lymphoma over time, and 5-year survival rates of the skin lesion itself vary from 50% to 100%, and often relate to the development of another internal serious blood neoplasm.

Therapy varies from excision, chemotherapy agents to topical radiation, such as skin electron beam therapy or combined chemotherapy and radiation treatment. In some cases, surgery provides control of local symptoms and apparent cure for limited lesions.

Basal Cell nevus Syndrome

Basal cell nevus syndrome or Gorlin syndrome or nevoid BCC syndrome is an inherited disorder that presents with multiple cutaneous basal cells, jaw cysts, musculoskeletal and neurologic abnormalities, and pitting of the palmar and plantar surfaces of the skin. The disease is autosomal dominant and frequently presents with odontogenic keratocysts, calcification of the falx cerebri, multiple cutaneous basal cells, and palmar and plantar pits. The lesions behave as BCC's and are usually managed with surgical excision. It is not infrequent that palmar and plantar pits contain BCC. The pits are usually small, 3 mm or less in depth. Patients will often have hundreds of BCC's over the course of their lifetime, and many eventually succumb to the disease. Topical chemotherapy agents such as Efudex have been used in an

FIG. 6 (A) Dermatofibrosarcoma protuberans looks like lumps of fibrous scar tissue, its distinct appearance helps to resolve character. The lesion must be confirmed by biopsy. Wide margins are necessary because of the tendency to extend local invasion along tissue septae. (B) Appearance of dermatofibrosarcoma protuberans in a white patient. (C) Appearance of a dermatofibrosarcoma protuberans in an African-American patient.

attempt to eradicate early superficial nonfacial basal cells but surgical excision are the treatment of choice.

Bowen's Disease

Bowen's disease is an erythematous, plaque-like lesion that represents a low grade, slow growing intraepithelial variant of SCC. Essentially, the growth of this tumor is intraepidermal and its history and progression are similar to other intradermal carcinomas such as erythroplasia of Queyrat. It is a less common malignancy that appears as a circumscribed, red or pink patch that can weep and present a scaly appearance. Many lesions occur on the trunk or lower extremities and genitalia, but the lesion can involve the head and neck region. The progression of the lesion is limited and extends normally over years. Invasive SCC can arise in these lesions, and if so, metastasis is possible. Excision to clear the margins with an initial 5-mm margin is recommended and Mohs excisions are favored. Lesions that occur in sensitive areas may require skin coverage, or lesions that are larger may require skin grafting. In the head and neck, cosmetically sensitive flap reconstructive techniques are preferred when primary closure is not possible.

Merkle Cell Carcinoma

This rare neuroendocrine skin cancer is characterized by rapid growth and very aggressive behavior. It is a firm, intradermal, red nodule that rapidly progresses to ulceration (Fig. 7). Recently, lesions have been traced to a polyomavirus infection and the disease is definitely more frequent in patients receiving immunosuppression. The disease progresses rapidly by intravascular and lymphatic spread, therefore, initial positron emission tomography imaging should evaluate the possibility of regional and distant spread. Survival is often predicted by positive regional nodes that occur in 50%, and the disease tends to be underrotated by limited surgical resections, and thus local failure is common (up to one third of patients). Local control may be improved by larger resection margins of 2 to 5 cm that often generate the need for skin grafting. Sentinel node biopsies are routinely recommended.

Periodic follow up with local, regional, and systemic monitoring by oncology is recommended. Although most recurrences occur in the first 2 to 3 years, survival is best predicted by the presence of nodal and distant disease. The behavior of Merkle cell cancer is usually more aggressive than significant invasive melanomas, and in fact, the mortality exceeds that of melanoma. The histologic diagnosis is confirmed by performing immunohistochemical staining. Because of the frequency of local failure in treatment when surgical margins are compromised, some have recommended postoperative radiation therapy for the primary tumor, draining lymphatics, and regional lymph node basins. The added value of this treatment when surgical margins are generous, sentinel lymph node biopsy is obtained, and positron emission tomography scans are negative has not been established. Adjuvant chemotherapy for regional disease has also been recommended (positive regional node disease) in addition to surgery, but its value is not proven.

FIG. 7 Merkle cell skin cancer looks like a cancerous lump that frequently grows rapidly and initially has no distinguishing characteristics. It must be differentiated by biopsy confirmed by immunostains.

Angiosarcoma

This rare vascular tumor of the skin generally occurs as a rapidly enlarging nodule or plaque, sometimes simulating a bruise (Fig. 8). Its transit metastasis occurs quickly and initial presentation with satellite nodules is not uncommon. There is a predilection for occurrence in the head and neck area and in the elderly. In one series, the mean age was 78 years and mimicked its lower male patients. Aggressive resection is indicated with 3- to 5-cm margins, frequently requiring flap or skin graft reconstructions. Sentinel lymph biopsy is recommended. Local recurrence is frequent because of the tendency for in transit metastasis, and the prognosis is quite limited with 20% or less survival being routine. These statistics and the proven aggressive behavior of this tumor have generated the recommendation that radiation and chemotherapy accompany the planned surgery. Despite these additions, the prognosis remains largely unaffected by additions to the surgical treatment proposed.

Adnexal Tumors of the Skin

Adnexal tumors occur from skin appendages such as eccrine, apocrine, sebaceous glands, and hair follicles. Some occur from fibrous or neural tissues. Sebaceous carcinomas usually present as a slightly nodulated nodule whose diagnosis is dependent on a biopsy. The prognosis varies with the aggressiveness of the lesion and wide excision with 2 cm margins to fascia are recommended. Although some practitioners perform

FIG. 8 Angiosarcoma is a rapidly growing aggressive cancer that often initially appears as a bruise or hemangioma. It is capable of early metastasis and systemic movement. (A) Angiosarcoma of the cheek with red cutaneous thickening and ulceration. (B) Angiosarcoma presenting as a nonblanching "bruise" of purple-red skin in the scalp.

sentinel lymph node evaluations in these more aggressive lesions, the value of these interventions remains to be proven.

Nonmelanoma skin cancers vary in severity from the relatively common and benign varieties to very aggressive and frequently lethal lesions. Treatment favors surgical resection predicated on accurate diagnosis and classification, with the appropriateness of treatment based on good pathologic definition of the lesion type.

Acknowledgment

We acknowledge the contributions of the panels who created the NCCN Guidelines, which form an excellent and carefully considered basis of the recommendations for diagnosis and treatment of these lesions that are summarized in this chapter. We recommend these guidelines in the strongest terms for those seeking further information and clarification, as they serve as a yearly up-to-date summary of current recommendations for diagnosis, evaluation, and treatment.

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Management of Cutaneous Melanoma

Michele M. Gage, MD, and Julia R. [illegible]ange, MD, ScM

Cutaneous melanoma is the fifth most common invasive cancer in men and the sixth most common invasive cancer in women in the United States. It is the largest cause of skin cancer mortality. Most melanomas are diagnosed early and can be expected to have a good prognosis with surgery as the only active therapy. The management of regional and distant disease has changed significantly in the last decade, with the evolution of a more restrained approach to the regional nodal basin and the development of immunotherapies and targeted therapies that improve survival for patients with regional and distant disease. This chapter reviews the recommended initial evaluation and workup of melanoma, indications for surgery, surgical technique, and postoperative follow-up.

INITIAL EVALUATION OF SUSPECTED MELANOMA WITH BIOPSY

Lesions suspicious for melanoma often (but not always) display classic features such as the ABCDEs: asymmetry, border irregularity, color variegation, large diameter, or evolution over time. Other features that may be considered concerning include a new pigmented lesion after age 30, a pigmented lesion that is out of character with the patient's mole pattern, and a lesion that becomes itchy or bleeds with minor injury. A focused history and physical examination should include review of potential risk factors, personal and family history, as well as a detailed physical evaluation of the lesion, the surrounding skin area, and all potential draining lymph node basins. Risk factors for melanoma include skin type, personal or family history of melanoma, multiple clinically atypical moles or dysplastic nevi, and inherited genetic mutations. Environmental factors, including excessive sun exposure and ultraviolet-based artificial tanning, should also be assessed. A complete skin examination should be done to assess for other primary skin cancers.

Suspicious lesions should undergo biopsy with a technique that allows full-thickness pathologic assessment preferred. Excisional biopsy with a narrow 1- to 2-mm gross margin may be considered. Punch biopsy may be considered either for very small lesions or for broader lesions where it is advantageous to establish a diagnosis before any larger excision. A punch biopsy should be taken from the darkest, most raised, or otherwise most suspicious appearing portion of the lesion. Regardless of biopsy technique, a full-thickness biopsy into the subcutaneous fat is important for accurate interpretation of tumor thickness. The orientation of a potential future surgical wide local excision should be considered when performing an excisional biopsy. For example, longitudinal or oblique incisions are preferred on the extremities, whereas head, neck, and trunk biopsies should be oriented parallel to skin lines.

Patients may sometimes present to a surgeon after a shave biopsy reveals melanoma, particularly when the initial clinical suspicion for melanoma was low. Thin shave biopsies often fail to provide accurate information on tumor thickness and should be avoided when melanoma is suspected. When a thin shave biopsy has a broadly positive base, repeat biopsy may be considered before proceeding to surgical wide local excision for more accurate tumor staging, particularly if there is visibly some tumor still present at the site.

Pathology results for a melanoma biopsy should include, at a minimum, the following information: thickness in millimeters, ulceration status, dermal mitotic rate (per millimeters squared), deep and peripheral margin status, presence or absence of microsatellites. Other features to be reported include histologic type, angiolymphatic invasion, radial or vertical growth phase, tumor-infiltrating lymphocytes, and regression.

Clinical staging evaluation is guided by the clinical stage at diagnosis. Patients with thin, early melanoma (≤1.0 mm) and clinically negative nodes should not have any systemic staging studies, unless signs or symptoms of disease spread are present. Patients with melanoma larger than 1.0 mm with clinically negative nodes and no signs or symptoms of metastatic disease can also forgo systemic staging. Patients with palpable adenopathy should have radiologic evaluation with ultrasound and needle biopsy if abnormal nodes are seen. Patients with confirmed nodal metastases or suspicious signs or symptoms of distant metastases should be evaluated with cross-sectional imaging, as well as baseline liver enzymes and lactate dehydrogenase.

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Management of Cutaneous Melanoma

Michelle M. Gaps, MD, and Julia R. Lange, MD, ScM

Cutaneous melanoma is the fifth most common invasive cancer in men and the sixth most common invasive cancer in women in the United States. It is the largest cause of skin cancer mortality. Most melanomas are diagnosed early and can be expected to have a good prognosis with surgery as the only active therapy. The management of regional and distant disease has changed significantly in the last decade, with the evolution of a more restrained approach to the regional node basin and the development of immunotherapies and targeted therapies that improve survival for patients with regional and distant disease. This chapter reviews the recommended initial evaluation and workup of melanoma, indications for surgery, surgical technique, and postoperative follow-up.

INITIAL EVALUATION OF SUSPECTED MELANOMA WITH BIOPSY

Lesions suspicious for melanoma often (but not always) display classic features such as the ABCDEs: asymmetry, border irregularity, color variegation, large diameter, or evolution over time. Other features that may be considered concerning include a new pigmented lesion after age 40, a pigmented lesion that is out of character with the patient's mole pattern, and a lesion that becomes itchy or bleeds with minor injury. A focused history and physical examination should include review of potential risk factors, personal and family history, as well as a detailed physical evaluation of the lesion, the surrounding skin area, and all potential draining lymph node basins. Risk factors for melanoma include skin type, personal or family history of melanoma, multiple clinically atypical moles or dysplastic nevi, and inherited genetic mutations. Environmental factors, including excessive sun exposure and ultraviolet–based artificial tanning, should also be assessed. A complete skin examination should be done to assess for other primary skin cancers.

Suspicious lesions should undergo biopsy with a technique that allows full thickness pathologic assessment preferred. Excisional biopsy with a narrow 1- to 2-mm gross margin may be considered. Punch biopsy may be considered either for very small lesions or for broader lesions where it is advantageous to establish a diagnosis before any larger excision. A punch biopsy should be taken from the darkest, most raised, or otherwise most suspicious appearing portion of the lesion. Regardless of biopsy technique, a full thickness biopsy into the subcutaneous fat is important for accurate interpretation of tumor thickness. The orientation of a potential future surgical wide local excision should be considered when performing an excisional biopsy. For example, longitudinal or oblique incisions are preferred on the extremities, whereas head, neck, and trunk biopsies should be oriented parallel to skin lines.

Patients may sometimes present to a surgeon after a shave biopsy reveals melanoma, particularly when the initial clinical suspicion for melanoma was low. Thin shave biopsies often fail to provide accurate information on tumor thickness and should be avoided when melanoma is suspected. When a thin shave biopsy has a clinically positive base, repeat biopsy may be considered before proceeding to surgical wide local excision for more accurate tumor staging, particularly if there is visibly some tumor still present at the site.

Pathology results for a melanoma biopsy should include, at a minimum, the following information: thickness in millimeters, ulceration status, dermal mitotic rate (per millimeters squared), deep and peripheral margin status, presence or absence of microsatellites. Other features to be reported include histologic type, lymphovascular invasion, radial or vertical growth phase, tumor infiltrating lymphocytes, and regression.

Clinical staging evaluation is guided by the clinical stage at diagnosis. Patients with thin, early melanoma (≤1.0 mm) and clinically negative nodes should not have any systemic staging studies, unless signs or symptoms of disease spread are present. Patients with melanoma larger than 1.0 mm with clinically negative nodes and no signs or symptoms of metastatic disease can also forgo systemic staging. Patients with palpable adenopathy should have radiologic evaluation with ultrasound and needle biopsy of abnormal nodes are seen. Patients with confirmed nodal metastases or suspicious signs or symptoms of distant metastases should be evaluated with cross sectional imaging, as well as baseline liver enzymes and lactate dehydrogenase.

Appropriate cross-sectional imaging could include computed tomography (CT) scanning of the chest, abdomen and pelvis (include neck CT in patients with head or neck primary tumor) with contrast, or whole-body positron emission CT. Brain magnetic resonance imaging with contrast is appropriate in patients with suspicious symptoms or as a baseline study in persons with melanoma stage IIIC or above.

Tumor mutation marker analysis (BRAF is the most frequent actionable marker) is necessary when the results are needed for clinical decision making. It should not be done in patients with early stage disease. Tumor mutation markers should be assessed for patients with stage III disease who are being considered for adjuvant therapies of immunotherapy or targeted therapy or clinical trials, and certainly in patients with stage IV disease when the result may determine whether targeted therapies may be considered.

SURGICAL MANAGEMENT OF MELANOMA: RATIONALE FOR SURGERY

Wide Local Excision

The surgical treatment of primary melanoma is based primarily on the thickness of the primary lesion. The purpose of the wide local excision is to remove the lesion in its entirety in clearly negative margins in such a way that the risk of local recurrence is minimized. Recommended margin widths are the ones measured in the operating room across the skin surface from the edge of the lesion. It is expected that some contraction of the skin specimen will occur, and that pathologic margins will be less than the measured surgical margin. Guidelines for wide local excision are based on several prospective randomized surgical trials spanning the last 3 decades (Table 1).

In brief, the recommended surgical treatment of melanoma in situ (Stage 0) is a 5 to 10 mm wide local excision. For melanomas 1 mm or smaller, a grossly measured margin of 1 cm results in excellent local control. Melanomas larger than 1 to 2 mm should be managed with a 1- to 2-cm excision, whereas melanomas larger than 2 mm in thickness should undergo wide local excision with a 2 cm margin. (Table 2) There may be occasions where margins can logically be modified for anatomic limitations or functional considerations in some patients.

TABLE 1 Recommended Surgical Margins of Excision of Melanoma Based on Randomized Surgical Trials and Meta-Analysis

Melanoma Thickness (mm)	Excision Margin (cm)
In situ	0.5–1.0
0.1–1.0	1.0
1.01–2.0	1.0 or 2.0
2.01–4.0	2.0
>4.0	2.0

Sentinel Lymph Node Biopsy and Lymph Node Dissection

The management of the regional node basin continues to change. Today, sentinel node biopsy is a standard staging tool for patients with primary melanoma and clinically negative regional node basin if the risk of having positive nodes is 5% or greater and if the patient wishes to have the prognostic information. In newly diagnosed patients with clinically negative nodes, national guidelines recommend sentinel lymph node biopsy for patients with melanoma more than 1 mm in thickness. Sentinel node biopsy may also be considered in select patients with thin melanoma, especially those with melanoma between 0.8 mm to 1.0 mm, particularly if there is ulceration or an elevated mitotic rate. Sentinel node biopsy for patients with melanoma 0.7 mm or less is generally discouraged but may be considered in unusual cases, such as when combined with mitotic rate of 2/mm² or more. There are patients for whom the decision whether to offer the sentinel node biopsy is unclear, such as to patients with unknown thickness as a result of a shave biopsy that yields a thickness of 0.7 mm with a transected base.

The purpose of the sentinel node biopsy is to provide prognostic information, but it does not by itself improve a patient's prognosis. However, when micrometastatic disease is detected in clinically negative nodes, the information identifies patients who may benefit from adjuvant treatment. Knowledge of the node status may be useful

TABLE 2 Randomized Controlled Trials Evaluating Surgical Margin for Melanoma

Study	Year	Number of Patients	Follow-up (yr)	Tumor Thickness (mm)	Margin (cm)
WHO[a]	1991	612	8	<2	1 vs. 3
Sweden	2000	989	11	>0.8–2.0	2 vs. 5
Intergroup	2004	468	10	1–4	2 vs. 4
France[b]	2003	326	14	<2	2 vs. 5
Sweden	2011	936	6.7	>2	1 vs. 3
United Kingdom[c]	2016	900	8	>2	2 vs. 4

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[c] Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. Ann Surg Oncol. 2001;8:101–108.

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[m] Wright FA, Rankin EM, Kelly AP, et al. Wide versus narrow excision margins for high risk, primary cutaneous melanomas: long term follow-up of survival in a randomised trial. Cancer Oncol. 2016;1:168–172.

WHO, World Health Organization.

to the patient to simply better informs the patient of their prognosis and help guide the type and frequency of follow-up plans. It is sometimes appropriate to decide not to perform a sentinel node biopsy in patients who are otherwise candidates for sentinel node biopsy. A decision to forego sentinel node biopsy can be a rational choice when the patient has significant comorbidities, a limited life expectancy, or simply chooses not to have it.

The role of completion lymph node dissection (CLND) in patients with a positive sentinel node has evolved with the results of two randomized clinical trials comparing CLND to nodal surveillance for patients with positive sentinel nodes. The Multicenter Selective Lymphadenectomy Trial II (MSLT-II) trial is the larger and more definitive of the two trials. The study found no significant difference in melanoma-specific survival or distant metastasis–free survival related to whether patient had completion node dissection or surveillance ultrasound scanning of the positive node basin. The observation group was monitored closely with serial nodal ultrasound scanning. CLND provided additional prognostic information and provided superior regional control but did not improve melanoma-specific survival compared with interval surveillance with ultrasound scanning. Additionally, lymphedema was reported in 24.9% of CLND patients and only 6.3% of the observation group. Today, for most patients with positive sentinel nodes, planned surveillance with serial node basin ultrasound scanning is a reasonable alternative to CLND for patients with low-risk, microscopic disease, with surveillance now preferred for most patients. The ideal patient for node basin surveillance is a patient with low-volume nodal metastases without extranodal extension who can adhere to the schedule of high-quality surveillance ultrasound scanning. Of those entering surveillance, about 25% are expected to recur in the node basin under surveillance, either with or without distant recurrence. It remains unclear whether we can define a group of sentinel node–positive patients who would gain a larger benefit from completion node dissection. Patients of concern include those excluded from randomization in MSLT-II or with high-risk features, such as those with three or more positive sentinel nodes, extranodal extension, microsatellites at the primary, more than two involved node basins, and patients who are immunosuppressed.

Clinically Positive Nodes

When clinically positive nodes (i.e., clinically palpable positive nodes) are present either at initial presentation or as a regional recurrence, staging with cross-sectional imaging must be done to rule out distant disease. If there is no disease beyond the node basin, the patient should undergo a therapeutic lymph node dissection of the affected basin. In cases of metastases to the inguinal nodes, ipsilateral obturator node dissection should be included if there are abnormal iliac or obturator nodes on cross-sectional imaging and may be considered if there are three or more positive inguinofemoral nodes or a positive Cloquet's node.

In Transit Disease

A substantial minority of patients will develop in-transit lesions over the course of their disease, usually recognized as tumor deposits in the dermis or subcutaneous tissue between the primary site (>2 cm away from the primary lesion) and the regional node basin. Patients found to have in-transit lesions have stage III melanoma and should have cross-sectional imaging for systemic staging and have the tumor sent for mutation analysis. If the patient has limited, low-volume disease, wide local excision may suffice as initial therapy, with consideration of systemic adjuvant therapy. Wide local excision of an in-transit lesion should be done with a surgical margin of 1 cm if feasible, but at least to a pathologically negative margin. If the patient has extensive in-transit disease that cannot be reasonably excised with low morbidity, then today systemic therapy is usually first line treatment, with consideration of regional perfusion or infusion techniques much less common than in the past.

Surgery in Stage IV Melanoma

Surgery in cases of advanced melanoma may be considered for two reasons: to eradicate all gross disease and for symptom palliation. Surgery in stage IV patients with a goal of rendering the patient free of disease is most likely to provide durable benefit to patients with oligometastatic disease and a long interval from primary diagnosis to the appearance of metastatic disease. In the era of newer and more effective systemic therapies, it is time to reassess the clinical scenarios in which patients might benefit from surgery. Additional clinical trials are needed to determine the optimal sequencing of surgery and medical therapies for patients with advanced melanoma.

Palliative surgery to relieve symptoms caused by metastases is appropriate when the anticipated benefit from palliation exceeds the morbidity of the procedure. For example, resection of bowel metastases to relieve obstruction or bleeding can yield palliation superior to other interventions. Expectant palliation can also be considered for control of disease that is progressing and is likely to cause disabling symptoms, such as enlarging, bulky but resectable nodal disease that may progress to symptomatic and unresectable disease if left unmanaged.

SURGICAL MANAGEMENT OF MELANOMA: TECHNIQUE

Wide Local Excision of Primary Melanoma

Cutaneous melanomas are managed with wide local excision with gross measured margins based on the melanoma thickness. Recommended excision margins refer to the gross measured margin across the skin surface from the edge of the lesion at the surgery and do not imply a necessary pathologic margin. For melanoma in situ, the excision should be a 5- to 10-mm margin, and the excision should be done into the subcutaneous tissue, but not deeper. For invasive melanoma, the radial margins to be taken are 1 cm for melanomas 1 mm or less in thickness; 1 to 2 cm for melanomas greater than 1 to 2 mm in thickness; and 2 cm for melanomas greater than 2 mm in thickness. Excision for invasive melanoma should be down to, but not including the deep fascia. Most wide local excisions on the trunk or proximal limbs can be excised with an elliptical excision and closed primarily. In many cases, primary closure is optimized with a length-to-width ratio of 3:1 (Fig. 1). The orientation of the ellipse should be chosen on the basis of the location of the melanoma. In general, the long axis of the ellipse should be parallel to the skin lines and tension lines, while also considering cosmesis. On the extremity, it can be advantageous to orient the ellipse obliquely, following the expected direction of lymphatics.

When simple primary closure is not possible, an alternate plan for coverage of the defect can be either local soft tissue coverage or

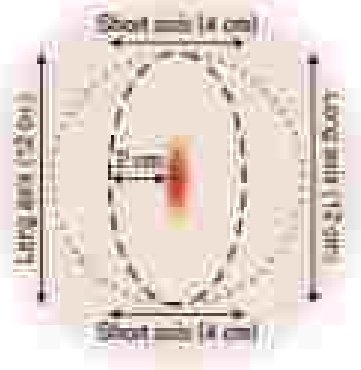

FIG. 1 Schematic of melanoma excision [illegible]

skin grafting. Soft tissue coverage with local advancement or rotation flaps preferred if possible. The overall time to healing after local advancement or rotation flap is less than with skin grafting, there is no separate donor wound to heal, and there is no need for immobilization during the initial postoperative period. The resultant surface after soft tissue advancement or rotation is likely to have a cosmetic similar to the original site. If a skin graft is necessary, greater attention to wound care is necessary, along with temporary immobilization of the area grafted. The total time to healing is greater, and there will be a resultant soft tissue defect at the site.

Wide excision for melanoma of the sole of the foot should be taken down to the plantar fascia. The defect requires coverage with skin graft or distant flap. Weight bearing must be restricted on the foot while the graft or flap heals, and healing can be difficult or delayed in patients with poor peripheral arterial flow. For melanoma of the toe, the excision margins remain the same as any other site (related to the thickness of the tumor) and therefore usually requires amputation. For a subungual melanoma, the great toe, if needed, can be amputated at the level of the proximal phalanx, with preservation of the metatarsophalangeal joint, which results in minimal change in ambulatory ability once healing is completed.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is a routine staging tool for melanomas with thickness 1 mm or greater (and for some thin melanomas) with clinically negative regional nodes at presentation. The sentinel node biopsy is ideally performed at the time of initial wide local excision, because its accuracy after wide excision is not well defined. The regional node basin that received lymphatic flow from a primary site is usually predictable, but in some cases there may be lymphatic flow to nodes that are outside the predicted basin. Close attention to preoperative lymphoscintigraphy is essential for accurate sentinel node identification.

Proper performance of lymphoscintigraphy and accurate communication with the nuclear medicine specialist is a critical first step in the sentinel node process. The dermis directly adjacent to the primary melanoma site is injected with technetium 99 sulfur colloid. The half-life of technetium 99 is 6 hours, and the timing of injection is optimally 1 to 18 hours before surgery. The lymphoscintigram is useful in identifying the location or locations of the sentinel node or nodes. Thoughtful attention should be given to the possibility of sentinel nodes at unexpected sites. In some cases, especially head and neck cases, preoperative localization may be aided by single photon emission CT. The surgeon should communicate directly with the nuclear medicine physician.

Once in the operating room, the location of the sentinel node should be confirmed with the gamma probe prior to final decisions regarding positioning. The gamma probe should also be used to interrogate possible lymphatic sites that did not appear on the lymphoscintigram; this will occasionally identify another basin with a sentinel node.

Some surgeons prefer the use of a second tracer, such as methylene blue, during surgery as a visual aid to sentinel node identification. Blue dye should not be used as a sole tracer without Tc sulfur colloid, because the identification rates are far lower than identification with the combination or with Tc sulfur colloid alone. Serious allergic reactions to methylene blue dye are uncommonly seen, and use of methylene blue dye is not recommended in pregnant patients. If blue dye is used, it is injected intradermally adjacent to the primary lesion a few minutes before incision at the lymph node basin site. The sentinel node procedure is found by identifying hot nodes with a gamma probe and excising the hottest nodes until the remaining nodal basin count is 10% or less of the hottest node. If blue dye is used, ideally the blue lymphatic channel coming from the injection site is visualized in the node basin and followed to the first blue node. The blue node is usually hot as well. It is common to retrieve 1 to 3 sentinel nodes per basin, but higher numbers are occasionally found. It is not necessary to place a drain at the sentinel node site.

Sentinel lymph node biopsy is associated with a low complication rate, with the most common complications being infection, seroma, and hematoma. It is expected that all patients will develop a small lymphocele at the site; it is usually small and will resolve without need for intervention. A small proportion of patients may need an office aspiration of the lymphocele if it is large or symptomatic. Lymphedema has been reported in a small proportion of patients after a groin sentinel node, especially in elderly or obese patients. When lymphedema occurs in this clinical context, it is usually mild and well tolerated and will often (but not always) resolve over several months.

Therapeutic Lymph Node Dissection

Complete lymphadenectomy for regional control of nodal disease remains important for many melanoma patients. It is necessary for patients with clinically positive nodes in the absence of distant disease and may be considered for select patients with positive sentinel nodes if they are felt to be not appropriate candidates for lymph node basin surveillance. Lymphadenectomy provides information regarding prognosis, as well as regional control of disease. The procedure should be anatomically based, excising the node basin in its entirety, while preserving key motor nerves and vasculature.

Axillary Dissection

An axillary lymph node dissection for melanoma involves complete resection of all lymph nodes at levels I, II, and III. The borders of dissection are the latissimus dorsi posteriorly, the subscapularis muscle posteriorly, the chest wall medially, and the axillary vein superiorly. The long thoracic nerve and thoracodorsal neurovascular bundle are preserved unless they are directly invaded by tumor. Level II and III nodes in some patients may be more easily accessed by drawing the arm in front of the patient's chest during the surgery, with strong retraction of the pectoral muscles. In some cases, the pectoralis minor muscle, if well developed, may be divided to obtain exposure of level III nodes to facilitate a complete resection. A closed suction drain is placed at the end of the case. Early mobilization of the arm to full range of motion and gentle physical therapy can facilitate recovery. There is approximately a 15% to 20% risk of symptomatic lymphedema. If lymphedema occurs, prompt referral to a lymphedema therapist can lessen the impact.

Inguinofemoral and Ilioobturator Dissection

The boundaries of the inguinofemoral node dissection (superficial groin dissection) are superiorly 3 to 4 cm above the inguinal ligament, medially to the pubic tubercle and the adductor longus, laterally to the anterior superior iliac spine and the lateral border of sartorius, and inferiorly to the apex of the femoral triangle. A common incision for the dissection is a modified sigmoid incision extending from medial to the anterior superior iliac spine, coursing downward and then medially below and parallel to the inguinal crease, ending near the apex of the femoral triangle. Incision design should be modified based on body habitus, preexisting incisions, need for en bloc skin resection, and location of involved nodes. Flaps are raised to expose the femoral triangle and external oblique. The spermatic cord should be undisturbed. Nodal contents are dissected down from the level of the external oblique to the inguinal ligament and from the anterior surface of the sartorius and the adductor longus. The greater saphenous vein can be identified in the medial inferior aspect of the dissection and ligated distally to assist with dissection. In patients with low volume disease and amenable anatomy, it may be reasonable to spare the greater saphenous vein. The nodes are then resected en bloc from the anterior surface of the femoral vessels taking care to secure branches of these vessels. Finally, the greater saphenous vein (if divided distally) is controlled and divided at the saphenofemoral junction. The femoral canal may be explored from beneath the inguinal ligament to excise Cloquet's node if this would be useful in determining whether to do an iliac dissection. Today, with high-quality

cross-sectional imaging, the decision of whether to do an ilioinguinal dissection is usually made before surgery, with rare need for evaluation of Cloquet's node. The sartorius muscle is often transposed medially for coverage and protection of the femoral vessels. The sartorius muscle is divided at its insertion into the anterior superior iliac spine, rotated over the femoral vessels, and sewn in place at the edge of the inguinal ligament superiorly and the fascia of the adductor longus medially. A closed suction drain is left in place.

Iliac and obturator lymph node dissection involves excision of the nodal tissue from the bifurcation of the common iliac vessels superiorly down to the distal part of the external iliac vessels, resecting nodal tissue anterior and medial to these vessels and including nodes in the obturator space medially. The iliac vessels, as well as the ureter, are to be identified and carefully preserved. A drain is not necessary in the dissected iliac/obturator space.

Inguinal dissection wounds have an infection rate of up to 15%, as well as symptomatic lymphedema rate of at least 20%. It is unclear whether lymphedema risk can be lessened with routine use a fitted compression garment at 20 to 30 mm Hg during the daytime for the first 6 months after surgery, although this is often prescribed, along with leg elevation whenever possible. Most patients after inguinofemoral or iliac/obturator dissection can expect to return to full function.

Cervical Dissection

The extent of cervical lymphadenectomy is dependent on the location of the disease and the presence or absence of direct invasion of surrounding structures. Whenever possible, a modified neck dissection is optimal, preserving the internal jugular vein, spinal accessory nerve, and sternal head of sternocleidomastoid. These structures should be excised only if there is direct tumor involvement. When there are metastases of the parotid lymph nodes, the lymph nodes in the upper neck are also at risk of harboring metastatic disease. For this reason, a neck dissection generally is performed in addition to a superficial parotidectomy.

A therapeutic neck dissection for melanoma can be associated with a 20% to 30% recurrence rate in the neck. Patients with suspected high risk of recurrence, for example, those with multiple positive nodes, extracapsular invasion, or both, may be considered for adjuvant radiation therapy.

Lymphedema

Lymphedema is a relatively common complication of axillary and inguinofemoral dissection and is often the dominant concern of patients facing these procedures. Lymphedema is an inherent risk of these procedures and can occur at any time after lymphadenectomy, even decades later. It is more frequent in patients who are elderly or obese, and those who have multiple positive nodes or postdissection radiation therapy. After surgery, all patients should take care to avoid injury or infection of the extremity at risk. It is not clear whether prophylactic limb elevation or compression garment use lowers risk in persons who do not have lymphedema. If lymphedema occurs, the patient should be evaluated promptly for precipitating factors such as soft tissue infection in the limb or disease recurrence. Patients with lymphedema without proximate cause requiring treatment (such as cellulitis or disease recurrence) should be referred to a lymphedema therapist for evaluation and management. Today, with active management, most cases can be maintained at a mild level. Attention to management of the lymphedema will be lifelong. Newer surgical techniques, such as lymph node transfer or lymphovenous bypass, are emerging as possible therapies for lymphedema, but assessment of their potential benefit requires further clinical trials.

MULTIDISCIPLINARY FOLLOW-UP

Patients with melanoma, regardless of stage, require lifelong surveillance for recurrence and possible second primary. The risk of a second primary melanoma is at least 8%, and melanoma patients are often at risk of other skin cancers, such as basal cell carcinoma and squamous cell carcinoma. All patients with melanoma require lifelong skin surveillance and evaluation of potential draining nodal basins.

Risk of recurrence of the melanoma depends on stage. Low risk patients (such as those with thin melanoma and negative nodes) may be monitored mainly by their dermatologist. Moderate- to high-risk patients should also be monitored by a surgical oncologist or a melanoma oncologist. Patients with positive nodes should have formal consultation with a medical oncologist. As newer medical therapies show survival benefit for high risk patients, adjuvant therapies with immunotherapy or targeted therapies should be strongly considered for all eligible patients. Clinical trial enrollment should be encouraged. Patients with thick melanoma with negative nodes are not currently routinely considered for systemic adjuvant therapies, but they are a high risk group that may benefit from follow-up with an oncologist.

There is no known benefit of routine cross-sectional imaging for surveillance in the absence of concerning symptoms. For patients who do not undergo lymph node dissection after a positive sentinel lymph node biopsy, node basin surveillance is critical. These patients require surveillance ultrasound scanning of the nodal basin with the positive sentinel node every 4 months for the first 2 years, and then every 6 months for years 3 to 5. Any suspicious nodes identified should be biopsied. If the biopsied node is positive, and cross-sectional imaging indicates that it is a single site of disease, the patient should proceed with surgical dissection of that basin.

FUTURE OF MELANOMA CARE

Melanoma care has evolved rapidly and will continue to change in the coming years. Care is best provided by specialists with a specific interest in melanoma. The past 2 decades have seen rapid change in management strategies for the regional node basin, and rapid development of new medical therapies for melanoma that are effective for some patients in improving survival in patients with stage III and stage IV disease. We anticipate that the development of additional treatment strategies, including neoadjuvant approaches and other multimodality plans, will continue to improve the outlook for melanoma patients.

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Management of Soft Tissue Sarcoma

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OVERVIEW

Soft tissue sarcomas (STSs) are malignant tumors that arise from mesodermal derived tissue, including fat, smooth/skeletal muscle, blood vessel, and connective tissue. Additional tumors classified as STS include malignant tumors of nerve sheath origin, derived from ectoderm. There are approximately 13,000 new cases of STS, representing 1% of all malignancies, with a slight male predominance, leading to approximately 5000 deaths per year in the United States. Although considered rare at all ages, in children, STS are the third most common solid malignancy, accounting for 15% of all pediatric cancers.

STS are a heterogeneous group of neoplasms that may be subclassified into more than 70 specific histologic conditions and may be distributed throughout the body. Approximately one-half arise in the extremities, and one-third arise in the abdomen, pelvis, and retroperitoneum. It is now recognized that the most common histologic subtype in adults is gastrointestinal stromal tumor (discussed elsewhere), followed by liposarcoma and leiomyosarcoma. In contrast, these subtypes are relatively less common in children, in whom pediatric (embryonal/alveolar) rhabdomyosarcoma and Ewing sarcoma account for more than half of all STS diagnoses.

Tumor related factors predictive of recurrence, survival, or both include size, grade (low, intermediate, or high), and histologic subtype, although the impact of these and other risk factors may vary depending on site of origin. These risk factors have recently been used to build validated nomograms for extremity and retroperitoneal sarcomas, available through a free smart phone app (www.sarcoma-score.com).

The most important treatment related factor predictive of recurrence is quality of surgical margins (negative/positive). This has been shown to be the strongest prognosticator of local failure, with a limited role, if any, in distant failure and final outcome, save for tumors located at critical sites. Pattern of failure depends on tumor grade, histology, and site of origin (which importantly influences the possibility of achieving clear surgical margins). In general, low grade tumors tend to recur locally or locoregionally, with only a low risk of distant spread. In contrast, high-grade tumors, which may also recur locally, have a much higher propensity for distant failure. Extremity STS most commonly spread to the lung when they metastasize, whereas retroperitoneal sarcomas generally recur in a locoregional pattern. Some histologic subtypes have peculiar natural histories. For example, myxoid/round cell liposarcomas tend to recur locally especially, with a lower risk to spread to distant sites even when high grade. Myxoid/round cell liposarcomas may spread to other organs (bone, abdominal cavity, paraspinal soft tissue, and bone) early in the course of the disease. Angiosarcomas are generally multifocal at presentation and very difficult to control surgically, and they can give rise to lymph node metastases and distant spread very early in the course of the disease.

Traditionally, surgical textbooks and peer reviewed literature have discussed the surgical management of STS based on site of origin. Although site of origin remains an important consideration, it has become increasingly clear that surgery must also be tailored to specific sarcoma histologic to more accurately reflect tumor biology and pattern of recurrence.

This chapter covers the management of nongastrointestinal stromal tumor STS. Surgical management is discussed both by specific histology as well as by site of origin. Although the focus of this chapter is surgery, additional treatments, such as radiation therapy or chemotherapy and imaging are considered as appropriate.

ETIOLOGY

Most sarcomas arise sporadically, without recognizable etiologic factors. Various chemical agents and herbicides have been associated with specific STS. For instance, vinyl chloride and thorium dioxide (Thorotrast) have been linked to hepatic angiosarcomas. Another well recognized risk factor is chronic lymphedema in the development of angiosarcoma, a phenomenon known as Stewart–Treves syndrome. Therapeutic and environmental exposure to radiation is associated with development of sarcomas within the treatment field at a median interval of approximately 7 to 10 years, with the most common histologic conditions being angiosarcoma and undifferentiated pleomorphic sarcoma (formerly called malignant fibrous histiocytoma or MFH, see below).

Germline genetic mutations and molecular alterations have been associated with the development of sarcomas. Li–Fraumeni syndrome, due to mutations of *p53*, is associated with both STS and osteosarcoma. Neurofibromatosis type 1 (von Recklinghausen disease), due to mutations of *NF1*, is associated with an approximately 10% risk of developing malignant peripheral nerve sheath tumors and an increased risk for developing gastrointestinal stromal tumors. Familial adenomatous polyposis, due to mutations in *APC*, is associated with desmoid tumors.

Chromosomal rearrangements may lead to gene fusions associated with sarcomas, such as the *SS18/SYT* rearrangement seen in synovial sarcoma and several others. Similarly, chromosomal amplifications may be associated with specific sarcoma histologic conditions, such as increased levels of MDM2 and CDK4 proteins in association with chromosomal 12 amplification in well differentiated and dedifferentiated liposarcoma.

GRADING

The American Joint Committee on Cancer (AJCC) has developed a staging system for sarcomas. The AJCC staging system not only incorporates the traditional variables of tumor size, nodal disease, and metastatic disease, but also tumor grade. Unlike the more common grading based on differentiation (well, moderate, or poor), STS grading is based on histology specific features, including differentiation, necrosis, and mitotic count, and is most commonly classified as low (grade I), intermediate (grade II), or high (grade III). Tumor stage incorporates both size (T1, ≤5 cm; T2, >5 cm) and depth with respect to fascia (superficial, T1a or 2a; deep, T1b or 2b). True nodal spread is rare.

However, there is considerable variability in outcome among patients within each stage. This is due in part to the fact that a critical factor, histology, is not incorporated into the AJCC staging system. Other prognostic factors, such as site of origin and patient age are also not weighted. To address this, modern nomograms (Figs. 1 and 2) based on STS histologic subtypes that consider specific prognostic factors as continuous rather than categorical variables have become available, some of which are included in the above mentioned app (www.sarcoma-score.com). They may be used immediately in the clinical setting with patients. In the long run, these may be more useful at identifying prognostically similar cohorts for future studies.

TREATMENT

Surgery remains the standard and only potentially curative therapy in the management of STS. In general, wide or radical resections are necessary to achieve negative margins. In other words, the tumor

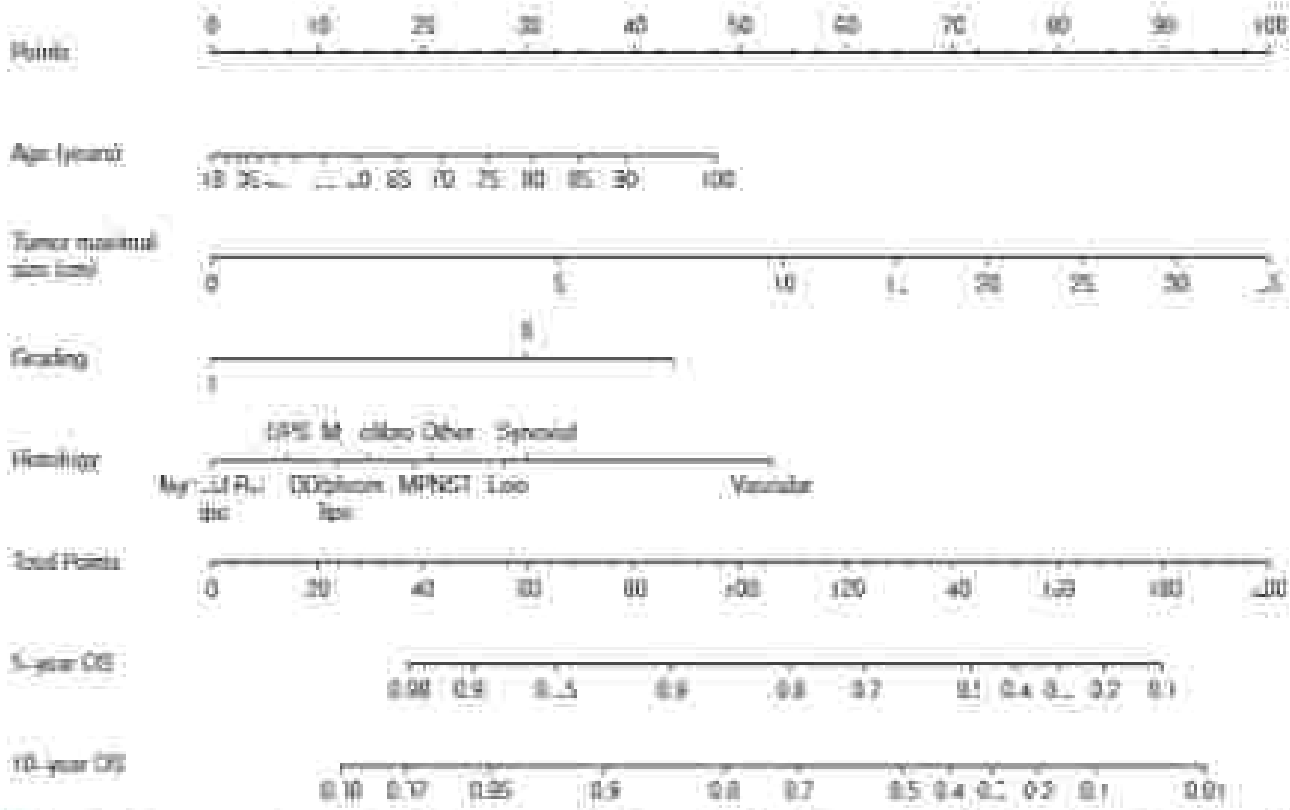

FIG. 1 Overall survival nomogram for secondary soft tissue sarcoma. DD, dedifferentiated; Leio, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumors; Myxof, myxofibrosarcoma; OS, overall survival; Plas, pleomorphic; RC, (L)S, round cell liposarcoma; UPS, undifferentiated pleomorphic sarcoma.

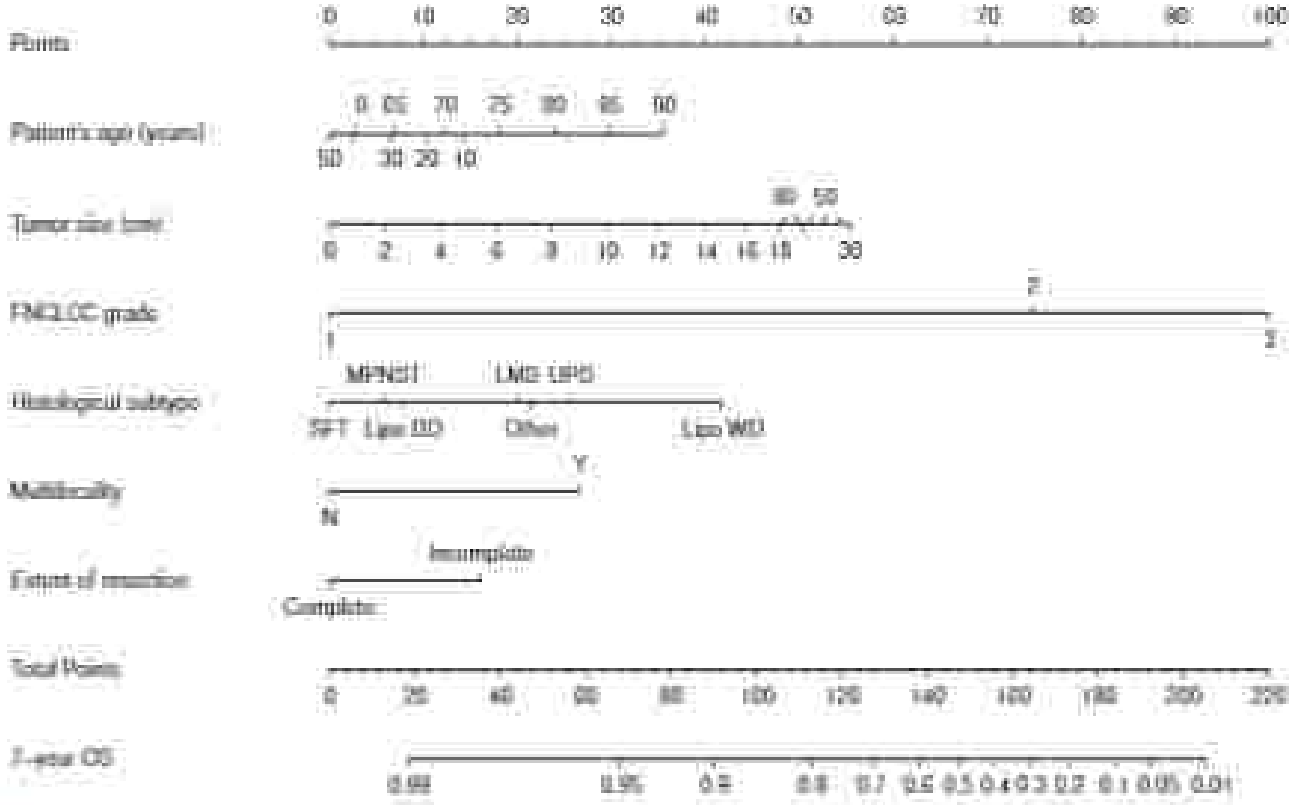

FIG. 2 Overall survival nomogram for retroperitoneal soft tissue sarcoma. Lipo DD, dedifferentiated liposarcoma; NCCC, National Federation of French Cancer Centers; "N", leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumors; OS, overall survival; "Y", solitary fibrous tumor; "PL, undifferentiated pleomorphic sarcoma; Lipo WD, well-differentiated liposarcoma.

must be resected en bloc with a cuff of healthy tissue all around to avoid contamination from tumor surface and removal of tumor microsatellites, which may be present in the healthy tissues surrounding the pseudocapsule. The extent of resection and adequacy of margins depends on a variety of factors, including histology and presence of an intact biologic barrier, such as muscular fascia, vascular adventitia, periosteum, or synovium.

Patients with STS should undergo evaluation at a sarcoma center because the administration of neoadjuvant or adjuvant therapy may be indicated. Generally, this involves multidisciplinary evaluation by a surgical oncologist and, depending on histology, a medical oncologist and a radiation oncologist. Reevaluation of pathology slides by a pathologist specializing in sarcomas is critical to confirm the exact histology and determine the most appropriate treatment. In fact approximately 25% of all sarcomas are initially designated with the incorrect histology, and approximately 10% are assigned the wrong histologic category in a clinically significant manner, thus impacting treatment plan. Given the complexity of many operations needed, support from other specialties, including plastic and reconstructive surgery, vascular surgery, urology, thoracic surgery, and anesthesia, is commonly required.

IMAGING

Histology and the specific imaging recommendations are discussed in further detail in the individual sections below. To better define the extent of extremity and truncal STS, including depth of invasion and relationship with neurovascular structures, an MRI of the affected site is the preferred imaging study. Further staging studies for patients with extremity STS should include chest imaging—radiography for low grade lesions and CT for intermediate- or high-grade lesions. Patients with abdominal visceral, pelvic, and retroperitoneal sarcomas should undergo CT imaging of the abdomen and pelvis and, in most cases, chest. Those with primary STS of the rectum or metastases to the liver may need further evaluation with MRIs of these sites. STS involving vascular structures, such as leiomyosarcomas arising in the wall of inferior vena cava, are usually sufficiently characterized by the standard MRI or CT imaging of the site, and CT angiography is not required. Patients with breast STS should undergo MRI imaging to define depth of extension; mammography is not routinely useful. Those with scalp STS may undergo either CT or MRI. There is no need for routine head CTs as a staging study. Although much has been written about the use of positron emission tomography (PET) in some sarcomas and many other malignancies, it is rarely indicated in routine sarcoma care. PET scans should only be ordered selectively, when attempting to resolve an ambiguous finding on other imaging or gauging treatment response under specific circumstances.

SITE-SPECIFIC TREATMENT

Extremity and Trunk Wall Soft Tissue Sarcoma

Clinical and Diagnostic Evaluation

Patients with extremity STS commonly present with a palpable mass. Initial clinical evaluation should include a thorough history and physical examination, with attention directed to size, precise location, and evidence of neurovascular compromise. No tumor markers are known for STS histology at present. After a thorough examination, MRI (or CT) of the affected site is indicated for most lesions; small, superficial lesions may be directly excised at the discretion of the surgeon. MRIs generally provide more detailed soft tissue definition but are less readily accessible, may be problematic for patients with claustrophobia, and cannot be performed in patients with retained ferromagnetic and certain types of aneurysm clips, cardiac devices, or other implants. Staging evaluation is completed by chest radiography (for low grade malignancies) or chest CT (for intermediate- or high-grade malignancies). There is no need for routine head CT (other than for shoulder soft part sarcoma) or PET scanning.

Imaging alone is rarely diagnostic of the specific sarcoma histology, with the exception of well-differentiated liposarcoma (also called atypical lipomatous tumor). Well-differentiated liposarcomas have a radiographic density similar to normal surrounding fat but tend to be well-encapsulated with thick internal septations. Such tumors may be treated with resection (complete excision with a margin of normal surrounding muscle, fat or fascia to minimize risk of local recurrence) and do not require a biopsy.

Other symptoms suspicious for sarcoma should be biopsied. We prefer to obtain core needle biopsies under radiographic guidance, although they may be performed without imaging, depending on location. Although biopsy tract recurrences are exceedingly rare, the site selected for the core needle biopsy should be planned such that it can be included in the excision used during the subsequent definitive resection or at least in the radiation field. Thus coordination between the surgeon and the interventional radiologist is required. It is important to specify "core needle biopsy" rather than fine needle aspiration because the latter rarely yields enough tissue and architecture information to distinguish between different sarcoma histologic conditions. A key advantage of core needle biopsy over an open biopsy is that the former can be directed toward a specific portion of the tumor. If a core needle biopsy fails to yield a diagnosis, an open incisional or excisional biopsy should be obtained. Although incisional biopsies have been used for diagnosis commonly, they are often performed improperly by inexperienced hands. Incisional biopsies should be performed through longitudinally oriented incisions placed such that the incision can be included in the final resection when a definitive resection is planned. If a transverse incision is used, then, when subsequent resection is required, challenges for reconstruction and risk of lymphatic disruption (depending on location) are magnified. Excisional biopsies should be confined to lesions less than 2 cm in size and superficial in location.

Surgical Treatment

Until the early 1980s, the standard of care for patients with extremity sarcomas was amputation. That changed after a seminal randomized, controlled trial conducted by Rosenberg and colleagues at the National Cancer Institute (NCI). In that trial, patients with high-grade extremity STS were randomized to undergo amputation or limb-sparing surgery with adjuvant radiation therapy. Those undergoing limb-sparing surgery headed toward a higher rate of local recurrence. Importantly, however, there was no difference in overall survival. This altered the standard treatment for extremity STS.

Currently, the goal of surgery is not only limb sparing, but also function sparing, while achieving appropriate biologic margins. Surgical resection should be carefully planned based on preoperative imaging. Resections should include not only the entire tumor (without rupture or violation of the surrounding pseudocapsule) but also an adequately wide margin (1–2 cm) of normal, noninvolved tissue. Resections performed with positive margins do result in higher risk of local recurrence and, to a lesser extent, death, especially if located at critical sites. However, a locally positive margin over a critical structure planned to adjuvant can still be accepted, provided adequate radiotherapy (generally preoperative) is performed, without compromising local control or overall survival. If the STS is close to the superficial skin, then an adequate skin paddle overlying the tumor should be resected en bloc with the tumor (Fig. 2). The surgeon should not compromise the margin by minimizing the skin resection just to avoid a skin graft or flap. Tumors extending toward but not involving the fascia should include the fascia as a margin. Superficial tumors involving the fascia should include the fascia and generally an additional margin of underlying muscle. By definition, when the investing fascia is infiltrated, the tumor is considered deep, even if it is mainly located in the superficial tissues. Similarly, deep tumors extending superficially to the fascia should include a margin of overlying subcutaneous and cutaneous tissues as a margin. It is uncommon for primary STS to violate a fascial plane, but that is not the case for recurrent STS. Deep tumors not extending into superficial tissues

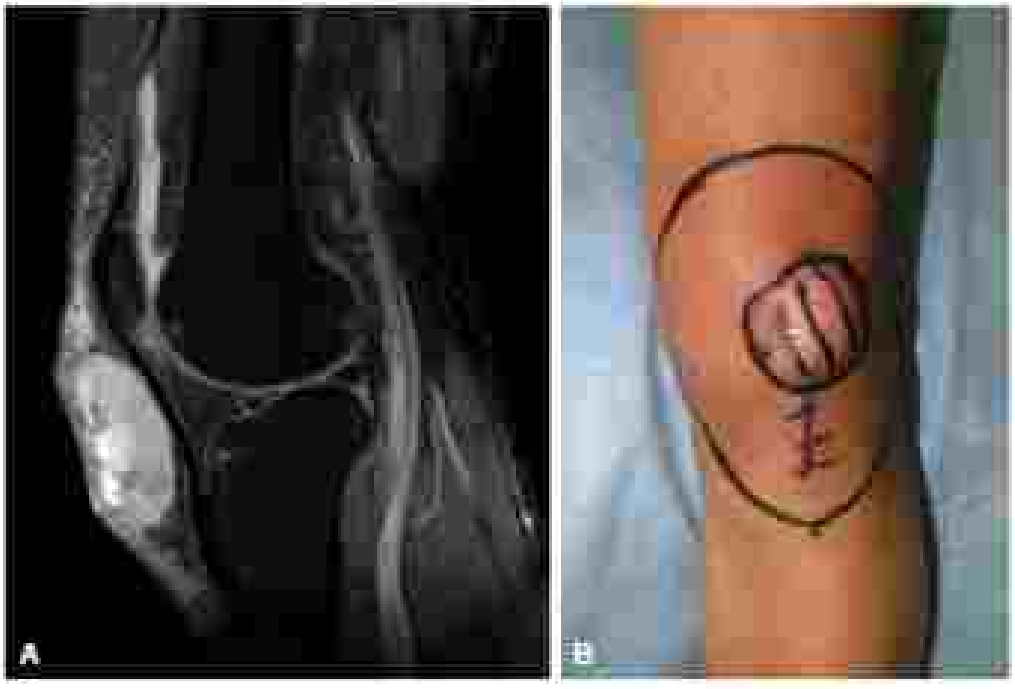

FIG. 5 (A) Sagittal magnetic resonance image of a superficial myxoid, mixed pleomorphic sarcoma. (B) Planned wide skin incision around the entire mass to achieve adequate skin margin.

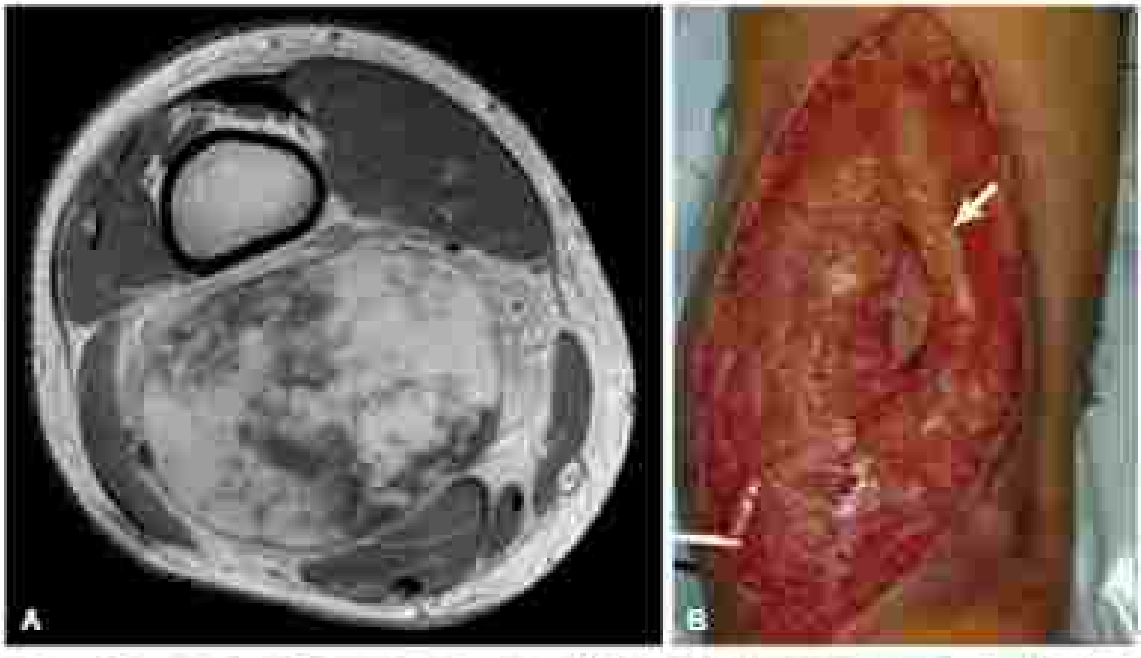

FIG. 6 (A) Axial magnetic resonance image of malignant solitary fibrous tumor of the thigh demonstrating deep location. (B) Due to its deep location only a minimal skin paddle around biopsy tract is needed at resection.

do not need a sizable resection of superficial tissues (Fig. 4). The tumor specimen should be oriented with marking sutures. When possible, additional margins may be sent separate from the main specimen, representing the superior, inferior, medial, lateral, superficial, and deep margins of dissection, with the true margins appropriately marked for orientation. Tumors tangentially involving bone, vessel, or nerve do not routinely require en bloc resection of these structures, as equivalent local control rates can be achieved with a carefully multidisciplinary approach of neoadjuvant radiation and surgery. Tumors abutting bone may include the periosteum as a margin if the bone is not directly invaded (Fig. 5). If bone is invaded or encased, composite resection and reconstruction may be necessary. If necessary, vascular resection and reconstruction should be considered for involved vessels (Fig. 6). If a critical nerve is encased, reconstruction with an interposition nerve graft should be considered (Fig. 7). Such reconstructions may be compromised if radiation is administered after surgery, and therefore preoperative radiation may be warranted. The specimen should be reviewed with the pathologist for optimal orientation.

Furthermore, it is critical to take into account the specific histology as described below. For instance resection for myxofibrosarcoma requires wider margins than resection for atypical lipomatous tumor

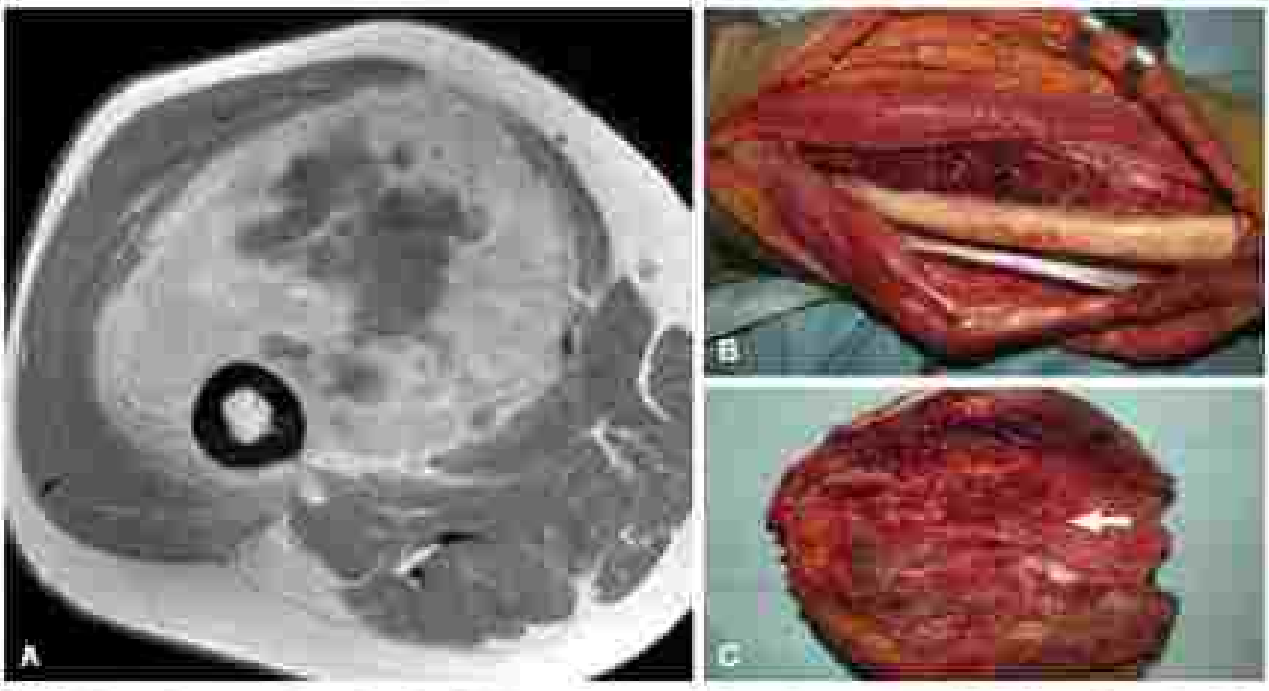

FIG. 5 (A) Axial magnetic resonance image of an unclassified pleomorphic sarcoma of the anterior compartment of the thigh partially causing the femoral shaft. The patient received preoperative conventional chemotherapy (3 courses of adriamycin + ifosfamide) and radiotherapy (for a total dose of 50 Gy). (B) Intraoperative image demonstrates periosteum stripped off en bloc with the tumor. (C) Surgical specimen, illustrating the deep margin over the bone (arrow).

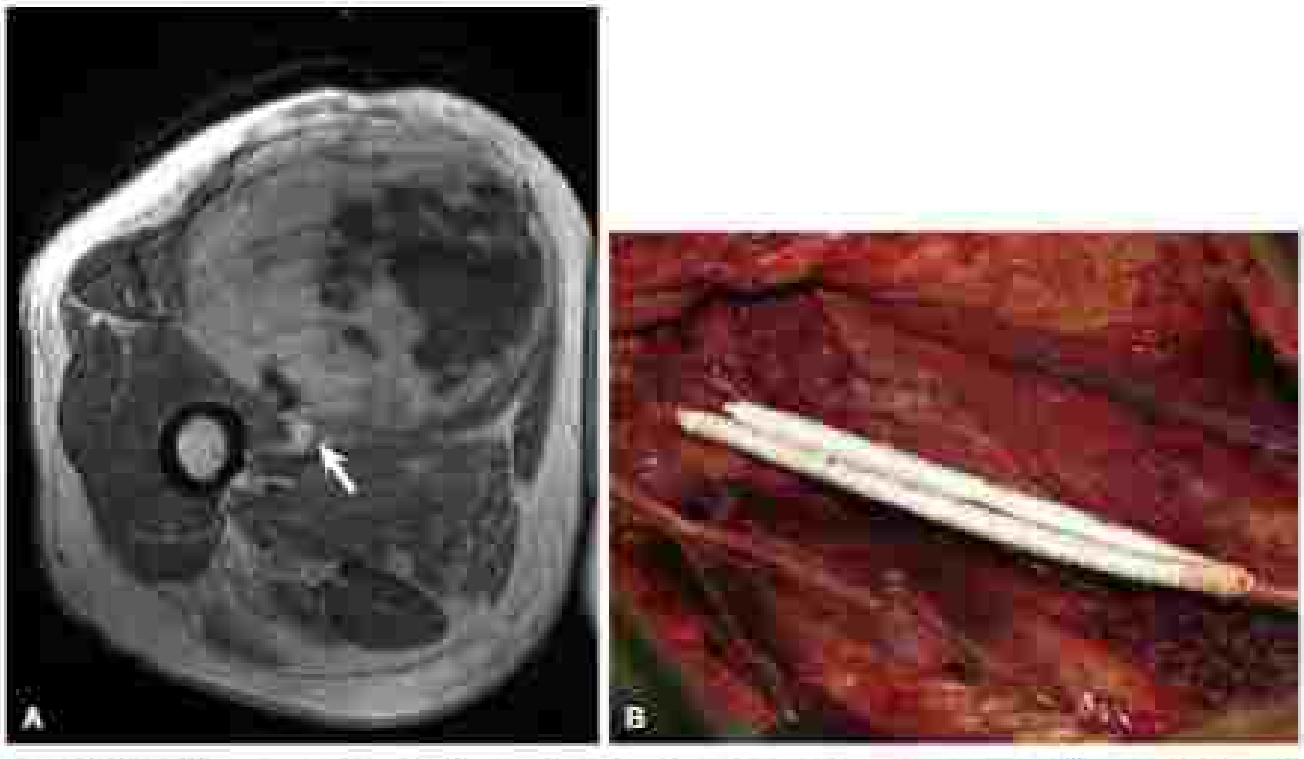

FIG. 6 (A) Axial MRI image of a monophasic synovial sarcoma of the thigh involving the femoral vessel (arrow). (B) Intraoperative image of the surgical field with vascular replacement, of both artery and vein.

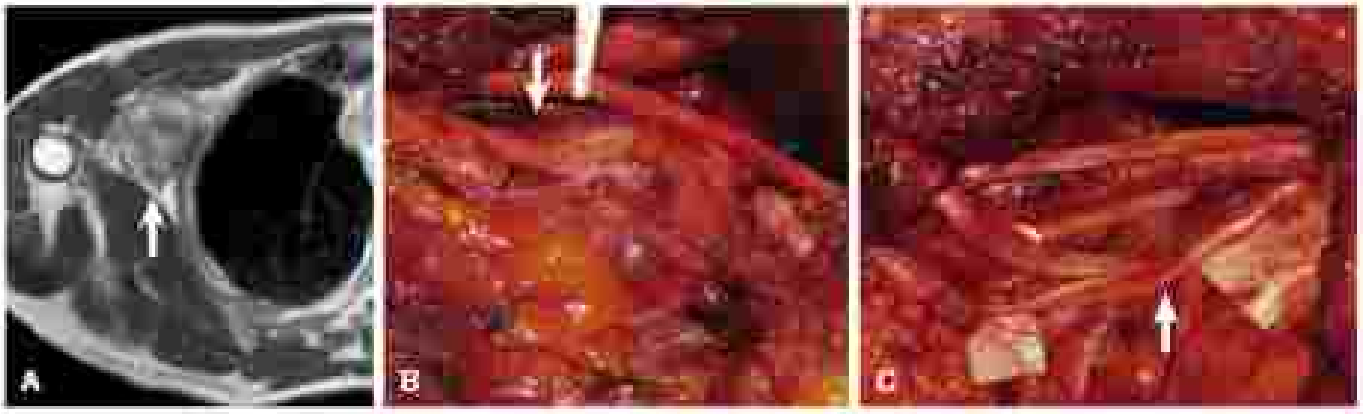

FIG. 7 (A) Axial magnetic resonance image of a myxoid liposarcoma involving the brachial plexus (arrow). Intraoperative image of the surgical field before (B, arrow shows involved nerve) and after resection (C, arrow shows the reconstruction using autograft).

(AJCC). Thus it is important for the surgeon to understand the different sarcoma histologic conditions, confirm the accuracy of the diagnosis with expert pathology review, and discuss the treatment plan in a multidisciplinary committee.

Wound closure should be meticulous to minimize risk of wound complications, which can be considerable as described in the next section. Drains may be necessary, particularly after preoperative radiation therapy or in the setting of recurrent tumors, as ongoing serous drainage may continue for weeks postoperatively. Flap reconstruction may be necessary for proper wound closure or if there is a large, potential dead space left behind (especially if preoperative radiation therapy had been administered).

Adjuvant/Neoadjuvant Radiation Therapy and Chemotherapy

Limb-sparing surgery generally relies on adjuvant/neoadjuvant radiation therapy to minimize risk of local recurrence, as demonstrated in the NCI trial. The goal of radiation is to treat the margin to minimize the risk of recurrence, not necessarily to reduce the size of the tumor per se. Radiation therapy reduces the risk of local recurrence from greater than 30% to less than 10% in most series but does not impact distant failure or overall survival rates.

Radiation therapy may be delivered as external beam radiation therapy (EBRT) or brachytherapy. EBRT may be delivered before or after surgery. One randomized trial, by O'Sullivan and colleagues, and sponsored by the Canadian NCI, compared preoperative EBRT with postoperative EBRT. There was no difference in local recurrence rates. Preoperative EBRT was associated with a doubling in the rate of wound complications (35% vs 17%) but essentially with a lower rate of late complications and tissue fibrosis and better functional outcomes. Postoperative EBRT generally covers a larger field (including drain sites) and to a higher dose than preoperative EBRT (approximately 66 Gy vs 50 Gy). This is particularly important in young adults of child-bearing age with proximal thigh STS; preoperative EBRT may spare the gonads whereas postoperative radiation may not. An ongoing North American trial is evaluating whether lower doses of postoperative radiation (50 Gy, matching the preoperative dose) provide equivalent rates of local control.

Brachytherapy may be delivered through afterloading catheters placed across the tumor bed at the end of surgery. The goal of brachytherapy is to deliver additional radiation to a close margin (including neurovascular structures) with minimal treatment to surrounding tissue, particularly when further EBRT is no longer feasible. When the final pathologic margins are confirmed, the appropriate catheters may be loaded with radioactive seeds once or twice a day for a defined treatment period concentrated over the close margins. To minimize wound complications, catheters should not be loaded until at least postoperative day 5. To minimize the risk of dislodging the catheters, any drains placed at the time of surgery should remain in place until the catheters have been removed.

Patients with small (<5 cm), superficial, well-circumscribed STS resected with an appropriately wide margin (>1 cm) of uninvolved tissue or biologic barrier (fascia) may not require radiation therapy, particularly if not high grade, provided that they can be reliably monitored.

Approximately 25% to 50% of patients with extremity STS develop distant metastatic disease. Those with large (>10 cm), deep, high-grade STS may be considered for preoperative or postoperative chemotherapy, usually with active agents such as doxorubicin and ifosfamide (response rates of 20% to 40% in patients with metastatic disease). A potential benefit in the more common histologic conditions at higher risk (i.e., synovial sarcoma, myxoid liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumor) has been recently suggested, and longer follow-up is awaited to draw more definitive conclusions. The implementation of the nomogram predicted risk, as described above, in the decision making will be critical in selecting proper patients for adjuvant/neoadjuvant chemotherapy in the future. Of note, chemotherapy may also be administered concurrent with radiotherapy and may help with maximizing tumor response, when limb/function preservation is an issue or positive margins over a critical structure are anticipated. The administration of concurrent chemoradiotherapy has been shown to offset the negative prognostic impact of locally positive surgical margins on local recurrence and final outcome.

Hyperthermic isolated limb perfusion (ILP) and infusion (ILI) have been investigated in several institutions as treatment for patients with locally advanced STS in whom limb-sparing, function-sparing surgery may not be possible. These procedures involve placing vascular access catheters into the main artery and vein of the affected extremity and perfusing with high-dose chemotherapy (usually melphalan) and tumor necrosis factor alpha under hyperthermic conditions. ILP is generally performed as an open procedure with catheters directly onto the vessels. ILI uses percutaneously placed catheters and is conducted under hypoxic conditions. Although both have proven efficacy in melanoma, the data for STS are more limited. No randomized trials have compared either technique over aggressive limb-sparing resection with EBRT for STS. Arguably, patients under consideration for ILP and ILI usually have locally advanced or multifocal STS and are not necessarily candidates for surgery with EBRT at first evaluation. ILP and ILI should be considered as potential therapies in appropriately selected patients, and eligible patients should be referred to centers where this therapy is available.

The utility of (neo)adjuvant immunotherapy for resectable extremity STS is under investigation and should only be considered on protocol. There is an ongoing U.S. randomized trial evaluating neoadjuvant radiation therapy with or without neoadjuvant/adjuvant pembrolizumab for certain subtypes of extremity STS.

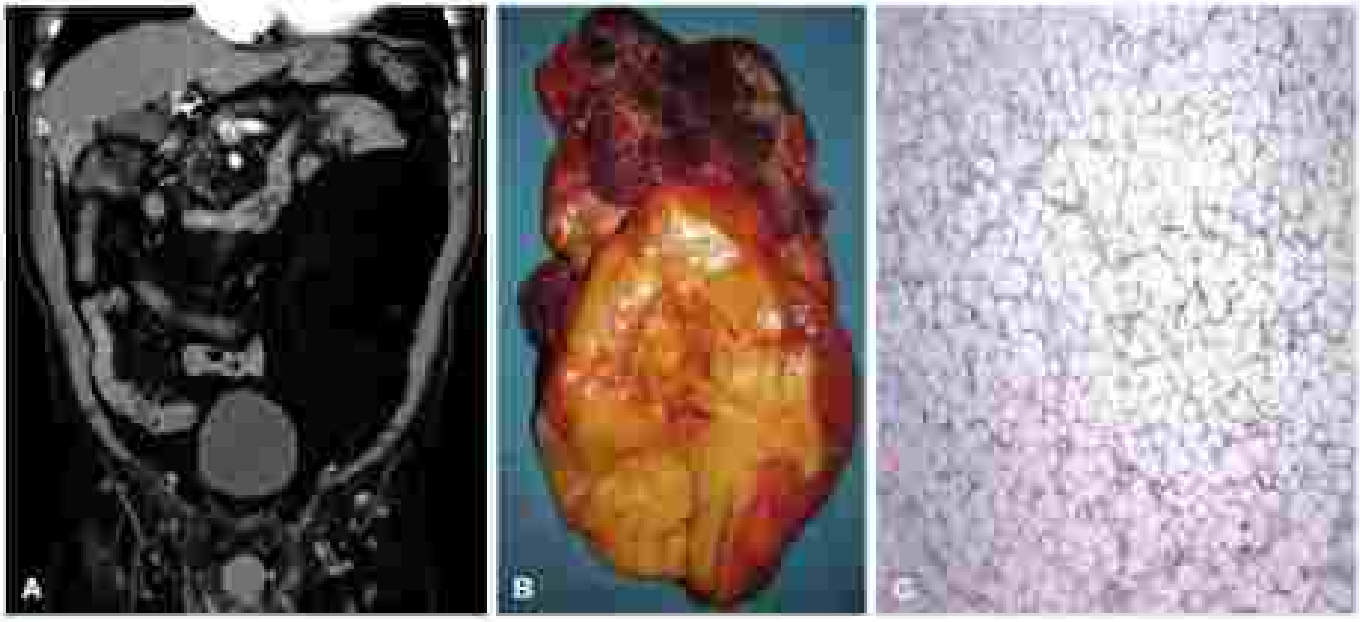

FIG. 8 (A) Coronal computed tomography view of a left-sided retroperitoneal well-differentiated liposarcoma, (B) surgical specimen, together with macroscopic (C) and microscopic appearance.

Retroperitoneal Soft Tissue Sarcoma

Clinical and Diagnostic Evaluation

Patients with retroperitoneal STS are often asymptomatic until the mass reaches a large size (often 15 cm or greater). Symptoms include a palpable mass, early satiety, abdominal discomfort, or occasionally a new varicocele in men. Others may be incidental findings during abdominal imaging for other reasons. Initial clinical evaluation should include a thorough history and physical examination, with attention directed to ruling out other diagnoses in the differential, including lymphoma, primary germ cell tumor and testicular cancer metastatic to retroperitoneal lymph nodes (if male). Although there are no tumor markers known for STS histologic conditions at present, screening studies exist for other diagnoses, including lactate dehydrogenase, human chorionic gonadotropin, and alpha fetoprotein. After a thorough examination, CT scanning of the abdomen and pelvis is indicated. Staging evaluation is completed by chest CT scanning. There is no need for routine head CT or PET scanning.

Imaging alone is rarely diagnostic of the specific sarcoma histologic condition, with the exception of well differentiated/dedifferentiated liposarcoma. As described in the extremity STS section above, well differentiated liposarcomas have a radiographic density similar to normal surrounding fat, but they tend to be well encapsulated, with thick internal septations. Giant lipomas are only identified incidentally in the retroperitoneum; therefore are mass consisting of very well differentiated fatty tissue should be considered as well differentiated liposarcoma and treated as such (Fig. 8). When a solid component is present within the fatty lesion, the diagnosis of dedifferentiated liposarcoma is very likely. However, all retroperitoneal masses should be biopsied to ensure the diagnosis before any treatment is undertaken. We prefer to obtain core needle biopsy specimens with coaxial needles, under radiographic guidance. Biopsy tract recurrences are exceedingly rare, usually associated with the use of the strong technique, and do not need to be resected during definitive surgery. Once the pathologic diagnosis is obtained, the strategy should be discussed within the multidisciplinary tumor board, which has to include at least a medical oncologist, radiation oncologist, radiologist, and pathologist. The first surgical approach is critical for cure and cannot be repeated, when inappropriate, by a second procedure.

Anatomic Features of Retroperitoneal Sarcomas (RPS)

In patients with extremity STS, distant failure is a common pattern of recurrence. In contrast, RPS most commonly recur in a locoregional manner, and mortality in RPS is more often associated with locoregional recurrence. Proper resection of RPS requires appreciation of the anatomic boundaries of the tumor. CT imaging should be reviewed to identify landmarks defining the extent of the mass to determine which structures may be safely resected and which must remain. The anterior margin of an RPS is generally the ipsilateral colon and mesocolon, pancreas, liver, or stomach. The posterior margin is generally the psoas and iliacus muscles inferiorly, the ipsilateral kidney and diaphragm superiorly, and the ipsilateral aorta and gonadal vessels medially. However, this may vary from tumor to tumor, and some or all of these structures could be anterior to the mass, in which case they would constitute a portion of the anterior margin. The medial margin usually includes the spine and paraspinous muscles, the inferior vena cava (for right sided tumors), and the aorta (for left sided tumors). The lateral margin is constituted by the lateral or flank musculoskeletal sidewall, although, depending on the size and location of the tumor, the kidney, colon, or both could also border the lateral portion of the mass. The superior margin is similarly dependent on the size and location of the mass and may include the diaphragm on either side, the right lobe of the liver, the duodenum, and the head/uncinate process of the pancreas for right sided tumors, and pancreatic tail, spleen, and splenic vessels for left sided tumors. The inferior margin may include the iliopsoas muscle, the femoral nerve, the common, internal, and external iliac vessels, and the pelvic sidewall. Clearly, the size and specific location of the mass determine which of the many structures mentioned above constitute which specific margin.

In general, the ipsilateral kidney, colon and mesocolon, and at least a portion of the psoas can be safely and routinely easily resected without much difficulty. Resection of the pancreatic tail and spleen can usually be performed with relatively low short term morbidity. Resection of other structures, including but not limited to the aorta, inferior vena cava, iliac vessels, femoral nerve, diaphragm, duodenum, pancreatic head or uncinate process, and liver, entail more significant resections, with entailing greater morbidity.

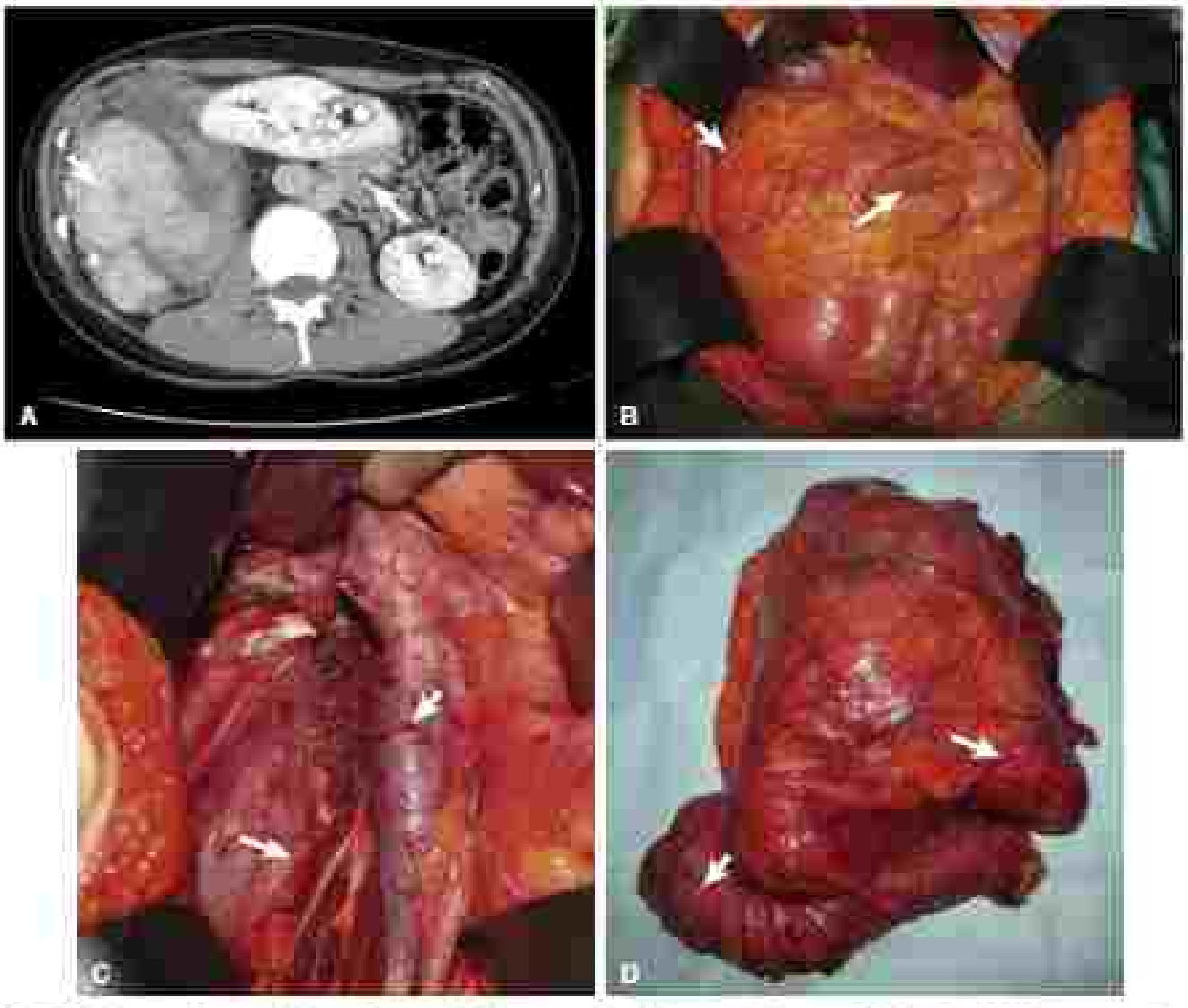

FIG. 9 (A) Axial computed tomography image of a synovial right retroperitoneal liposarcoma (*thin arrow*) displacing the right kidney anteromedially (*thick arrow*). (B) Intraoperative image of the same right retroperitoneal sarcoma (*thin arrow*) with the kidney displaced anteromedially (*thick arrow*). (C) Surgical field after tumor removal demonstrating a clean right retroperitoneal space with viable femoral nerve, psoas muscle (*long arrow*), tissue psoas resection and exposed ureteral wall (*thin arrow*). (D) Surgical specimen including right colon (*short arrow*) and right kidney (*big arrow*); psoas not shown but present.

Technical Aspects of Retroperitoneal Sarcoma Resection

Before surgery, contralateral renal function should be assessed with a nuclear scan if an epithelial nephrectomy is planned. Patients should undergo bowel prep. Patients may be placed in either a lithotomy or modified lateral decubitus position. The abdomen may be entered through a midline, oblique, flank, or thoracoabdominal incision, depending on the precise anatomic location. It is important to adjust the incision to the extent of tumor to provide optimal exposure.

The goal of primary surgery should be an extended resection, removing involved or adherent surrounding organs and retroperitoneal fat en bloc with the tumor in an effort to maximally clear the margins and avoid spilling tumor (Figs. 9 and 10). Special consideration may apply to histologic subtypes different from liposarcomas. A more conservative resection, albeit wide, can be considered, if visceral organs are not directly involved. This is typically the case of solitary fibrous tumors, as well as of leiomyosarcoma because they present as well circumscribed masses, readily distinguishable from the retroperitoneal fat/soft tissues (Figs. 11 and 12), and have a much more limited local recurrence risk. Due to the size of the tumors, exposure and retraction may need to be shifted periodically. Ideally, the operation is conducted with carefully circumferential dissection around the expected specimen, enabling optimistic exposure on a broad front. It is important to approach surgery with curative intent. A macroscopically incomplete resection is no more beneficial than nonoperative management. The resection specimen should be reviewed with the pathologist immediately after removal for orientation and identification of margins of concern.

Adjuvant/Neoadjuvant Radiation Therapy and Chemotherapy

The role of radiation therapy is controversial. Radiation therapy unquestionably reduces the risk of local recurrence in patients with extremity STS, but this has not been proven in RPS. Furthermore, the proximity of radiosensitive tissues and organs, such as liver and small intestine, together with the large size of the radiation field, limits its utility in some patients. Those who use radiation

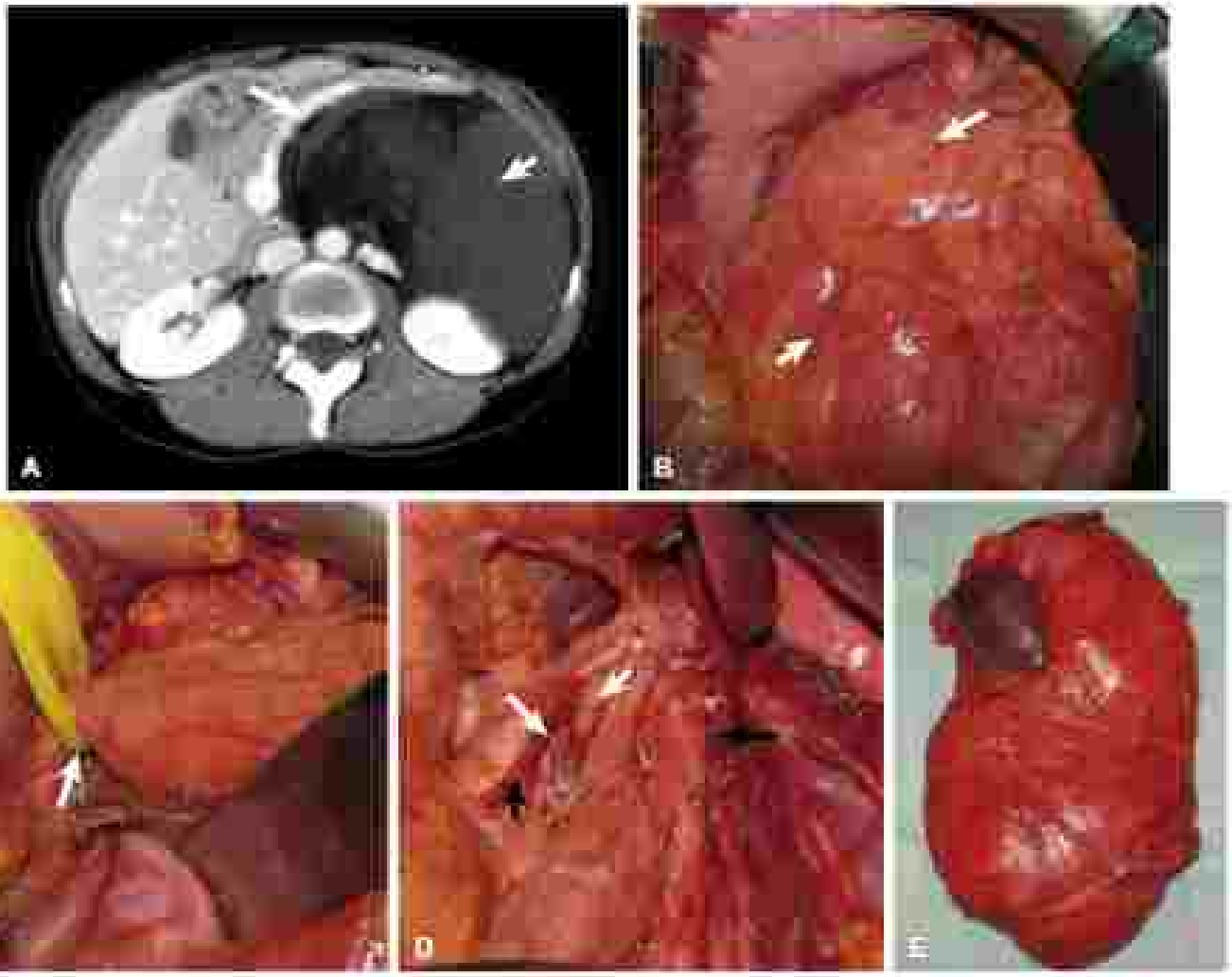

FIG. 10 Axial computed tomography (A) and intraoperative image (B) of a left retroperitoneal liposarcoma (short arrow) displacing the pancreas anteriorly (long arrow). (C) Preparation of pancreatic body for transection (arrow). (D) Surgical field after tumor removal demonstrating a clean left retroperitoneal space with visible ventral vein (long white arrow), superior mesenteric artery (short white arrow), pancreatic stump (short thin arrow), and aorta (long thin arrow). (E) Surgical specimen including left colon, left kidney, left psoas, distal pancreas, and spleen.

therapy generally favor delivering it before surgery, when the bulk of the tumor itself displaces uninvolved organs out of the radiation field. There is one recently completed randomized trial evaluating the utility of preoperative radiation therapy in patients with RPS, based in Europe and open to selected North American centers.

Similarly, the role of chemotherapy even for the subtypes at higher risk of distant spread (G3 dedifferentiated liposarcoma and leiomyosarcoma), is controversial. If considered, the neoadjuvant setting is usually preferable. There are no randomized trials addressing the role of standard chemotherapy in this disease as of yet. International collaboration is a key for maximizing the chance to enroll successfully in prospective studies for these rare diseases.

Breast Sarcoma

The most common sarcoma histologic conditions arising in the breast are angiosarcoma and phyllodes. Angiosarcoma may arise either primarily within the breast parenchyma or secondarily within the breast skin as a consequence of lymphedema or, more commonly, radiation therapy delivered as a part of breast conservation therapy for breast cancer. Each of these malignancies will be considered individually.

Primary Angiosarcoma

Primary angiosarcoma is a disease of the breast parenchyma arising in young women. Angiosarcoma, irrespective of site, is in general responsive to systemic chemotherapy. However, once chemotherapy is stopped, the disease tends to regrow. Furthermore, despite its sensitivity to chemotherapy, there is no proven survival benefit from systemic therapy. The only potentially curative therapy is surgery. Although breast cancer may be treated with breast conservation limited surgery due to the proven benefit of radiation therapy and hormonal therapy, there are no such proven beneficial adjuvant therapies for primary breast angiosarcoma. Therefore patients should be offered a simple mastectomy instead of lumpectomy. Partial resection of the pectoralis major may be necessary to achieve negative margins. The skin may be closed primarily. Before surgery, the patient should undergo staging with chest, abdomen, and pelvis CT scanning and an MRI of the breast. Initial physical examination should include a contralateral breast examination. The contralateral breast may be a site for metastatic disease, but, to date, there is no proven benefit from a contralateral prophylactic mastectomy.

Secondary Breast Angiosarcoma

Secondary breast angiosarcoma is a disease affecting older women. Historically, secondary angiosarcoma arose in the setting of

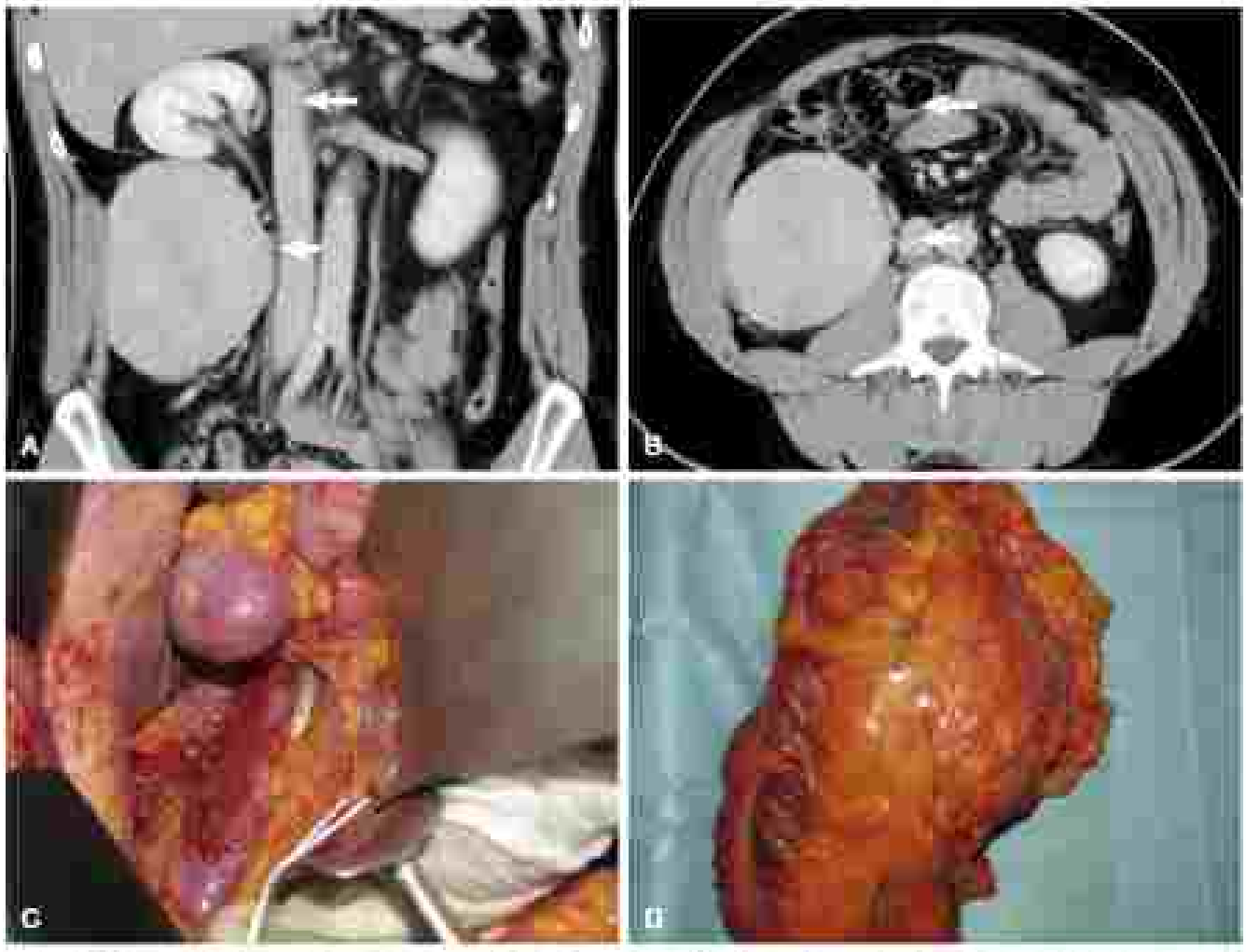

FIG. 11 (A–B) Coronal/axial computed tomography images of a right retroperitoneal solitary fibrous tumor (short arrow) displacing the right kidney and the right colon (long arrow). Surgical field (C) after tumor removal en bloc with peritoneal capsule, psoas muscle fascia, and right colon (D).

lymphedema. Now, it is more commonly seen as a consequence of RT. RT associated angiosarcoma is a cutaneous malignancy that may extend into breast parenchyma, whereas primary angiosarcoma is a disease of the breast parenchyma. Thus the operation for secondary angiosarcoma is different than that for primary angiosarcoma. Patients with secondary RT- associated angiosarcoma should undergo not only a total mastectomy but also, more importantly, resection of the affected organ—all of the breast skin. The disease is often multifocal, and therefore as much of the irradiated skin should be removed en bloc with the breast as possible. This is critical—a simple mastectomy alone does not remove the organ (skin) involved, and recurrence may be noted within weeks to months. If the tumor extends to the pectoralis major, then the muscle should be removed as well. All patients require extensive reconstruction, including skin grafting just to recover a flat, closed chest wall. Preoperative staging should include an MRI of the breast and a CT of the chest, abdomen, and pelvis. Follow up imaging should include CT of the chest, abdomen, and pelvis. MRI of the chest wall is not usually necessary because local recurrences are often apparent on clinical examination alone.

Phyllodes Tumor

Phyllodes tumors of the breast can grow to be quite large. Surgery alone is the primary therapy. Tumors should be resected with a negative margin; for smaller tumors, a lumpectomy may be possible, but, for larger tumors, a simple mastectomy may be necessary. Lymph node biopsy is not necessary. Recurrence may be observed in approximately 15% of patients, including local recurrence in the ipsilateral breast and distant recurrence in locations such as the lung and liver. Contralateral breast recurrences are exceedingly rare, and thus contralateral prophylactic mastectomy is not indicated.

HISTOLOGY-SPECIFIC TREATMENT

ALT/Well-Differentiated Liposarcoma

This low grade tumor, when arising in the extremity, has a relatively low rate of recurrence, may not recur for quite some time, and has no risk of distant metastatic spread and death, unless dedifferentiation occurs over its natural history. Dedifferentiation, if it occurs, in fact entails a risk of metastatic spread as high as 20%. In contrast, low-grade locally recurrent ALT may grow slowly for years. Therefore such tumors arising in the extremity can be resected with a limited negative or even a positive margin, especially when preserving limb function is an issue (Fig. 13). Radiographically, ALT may be difficult to distinguish from an intramuscular lipoma, a benign entity that can also arise in deep muscle tissue. ALT/well-differentiated liposarcoma is a more threatening neoplasm when located in the retroperitoneum, even in absence of areas of dedifferentiation. In fact, as discussed above, local control is an issue at this site, and patients often die of locoregional failure, without developing distant metastases (Fig. 14).

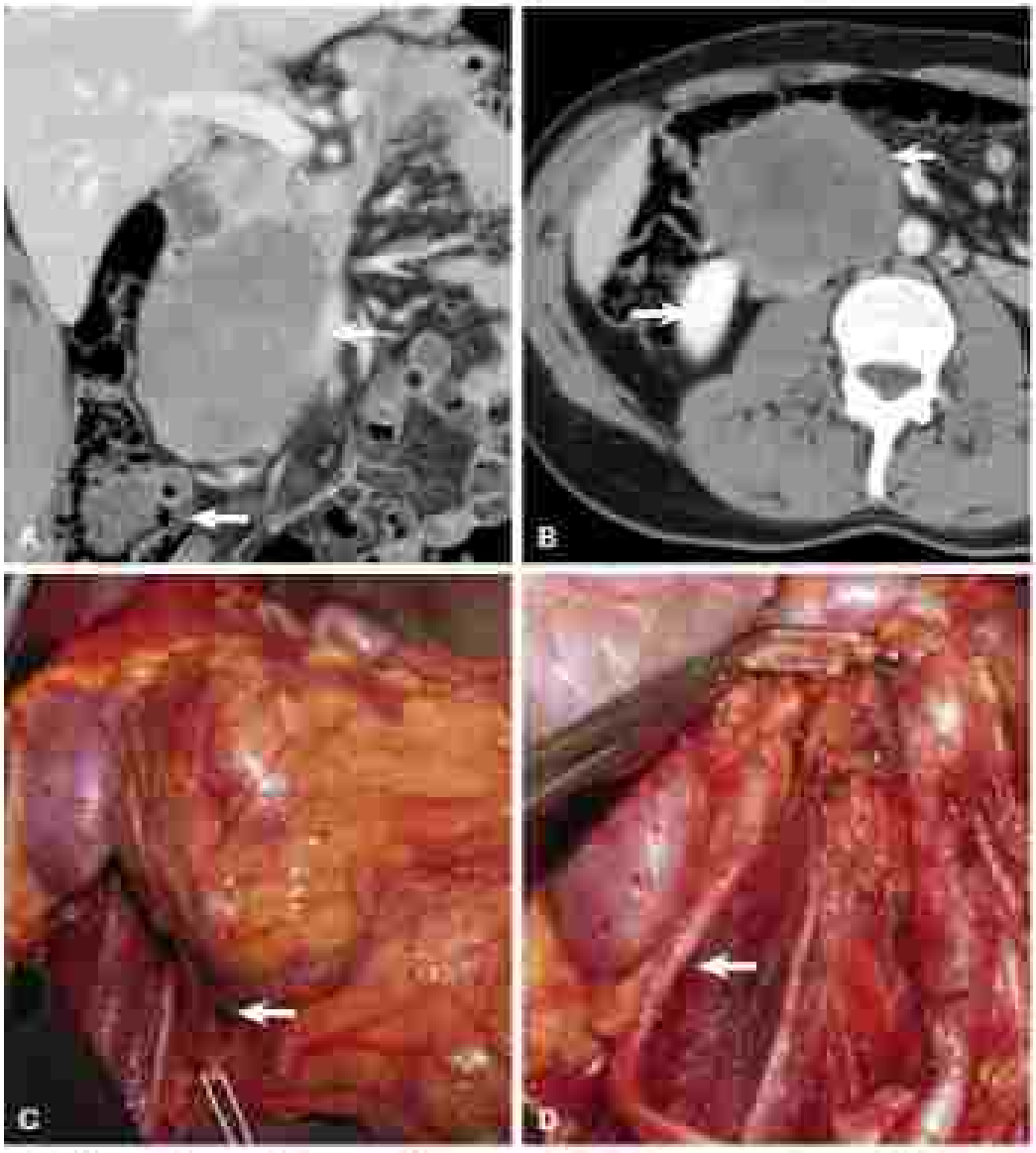

FIG. 12 (A–B) Contrast-enhanced computed tomography images of a leiomyosarcoma of the inferior vena cava (short arrow) displacing the right kidney and the right colon (long arrow). Intraoperative images showing displacement (C, arrow) and preservation of the right ureter and kidney (D, arrow).

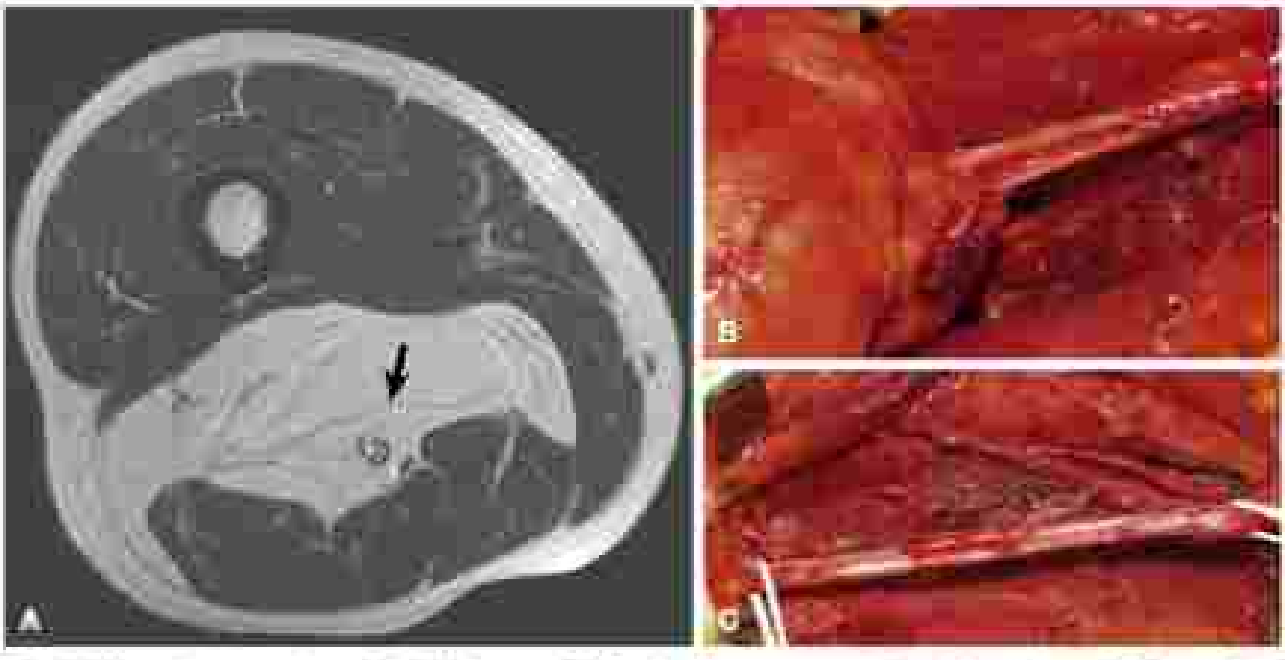

FIG. 13 (A) Axial magnetic resonance image of the thigh shows a well-differentiated liposarcoma encasing the sciatic nerve (arrow). (B) Tumor pushed off the sciatic nerve. (C) Surgical field after resection of the tumor with demonstrated nerve.

Myxoid Liposarcoma

Myxoid liposarcoma is a subtype of liposarcoma, commonly arising in extremities and notable for two key unusual characteristics that impact treatment and surveillance. First, it is particularly sensitive to chemotherapy and radiation therapy, such that the use of either or both in the neoadjuvant setting can result in significant tumor shrinkage (Fig. 13). This can be particularly beneficial if the tumor is abutting a critical structure, such as bone, vessel, or nerve. In fact, the sensitivity of this histologic subtype to radiation serves as the basis of an ongoing noninferiority trial evaluating lower doses of neoadjuvant radiation (36 Gy) instead of the traditional neoadjuvant dose (50 Gy). Second, myxoid liposarcoma has a propensity to metastasize to unusual sites, including extraspinal tissue. Therefore we recommend periodic imaging of extraspinal tissue (including muscle and bone).

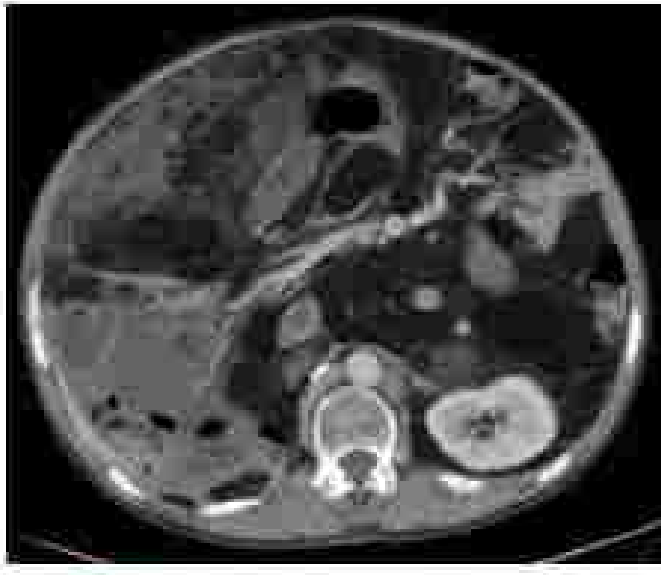

FIG. 14 Locally advanced well-differentiated liposarcoma.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a superficial tumor that infiltrates soft tissue for centimeters beyond the obvious margins of the lesion and can recur locally after an inadequate resection. However, the more common variety of DFSP does not display metastatic behavior. Therefore the goal of surgery should be negative margins, often necessitating reconstruction by plastic surgery. When cosmesis is an issue, limited positive margins may be accepted, and a wider resection postponed until DFSP locally recurs. Due to the relatively indolent nature of the growth of DFSP, a tissue expander may be placed, and resection may be delayed to allow a single stage resection and reconstruction (Fig. 16). Because DFSP is usually a relatively superficial tumor, resection of muscle deep to the tumor is not often necessary. Intraoperative frozen section margin analysis is not generally helpful because the surrounding fat rarely freezes well for analysis. Mohs' micrographic surgery has been reported as a treatment for this neoplasm, but long-term results are lacking. Follow-up should consist of a physical examination, and imaging may be reserved for patients with a suspicious mass in the tumor bed. Approximately 5% to 10% of patients with DFSP have a more aggressive fibrosarcomatous variant that may recur locally and potentially spread. These individuals should be treated as a "conventional" sarcoma and followed up with systematic imaging. Radiation therapy is not usually recommended. Imatinib is approved for the management of locally advanced/metastatic DFSP. However, it should be noted that neoadjuvant imatinib does not change the original extent of the resection, even after shrinkage. In locally advanced disease, it is usually given as a bridge therapy when tissue expansion (for subsequent flap reconstruction) is required before performing the excision, especially when a fibrosarcomatous component is present.

Myxofibrosarcoma

This tumor, when located superficially, infiltrates through soft tissue (subcutaneous fat and investing fascia) centimeters beyond the macroscopic margins of the visible or palpable mass (Fig. 17). When located intramuscularly, the extension of the infiltration is usually limited by anatomic barriers, although it has a higher propensity to invade into these anatomic boundaries compared with other histologic subtypes. Myxofibrosarcoma most commonly arises in the extremities of elderly individuals. It demonstrates a 30% rate of local recurrence

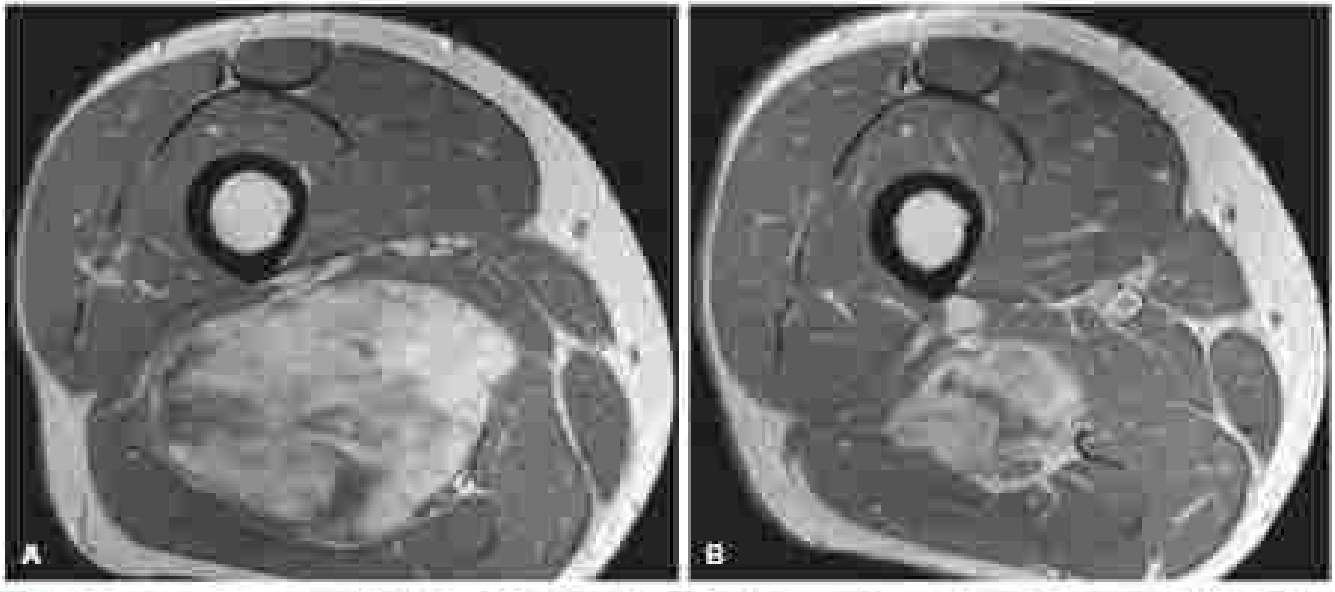

FIG. 15 High-grade myxoid liposarcoma of the right thigh. Contrast-enhanced T1-weighted magnetic resonance image, axial view at baseline (A) and after administration of neoadjuvant chemotherapy (B) (three courses of anthracycline + ifosfamide) and radiotherapy (to a total dose of 50 Gy).

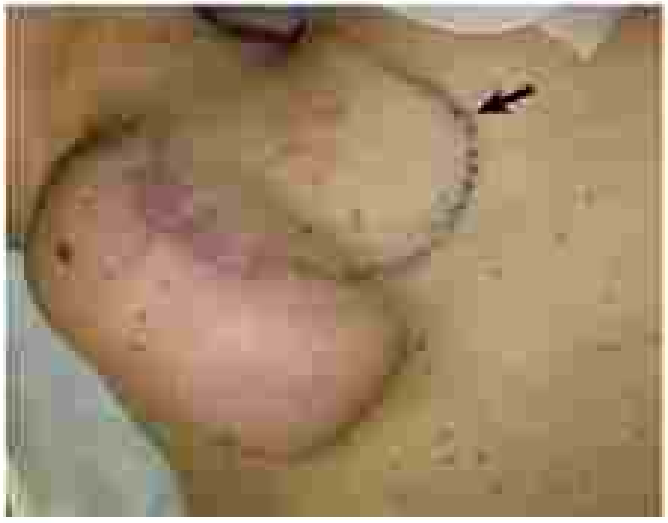

FIG. 16 Dermatofibrosarcoma protuberans repaired by a rotational flap after prior tissue expander placement. Residual tan of incision line marked in black (arrow).

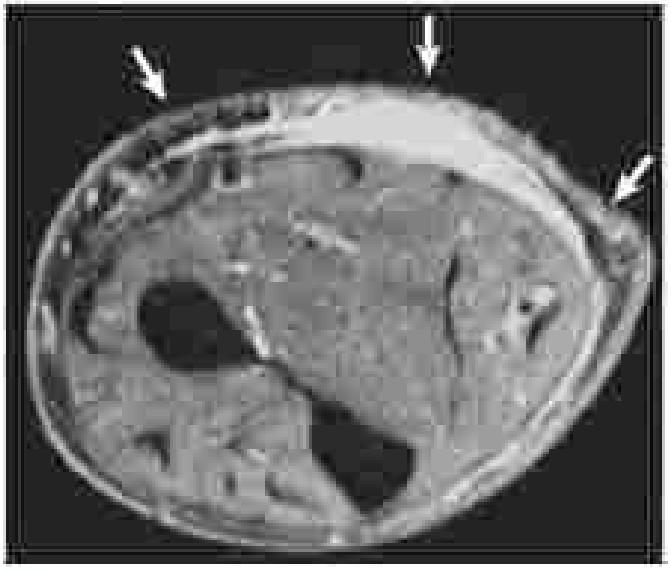

FIG. 17 Superficial myxofibrosarcoma of the forearm, with infiltration of the surrounding tissue extending 2 to 3 cm from the mass. The effect is shown by arrows.

and 10% rate of distant recurrence. Multiple local recurrences have been associated with eventual amputation. Therefore it is critical to pursue aggressive local therapy. Wide surgical margins (2- to 4-cm radial margins beyond the clinical boundaries of the palpable mass, especially in more superficial tumors) should be the goal of surgery, which often requires complex wound closure or flap reconstruction by a plastic and reconstructive surgeon, as well as resection and reconstruction of vessels, nerves, or both. Radiation therapy, either before or after surgery (described below), may be considered because this specific histology is one of the most sensitive to this treatment modality. Follow-up imaging should include the primary site (usually with an MRI), as well as the lungs (chest CT).

Angiosarcoma

Management of primary and radiation-associated (secondary) angiosarcoma of the breast is discussed in the section on breast carcinoma above. Scalp angiosarcoma (Fig. 18) is a particularly insidious malignancy. Scalp angiosarcomas are commonly multifocal, by both clinical examination and CT or MRI imaging. Although radical surgery is possible (requiring complex flap reconstruction), it is not uncommon for patients to develop local recurrences immediately outside the margins of resection, even if the margins of the initial resection were widely negative and with or without radiation therapy. Angiosarcoma is sensitive to systemic chemotherapy and to radiation therapy. Because surgery is rarely curative, it should not be considered first-line therapy for scalp angiosarcoma. Surgery may be reserved for patients who are experiencing problems with local control (bleeding from a fungating tumor) or who only appear to have a solitary site of disease by both clinical examination and imaging while undergoing systemic therapy.

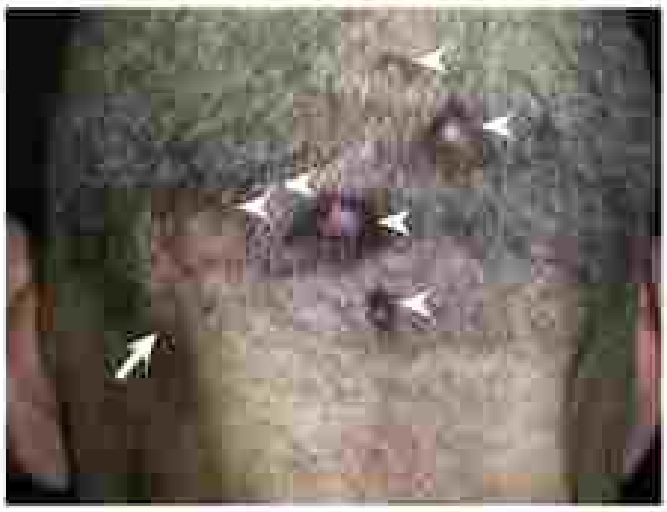

FIG. 18 Multifocal angiosarcoma (arrow) on scalp with necrotic tumor rarely penetrated.

Radiation-Induced Sarcomas

Radiation-induced sarcomas are rare and include a variety of histologic subtypes, the most common of which are undifferentiated pleomorphic sarcoma, angiosarcoma, malignant peripheral nerve sheath tumors, and leiomyosarcoma. In addition to the intrinsic characteristics of each histologic subtype, all characterized by a high propensity to locally recur, given the difficulty of obtaining clear margins. This is due in part to the difficulty in distinguishing tumor infiltration of healthy tissues from radiation-induced soft tissue changes around the tumor site and in part to the discontiguous and multifocal involvement of tissue within the radiation field (Fig. 19). The tumor should be excised with as much tissue around it as possible. This often, if not always, requires reconstruction and coverage by a plastic surgeon and potentially a more liberal policy of neurovascular resection and reconstruction. Systemic chemotherapy and reirradiation are often considered, given the overall dismal prognosis, although the use of the latter must be weighed with caution.

Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNSTs) often arise from a major peripheral nerve, which can be identified macroscopically. They can occur sporadically or in the context of neurofibromatosis type 1. The high-grade variant is marked by an early propensity for distant metastasis. When originating from a peripheral nerve, MPNST also may spread along the nerve fibers proximally or distally. Wider margins at this level should be obtained (if possible, at least 4 cm of macroscopic healthy nerve, Fig. 20) to limit locoregional failure, which eventually may reach the spinal cord. Intraoperative

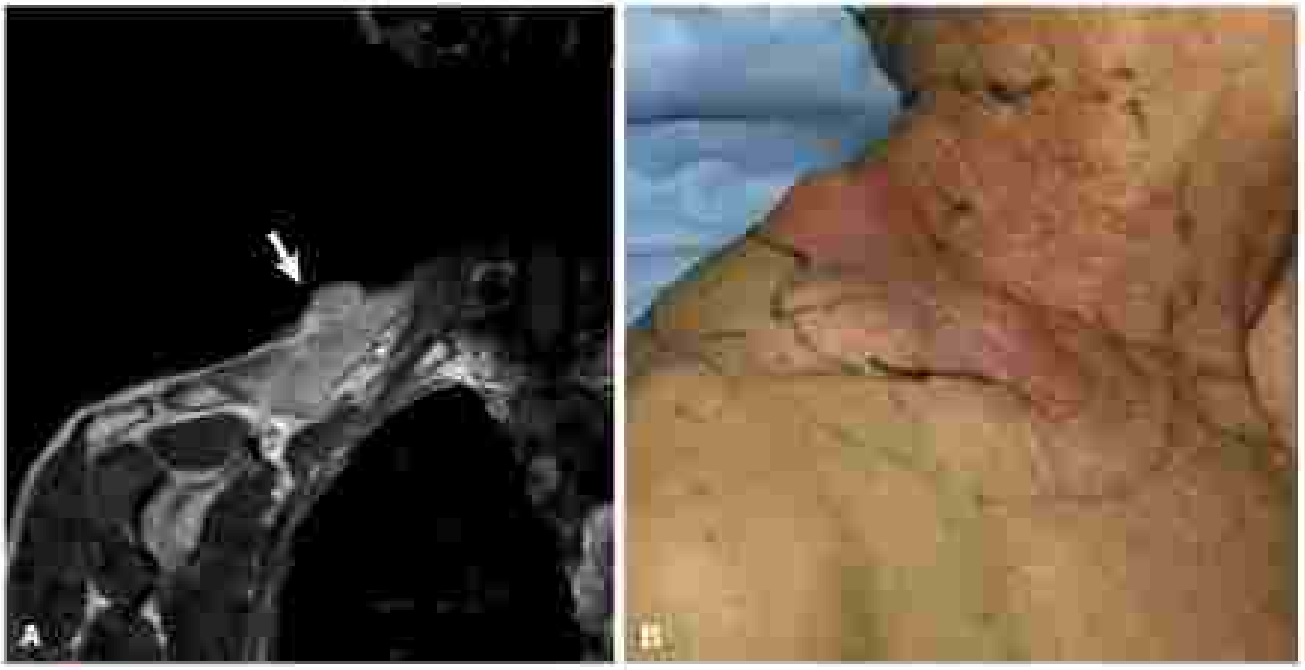

FIG. 19 Radiographic appearance (A, inset) and clinical appearance (B) of a multifibrinoid sarcoma of the right supraclavicular area.

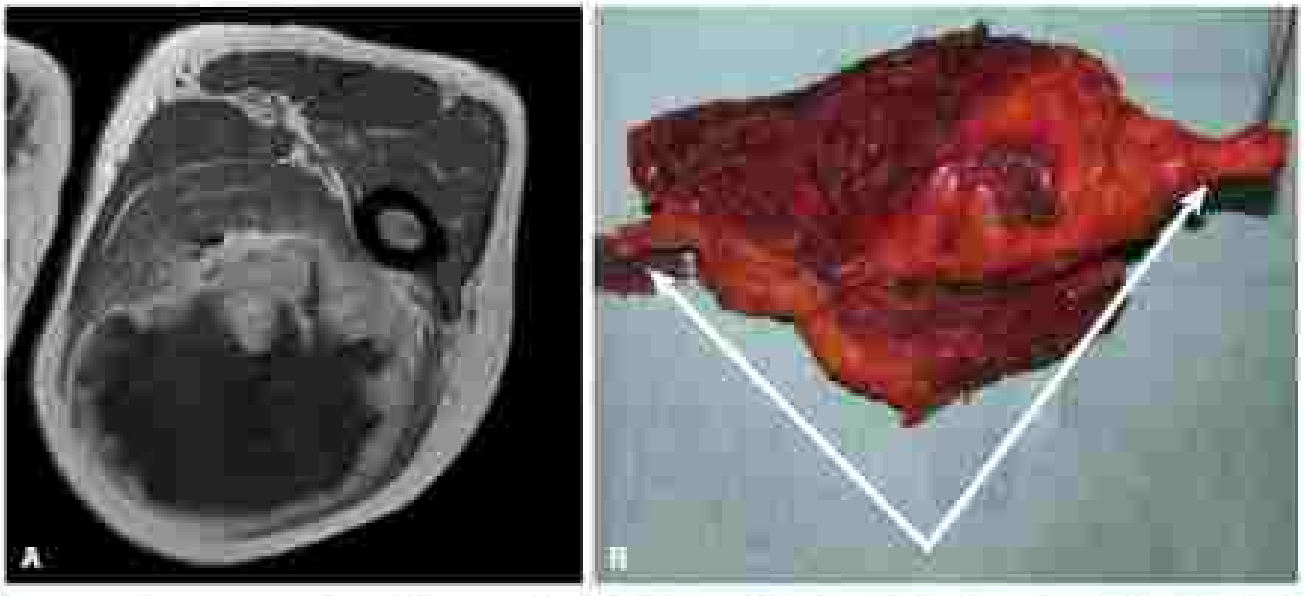

FIG. 20 Preoperative magnetic resonance image (A) and surgical specimen (B) demonstrating malignant peripheral nerve sheath tumor arising from the sciatic nerve (arrows indicating nerve margin).

tissue sarcoma analysis may help ensure clear margins. Systemic chemotherapy is used in an individualized basis.

Desmoid Fibromatosis

Desmoid fibromatosis is a noninvasive neoplasm that displays malignant local behavior. Desmoids may arise in the context of familial adenomatous polyposis (FAP), concurrent with a pregnancy, or sporadically. Those arising in the context of FAP may be quite aggressive, often involving the bowel mesentery and occasionally encasing the mesenteric vessels. In fact, local complications secondary to desmoids are the most common cause of death after colon cancer in individuals with FAP. Those arising during pregnancy may grow during pregnancy, but often this growth stabilizes postpartum.

Recently, there has been a trend toward less radical surgery and more nonoperative management. The natural history of desmoids may vary, and often tumors stop growing or even shrink without intervention (Fig. 21). Therefore primary nonoperative management is now considered the primary approach, particularly for tumors situated in difficult locations. In case of persistent progression, different management is considered, depending on the location. Systemic therapy, including cytotoxic intravenous chemotherapy with different agents and schedules, oral tyrosine kinase inhibitors (imatinib,

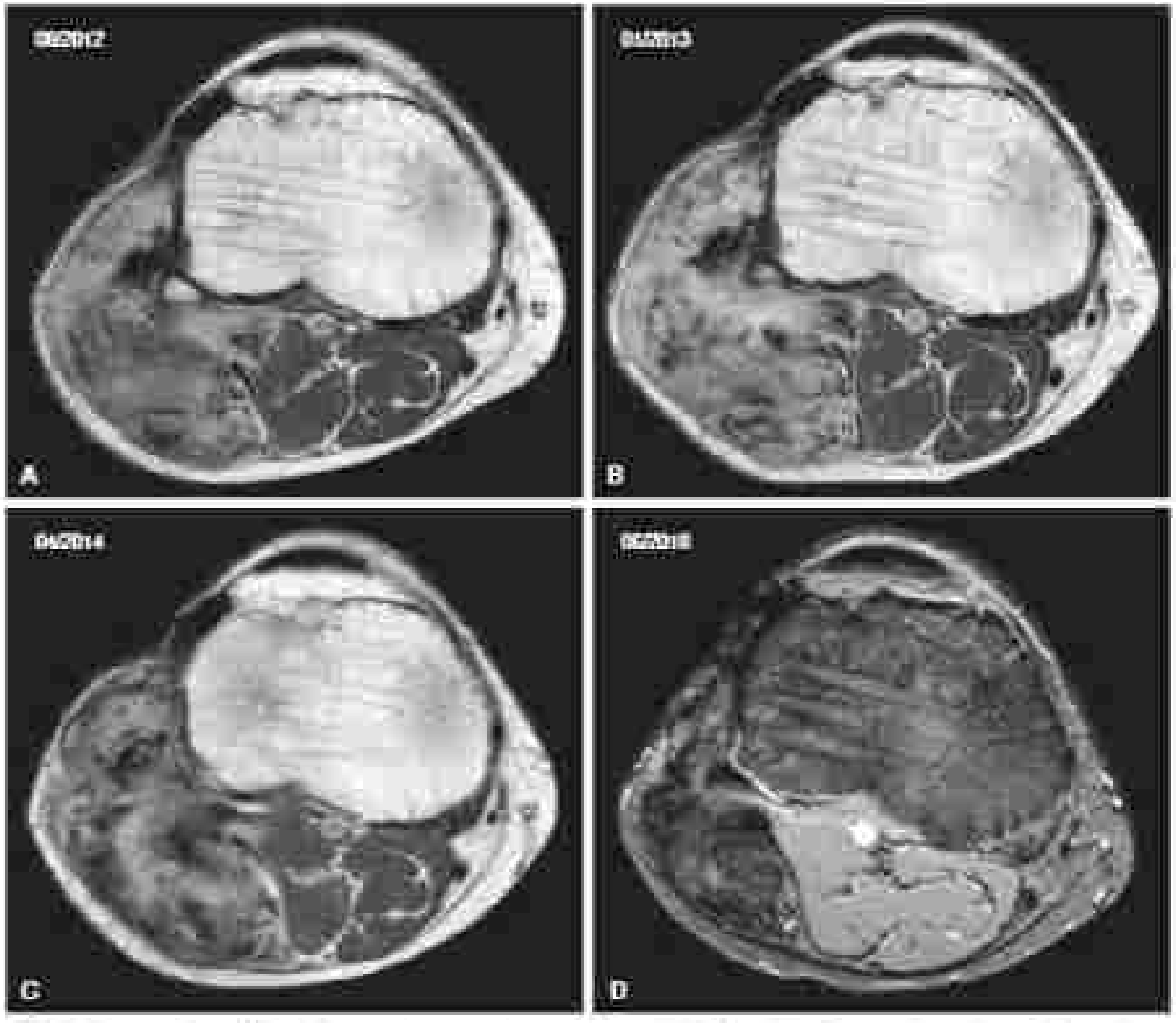

FIG. 21 Axial contrast-enhanced T1-weighted magnetic resonance images of right proximal leg dermatofibrosarcoma on active surveillance only at baseline (A), 6 months (B), 12 months (C), and 20 months (D) later. A lack progression after initial slight progression and subsequent stabilization is clearly seen.

steroids), nonsteroidal antiinflammatory drugs, and hormonal agents such as tamoxifen have varying degrees of efficacy and are often considered before resorting to surgery, with the only possible exception of sporadic abdominal wall desmoids, which are characterized by an optimal postsurgical outcome.

When surgery is undertaken, it is important to avoid compromising function when possible. Mesenteric desmoids may be particularly problematic to resect, especially those associated with FAP, and surgery should be approached with caution. Every care should be taken to avoid a modality that determines higher morbidity than the one determined by the presence of the disease itself.

SUMMARY

Soft tissue sarcomas may arise in a variety of body sites and within a variety of tissues. The management of STS requires a thorough understanding of the biology of the different histologic conditions. Limb- and function-sparing approaches should be used when feasible, but extent of surgery should not be compromised for sake of chosen. Margins of resection and use of adjuvant radiation therapy and chemotherapy are contingent on accurate histologic diagnosis. However, adjuvant therapy after a marginal resection is not an appropriate substitute for a margin negative operation. Treatment planning should include multidisciplinary consultation to determine optimal therapy, taking into consideration the size and extent of the disease, its natural history and sensitivity to available treatments, surgical challenges, and, of course, the wishes of the patient.

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MANAGEMENT OF SOLITARY NECK MASS

Allison N. Martin, MD, MPH, John B. Hanks, MD, and Philip A.S. Ash, MD

A isolated neck mass is a common clinical scenario in patients of all ages. Management varies widely with the multiple etiologies. Success in this scenario requires familiarity with cervical anatomy, an organized approach to differential diagnosis, and a stepwise evaluation as summarized in Fig. 1. Tissue acquisition for diagnosis often is required, and surgical treatment is indicated for many etiologies of neck mass. Therefore the prepared surgeon is well positioned to play a central role in the clinical evaluation, diagnostic workup, and management of neck masses.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the isolated neck mass is broad and includes congenital, inflammatory, and neoplastic processes (Box 1). Between 2% and 9% of head and neck cancers present as cervical masses without a known primary. Although malignancy must be considered in all cases of neck mass, the likelihood varies significantly with age. In the pediatric population, less than 10% of neck masses are neoplastic, whereas as many as 80% of neck masses that occur outside of the thyroid are neoplastic in adults over the age of 40 years. Additionally, human papillomavirus (HPV) has been increasingly associated with the development of head and neck cancers in the United States.

WORKUP

History

The clinical history gives indications regarding the likelihood that a given neck mass is benign or malignant. The importance of patient age helps to stratify the most likely cause of the neck mass: young patients (<16 years) are most likely to have an inflammatory or congenital lesion; the cause of a neck mass in patients ages 16 to 40 is still most often inflammatory or congenital but may also be malignant; masses in patients older than 40 years should be considered malignant until proven otherwise. Other history items concerning for malignancy include a personal history of malignancy, family history of malignancy, smoking or other tobacco use, heavy alcohol use, sun exposure, and radiation exposure. Neck specific history items that are concerning for malignancy include persistent mass, dysphagia, hoarseness or other neurologic deficit, epistaxis, and radiating pain, including otalgia. Constitutional symptoms such as sweats, fevers, fatigue, and weight loss are concerning for lymphoma or other malignancy but also may be present with infectious etiologies. Rapidly developing tender masses are often infectious or inflammatory. It is important to fully characterize the timing of onset of the mass and how it has changed over time, in either size or character, since it was first noted.

One also should ask about prior treatments, biopsies, and surgical interventions. More often in children, but also in adults, lymphadenopathy may already have been treated with antibiotics. Persistence of lymphadenopathy after antibiotics should be considered concerning for malignancy. Retrieval of relevant prior imaging, operative reports, pathology reports, and pathology specimens is imperative whenever possible.

A history of severe or episodic hypertension rarely may be associated with a head and neck paraganglioma, although only a small minority of head and neck paragangliomas are functional. Cough provoked by pressure on the mass has been associated with schwannomas of the vagus nerve. This can be confirmed with palpation on physical examination.

Finally, the incidence of HPV-associated oropharyngeal squamous cell carcinomas has more than doubled in recent years. Diagnostic delay for these lesions is typically due to differential epidemiology and presentation compared with classical head and neck cancers in that affected individuals are (1) younger and lack exposure to tobacco, alcohol, or both and (2) present as neck metastases without a known primary and can be cystic in nature, causing diagnostic confusion with branchial cleft cysts.

Physical Examination

A focused physical examination of the head and neck is essential to properly evaluate a neck mass. Important examination findings include firmness, nonmotion, asymmetry in the contralateral neck, fixation to surrounding structures, midline mass, and neurologic deficit, including cranial nerve (CN) function (see the "Surgical Considerations" section for a detailed discussion of CNs at risk for injury). All other aspects of the neck also should be examined, including the thyroid and salivary glands, as well as all nodal basins. The examiner can typically distinguish thyroid from nonthyroid tissue on physical examination, otherwise ultrasonography can make this clear. Visualization of the mucosal surface of the upper aerodigestive tract is important, as is evaluation of the skin of the head and neck, including the scalp and auditory canal. Palpation with the gloved hand, including bimanual palpation of the floor of the mouth, may help with identification of abnormalities that exist deep to normal-appearing mucosa. Examination of dentition could reveal dental infection that can result in cervical lymphadenopathy.

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Physical Examination

A focused physical examination of the head and neck is essential to properly evaluate a neck mass. Important examination findings include firmness, nonmotion, asymmetry in the contralateral neck, fixation to surrounding structures, midline mass, and neurologic deficit, including cranial nerve (CN) function (see the "Surgical Considerations" section for a detailed discussion of CNs at risk for injury). All other aspects of the neck also should be examined, including the thyroid and salivary glands, as well as all nodal basins. The examiner can typically distinguish thyroid from nonthyroid tissue on physical examination, otherwise ultrasonography can make this clear. Visualization of the mucosal surface of the upper aerodigestive tract is important, as is evaluation of the skin of the head and neck, including the scalp and auditory canal. Palpation with the gloved hand, including bimanual palpation of the floor of the mouth, may help with identification of abnormalities that exist deep to normal-appearing mucosa. Examination of dentition could reveal dental infection that can result in cervical lymphadenopathy.

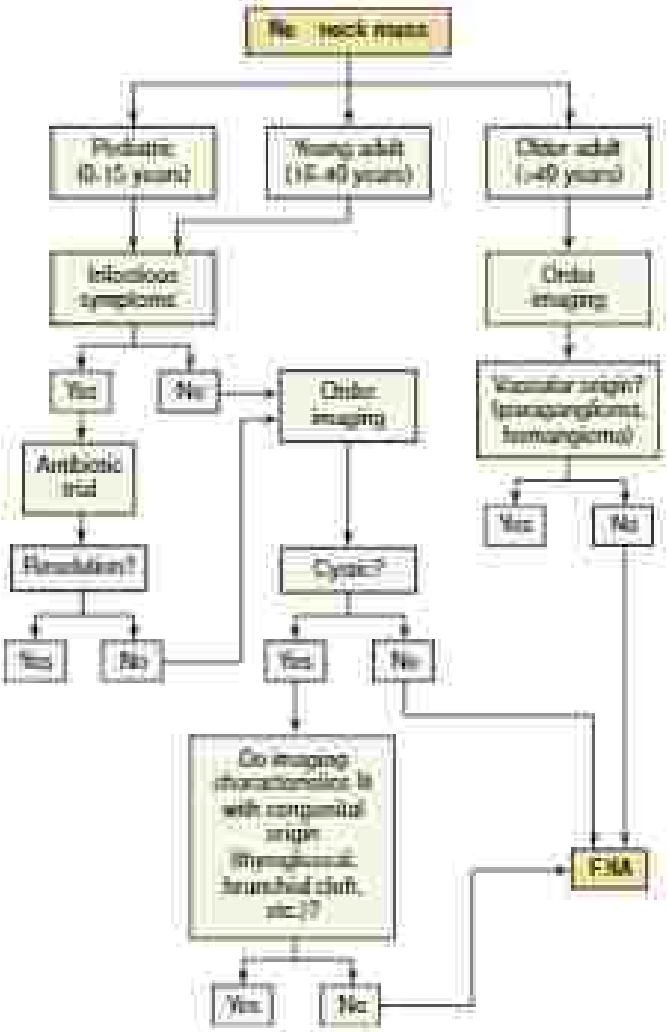

FIG. 1 Diagnostic algorithm for a new neck mass. The distinction made based on age of 40 years should be taken as a general guideline to be adjusted based on clinical evaluation and not as an absolute rule. FNA, fine-needle aspiration. *(Modified from Hui FW, Hughes RJ, Lund VJ, et al. Infra-Carotid Digastric Triangle Lymphadenopathy: A New Classification. Philadelphia: Elsevier; 2010.)*

BOX 1 Differential Diagnosis of Neck Masses

Developmental

Inclusion cyst
Thyroglossal duct cyst
Congenital vascular malformations
Branchial cleft cyst
Cystic hygroma
Laryngocele
Teratoma
Bronchogenic cyst
Infections
Bacterial lymphadenitis (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Bartonella*, *Brucella*)
Viral (Epstein-Barr, HIV, other common viruses)
Protozoal (toxoplasmosis, leishmaniasis)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis)

Inflammatory

Sarcoidosis, tuberculosis
IgG4 disease
Sarcoidosis
Aneurysm

Benign Neoplasia

Lipoma
Thyroid nodule/diffuse goiter
Parathyroid adenoma (rarely palpable)
Fibroma
Neurofibroma
Schwannoma (cyst)
Benign salivary tumors (pleomorphic adenoma, Warthin's tumor)

Malignancies

Lymphoma
Carotid body tumor
Thyroid cancer
Malignant salivary tumors (mucoepidermoid, adenoid cystic)
Parathyroid cancer
Pheochromocytoma
Carcinoid
Metastasis to cervical lymph nodes (thyroid, squamous cell carcinoma, adenocarcinoma, melanoma)

Patients and even referring physicians may mistake normal structures for pathology. Such structures may include gnathic salivary glands, the horn of the thyroid cartilage, the hyoid bone, or spinal transverse processes (particularly C2). Therefore examination of the neck should first confirm the presence of a pathologic finding. If an abnormality is present, a detailed examination ensues. The mass should be measured in at least two dimensions with a tape measure and the findings documented. Photographs for the medical record may also be valuable. The location of the mass should be precisely defined. The location should be defined not only in a descriptive fashion relative to normal anatomy (e.g., "at the anterior border of the sternocleidomastoid muscle [SCM] at the level of the cricothyroid") but also by the nodal level based on the system outlined in Fig. 2A and Table 1. This system of nodal levels is of value for several reasons: (1) it allows reproducible communication between caregivers and referral boundaries with physical examination, imaging, and operative anatomy; (2) nodal levels are diagnostically important because malignancies of different origins spread characteristically to different nodal levels (see Table 1); and (3) lymph node levels are important therapeutically because lymph node dissection typically proceeds based on nodal level compartment dissection. The location of a neck lesion may also be noted in reference to the anatomic triangles of the neck as delineated by the SCM (Fig. 2B).

Mirror examination or flexible fiberoptic laryngoscopy allows significantly improved visualization and can be performed in the office setting. Evaluation of all mucosal surfaces is possible, from the nasal cavity to the vocal cords. The location of the neck lesion that is concerning for metastatic lymphadenopathy helps to determine the most likely primary sites and can guide this evaluation. Attention should be paid to all visible surfaces, especially the lymphoid regions of the nasopharynx, base of the tongue, and oropharynx (Waldeyer's ring).

In addition to examination of the head and neck, a thorough physical examination is warranted in all cases of neck mass. One should note the presence of cachexia and stigmata of alcoholism or tobacco abuse. Examination of skin, lungs, and abdomen may provide clues with regard to a primary source of metastatic disease in the neck. Axillary and femoral lymph node basins should be examined and may be revealing in a systemic disease process. General examination also helps the surgeon understand a patient's general fitness to tolerate medical and surgical interventions. The clinician also should look for any prior incisions that indicate diagnostic or therapeutic interventions that the patient may have neglected to describe.

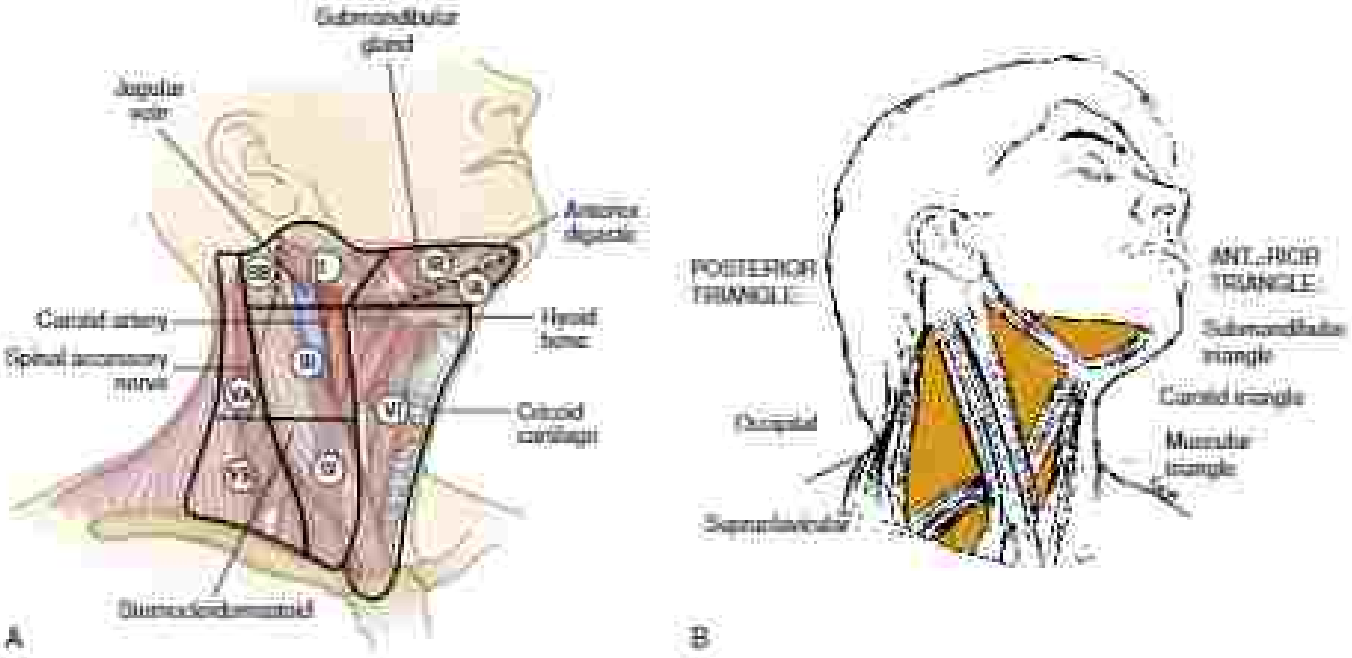

FIG. 2. (A) Head and neck lymph node levels of the neck. Boundaries are given in Table 1. Criteria exist to define these levels clinically, radiographically, and surgically. (B) The neck is divided into two major triangles, anterior and posterior, by the sternocleidomastoid muscle. The anterior triangle may be further subdivided into the carotid, submandibular, submental, and muscular triangles; the posterior belly of the omohyoid divides the posterior triangle into occipital and supraclavicular triangles. (A, From Smith PW, Saboorian MH, Haffty B, Ogunbiyi O. Cancer control in the United States. Lancet Oncol. 2002;3:698–707. Modified from Lingeman RE. Surgical anatomy. In: Cummings CW, et al, eds. Otolaryngology—Head & Neck Surgery. 2nd ed. St Louis: Mosby; 1993.)

TABLE 1 Boundaries of Cervical Lymph Node Levels and Considerations for Primary Site for Metastatic Disease

Boundaries and Contents		Metastatic Primary Sites
Level I	Submandibular and submental nodes. Bounded by the mandible superiorly, the midline anteriorly, the hyoid inferiorly, and the stylohyoid muscle posteriorly. Subdivided into IA and IB by the anterior belly of the digastric muscle. IA crosses the midline to the contralateral anterior belly of the digastric.	IA: Floor of mouth, lower lip, anterior tongue, lower gum. IB: Oral cavity, anterior nasal cavity, submandibular gland, midface soft tissues.
Level II	Upper jugular nodes. Bounded by the skull base superiorly, the stylohyoid muscle anteriorly, the inferior border of the hyoid bone inferiorly, and the posterior border of the SCM posteriorly. Subdivided into IIA and IIB by the spinal accessory nerve.	Oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, parotid gland
Level III	Middle jugular nodes. Bounded by the inferior border of the hyoid bone superiorly, the sternohyoid muscle anteriorly, the inferior border of the cricoid cartilage inferiorly, and the posterior border of the SCM posteriorly.	Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, cervical esophagus, thyroid
Level IV	Lower jugular nodes. Bounded by the inferior border of the cricoid cartilage superiorly, the sternohyoid muscle anteriorly, the clavicle inferiorly, and the posterior border of the SCM posteriorly.	Hypopharynx, thyroid, cervical esophagus, larynx, Virchow's node (lung or abdominal malignancy)
Level V	Posterior triangle nodes. Bounded by the junction of the trapezius and SCM superiorly, the posterior border of the SCM anteriorly, the clavicle inferiorly, and the anterior border of the trapezius laterally. Subdivided into VA and VB by the plane of the inferior border of the cricoid cartilage.	Nasopharynx, oropharynx, thyroid, cutaneous structures of scalp and neck, breast
Level VI	Also known as the central compartment. Prelaryngeal, pretracheal, delphian, paratracheal nodes, and parathyroidal nodes. Bounded by the hyoid bone superiorly, the carotid sheath laterally, and the sternum inferiorly.	Thyroid, glottic and subglottic larynx, piriform sinus, cervical esophagus
Level VII (variably defined)	This level is variably defined and is the substernal extension of level VI to the level of the innominate artery.	Similar to level VI

SCM, Sternocleidomastoid muscle.

Two congenital lesions are worth highlighting for their specific physical examination findings: thyroglossal duct cysts and branchial cleft cysts. Thyroglossal duct cysts are found in or near the midline of the neck and typically just below the hyoid bone and occur along the thyroglossal tract between the thyroid and the base of the tongue. They may become infected, which frequently follows an upper respiratory infection, or they may present as an asymptomatic mass. Most are diagnosed before adulthood, but initial presentation to adults is not uncommon. Protrusion of the tongue typically results in cephalad movement of the mass. This feature may be more easily appreciable by first applying inferior digital pressure on the mass before tongue protrusion. Thyroglossal duct cysts may create a mass effect or develop recurrent infections, and about 1% harbor malignancy. Therefore, when these cysts are found, excision of the cyst, presumptive labs, if present, and the tract up to the base of the tongue, including the central portion of the hyoid bone, is indicated (the Sistrunk procedure). Confirmation of the presence of normal thyroid tissue in the thyroid bed with examination or imaging before excision is important.

Branchial cleft cysts are also congenital lesions and, similar to thyroglossal duct cysts, may present with an inflammatory picture after an upper respiratory infection. These cysts are almost always diagnosed before age 30 years and account for 20% of pediatric neck masses. First branchial cleft cysts present inferior to the auricle or just below the angle of the mandible. These may communicate with the auditory canal and may be closely associated with the facial nerve. Second branchial cleft cysts are the most common (95%). They are found inferior to the angle of the mandible on the anterior border of the SCM and communicate with the tonsillar fossa. Third branchial cleft cysts also present on the anterior border of the SCM, lower than a second cleft cyst, and communicate with the pharynx at the thyrohyoid membrane or piriform sinus. Branchial cleft cysts and their tracts are typically excised with care given the relationship of these tracts to cranial nerves and other deep structures.

Imaging

Imaging of a neck mass may be valuable in characterizing the primary lesion, in searching for a primary source of a metastasis, and in follow up after an intervention. Anteroposterior and lateral chest radiographs should be obtained if concern exists that the neck mass is related to an atypical infectious or inflammatory source and in those with a history of cough or recent travel. Chest imaging also is indicated for those masses whose location and biopsy findings are concerning for a primary thoracic malignancy, such as lung cancer, and for patients with a new diagnosis of cancer to evaluate for pulmonary metastasis.

CT scanning of the neck requires ionizing radiation to the thyroid and is most valuable if performed with intravenous contrast. Contrast may be contraindicated because of renal disease or allergy. Despite this, contrast CT scanning is an excellent and widely available imaging modality and is superior to ultrasound scanning in providing three-dimensional resolution of the anatomy of the lesion and evidence of invasion or distortion of normal anatomy. Also, if the presenting lesion is thought to be nodal metastasis from a head and neck primary malignancy, high-quality CT scanning of the head and neck can identify a primary source in 20% of cases. Therefore contrast CT scanning of the head and neck is valuable and is indicated in many neck masses to which the diagnosis or primary source is not already defined.

Magnetic resonance imaging (MRI) is often better than CT scanning in defining the presence or absence of invasion by the mass into surrounding structures, particularly vascular and neural structures. It may also be helpful in patients with significant dental artifact, in pregnant patients, or in those with indicated contrast reactions. MRI is helpful in the diagnosis and evaluation of carotid body tumors, glomus tumors, and schwannomas.

Ultrasound scanning can serve as an extension of the physical examination during the initial office evaluation of the mass or through formal radiology performed scan. Ultrasound scanning avoids exposure to ionizing radiation or contrast and allows precise measurements of size and definition of the relationship to normal anatomy; distinguishes cystic from solid lesions; allows assessment of vascularity; characterization of lymph nodes and may help distinguish whether the mass is invasive into surrounding structures. Ultrasonographic features that suggest malignancy include loss of the normal hyperechoic fatty hilum, hyperechogenicity or hypoechogenicity, cystic degeneration, punctuate calcifications, unclear borders with surrounding structures, and perinodal edema (Fig. 3). Ultrasound scanning also is ideal for evaluation of thyroid nodules.

The role of positron emission tomography (PET) or fusion imaging of PET with CT scan (PET/CT) continues to be elucidated. PET and PET/CT are not appropriate first line studies for the initial evaluation of a neck mass. However, PET is an appropriate secondary imaging technique for patients who are being evaluated for a metastatic squamous cell carcinoma of unknown primary when CT scanning or MRI have been unrevealing.

With improvements in the capabilities of CT scanning and MRI, diagnostic arteriography is rarely necessary for neck masses. Arteriography may be indicated therapeutically, particularly for embolization of some highly vascular lesions before resection.

Tissue Diagnosis

The presence of an isolated neck mass in an adult over age 40 years should be considered malignant until proven otherwise. These masses may represent metastatic squamous cell carcinomas from the upper aerodigestive tract. Fine needle aspiration (FNA) biopsy plays a central role in the diagnostic evaluation of neck masses and should be considered the standard of care in undiagnosed adult neck masses. FNA can be performed with simple equipment, is widely available, is generally safe, and is diagnostic in 90% or more of cases. Samples can be evaluated for both pathology and microbiology, depending on the clinical scenario. Risks associated with this procedure include bleeding and sampling error. Furthermore, FNA can provide tissue for microbiologic testing, which is essential in the diagnosis and management of infectious processes, such as infectious lymphadenitis or HPV/Epstein-Barr virus–positive nodules.

Readily palpable lesions may be amenable to simple manual biopsy, but ultrasound scanning is now readily available, and real-time ultrasound guidance should most often be used to decrease risk and increase diagnostic yield. In cases of a cystic lymph node, ultrasound scanning should be used to ensure that the wall is sampled. Ultrasound guidance also helps to avoid needle biopsy of vascular lesions that are mistaken as a solid mass with examination if imaging is not already completed.

FNA typically can be performed on an outpatient basis. Because multiple passes should be taken, the use of local anesthetic is suggested. If manual palpation guidance is used, the mass should be transfixed between the thumb and forefinger of the nondominant hand. If ultrasound scanning is used, a 22- to 30-gauge is appropriate in most cases (Fig. 4). The needle should be passed along the long axis of the probe at an oblique angle so that the entire needle course can be imaged in real time. A short-axis technique also can be used, in which the needle is inserted perpendicular to the probe and is lateral by some. Needle guides are available with some ultrasound equipment and may be used if desired. A 22-gauge or 25-gauge needle is affixed to a 10-mL syringe with several milliliters of air already in the syringe. The syringe may be placed in a special control handle, but this is not required. The mass should be entered with negative pressure on the syringe. There is four aspirates should be made per pass, and multiple angled passes should be made to ensure adequate sampling. Suction on the syringe plunger should be released before exiting the mass to avoid aspiration of the sample into the body of the syringe. The syringe is then removed from the needle, filled with air, and placed back on the needle. The specimen is then expelled from the needle onto a glass slide. The slide containing the specimen is immediately

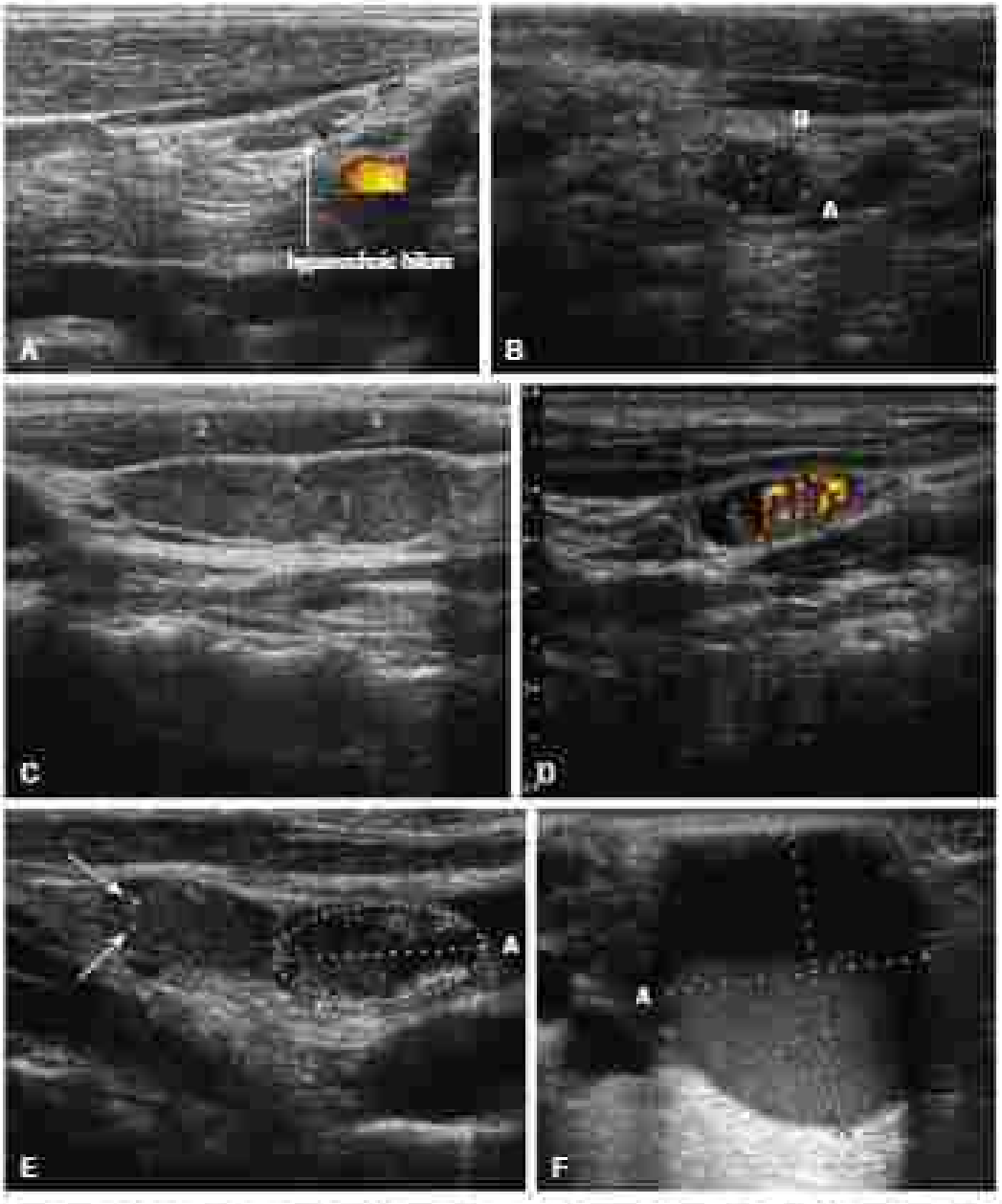

FIG. 3. (A) Benign lymph node shows hyperechoic fibers. (B) Malignancy mixed cystic and hyperechoic lymph node. (C) Malignant lymph node with loss of hyperechoic fatty fibers. (D) Malignant lymph node with peripheral and central vascularization. (E) Malignant lymph node with hyperechoic punctuate calcifications. (F) Malignant lymph node with cystic degeneration. (From Ghaedian T, Ozaki T, Ryan M, et al. Ultrasound features of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. Clin Endocrinol Meta. 2020;92:690–694.)

smeared with another slide. The specimen is then promptly placed in formalin or ethanol to prevent desiccation. The presence of a cytologist for immediate review of the slides helps ensure that adequate specimen is achieved and increases diagnostic yield.

If initial FNA biopsy results are nondiagnostic, the surgeon should communicate with the pathologist to determine whether the specimen is inadequate or whether a different type of biopsy is needed. If inadequate biopsy is the problem, then repeat FNA with ultrasound guidance and immediate cytopathology review is indicated.

FNA biopsy provides the cytopathologist with the opportunity to comment on abnormalities at the cellular level but with minimal ability to comment on architectural characteristics. This may render specific diagnosis impossible, which is particularly a challenge for lymphoma and follicular thyroid cancer. In situations in which FNA biopsy is inadequate, core needle biopsy provides a small plug of tissue with some preservation of architectural features. A conversation with the pathologist familiar with the case is the best approach to ascertain whether a core needle biopsy is expected to be helpful beyond an FNA and therefore worth the slightly increased risk of hematoma or other injury. Core biopsy also typically should be performed with real-time ultrasound guidance. If lymphoma is suspected, this should be communicated to the pathologist to ensure appropriate specimen handling, including sending the specimen unfixed.

Excisional biopsy may be necessary in a minority of cases, roughly 10% of those with malignant neck mass. Advantages include excellent tissue acquisition for pathologic analysis and the potential of therapeutic benefit in some cases. Excisional biopsy also allows the surgeon to allocate a significant sample of tissue for culture. It is important to communicate directly with the pathologist so that the fresh tissue is handled appropriately, because incorrect processing in formalin

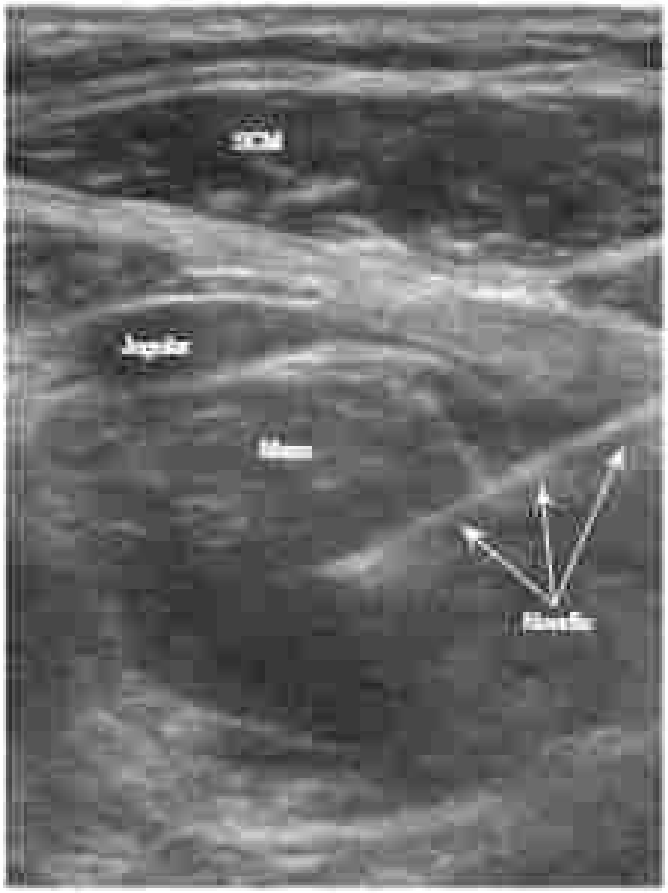

FIG. 4 Ultrasound-guided fine-needle aspiration biopsy of a neck mass lying posterior to the jugular vein. The biopsy was performed with a 22-gauge needle and confirmed metastatic papillary thyroid cancer. SCM, Sternocleidomastoid muscle.

can rule the sample for culture or cytology. Disadvantages include soreness, potential poor wound healing, particularly if therapeutic radiation may ensue, potential spread of disease, need for anesthesia, risk of surgical complication, such as nerve injury, and creation of a cooperative field if subsequent compartment-based dissection proves necessary. With the excellent success of FNA in diagnosis of squamous cell cancer, open biopsy should rarely be necessary. Not only does it expose the patient to anesthetic and procedural risks, but it may worsen the prognosis and increase the local failure rate. If squamous cell cancers remain a possibility and an excisional biopsy is planned, the surgeon should discuss proceeding directly to formal compartment-oriented neck dissection with the same anesthetic if squamous cell carcinoma ultimately is identified. Obviously, a thorough examination for a primary malignancy should be completed before this approach.

Although most thyroid masses are benign, a thorough and thoughtful evaluation of thyroid nodules should be pursued. This workup is detailed elsewhere in this text, but FNA also plays a prominent role for thyroid lesions and is particularly effective in diagnosis of papillary thyroid cancer. On occasion, a biopsy of a lateral neck mass shows thyroid follicular cells in a patient without known thyroid disease. This finding should be construed as indication for a primary thyroid malignancy within the thyroid, most often a papillary thyroid cancer.

Carotid body paragangliomas typically can be diagnosed on the basis of classic imaging features on CT/CT angiography, MRI, or angiography, including splaying of the internal and external carotid arteries. These lesions are highly vascular. Biopsy of carotid body tumors is not needed and should be discouraged.

Endoscopy and Biopsy

When FNA of a neck mass reveals squamous cell cancer, the surgeon must seek the primary lesion. As previously reviewed, the nodal level may direct the initial evaluation. A thorough history and physical examination, including mirror examination or flexible fiberoptic laryngoscopy, should be completed. Initial imaging consists of CT scanning of the neck, which results in identification of a primary malignancy in 20% of cases. Chest imaging (plain x-ray or CT scanning) aids in the search and is particularly useful for lower neck nodal disease. PET may be a useful secondary imaging study. If PET is used as part of the diagnostic approach, it should be completed before endoscopy and biopsy, both to aid in targeting the evaluation and to prevent false-positive PET findings from recently manipulated tissue.

When the primary tumor site remains occult after these studies, panendoscopy and biopsy should follow. Panendoscopy includes laryngoscopy, bronchoscopy, and esophagoscopy. If a primary tumor still is not identified, then at the same setting, biopsy should be performed. If the tonsils are still present, ipsilateral tonsillectomy should be performed; tonsils are found to be the primary source in 20% to 40% of these patients. Bilateral tonsillectomy also is reasonable, but, if this is not performed, then the contralateral tonsil should at least be biopsied. Directed biopsy also should be performed of the nasopharynx, hypopharynx, tongue base, and piriform sinus. Special attention should be paid to any area that was at all suspicious on the imaging evaluation.

SURGICAL CONSIDERATIONS

Anesthesia and Airway Considerations

Many neck masses feel superficial or prominent but can be misleading. Neck masses usually lie deep to the platysma, and major neurovascular structures are often within the intended operative field. Local anesthetic can impair motor response of nerves at risk. Therefore most neck mass surgical biopsies or excisions are performed with general anesthetic. In cases in which clinical or radiographic evaluation suggests significant airway compromise or distortion, communication with the anesthesiologist is imperative to plan for difficult airway management. If the airway is markedly compromised, a planned tracheostomy may be appropriate and should be performed before patient decline develops. Communication again is important regarding avoidance of long-acting paralytics to permit monitoring of motor nerve response.

Incisions

Transverse skin incisions that are placed in a preexisting skin crease are preferred for optimal cosmetic results. When possible, the incision should be placed along the same line as would be used if a subsequent more radical procedure, such as neck dissection, followed the initial procedure. If a small incision is initially used and a need for more exposure occurs, neck incisions can be widened with either transverse or oblique extensions (e.g., along the anterior border of SCM) for better visibility. Although cosmesis is important, it is more important to have adequate exposure to identify anatomic landmarks and protect vessels and nerves.

Potential Nerve Injuries

Neurologic injury may occur with both diagnostic and therapeutic interventions. An understanding of the anatomy is essential to minimize the rate of injury, as is discussion of potential temporary dysfunction or permanent injury with the patient before intervention. Low-energy nerve stimulating devices may aid in identification of motor nerves in the course of dissection but cannot substitute for knowledge of anatomy and meticulous technique. Among the most frequently at risk and commonly injured nerves in the neck are the spinal accessory nerve (cranial nerve [CN] XI) and the marginal mandibular branch of the facial nerve (CN VII). Both injuries cause significant morbidity.

The marginal branch of CN VII is at risk below the body of the mandible. It courses from the main trunk of the nerve in the parotid gland over the body of the mandible (at the area of the facial artery) into the fascia of the submandibular gland, deep to the platysma. The nerve then courses superiorly to cross over the mandible and ultimately becomes more superficial at the level of the platysma and innervates the depressors of the lower lip. The nerve thus lies below the inferior aspect of the mandible for several centimeters. Avoiding the region of the body of the mandible can minimize chances of injury to this nerve. To avoid injury to this nerve, which may be diminutive in size, incisions should be made at least two fingerbreadths below the inferior edge of the body of the mandible. In dissection of the submandibular region, the fascia of the gland should be elevated with the skin flap and the facial vein should be ligated and divided low. Dissection should proceed bluntly, spreading in the expected direction of the nerve.

The vagus nerve (CN X) descends within the carotid sheath, typically posterior to the vascular structures. Unlike division of the vagus in the chest or abdomen, a vagal injury or sacrifice in the neck carries the added morbidity of creating an ipsilateral vocal fold paralysis. This occurs because the recurrent laryngeal nerve has not branched from the vagus nerve until after the latter has descended from the neck. If a vagus nerve injury occurs, neurorrhaphy is not expected to restore normal function but may help to prevent atrophy of the vocal fold complex, which improves the functional result of subsequent vocal cord medialization procedures. In the right neck, the potential exists for a nonrecurrent laryngeal nerve that courses directly medially from the vagus. This aberrant nerve may course with the superior thyroid artery or more inferiorly. Nonrecurrent right laryngeal nerves occur in the setting of an aberrant right subclavian artery (arteria lusoria), and could be injured in the carotid sheath or central compartment if not recognized.

The spinal accessory nerve (CN XI) is at risk for surgical injury in cervical levels II and V. It exits the jugular foramen together with the vagus and glossopharyngeal nerves and courses inferior laterally deep to the posterior belly of the digastric. It passes either superficial or deep to the internal jugular vein. It gives off branches to the SCM and passes either through or deep to the SCM into the posterior triangle. It exits the posterior border of the SCM at approximately the junction of the upper and middle third of the posterior border of the SCM, typically 5 to 8 cm from the mastoid tip. This is approximately 1 cm cephalad to Erb's point, where cutaneous nerves including the greater auricular nerve can be found at the posterior border of the SCM. CN XI then runs superficially overlying the levator scapula muscle in the posterior triangle to the trapezius and courses and may connect with branches of the cervical plexus in its course. It frequently has a more distal course in level V, and the absence of a defined platysma in the posterior triangle renders it even more susceptible to injury.

The hypoglossal nerve (CN XII) provides motor innervation to the tongue. It traverses levels I and II. It descends between the internal jugular vein and the carotid artery and then courses medially. It runs deep to the posterior belly of the digastric muscle, where it is surrounded by the ranine veins. Injuries to this nerve may occur during attempts to control bleeding from these veins.

Other Potential Complications

Although these procedures are usually clean, wound infection sometimes occurs and may be related to the smoking and nutritional status of the patient or irradiated tissue. Chyle leak also may occur and is most likely with procedures on the left side at level IV. The thoracic duct runs deep to the carotid artery low in the left neck and empties into the internal jugular vein deep to its junction with the subclavian vein. All tissue divided in this area lying between the pleura and vagus nerves should be carefully ligated. When they occur, chyle leaks are initially managed conservatively with a low fat diet and medium chain triglyceride diet. High volume or persistent leaks occasionally require reoperation for definitive repair, which usually is accomplished with the placement of Weck clips once the leak is identified and isolated from other structures.

Suggested Readings

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Surgical Infections of the Hand

E. Gene Deune, MD, and Nicholas A. Caloras, MD

BACKGROUND

The hand is continuously subjected to insults that could result in serious infections. With all these sources, it is a wonder that the hands and fingers are not infected more often. Cases of suspected hand or finger infections demand accurate diagnosis, appropriate and timely antimicrobial drugs, and well-thought-out surgical interventions, when necessary. Failure to do so can result in significant functional and cosmetic deficits caused by contractures, stiffness, or amputations.

General Principles

Initial management of hand infections depends on a thorough history regarding the mechanism and the environment of the injury, duration of the infection, possible inciting organisms, and any contributing systemic illness. The occupation, location, and circumstance of the injury can be exceptionally informative regarding the causative organism, such as herpes simplex in dental and healthcare workers or *Pasteurella multocida* in cat and dog bites. Diabetes, injection drug use, or an acquired immunocompromised state (for example, active chemotherapy, human immunodeficiency virus, or long-term steroid use) may potentiate infections by an otherwise nonvirulent organism.

Examination

Remove all clothing, jewelry, and dressings from the fingers to the shoulder, bilaterally so that nothing interferes with the visual inspection of the hand. This is one of the most important aspects of assessing hand infections. Note the skin color, size, shape, and position of the hand and fingers. Look for any cuts or wounds on the hand and any deformities that may indicate a structural injury. Assess motion of the hand and fingers at each joint to evaluate for functional integrity. Hand infections oftentimes result from an injury that may be associated with tendon lacerations, fractures, or foreign objects, conversely, infections often lead to pain and limited range of motion.

Tests and Studies

Laboratory tests should include a complete blood count and electrolytes; sedimentation rate and C-reactive protein are helpful in cases

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The vagus nerve (CN X) descends within the carotid sheath, typically posterior to the vascular structures. Unlike division of the vagus in the chest or abdomen, a vagal injury or sacrifice in the neck carries the added morbidity of creating an ipsilateral vocal fold paralysis. This occurs because the recurrent laryngeal nerve has not branched from the vagus nerve until after the latter has descended from the neck. If a vagus nerve injury occurs, neurorrhaphy is not expected to restore normal function but may help to prevent atrophy of the vocal fold complex, which improves the functional result of subsequent vocal cord medialization procedures. In the right neck, the potential exists for a nonrecurrent laryngeal nerve that courses directly medially from the vagus. This aberrant nerve may course with the superior thyroid artery or more inferiorly. Nonrecurrent right laryngeal nerves occur in the setting of an aberrant right subclavian artery (arteria lusoria), and could be injured in the carotid sheath or central compartment if not recognized.

The spinal accessory nerve (CN XI) is at risk for surgical injury in cervical levels II and V. It exits the jugular foramen together with the vagus and glossopharyngeal nerves and courses inferior laterally deep to the posterior belly of the digastric. It passes either superficial or deep to the internal jugular vein. It gives off branches to the SCM and passes either through or deep to the SCM into the posterior triangle. It exits the posterior border of the SCM at approximately the junction of the upper and middle third of the posterior border of the SCM, typically 5 to 8 cm from the mastoid tip. This is approximately 1 cm cephalad to Erb's point, where cutaneous nerves including the greater auricular nerve can be found at the posterior border of the SCM. CN XI then runs superficially overlying the levator scapula muscle in the posterior triangle to the trapezius and courses and may connect with branches of the cervical plexus in its course. It frequently has a more distal course in level V, and the absence of a defined platysma in the posterior triangle renders it even more susceptible to injury.

The hypoglossal nerve (CN XII) provides motor innervation to the tongue. It traverses levels I and II. It descends between the internal jugular vein and the carotid artery and then courses medially. It runs deep to the posterior belly of the digastric muscle, where it is surrounded by the ranine veins. Injuries to this nerve may occur during attempts to control bleeding from these veins.

Other Potential Complications

Although these procedures are usually clean, wound infection sometimes occurs and may be related to the smoking and nutritional status of the patient or irradiated tissue. Chyle leak also may occur and is most likely with procedures on the left side at level IV. The thoracic duct runs deep to the carotid artery low in the left neck and empties into the internal jugular vein deep to its junction with the subclavian vein. All tissue divided in this area lying between the pleura and supraclavicular should be carefully ligated. When they occur, chyle leaks are initially managed conservatively with a low fat diet and medium chain triglyceride diet. High volume or persistent leaks occasionally require reoperation for definitive repair, which usually is accomplished with the placement of Weck clips once the leak is identified and isolated from other structures.

Suggested Readings

Chen A, Otto KJ. Differential diagnosis of neck masses. Cummings Otolaryngology Head & Neck Surgery. 5th ed. Philadelphia: Elsevier; 2010:1436–1442.

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Surgical Infections of the Hand

E. Gene Deune, MD, and Nicholas A. Caloras, MD

Background

The hand is continuously subjected to insults that could result in serious infections. With all these sources, it is a wonder that the hands and fingers are not infected more often. Cases of suspected hand or finger infections demand accurate diagnosis, appropriate and timely antimicrobial drugs, and well thought out surgical interventions, when necessary. Failure to do so can result in significant functional and expressive deficits caused by contractures, stiffness, or amputations.

General Principles

Initial management of hand infections depends on a thorough history regarding the mechanism and the environment of the injury, duration of the infection, possible inciting organisms, and any contributing systemic illness. The occupation, location, and circumstance of the injury can be exceptionally informative regarding the causative organism, such as herpes simplex in dental and healthcare workers or *Pasteurella multocida* in cat and dog bites. Diabetes, injection drug use, or an acquired immunocompromised state (for example, active chemotherapy, human immunodeficiency virus, or long-term steroid use) may potentiate infections by an otherwise nontributed organism.

Examination

Remove all clothing, jewelry, and dressings from the fingers to the shoulder, bilaterally so that nothing interferes with the visual inspection of the hand. This is one of the most important aspects of assessing hand infections. Note the skin color, size, shape, and position of the hand and fingers. Look for any cuts or wounds on the hand and any deformities that may indicate a structural injury. Assess motion of the hand and fingers at each joint to evaluate for functional integrity. Hand infections oftentimes result from an injury that may be associated with tendon lacerations, fractures, or foreign objects, conversely, infections often lead to pain and limited range of motion.

Tests and Studies

Laboratory tests should include a complete blood count and electrolytes; sedimentation rate and C-reactive protein are helpful in cases

of suspected osteomyelitis. Cultures and gram stains are rarely useful for chronic cutaneous infections but are vital in cases of abscess or deep space infections. If there is a strong suspicion, cultures should also be sent for atypical bacteria, mycobacteria, fungi, and viruses. All patients should have three plain radiographs of the hand to look for foreign bodies, subcutaneous air, or fractures. Arthrocentesis should be strongly considered when septic arthritis is a prominent feature of the differential diagnosis. Computed tomography is indicated in cases of multiple fractures or when there is concern for abscess, deep space collection, or concomitant vascular injury. Magnetic resonance imaging is most useful in the evaluation of osteomyelitis.

Treatment

Treatment in the first 24 to 48 hours consists of antibiotics, immobilization, and elevation. Elevation is especially useful in greatly edematous infections. In a stable patient, antibiotics can be delayed if meaningful cultures can be obtained promptly. A bedside procedure, under local anesthetic infiltration or nerve block, is often indicated in cases of superficial abscess, easily extractable foreign body, or grossly contaminated lacerations. If there is no improvement after the first 48 hours, it is highly unlikely that prolonged antibiotics alone will be effective. Thrombosis of local vessels at the infection site prevents adequate circulation; furthermore, compartments and closed spaces of the hand tend to wall off infections, preventing systemic antibiotics from reaching the infection.

Progression of the symptoms, delayed presentation (>48 hours), or deep abscess formation are all indications for operative intervention. When operating in the hand, placement of incisions is crucial to long-term success. General principles of operative treatment consist of thorough irrigation and debridement of nonviral tissue. Even after thorough debridement, the wound may still require closed or open postoperative drainage. We recommend using tourniquet control without limb exsanguination, the latter of which risks propagating bacteria into systemic circulation. Instead, the arm should be elevated and direct pressure applied to the brachial artery for 1 minute before tourniquet inflation. Intraoperative cultures should be acquired and the hand then splinted for at least 3 days. Occasionally, more debridement may be necessary to control the infection.

MINOR INFECTIONS

Cellulitis

Cellulitis is infection of the dermis; it may be the cutaneous representation of a deeper or distant infection or abscess. Inciting causes can be a skin abrasion, a puncture, or a retained foreign object. The most common organisms are *Staphylococcus aureus* and group A β-hemolytic *Streptococcus*.

Symptoms

Warmth, erythema, swelling, lymphangitis, and adenopathy are all common. Moderate to severe discomfort on palpation or range of motion in the involved region is also typical.

Treatment

Initial management involves marking the extent of infection, hand immobilization, elevation, antibiotics, and removal of the offending agent (e.g., foreign object, distant source of infection, or an unlikely drug allergen). It is of utmost importance not to use the affected limb for venipuncture. The severity of the cellulitis dictates whether the patient receives treatment as an outpatient or an inpatient. If the cellulitis increases, if there is no response to oral antibiotics, or if there is purulence, the patient needs to be hospitalized. Anti-staphylococcal penicillins or first generation cephalosporins should be the first-line antibiotics. Clindamycin or a quinolone may be used in cases of penicillin allergy. Vancomycin is indicated if there are risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA). Failure of first-line antibiotics is most often due to bacterial resistance or perpetuation of an underlying abscess.

Paronychia

Although it is the most common hand infection, paronychia is usually seen first by either the patient's primary care physician or the emergency room physician. Paronychia is an infection along the paronychium, the lateral folds of the fingernail. The eponychium is the proximal boundary, and the hyponychium is the distal boundary. Thus an eponychia that occurs at the base of the nail refers to the infection along the eponychium. If both the paronychium and the eponychium are involved, it is called a *circumferential infection*. A paronychia is caused by bacteria introduced into the soft tissue through a break in the nailfold from a hangnail, manicure, nail biting, or penetrating trauma. Common organisms are *S. aureus* or oral anaerobes. A ruptured ganglion cyst emanating from the distal interphalangeal (DIP) joint can also be a cause for an infection along the nailfold.

Symptoms

The symptoms vary depending on the severity and duration of the paronychia. Initially there is mild swelling and erythema at the site of the inciting source, with involvement of the adjacent nailfold. If neglected, the infection may progress to fluctuance and local purulence with spontaneous drainage. Purulence distal to the nail plate indicates that there is involvement of the nail matrix. With severe infections an accompanying cellulitis involving the finger and the hand may occur.

Treatment

The treatment is tailored to the severity of the infection. Prevention is the major deterrent, particularly if the cause is nail biting or manicures. In early paronychia, when there is no purulence and only erythema and swelling, oral antibiotics, warm soapy soaks, and splint immobilization can be successful.

When surgical drainage becomes necessary, the finger needs to be anesthetized with a digital block. A Penrose drain is placed around the base of the finger as a digital tourniquet. Next, a large-bore intravenous needle (19- or 18-gauge) is inserted beneath the nailfold with the bevel side down and gently passed back and forth to lift the nailfold off the nail plate (Fig. 1). This action allows for localization and puncturing of the abscess. Once the location of the abscess is noted, the needle can be turned 90 degrees and the sharp beveled edge used as a knife. With this technique, the nailfold is incised directly over the abscess to allow for drainage. If the abscess is underneath the nail plate, or an ingrown nail is the causative factor, a portion of the nail plate can be elevated off the nail bed. The nail is then cut longitudinally with sharp scissors or scalpel and gently removed. We recommend routinely obtaining cultures if a paronychia requires intervention for drainage. The wound should be packed with ¼ 25 inch ribbon gauze and the finger wrapped. Other wound care includes twice daily warm soapy soaks and replacement of the packing twice a day. An oral anti-staphylococcal antibiotic should be administered for at least 5 days, with a plan to follow up in 1 week.

Chronic paronychia is a clinically different entity than acute paronychia. It occurs in patients whose hands are constantly exposed to water containing irritants, alkali, or microorganisms. Its treatment involves the removal of the overlying dorsal skin as a nonpainful outpatient procedure. The reader is referred to the references listed below for more information.

Herpetic Whitlow

Herpetic whitlow is a cytolytic skin infection of the pulp and nailfold of the fingers. The causative agent is herpes simplex virus, type 1 or type 2. Infection occurs from direct contact with another infected individual or from self-inoculation by an infected body part. Dental and medical personnel are at slightly higher risk of infection because of the increased contact with potentially infected secretions. Immunocompromised patients are also at high risk. It is important to distinguish between a paronychia and herpetic whitlow because incision and drainage of a herpetic whitlow is not recommended for fear of a bacterial superinfection.

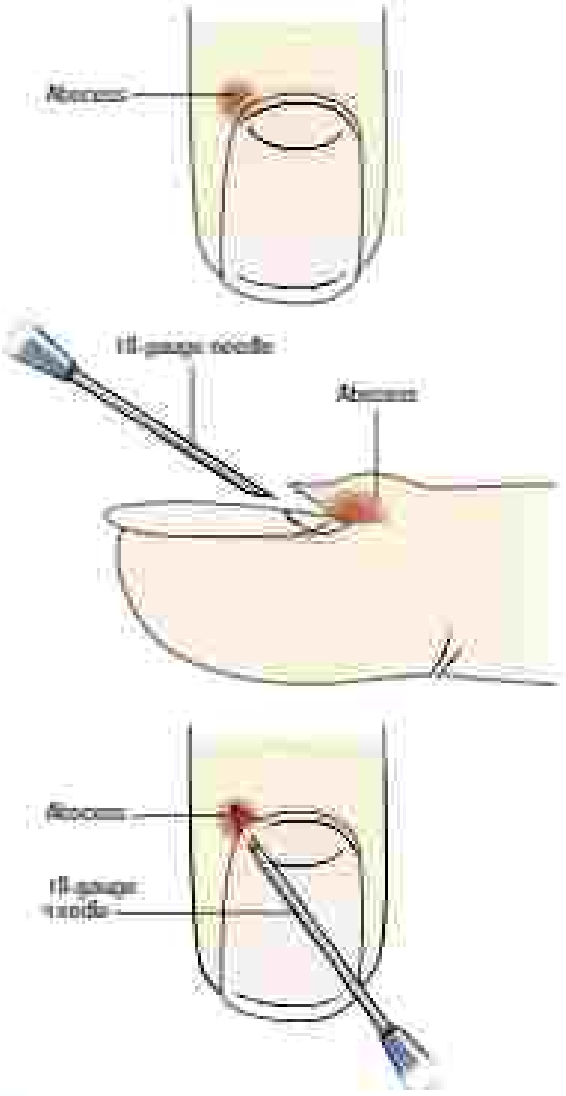

FIG. 1 Paronychia drainage. A large-bore intravenous needle (16- or 18-gauge) is inserted beneath the eponychium with the bevel side down and gently passed back and forth to lift the margin of the nail plate (A). The abscess is then entered with the needle tip, and pus is drained (B). The nail plate may be removed to expose the entire abscess cavity (C).

Symptoms

After the inoculation, there is usually a 48- to 72-hour prodrome of severe pain, followed by erythema. Ten to 14 days later, small clear vesicles, which may be turbid, appear and then coalesce. The overlying skin sloughs and ulcerates. Fever, malaise, and lymphangitis may occur. In susceptible hosts, signs and symptoms of disseminated virus can be observed.

Diagnosis and Treatment

Tzanck smear or viral cultures of the vesicle fluid will secure the diagnosis. Often these tests are unnecessary because the diagnosis can be made on the symptoms alone. The infection is usually self-limiting and lasts 3 to 4 weeks, so antiviral medication is not indicated, unless there is concern for visceral and disseminated infection. Removing the nail plate has been advocated to relieve pain if the nail plate is involved, but surgical intervention increases the risk of bacterial superinfection and systemic viral infection. Patients should cover the area with a clean, dry dressing at all times to prevent spread of the virus. Twenty percent of patients will experience a recurrence, which is usually milder and of shorter duration than the initial infection.

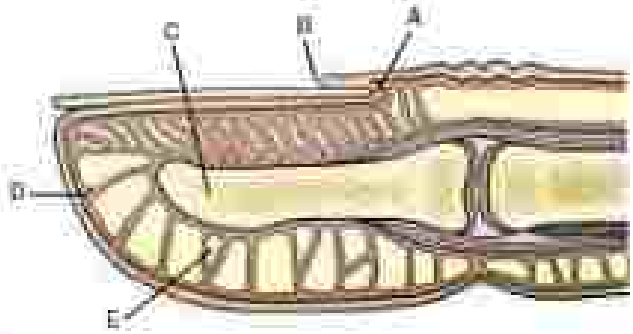

FIG. 2 Anatomy of the distal fingertip. Note the compartments formed by the vertical septae. A, nail matrix. B, eponychium. C, distal phalanx. D, septum. E, fingertip pulp.

Felon

A felon is a subcutaneous abscess in the volar fingertip pulp, within the multiseptated compartments created by vertical fibers extending from the distal phalangeal periosteum into the epidermis (Fig. 2). Felons are usually due to penetrating trauma from a needle, wood splinter, or minor cut. Iatrogenic trauma from finger sticks for blood glucose monitoring can also be a cause. The most common organism is *S. aureus*. Gram-negative rods or polymicrobial infections should also be suspected in immunocompromised patients. Left untreated, a felon may progress to localized tissue necrosis, septic destruction, cellulitis, distal phalangeal osteomyelitis, and DIP joint septic arthritis. Proximal spread may also result in pyogenic flexor tenosynovitis.

Symptoms

Usually, the patient presents a few days after the injury with a rapid onset of pain, erythema, and tense swelling of the entire pulp. The swelling does not usually extend to the DIP crease unless there is an associated cellulitis, pyogenic flexor tenosynovitis, or septic arthritis of the DIP joint.

Treatment

If seen in the first 24 to 48 hours, oral antibiotics, warm soapy soaks, and elevation may abort the progression. Failure to improve, worsening symptoms, or fluctuance in the finger pulp are all indications for drainage. There are several locations for the surgical incision (Fig. 3). Regardless of which one is used, the digital neurovascular structures (found in the midline of the volar-distal dimension), the flexor tendons, nail matrix, and the DIP joint space should be protected to avoid injuries. The two preferred incisions are the single longitudinal palmar incision and the unilateral longitudinal incision. The abscess should be drained, irrigated, and packed; cultures should be obtained from any discrete infectious collections. A first-generation cephalosporin or clindamycin (penicillin allergy) is recommended and wound care continued until the felon has resolved.

MAJOR INFECTIONS

Pyogenic Flexor Tenosynovitis

Pyogenic flexor tenosynovitis is infection within the potential space formed by the visceral and parietal layers of the synoviovium that constitute the flexor tendon synovial sheath. The visceral layer invests the flexor tendon, which is then surrounded by the parietal layer. The synovial sheath begins just proximal to the first annular pulley (A1) at the distal metacarpal neck and ends at the insertion of the flexor digitorum profundus distal to the A1 pulley. The small finger sheath

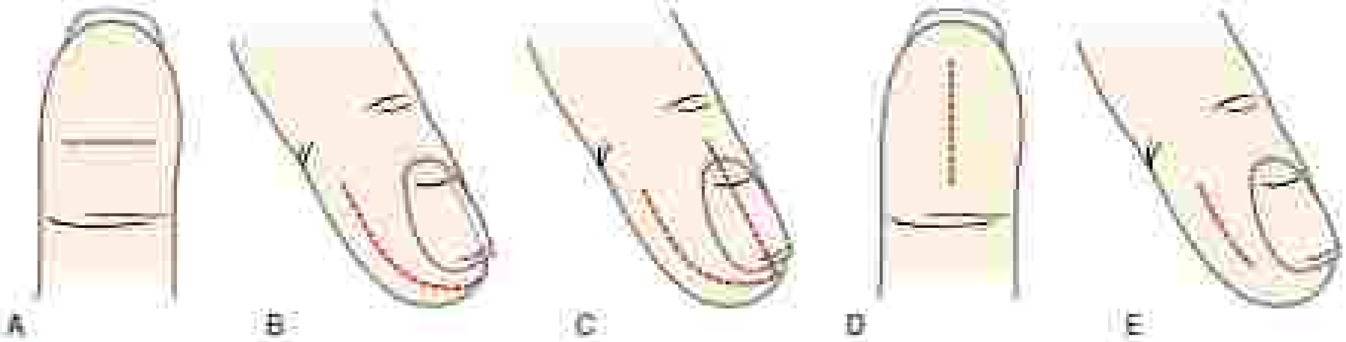

FIG. 3 Incisions used for draining felons (A) Transverse palmar incision. (B) Fish-mouth incision; note the incision goes to the other side of the finger. (C) Hockey-stick, or J-incision. The two preferred incisions are ( ) the longitudinal palmar incision and (E) unilateral longitudinal incision.

is continuous with the ulnar bursa, and the thumb flexor sheath is continuous with the radial bursa.

[illegible]

[illegible]

Treatment

[illegible]

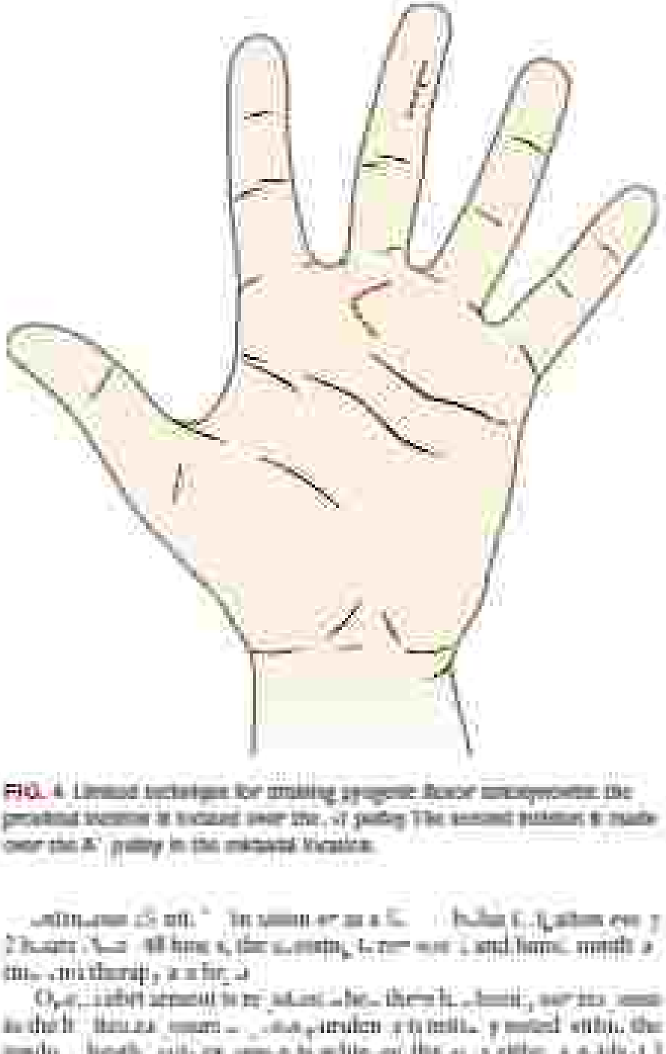

FIG. 4 Limited technique for draining pyogenic flexor tenosynovitis: the proximal incision is located over the A1 pulley. The second incision is made over the A5 pulley in the midlateral location.

[illegible]

Deep Space Infections

[illegible]

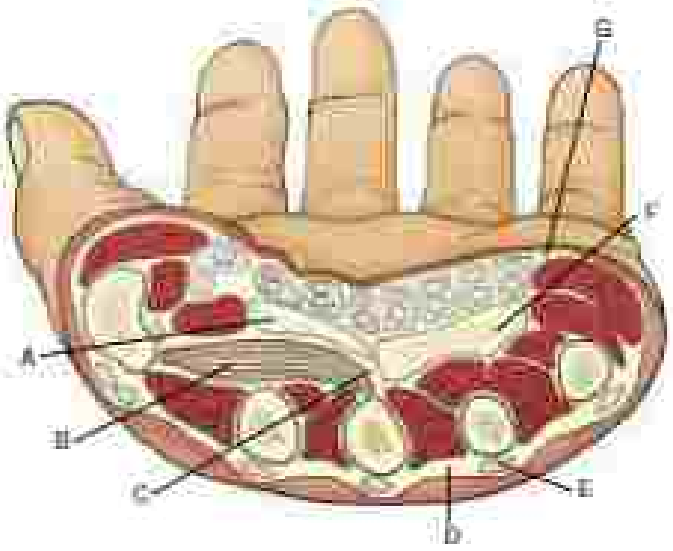

FIG. 3 Anatomy of the hand, cross-sectional view. The deep spaces are demonstrated: thenar space, midpalmar space, hypothenar space, and the dorsal subaponeurotic space. The interdigital web spaces and the space of Parona are not shown. A, Thenar space; B, adductor pollicis muscle; C, midpalmar space; D, dorsal subaponeurotic space; E, extensor tendon surrounded by dorsal aponeurosis; F, midpalmar space; G, palmar aponeurosis.

space, and interdigital webspaces, one in the dorsal hand (the dorsal subaponeurotic space), and the sixth in the volar forearm (space of Parona). The most hand infections, the most common organisms are *S. aureus* and Streptococcus species. Penetrating trauma is the most common cause of infection. In the absence of trauma, the most likely cause for the infection is contiguous spread from an adjacent deep space infection, a concurrent subcutaneous abscess, or pyogenic flexor tenosynovitis. Swelling and tenderness are symptoms shared by all deep space infections. A deep space infection requires surgical incision, drainage, irrigation, and debridement of all necrotic tissue, followed by elevation, immobilization, and intravenous antibiotics. Gram stains and culture are essential at the time of the incision and drainage.

Thenar Space

The thenar space is located on the radial palmar aspect of the hand just distal to the thenar eminence. The dorsal floor is defined by the first metacarpal muscles and the adductor pollicis longus, which inserts into the volar aspect of the long finger metacarpal. Ulnarly, it is separated by the oblique fascial septum from the midpalmar space (see diagram), which also inserts into the long finger metacarpal at the same place as the adductor pollicis longus fascia. Radially the border is formed by the convergence of the adductor pollicis tendon and fascia at the thumb proximal phalanx.

Symptoms

The thenar region and first webspace are characteristically swollen and exquisitely tender to palpation. Thumb motion, both passive and active, induces severe pain. The swelling often results in thumb abduction as the volume of the thenar space increases due to the expanding purulence or swelling. Because of the higher compliance of the dorsal skin, the swelling and purulence may be more noticeable dorsally.

Treatment

Surgical drainage is performed through a combination of volar and dorsal incisions (Fig. 4). A dorsal incision alone is not recommended because it offers incomplete access to the thenar plate deep to the radial finger flexor tendons. The volar incision can be approached through a transverse or longitudinal approach. The longitudinal

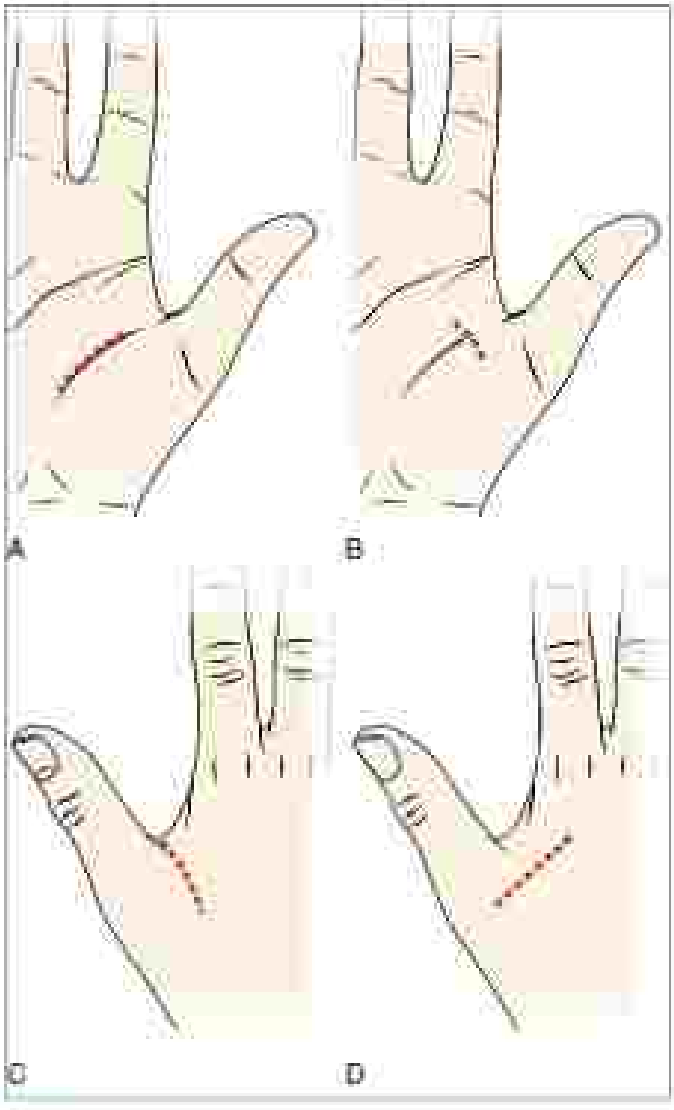

FIG. 4 Thenar space infection. (A) The palmar longitudinal incision is made parallel to or in the thenar crease. The incision is performed over the palmar transverse incision (B), dorsal and then longitudinal incision (C), and the transverse incision (D).

approach is preferred because of the decreased risk of injuring the neurovascular structures. The longitudinal incision is made parallel to or in the thenar crease. Care is taken to protect the palmar cutaneous branch of the median nerve, which lies subcutaneously in this region, as well as the recurrent branch of the median nerve, which lies deeper at the distal border of the transverse carpal ligament. The dissection is done bluntly between the first and second metacarpal entering through the palmar fascia. The dorsal compartment between the adductor and the first dorsal interosseous muscle is also decompressed.

The dorsal incision is made either longitudinally or transversely. Again, the longitudinal incision, performed by us, is placed 'in proximal to the web, centered over the dome of the dorsal extension of the infection and then extended proximally by 1 to 2 cm. To avoid a potential webspace contracture, the incision should not extend to the web edges. Care is taken to protect any sensory branches or large dorsal veins. Blunt dissection is directed deeply toward the palm, between the first dorsal interosseous and adductor pollicis muscles, to fully evacuate the space. The wound is then thoroughly debrided, irrigated, and packed.

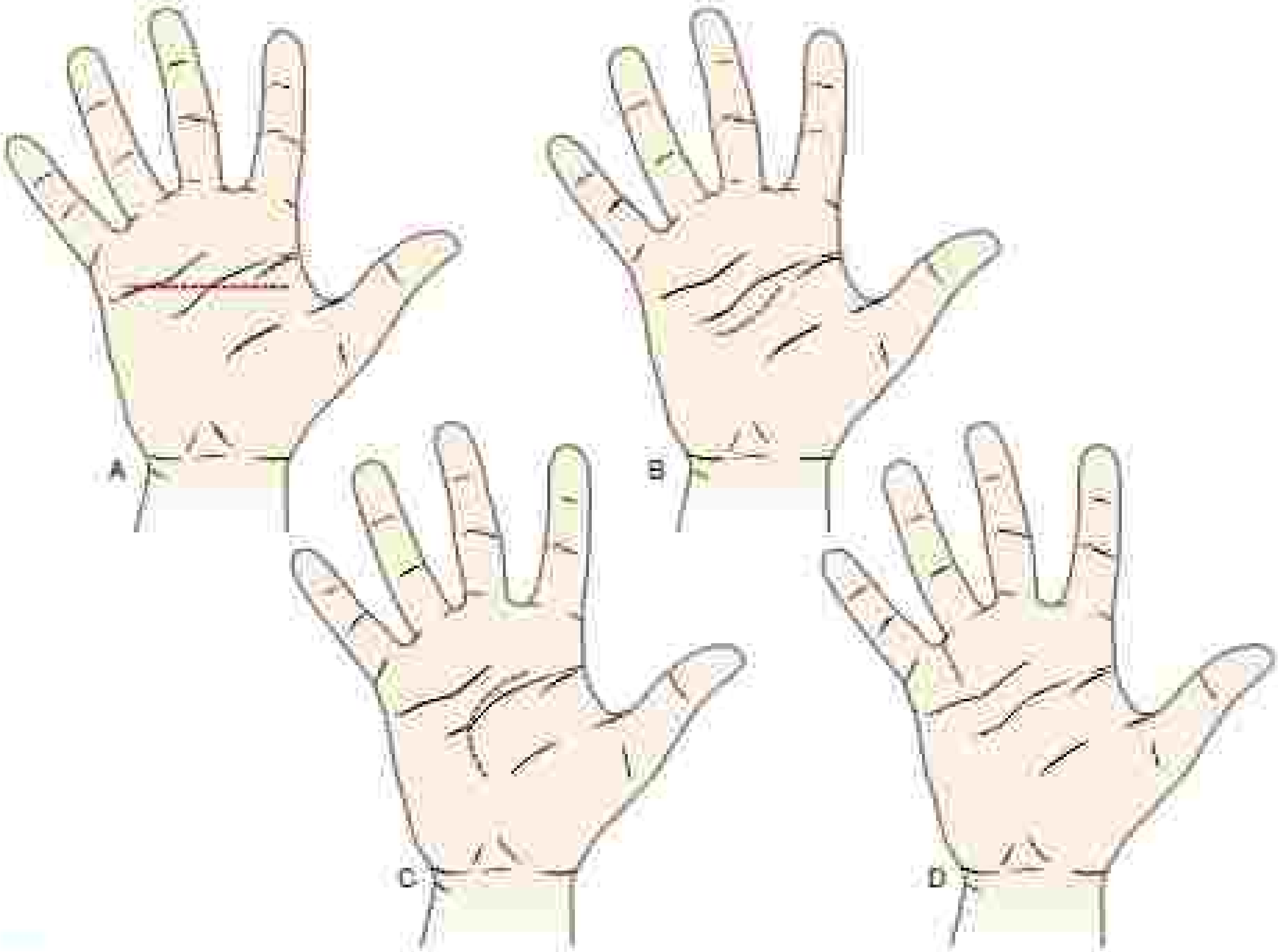

FIG. [illegible] Incisions used for draining midpalmar space infections. (A) Transverse incision. (B) Longitudinal or oblique incision. (C) [illegible] transverse and longitudinal incision. (D) Approach through the [illegible] lumbrical.

Midpalmar Space

[illegible]

FIG. 8 Longitudinal incision for drainage of a hypothenar space is placed along the axis of the ring finger metacarpal in the proximal palm.

and the dorsal skin, and the other on the palmar surface centered on the ulnar border of the ring finger metacarpal axis above the hypothenar eminence (Fig. 8). Blunt dissection is continued until the space is reached. Neither of the two incisions should cross the wrist crease, and care is taken not to injure any neurovascular structures, particularly with the palmar approach because the ulnar nerve and artery are in close proximity to Guyon canal.

Subcutaneous (Web) Space

The triangular spaces at the base of the fingers are prone to direct penetrating trauma or irritation by insects. The roof is defined by the dorsal hand fascia and skin. The radial and ulnar borders are composed of the extensor tendon mechanism and the metacarpophalangeal joint capsular structures. The ventral septae of the palmar fascia form the distal boundary, thus limiting the extension into the palm.

Pathogenesis

Because of the limitations of the fibrous palmar fascial attachment to the palmar skin, the swelling tracks distally around the palmar fascia into the dorsal subcutaneous web space, producing a collar button abscess. Erythema, fluctuance, and sometimes cellulitis of the dorsal hand are seen. Finger abduction is seen if the pathogenesis is predominantly on the volar aspect; on the contrary, lack of abduction suggests a dorsal location of the abscess.

Treatment

Intravenous antibiotics, followed by prompt surgical drainage, are required through either the volar or the dorsal surface or both. A single longitudinal volar incision does not provide sufficient exposure, and a single transverse incision placed either dorsally or volarly may result in a web space contracture (Fig. 9). A volar zigzag incision is made first, placed between the metacarpal and beginning proximally at the level of the metacarpophalangeal joint and extending distally to the base of the involved web. Blunt dissection is done. The subcutaneous and deep tissues are divided, and the dorsal and palmar spaces are connected. Care is taken to protect the neurovascular structures as they enter either of the involved fingers. If there is a collar button abscess, a dorsal incision is made. The pus/debris is then thoroughly evacuated and the wound copiously irrigated before packing is left.

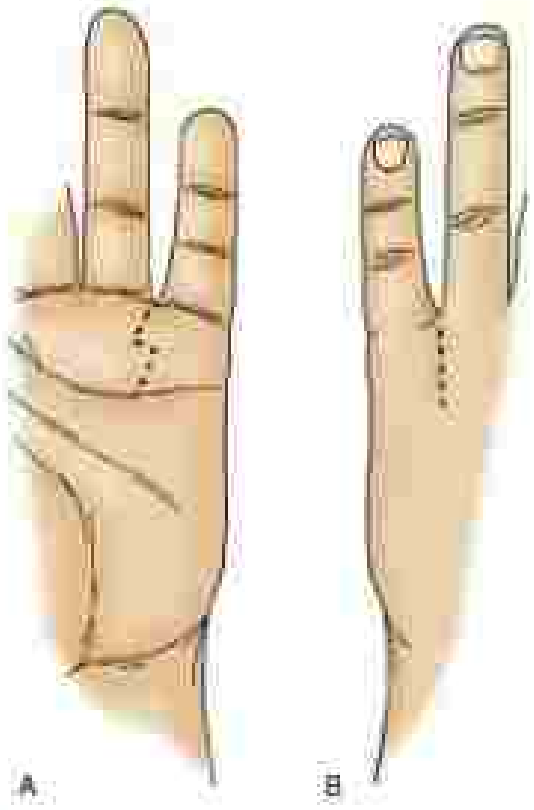

FIG. 9 Incisions for an interdigital web space infection: zigzag palmar incision (A) and dorsal longitudinal incision (B).

Deep or Subaponeurotic Space

The dorsal subaponeurotic space is a potential space located on the dorsum of the hand composed of loose areolar tissue deep to the extensor tendons and superficial to the interosseous muscle fascia and the metacarpal periosteum. Infections are usually due to a penetrating injury. Due to the overlapping presentation of cellulitis and deep space infection, advanced imaging can be helpful in establishing this diagnosis.

Symptoms

The dorsal hand is swollen and erythematous with warmth, fluctuance, and tenderness, similar to cellulitis. Finger extension is difficult and painful. The palm of the hand is usually unremarkable.

Treatment

Failure of conservative treatment, a high suspicion of a subaponeurotic space infection, or both are indications for surgical exploration. If the abscess is small and well localized, one dorsal longitudinal incision is used. A more diffuse and extensive infection, two dorsal longitudinal incisions, made over the second and fourth metacarpals, are used (Fig. 10). Care is taken not to injure the extensor tendons, and incisions are made in the fascia between the tendons to allow entry into the subaponeurotic space.

Space of Parona

The space of Parona is located in the distal forearm dorsal (deep) to the flexor digitorum profundus tendons and volar to the pronator quadratus. This space is continuous with the radial and ulnar bursae and the midpalmar space and thus is very susceptible to infections from contiguous spread. This is the most common cause of the infection. Pyogenic flexor tenosynovitis is the second most common.

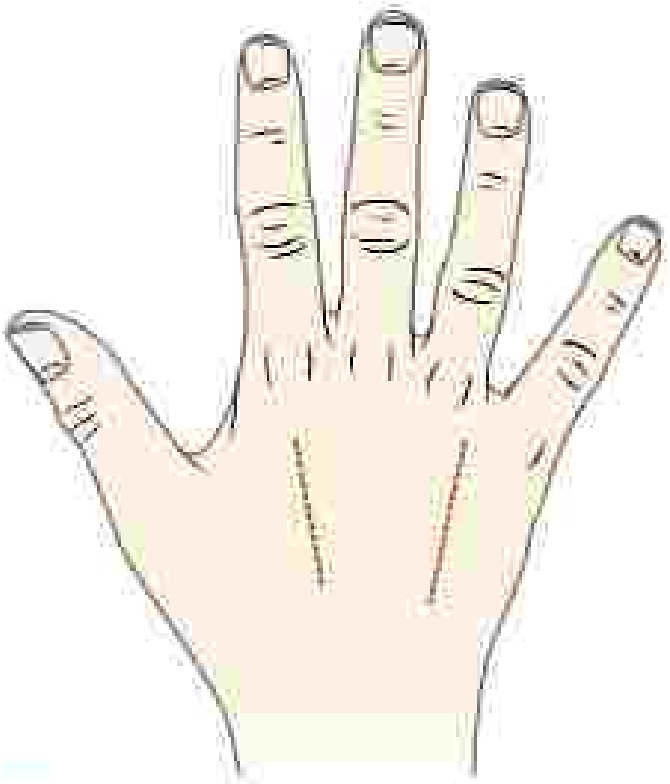

FIG. 59 Location of the two dorsal incisions for draining a subperiosteal space infection.

Symptoms

Swelling, tenderness, and occasional fluctuance are noted in the distal volar forearm. Flexion of the fingers is difficult and painful. Numbness and weakness in the thumb, index, and ring finger should raise concern for acute carpal tunnel syndrome.

Treatment

A longitudinal incision is made ulnar to the palmaris longus tendon from the wrist flexion crease to the distal third of the forearm. Care is taken to protect the median nerve. The sheath and tendons are retracted radially to gain access to the space of Parona. The abscess is decompressed, and the space is thoroughly irrigated. If a subpalmar space infection is present, two separate incisions may be made to preserve the transverse carpal ligament. If there is concern for median nerve entrapment, the incision can be taken distally as a single line from the forearm across the carpal tunnel to the midpalm.

OTHER INFECTIONS

Septic Arthritis

Septic arthritis involving joints in the fingers and hand is unusual. Penetrating trauma is the most common cause. Other causes include hematogenous spread or contiguous spread from an adjacent infection. The most common organisms are [illegible] and *S. epidermidis*; a species of *Eikenella* may be present if the cause was a human bite. Signs and recognition are important because timely treatment can prevent the destruction of the articular cartilage by the infection.

Symptoms

The patient may have low-grade fever, chills, and night sweats associated with pain, erythema, and swelling to the involved joint. Because the joint space is distended with fluid, active or passive motion will result in pain.

Treatment

Aspiration of purulence from the joint confirms the diagnosis. Samples should be sent for cell counts and microscopy because crystalline arthropathy can present identically. Radiographs are usually normal but, in severe cases, may show osteomyelitis. Septic arthritis is a surgical emergence and requires immediate drainage. Arthrotomy remains the most appropriate and preferred method. In the wrist, a longitudinal incision between the third and fourth dorsal compartments is preferred. For the metacarpophalangeal joint, a dorsal midline incision is made and the joint is exposed through an incision in the extensor hood; care should be taken to preserve the sagittal bands. The joint is then thoroughly irrigated with copious saline (3–4 L). For the proximal interphalangeal (PIP) joints, a midaxial incision from the DIP joint to the subplatar is used to avoid injury to the central slip. The transverse retinacular ligament and the accessory collateral ligaments are identified and incised to expose the PIP joint. The joint is then debrided of any necrotic tissue and copiously irrigated. The wounds are closed primarily over a small Penrose drain, which is then removed on postoperative day 1. Hand motion and therapy are started on postoperative day 2 or 3, when the pain has decreased. Antibiotics should be administered intravenously for several days, followed by a course of oral antibiotics, as directed by surgical cultures.

Human and Animal Bites

As causes of penetrating injury to the hand and joints, bite injuries cause considerable morbidity and disability to the human hand. Human bites tend to be more virulent than animal bites. These bites often result after an altercation ("fight bites"), where there is a direct bite by the assailant in the finger or the hand, or the tooth penetrates the dorsal PIP or MP joints during a clenched fist punch. Human bites, regardless of where they are located, must be explored aggressively due to very high risk of joint and periosteum violation and osteolysis. The wound should be extended to allow for complete arthrotomy, liberal culturing of involved tissue, and copious irrigation. After adequate surgical drainage, the hand is immobilized and elevated. Motion is initiated as soon as feasible on postoperative day 1 or 2. Intravenous antibiotics are necessary. Recommended empiric regimens include a third-generation cephalosporin or gentamicin and penicillinase-resistant penicillin.

Of the animal bites, dog bites rarely become infected, but more than half of all cat bites become infected. Organisms tend to be mixed and include *S. aureus*, *Streptococcus viridans*, and *Pasteurella multocida*. Most dog and cat bites tend to be small but still require local wound care, including initial copious irrigation. Empiric antibiotics, usually oral amoxicillin–clavulanate or intravenous ampicillin–sulbactam (penicillin allergy: patients can benefit from a quinolone and clindamycin) are recommended. Treatment with a prophylaxis of tetanus, rabies, or both is indicated as well. Open wounds require appropriate surgical care, depending on the extent of injury and the structures damaged.

Necrotizing Infections

Necrotizing fasciitis is a true surgical emergency because infection in the hand or upper extremity can frequently lead to multisystem organ failure, amputations, and death. The typical presentation of these infections is similar to cellulitis with erythema, swelling, and pain. Concerning signs, however, include hypotension, tachycardia, soft tissue crepitus, skin sloughing or blistering, and dusky appearing skin. Any time is clinical suspicion for this infection, emergent debridement and intravenous antibiotics must happen immediately. With regard to operative treatment, involved tissue is superficial to the fascia and may appear pale gray, with a dull gray liquid discharge. This must be debrided back to bleeding tissue, with minimal regard for conventional anatomic boundaries. Repeat debridements must occur every 24 to 48 hours as needed. Amputation is a useful adjunct for severe infections but does not provide a mortality benefit.

initial empiric antibiotic therapy must cover the most likely causative organisms—group A *Streptococcus*, *Staphylococcus* species, and anaerobes. Multidrug regimens are usually required and can include vancomycin, piperacillin/tazobactam, and clindamycin or ampicillin/sulbactam, ciprofloxacin, and clindamycin. Intraoperative cultures can then be used to narrow therapy.

SUMMARY

Hand infections can have devastating effects leading to significant compromise and morbidity in the affected individual. As present this, hand infections need to be accurately diagnosed and treated appropriately and aggressively to avoid devastating and permanent [illegible].

SUGGESTED READINGS

[illegible]

NERVE INJURY AND REPAIR

Christopher Frost, MD, and Gudjon D. Ronson, MD

During the past [illegible] years, and mainly due to the development of microsurgical technique, surgeons have been routinely repairing severed peripheral nerves. This has paralleled the advances in macrovascular reconstruction and digital replantation. Performance of nerve repair requires meticulous microsurgical technique and the use of both the science and art of peripheral nerve surgery. Furthermore, nerve repair is often an exercise in delayed gratification because many injuries can take months or even years to recover after repair.

BASIC ANATOMY

Nerve anatomy and physiology is fundamental to peripheral nerve surgery and guides the diagnosis of nerve injury. The basic subunit of the peripheral nerve is the axon. These axons are surrounded by endoneurium and grouped into fascicles. Each fascicle is encapsulated by a perineurium, and groups of fascicles are in turn surrounded by an interfascicular epineurium. Each peripheral nerve is comprised of a group of fascicles surrounded by an external epineurium. Finally, the nerve sheath is contained within a mesoneurium, which both allows for nerve gliding during normal range of motion and contains the segmental blood supply to the nerve (Fig. 1).

FACIAL TOPOGRAPHY

When performing peripheral nerve surgery, it is important that proximal motor and sensory axons connect to their corresponding distal fascicles. More proximally there can be significant intermingling between sensory and motor axons with plexus formation in the nerve trunks proximally. As the nerves travel more distally, motor and sensory axons more clearly develop into distinct fascicles. This can have important clinical consequences after nerve repair. For example, repairing facial nerve injuries within the temporal bone often leads to improper connections between proximal and distal nerves. This can lead to a significant amount of disabling synkinesis and dyskinesis secondary to the lack of distinct fascicular architecture to the proximal facial nerve trunk. This is opposed to injuries distal within the face because these fascicles are separated into clear branches and errant innervation less likely to occur.

PATHOPHYSIOLOGY

A clear understanding of the mechanism of injury, zone of injury and degree of nerve injury is critical for successful management. Based on the mechanism of injury, lesions can be classified as open (laceration) or closed (stretching, blast, compressive trauma). Gunshot wounds behave like closed injuries typically because nerve injury is more likely due to blast effect rather than transection. Initial zone of injury can vary widely depending on the mechanism of injury. Sharp injury such as a scalpel blade produces a small zone of injury. More blunt mechanism such as a table saw on the other hand can produce a very wide zone of injury. The zone of injury can be difficult to discern on initial exploration of there is evidence of blunt trauma, crush, or nerve avulsion.

The degree of injury can be classified using several different systems (Table 1). The Seddon classification divides injuries into neurapraxia, axonotmesis, and neurotmesis based on the anatomic nerve component that is damaged. The Sunderland classification I to V is based on the degree of injury and expected recovery. Mackinnon and Dellon added a VI degree to this system (combined nerve injury).

Focal or segmental demyelination with preservation of axon continuity is termed neurapraxia (Sunderland class I). In this case functional recovery is expected to occur spontaneously as the myelin heals. This recovery occurs over a period of hours or days up to a weeks. Iatrogenic surgical intervention is required in this case. A distal nerve compression ("Saturday night palsy") with resulting wrist drop that spontaneously recovers is one common example.

Axonal injury with preservation of the endo and epineurial sheath is known as axonotmesis (Sunderland class II–IV). In this case the axon will die back to the nearest node of Ranvier. After initial stabilization the axon will begin to form multiple "growth cones" and will regrow at a rate of 1 mm/day or 1 inch/month through the distal endoneurial tubes. The axons distal to the injury site undergo Wallerian degeneration whereby myelin and cellular debris are phagocytosed, and the axon replaced. Axonotmesis can result in a range from complete recovery to minimal or no recovery. Degree of recovery is dependent on the degree of damage to the surrounding structures (endoneurium, perineurium and epineurium) and the resulting scar tissue. If the surrounding tissues remain intact the axons will usually reach the distal endoneurial tubes and spontaneous recovery will occur (Sunderland class II–III). On the other hand, if the sprouting axons are unable to reach the distal endoneurium, then a neuroma in continuity will develop, and no spontaneous recovery will occur (Sunderland class IV).

Finally, complete transection of all neural structures is termed neurotmesis (Sunderland class V). Spontaneous recovery in this case is not expected. Surgical intervention is required in all cases of neurotmesis and in cases of axonotmesis where regenerating axons are unable to regenerate successfully through the distal endoneurium.

Importantly, the distal axons in all cases of nerve injury will have viable axons that can transmit electrical signals for between 72 and [illegible] hours after injury. After this time period the distal axons will irreversibly degrade and undergo Wallerian degeneration. In cases where it is critical to stimulate distal motor branches during repair such as in facial nerve injury, patients should be brought to the operating room within 72 hours of initial injury. Nerve repair between

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NERVE INJURY AND REPAIR

Christopher Frost, MD, and Gudjon D. Runnon, MD

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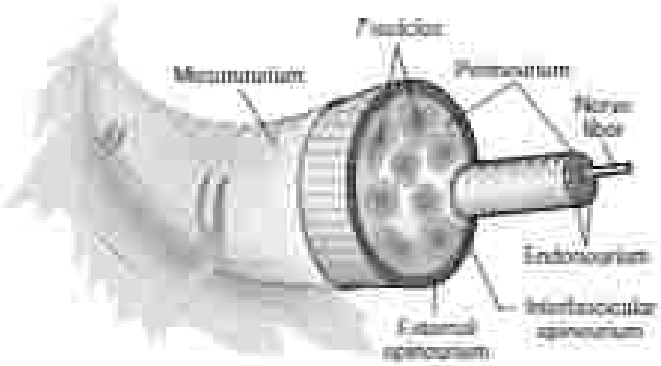

FIG. 1 Anatomy of a peripheral nerve.

inappropriate proximal and distal motor muscles can lead to weakness and dysfunction.

After muscles lose innervation they begin to degenerate from both chronic atrophy and denervation atrophy. Motor endplates within the muscle will irreversibly degenerate after 12 months and will be gone by 18 to 24 months. After this point, the muscle cannot be reinnervated, creating a relative deadline for recovery of motor function at 1 year after injury. On the other hand, sensory end organs do not undergo degeneration and reports have been made of successful sensory reinnervation many years after initial injury (Table 2).

TIMING

Optimal surgical timing is essential for successful nerve repair. Closed injuries should be approached differently from open injuries. Early recognition and treatment of nerves unlikely to recover

TABLE 1 Classification and Expected Recovery of Nerve Injuries

Classifications		Nerve Components Injured					Expected Recovery		
Seddon	Sunderland Degree of Axonotmesis	Myelin	Axon	Endoneurium	Perineurium	Epineurium	Extent	Rate	Surgery Indicated
Neurapraxia	First	+					Complete	Fast	No
Axonotmesis	Second	+	+				Good	Slow	Not usually
	Third	+	+	+			Variable	Slow	Variable
	Fourth	+	+	+	+		None	None	Yes
Neurotmesis	Fifth	+	+	+	+	+	None	None	Yes
	Sixth	Combination of injury					Variable	Variable	Variable

+, Injury.

TABLE 2 Treatment Options and Indications for Repair of Nerve Injuries

Options	Indications
Observation	Recovering nerve injury Partial nerve injury
Neurapraxia	Nerve in continuity, but with NAP
Axonotmesis	Axonotmesis Some preservation of axons in nerve, but with poor NAP
Neurotmesis	Axonotmesis (i.e., disruption of endoneurium, perineurium, and epineurium) Nerve in which stimulation distal to the injury does not produce a muscle contraction
Nerve repair (end-to-end neurorrhaphy)	Sharp nerve transection in which the nerve ends can be approximated without tension
Nerve graft	Nerve gap in which tension would be excessive if the nerve ends were sutured directly together Nerve injury in which end-to-end repair would result in a poor functional outcome (e.g., proximal nerve grafting in the upper arm)
Nerve transfer (neurotization)	Nerve injury proximal to the target muscle, with the donor nerve innervating a muscle that is less important than the target muscle
Nerve transplantation	Nerve injury proximal to the target muscle
Functional muscle transfer	Irreparable nerve injury, with no donor nerve available
Free muscle transplantation	Irreparable nerve injury, with no donor nerve available
Amputation	Irreparable nerve injury, with no donor nerve available, and the patient desires amputation

NAP, Nerve action potential.

TABLE 3 3+1 Rule for Timing of Nerve Repair

Timing	Time	Injury Type	Injury Classification
Early	3 days	Sharp laceration or transection Acute nerve compression resulting from vascular (e.g., hematoma, pseudoaneurysm) or bony injuries Acute neurologic worsening under close observation	Neurotmesis
Subacute	3 weeks	Blunt transection Ragged transection	Neurotmesis
Delayed	3 months	Lesions in continuity (nonpenetrating injuries such as stretch injuries, contusive injuries, gunshot wounds)	Axonotmesis
Late	>1 year	Salvage procedures	Neurotmesis or axonotmesis

spontaneously to key and "time to muscle" remains a fundamental concept. Surgical timing can be summarized by the 3+1 rule (Table 3), with early repair occurring within 3 days, subacute repair at 3 weeks, delayed repair at 3 to 6 months, and late repair after 1 year.

Early repair, occurring within 3 days after the injury or at presentation if evaluated after 3 days, is indicated in cases of suspected transection with sharp injuries. In this case, any neural deficits are likely to represent nerve transection (neurotmesis or Sunderland class V) and will require surgical intervention. It is also indicated in situations with vascular (e.g., hematoma, pseudoaneurysm) or bony injuries causing acute nerve compression, especially if they occur in the vicinity of a closed compartment. If a neurologic examination worsens acutely under close observation, the nerve damage potentially can be reversed or reduced by immediate surgical intervention.

Subacute repair, occurring around 3 weeks after injury, is advocated by some for blunt or ragged transections (e.g., by projectiles, blades or chainsaws), but others still treat these injuries acutely. These injuries clearly represent neurotmesis and surgical intervention is required. Such injury can cause a large and unpredictable zone of injury; however. Delaying repair for a few weeks allows Wallerian degeneration to begin occurring, better defining the zone of injury. At the time of repair, the nerve endings can be resected back to healthy tissue. This could be difficult to evaluate if the injured nerves were explored immediately after the injury.

In contrast, advocates for earlier surgery feel that surgery is easier and more practical at an earlier time, especially if done at the same time that surgical intervention is performed by another team, such as a general, vascular, or orthopedic surgical team. Furthermore, the additional technical challenges of dealing with scarring can be avoided. For example, if a patient with a fracture and associated nerve palsy is being examined by an orthopedist, it would be reasonable to explore the nerve at the same time. If the nerve is found to be in continuity but nonfunctional, observation for several months is indicated. Note that because Wallerian degeneration does not occur until 2 to 3 hours after injury, intraoperative electrophysiologic testing would not be reliable or helpful in predicting recovery or acutely determining the grade of injury. If the nerve is found to be ruptured, some would repair it at the same time. Others would perform the surgery at a second stage, when the zone of injury can be better defined; nerve ends are tacked down under tension as they do not retract, using radiopaque clips or sutures so that they can be identified easily. At a later time, a subacute nerve repair can be done.

Delayed repair, occurring approximately 3 months but up to 6 months after injury, is indicated for lesions in continuity, such as the majority of stretch injuries, contusive injuries, and gunshot wounds. In these cases, it is difficult to predict with certainty which path the nerve injury will follow from those described previously and whether the injury will recover spontaneously or require surgical repair. Nonoperative treatment can be continued in patients with early signs of spontaneous recovery or in partial lesions. Note that 90% of nerves that recover do so within 6 months. Surgery is indicated when there has been no evidence of clinical or electrical recovery after this period of observation. In these cases, the delay also will allow lesions in continuity to be evaluated during surgery with nerve action potential (NAP) testing to distinguish between recovering lesions (Sunderland class II–III) and nonrecovering (Sunderland class IV) lesions that require repair.

Late repair, occurring more than 1 year after injury, may be considered a salvage procedure in patients who are seen for a delayed fashion or in those who either have not recovered or have recovered incompletely after spontaneous recovery or previous nerve surgery. Nerve repair and reconstruction typically does not work well after this period, which can be considered as short as 9 months by some surgeons because of permanent changes at the muscular level. The one exception might be distal nerve transfers (those performed close to the end organ), which can be performed in select cases even up to 18 months after injury. However, reconstructive options addressing muscles, tendons, bones, and joints may be useful.

TREATMENT FOR NERVE INJURY

The management and surgical treatment of nerve injury involves the application of general principles that are relevant to all nerve surgeries and of specific nerve repair techniques particular to each situation.

GENERAL PRINCIPLES

Preoperative Assessment

The optimal approach to nerve injury assessment includes a detailed history of the mechanism of injury and the onset of the deficit, a physical examination (neurologic, vascular, and musculoskeletal examination), and electrodiagnostic studies, such as electromyography and nerve conduction studies. These three pillars (history, physical examination, and electrodiagnostic studies) help the clinician to determine the extent and severity of the nerve injury. Additionally, imaging studies (radiography, ultrasonography, computed tomography, magnetic resonance imaging, and neurography, or myelography) can further enlighten the clinical scenario and the operative planning. Specifically, high resolution (3 Tesla) magnetic resonance neurography (MRN) has been increasingly used to better define the anatomy of injured nerves. MRN provides a substantial benefit for the evaluation of large proximal nerve elements such as the brachial plexus, the lumbosacral plexus, the sciatic nerve in the pelvis, and other nerves that follow deep or complex courses, where electrodiagnostic studies are difficult to use. The clinician must also remember to use sensory and motor function grading scales, which will facilitate follow-up and assessment of the results of interventions (including observation).

Key Operative Principles

At surgery, the steps taken to expose the injured nerve before the nerve repair itself are important. Knowledge of the anatomy is crucial, especially when scarring from the injury is expected and likely will distort the anatomy. Adequate exposure should be planned, including the possibility of harvesting nerve grafts. Dissection usually is done between two muscle groups parallel to the long axis of the nerve. Ideally, a normal segment of the nerve is identified first, both proximally and distally, before dissection is carried toward the injured segment. If the injured segment is near a compression site, such as the median nerve near the carpal tunnel, then the site of compression should be released at this time. For practical purposes, there are two possibilities: the identification of a neuroma in continuity or nerve stumps.

If there is a neuroma in continuity, intraoperative NAP recordings can be performed to assess the degree of injury (recovery or no recovery) (Fig. 2). These are helpful because gross inspection or palpation of a neuroma in continuity does not predict histology, recovery, or outcomes. Furthermore, NAP can determine recovery across a short segment of nerve (i.e., proximal and distal to an injury) before recovery can be seen by physical examination or conventional electromyogram. When a NAP is present across a lesion, the lesion should not be resected because the outcome generally will be better with neurolysis alone. If a NAP is absent across a lesion, the outcomes are generally poor if the lesion is left intact, therefore surgical repair is indicated.

If two nerve ends suggestive of a rupture or transection are identified or if a nerve end suspicious for an avulsion is found, a nerve repair or reconstruction is indicated. The use of NAP recordings still can be helpful in these situations and can allow identification of the proximal location at which nerve grafting can be performed. Some use NAP to brachial plexus avulsion injuries to define preganglionic responses. Others use other techniques, including somatosensory evoked potential and motor evoked potential, to assess whether the proximal nerve stump is intact and can be used for reinnervation.

For the nerve repair, microsurgical techniques, which involve the use of micro instruments and of a microscope or magnifying loupes, should be used. The nerve ends on both sides should be prepared by removing sharply the neuroma and scar tissue, until normal fascicular structures are obtained. The nerve stumps should be sliced proximally and distally (like slicing a loaf of bread) until a healthy fascicular pattern is visualized. This is called the nerve divergent (snail's eyes). This pattern of healthy fascicles protruding from the cut nerve endings is due to the pressure within the endoneurium. The fascicles that protrude past the cut nerve ending should be divided further until all of the fascicles fit "flush" with the epineurial sheath. This is critical so that the fascicles do not overlap once the epineurium is sutured. Optimal microsurgical technique will cause minimal surgical trauma and permit an end to end repair or interfascicular grafting. It is further recommended that 8-, 9-, or 10-0 sutures be used, and using the fewest number of sutures to approximate the nerve accurately is preferred. The repair must be without tension to obtain good results. Fibrin glue may be used to reinforce the suture line, but other methods involve the use of fibrin glue alone or with a variety of nerve conduits (conduitation).

If repair of a motor nerve is planned (and it is within 72 hours of the original injury), it is crucial to remember that a tourniquet applied longer than 30 minutes can cause ischemia of the distal nerve, and intraoperative nerve stimulation will no longer be possible. Thus the initial dissection must be well planned, focused, and directed to ensure there is enough time to dissect the injured distal nerve and apply stimulation for 5- minutes afterward.

FIG. 2 Intraoperative photograph showing [illegible] nerve [illegible] the upper trunk [illegible] the UT [illegible] the [illegible] nerve [illegible] the [illegible] nerve [illegible] the [illegible] nerve [illegible] proximal [illegible] distal to it.

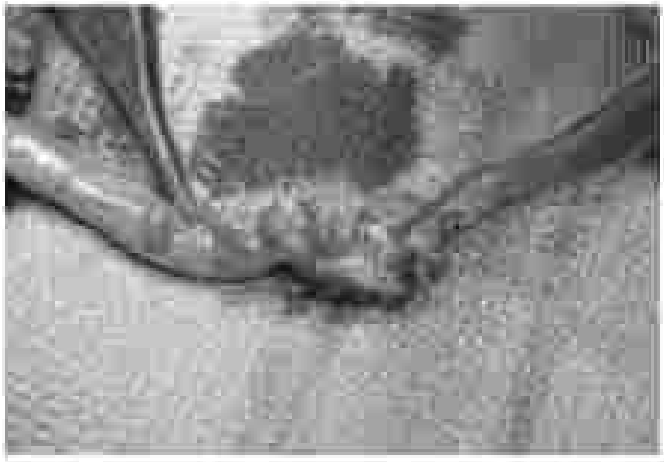

FIG. 3 Nerve ruptured [illegible] with healthy fascicles are uncovered in a sagittal manner to the end a neuroma is resected from the proximal nerve end.

TECHNIQUES FOR NERVE SURGERY

Neurolysis

Neurolysis, defined as releasing scar tissue surrounding the injured nerve, is indicated when a neuroma in continuity with intact NAP conduction is found. In general, external neurolysis, which is completed during the nerve exposition, is sufficient. In select instances, some advocate limited internal neurolysis or removal of the scar tissue between the various nerve fascicles.

Direct Repair

Direct nerve repair is the end to end suture of nerve stumps. It is indicated when a short nerve gap exists, either from a sharply transected nerve (such as a cut from glass, a knife, or a razor) or after removing a focal neuroma in continuity that did not conduct a NAP. Direct repair is the preferred method of nerve repair whenever possible, assuming that the damaged segment of the nerve has been resected and that the sutures are without tension. This method allows direct delivery of proximal axons to the distal stump via a single suture line. It also usually permits fascicular alignment, which increases matching between motor and sensory axons and their targets.

For primary nerve repair, an epineurial repair is usually the most predictable (Figs. 3, 4, and 5). The external epineurial vessels can be arranged to ensure that the fascicles are appropriately aligned.

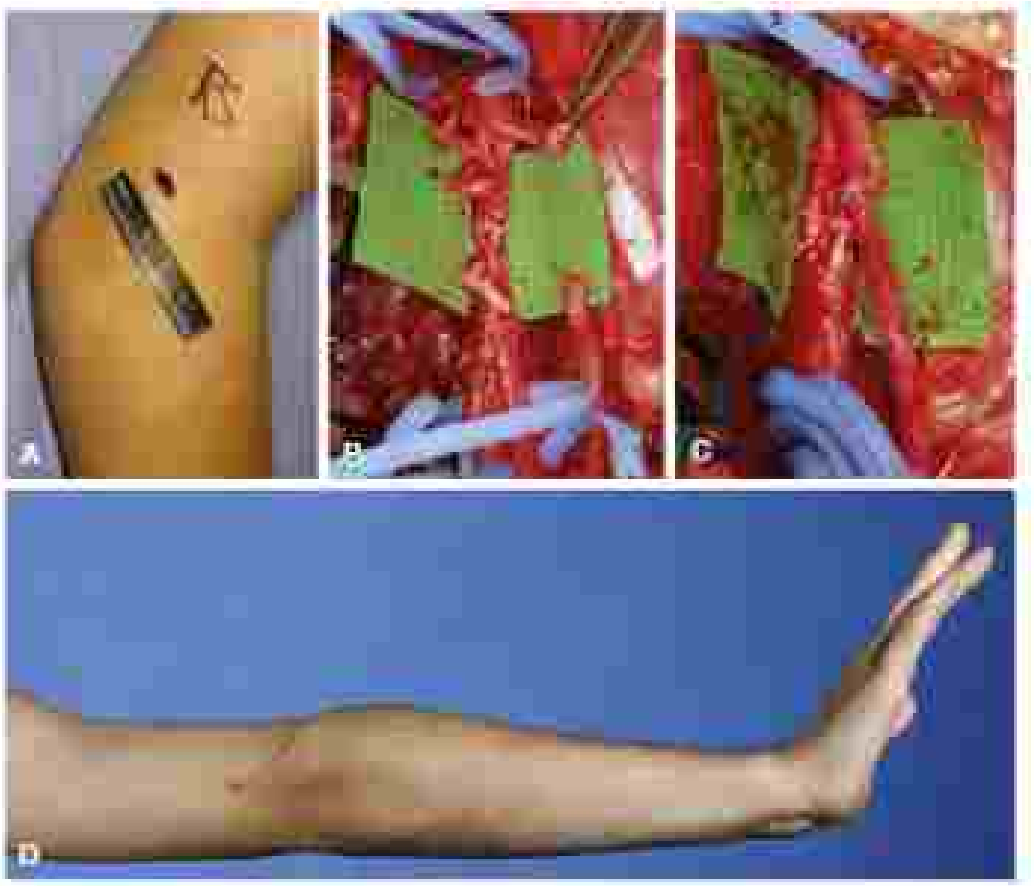

FIG. 8 Patient with a partial laceration of the radial nerve trunk at presentation 1 week after injury. (A) The open knife injury wound is seen in the right arm slightly proximal to the elbow near the interval between the brachioradialis and triceps. The knife blade had penetrated the arm to a depth of approximately 5 cm (2 inches). The patient had no motor, sensation, partial weakness of the finger extensors and wrist extension, and decreased sensation in the domain of the radial nerve. (B) At exploration the radial nerve was found to be partially lacerated at its bifurcation into the deep and superficial radial nerve. The complete laceration of the superficial (sensory) radial nerve is seen, as is the partial injury to multiple fascicles of the deep (motor) branch of the radial nerve. (C) Direct repair of the superficial sensory radial nerve and the fascicles of the deep branch of the radial nerve are shown. A nerve graft was used to perform a side repair. (D) After 6 months, the patient had already regained good finger and wrist extension (medical research council [MRC] grade 4). Thumb extension (the most distal motor target) improved to MRC grade 3, although the patient still had sensory abnormality in the domain of the hand.

Additionally, to facilitate maximization of fascicular orientation, it is important to be familiar with the serial cross sectional fascicular topography, fascicular stimulation, histochemical stains, and gross fascicular matching. Often, only two or three interrupted sutures are necessary to align and coapt the nerve endings. It is critical at this stage to ensure there is no overlapping of the fascicles (Fig. 6). The fascicles should just be gently coapted within the epineurium. It is also important to make sure the needle passes only through the epineurium and does not catch a portion of one of the fascicles because this can lead to a small intraneural neuroma and the fascicle will not heal properly.

Occasionally, it is appropriate to perform fascicular or grouped fascicular repairs. In a large nerve where the fascicles are easily identifiable, it may be possible to suture the internal epineurium between the fascicles with a few small, interrupted nylon sutures and then perform the epineurial repair. Some researchers have reported that grouped fascicular repair results in more intraneural scarring, so most peripheral nerve surgeons continue to use the epineurial repair. When performing nerve repairs, it is important to understand the difference between the fascicular topography in the proximal nerve trunk and the fascicular topography in the distal nerve (Fig. 7). Most nerves have a significant intermingling of sensory and motor fibers with plexus formation proximally, whereas more distally they usually become groups of sensory or motor fibers. This partially explains why more distal nerve repairs have better long-term functional outcomes.

If a small nerve gap is present, several methods can be used to reduce the gap and achieve a direct repair. Commonly used methods include nerve mobilization, nerve transposition, as with the ulnar and radial nerves, and joint positioning, such as repair and immobilization of a joint in some degree of extension with gradual postoperative extension beginning at about 3 weeks. In some cases, bone shortening, as with comminuted fracture, may offer an opportunity for decreasing a nerve gap.

Nerve Graft

Nerve graft repair is performed when nerve stumps on either side of a gap cannot be opposed for a direct end to end repair without tension. Often this technique is necessary for recurrent or continuity of moderate or longer lengths with unrecordable (negative) NAP or for transected nerves with retracted stumps, which occurs when the initial surgery is delayed.

The most frequent source of nerve graft is the sural nerve (Fig. 8). However, the medial or lateral antebrachial cutaneous nerves, superficial sensory radial nerve, superficial peroneal nerve, distal posterior interosseous nerve, great auricular nerve, and cervical plexus nerves are alternatives. The nerve graft should be sutured into place in a reversed fashion from its usual anatomic course (i.e., the more distal end of the nerve graft should be sutured to the proximal end of the

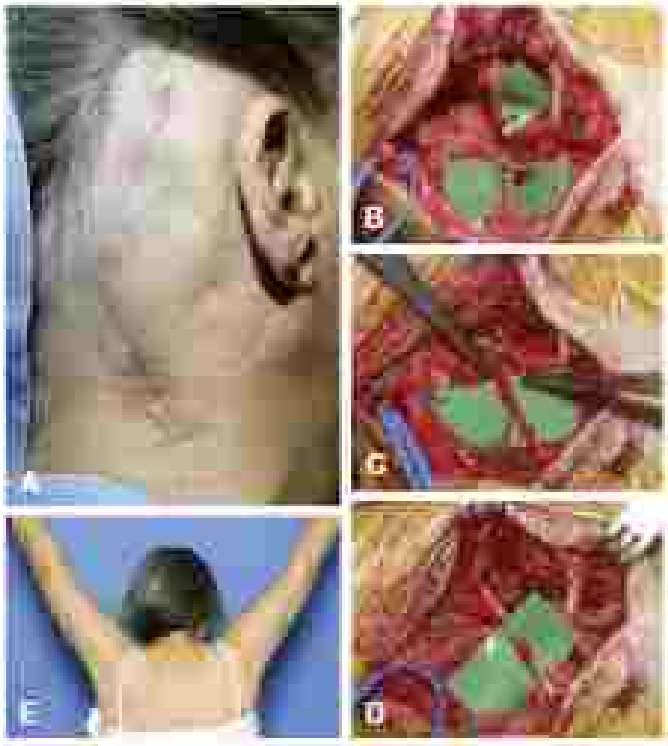

FIG. 5 Patient with a spinal accessory nerve injury after a right retrosigmoid craniotomy for removal of a vestibular schwannoma. (A) Surgical incision used for the resection of the right vestibular schwannoma. After surgery, the patient developed prominent scapular winging, atrophy of the right trapezius muscle, and significant difficulty in abducting the right arm. Electromyography 1 months after surgery confirmed a right spinal accessory neuropathy affecting the motor branch to the trapezius (normal sternocleidomastoid) without evidence of reinnervation. (B) At exploration, soon thereafter, the great auricular nerve (at the right of the nerve stump) and the greater occipital nerve (blue vessel loop) were identified. The proximal and distal stumps (stapled to a green background) of the spinal accessory nerve were found within the area of the prior surgical exposure. (C) To achieve a direct repair the two nerve stumps were mobilized proximally and distally. (D) A direct end-to-end repair was performed using an 8-0 suture. (E) The patient regained excellent function, scapular stability, and range of motion, shown here at 15 months after the repair.

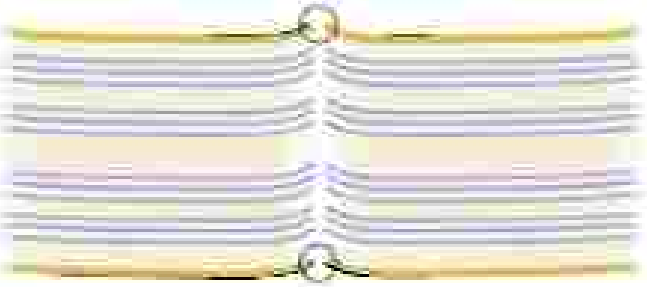

FIG. 6 Nerve ends should be trimmed to remove scarred tissue and ma [illegible] healthy-appearing fascicles in a way that will allow fascicles (about the) to be trimmed, both with the epineurium. Fiber sutures a the spine should be placed with 8-0, 9-0, or 10-0 suture and should be done carefully to prevent twisting of the ends. A tradivercular suturing through a fascicle. Coronal topography can a aligned by counting of cut vessels along the epineurium.

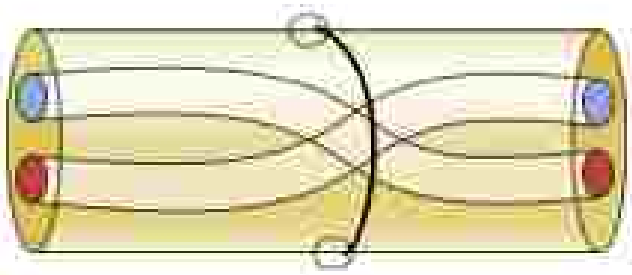

FIG. 7 Proximal nerve fascicles should be aligned to their corresponding distal fascicles. Mismatch between proximal and distal axonal can lead to errant innervation o inappropriate distal targets and lead to painful or dysfunctional.

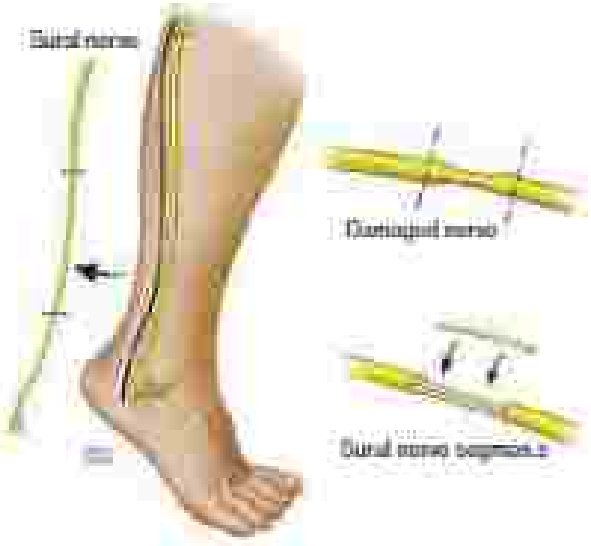

FIG. 8 The distal nerve A the most common source of nerve graft. A purely sensory nerve, it supplies sensation to a small area of the dorsolateral aspect of the foot. The distal nerve is up to ~8 cm long in each leg; nerve grafts may be harvested bilaterally and distal nerve segments are used to bridge the nerve gap.

nerve gap being repaired, and the proximal end of the nerve graft should be sutured to the distal end of the nerve gap). This ensures that axons will not be lost through small side branches in the nerve graft as the axons grow through the graft. When the diameter of the nerve at the site of repair is much larger than the diameter of the nerve graft, grouped fascicular repair may be used (Fig. 9). The disadvantage of nerve grafting is related to the donor sequelae associated with donor morbidity from the nerve harvest, such as expected permanent sensory loss and small chance of neuropathic pain.

The graft length is calculated by measuring the nerve gap and adding 10% to account for some elongation of the graft and to avoid tension. One graft or several "cable" grafts are placed to maximize the surface area at the repair sites and to prevent mismatch. Interfascicular grafts may be sutured individually at both ends or may be placed together and then sutured as a single unit.

Vascularized nerve grafts have been advocated by some to improve the speed and quality of regeneration compared with standard, non-vascularized nerve grafts; however, this practice is controversial. Autogenous or synthetic conduits may be used for short gaps (<3 cm) of small diameter, usually sensory nerves (e.g., digital nerves). Using a nerve conduit requires an coaptation technique. The nerve conduit must be the correct diameter to accommodate the nerve and should be approximately 10 mm longer than the nerve gap. The coaptation technique involves placing the proximal nerve ending 5 mm within

FIG. 9 Intraoperative image of three sural nerve segments bridging a radial nerve gap in the distal arm after a humeral fracture.

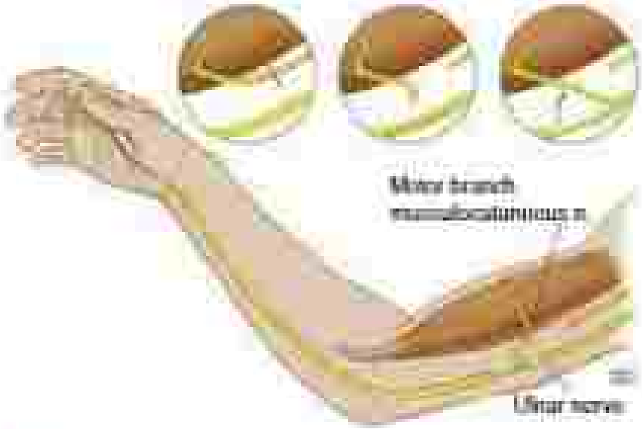

FIG. 1[illegible] Oberlin nerve transfer technique (Oberlin procedure) used for the repair of injury to the brachial plexus or musculocutaneous nerve leading to loss of biceps motor function. To perform this transfer the ulnar nerve function must be preserved. At the level of the middle or proximal third of the arm, a functioning ulnar nerve fascicle is used to reinnervate the biceps motor branch originating from the musculocutaneous nerve. In general, ulnar motor function is preserved [illegible], but the patient may experience transient sensory changes in the distribution of the ulnar nerve. [illegible] series using this technique reports that [illegible] of patients recovered good elbow flexion after surgery.

one end of the nerve tube and the distal nerve [illegible] 5 mm within [illegible] end [illegible] the [illegible] with [illegible] sutures [illegible] on [illegible] nerve conduit.

Nerve Allografts

[illegible]

Nerve Transfers

[illegible]

distal nerve [illegible] closer to the end organ as opposed to proximal nerve grafting farther from the end organ (Table [illegible]).

Muscle and Tendon Transfer and Bone and Joint Procedures

These various procedures usually are performed in a delayed fashion, sometimes more than a year after the injury. Muscle or tendon transfer is the transfer of a muscle or tendon that is working and is expendable to achieve a new function. This technique, similar to nerve transfer, requires a functional expendable innervated muscle in the vicinity. Examples of reliable tendon transfers include opponensplasty, anticlaw procedure, thumb adductorplasty, flexor to extensor transfers, elbow flexorplasty, transfers for shoulder external rotation, antiwing (scapular) transfers, transfers for pronation, and extensor to flexor transfers. An alternative is the transfer of a free functioning muscle, such as the gracilis muscle from the lower extremity, which can be transferred at a late stage for elbow flexion or finger flexion. This requires the presence of an arterial and venous supply, as well as a functioning nerve to reinnervate the muscle. Bone and joint procedures, such as osteotomies and arthrodeses, also may improve function. Shoulder fusion may be an option for patients with brachial plexus palsy and refractory instability with pain.

EXPECTED OUTCOMES FROM REPAIR AND RECONSTRUCTION

Outcomes after nerve injury and repair are variable owing to a multitude of underlying factors. The best outcomes are achieved when spontaneous neural recovery occurs (i.e., when surgery is not indicated). Other factors influencing the recovery of nerve repair and reconstruction include the following:

1. Patient age. The younger the patient, the better the recovery because of inherent physiologic factors related to regeneration, limb length, and capacity for cortical reorganization and reeducation.
2. Level of injury. Distal injuries fare better because of the shorter distance to the end organ.

TABLE 4 Common Motor Nerve Transfers of Upper Extremity

Motor Deficit	Recipient Nerve(s)	Donor Nerve(s)
Elbow flexion	Biceps, brachialis branches of MCN	Ulnar nerve fascicle to FCU Median nerve fascicle to FDS/PL/FCR
Elbow flexion	MCN	Medial pectoral nerve branches
Elbow flexion	MCN	Thoracodorsal nerve
Elbow flexion	MCN	Distal accessory nerve
Elbow flexion	MCN	Intercostal nerves
Shoulder abduction, external rotation	Suprascapular nerve	Accessory nerve (distal end-to-end or end-to-side with neurotomy and proximal crush injury) Pectoral fascicle of C7, middle trunk
Shoulder abduction	Axillary nerve	Medial triceps branch
Shoulder abduction	Axillary nerve	Medial pectoral nerve
Shoulder abduction	Axillary nerve	Thoracodorsal nerve
Shoulder abduction	Axillary nerve	Intercostal nerves
Scapular winging, instability	Long thoracic nerve	Thoracodorsal nerve[a]
Scapular winging, instability	Long thoracic nerve	Pectoral fascicle of C7, middle trunk[b]
Scapular winging, instability	Long thoracic nerve	Intercostal nerves
Intrinsic hand	Deep motor branch/fascicle of ulnar nerve	Distal AIN
Pronation	Pronator teres branches of median nerve	ECRB branch of radial nerve FDS or ECRB/palmaris longus branch of median nerve
Wrist, finger extension	ECRB, PIN branches of radial nerve	FDS, FCR/PL branches of median nerve
Finger flexion	AIN branch of median nerve	Brachialis branch of MCN ECRB, supinator branches of radial nerve
Elbow extension	Triceps branch of radial nerve	FCU fascicle of ulnar nerve ECRL fascicle of radial nerve
Elbow extension	Triceps branch of radial nerve	Intercostal nerves

[illegible]

1. Type of nerve injured: Pure nerves fare better than mixed nerves because there is less chance of fascicular mismatch.
4. Specific nerve involved: Radial nerve recovers better than median nerve, which recovers better than ulnar nerve; nerves C5 and C6 and those of the upper trunk recover better than nerves C8 and T1 and those of the lower trunk; and tibial nerve recovers better than peroneal nerve.
5. Mechanism of injury: Lacerations have better outcomes than low-velocity gunshot injuries, which in turn have better outcomes than high-velocity gunshot injuries; transections have better outcomes than crush or avulsion injuries; and stretch injuries generally have better outcomes than ruptures, which fare better than avulsions. These variations in outcomes are related to the zone of injury and associated soft tissue and vascular damage.
6. Timing of repair and reconstruction: The earlier the better; outcomes are typically best before 6 months, but they depend on the size of the gap, the status of the end plate, and the status of the alpha motor neurons.
7. Type of repair or reconstruction: Patients in whom exploratory surgery is indicated, but in whom only neurolysis is performed because of a positive NAP, generally have favorable outcomes. Patients in whom direct end-to-end nerve repair can be performed generally have better outcomes than patients who undergo conventional interpositional nerve grafting. Improved techniques with nerve transfers, especially distal nerve transfers, have improved outcomes in peripheral nerve surgery in recent years. Direct nerve transfers have better outcomes than nerve transfers with interpositional grafts.

WHO SHOULD OPERATE

By extrapolation based on data related to other surgical techniques, it seems reasonable to expect improved outcomes in centers performing high-volume practice. Timely referral to centers specializing in evaluation and management of nerve injuries is important and should be considered.

SUMMARY

The treatment and management of nerve injuries require thorough knowledge of anatomy, of the nerve injury process, and of the available repair and reconstructive options. It also requires specific microsurgical skills in the context of a multidisciplinary team able to address the peripheral nerves and associated muscles, tendons, and joint problems, as well as concomitant injuries in the central nervous system (spinal cord and brain) and other systems.

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GAS GANGRENE OF THE EXTREMITY

Sharon Henry, MD, FACS, and Christine Cole, MD

Gas gangrene is a term generally reserved for a devastating infection caused by Clostridium species. Its occurrence is a medical and surgical emergency. Gas gangrene rapidly affects muscle and results in necrosis. Once a dreaded complication of battlefield wounds, in civilian populations it most commonly follows traumatic injury, particularly those occurring during natural disasters such as earthquakes, after operative procedures, or in association with drug injection, either medical or recreational, or spontaneously in the immunosuppressed or those with occult malignancy. Contaminated wounds can progress rapidly to gas gangrene when they are inappropriately closed or inadequately debrided. C. perfringens is the organism most commonly involved, but several other species are pathogenic. Clostridia produce exotoxins that lead to systemic phenomena, derangements and all its ability to invade locally. Early detection and treatment limit mortality and morbidity.

EPIDEMIOLOGY

Gas gangrene is rare, an estimated 0.1 to 1.5 cases occur per 1 million people. In the United States, 1000 cases are estimated to occur annually. Before the twentieth century, gas gangrene was a common cause of limb loss and death in wartime. The introduction of gunpowder increased the complexity of extremity wounds on the battlefield. Large, rubble lead ammunition of the Civil War produced compound fractures with tissue injury that favored the development of gas gangrene. The mortality rate from gas gangrene during the Civil War was 45%. Fleming, in a description of the bacteriology of wounds during World War I, identified C. perfringens (then w...ani) to be present in 41% of wounds in the first 7 days after injury. Five percent of the wounded developed gas gangrene. During World War II, early debridement, delayed closure, antitetanus, and penicillin administration combined to decrease the mortality rate of gas gangrene from 5... in 1 80 to 1902 to 22% by 1.36 to 1.45. Subsequent wars have seen a further decline in the incidence of gas gangrene in wounds. During the Vietnam War, the incidence declined to 0.02%. Rapid evacuation of the injured soldier with prompt wound debridement is responsible for the improvement. Civilian disasters continue to be a source of potential outbreaks of gas gangrene. The Wenchuan earthqua... e of 200... in China saw a 2.4% incidence of gas gangrene among hospitalized patients.

Gas gangrene occurs in three clinical settings: traumatic, postoperative/cultural, and spontaneous. A shift in the epidemiology of gas gangrene has occurred in recent decades, from traumatic injuries to postoperative wounds and sites of intravenous drug administration (Box 1). Traumatic causes include penetrating wounds from gunshots and stab injuries, crush injuries, and fractures, especially those injuries contaminated by soil. Nontraumatic cases are seen in postoperative wounds and among intravenous drug users. Central are colonization of the gut is a potential source of nontraumatic cases of spontaneous clostridial myonecrosis. These patients often have a hematologic or occult malignancy as their underlying predisposition to seeding from a gastrointestinal source, leading to "bland" myonecrosis. Mortality rates have decreased considerably in recent decades, but case fatality rates remain as high as 2...%.

PATHOGENESIS

George Nuttall and William Welch discovered C. perfringens in 1892. This gram-positive bacillus was initially called C. welchii but was renamed C. perfringens. This species is part of the normal flora of the human gastrointestinal, biliary, and genitourinary tracts. Soil, especially of farms or ranches, can be heavily contaminated with Clostridium species. It logically follows that traumatic open wounds that are heavily contaminated with soil are at risk from these organisms. C. perfringens is anaerobic but is somewhat aerotolerant. It forms spores that are heat resistant. The spores are capable of surviving in harsh environments and so can be difficult to eradicate. Under the proper conditions, this organism is capable of rapid multiplication and can have a generation time as short as 8 to 10 minutes with the production of a significant amount of gas.

Predisposing factors to the development of gas gangrene are lacerations, punctures, or crush wounds contaminated with soil that contain the spores. Immunocompromise is implicated in nontraumatic cases.

Initial growth of the organism begins within the area of devitalized tissue in an anaerobic environment. The infection advances through healthy living tissue, producing destruction and necrosis. It can advance at alarmingly rapid rates. Gas gangrene proceeds in four stages. Contamination and proliferation is the first stage. The degree and type of tissue injury and hypoxia and the amount of contamination are essential at this stage. A low pH favors the growth of clostridia. Muscle hypoxia leads to the release of amino acids and glycogen supporting survival and replication of the bacteria. Phagocytes are ineffective in the hypoxic environment. The bacteria elaborate toxins in stage 2. Muscle destruction provides nutrients such as

SUMMARY

The treatment and management of nerve injuries require thorough knowledge of anatomy, of the nerve injury process, and of the available repair and reconstructive options. It also requires specific microsurgical skills in the context of a multidisciplinary team able to address the peripheral nerves and associated muscles, tendons, and joint problems, as well as concomitant injuries in the central nervous system (spinal cord and brain) and other systems.

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BOX 1 Settings for Clostridial Myonecrosis

Trauma

Penetrating wounds
Crush injuries
Open fractures
Blast injuries
Natural disasters
Industrial injuries

Procedural

Gynecologic surgery
Postpartum
Gastrointestinal surgery
Injections
Radiation therapy

Spontaneous

Diabetes mellitus
Leukemia
Gastrointestinal malignancy
Diverticulitis
Drug-induced immunosuppression
HIV/AIDS
Peripheral vascular disease
Intravenous drug use
Malnutrition

TABLE 1 Clostridial Species

Species	Frequency
Clostridium perfringens	80%–90%
Clostridium novyi	8%
Clostridium septicum	6%
Clostridium histolyticum	<3%
Clostridium sordellii	<3%
Clostridium fallax	<1%

FIG. 1 Classic skin changes. Bullae forming and widespread skin discoloration.

branched chain amino acids and carbohydrates. An acidic environment with higher sodium to potassium ratio is ideal for continued bacterial growth and toxin production. Stage 3 is tissue destruction. The toxins create their effect systemically and locally. A hallmark of clostridial infection is the lack of inflammatory response. The α toxin produced increases the adherence of platelets and neutrophils causing vascular occlusion. This occlusion results in tissue ischemia and death and accounts for the pain noted clinically. The last stage is systemic toxicity. θ- and ι1 toxins combine to interact with macrophages, platelets, and endothelial cells to induce cytokine production. Tumor necrosis factor-α and interleukin 1 and 6 contribute to the development of shock and multiple organ dysfunction. The toxins also have direct effects on phagocyte and macrophage function, as well as on endothelial integrity. Toxins induce hemolysis and directly affect cardiac output, heart rate, and systemic vascular resistance.

C. perfringens is the organism most commonly cultured from traumatic wounds that have developed gas gangrene. *C. perfringens* is the causative organism in 80% to 95% of cases (Table 1). Other clostridial species cultured include *Clostridium novyi* (8%), *Clostridium septicum* (6%), and *Clostridium histolyticum*, *Clostridium fallax*, and *Clostridium sordellii* (1%). *C. septicum* infections frequently spread from a hematogenous or gastrointestinal source. Patients who survive an episode of gas gangrene with this organism should be evaluated for occult gastrointestinal malignancy. Nearly three-quarters of patients with *C. septicum* gas gangrene have a malignancy. A gastrointestinal malignancy was noted in about one-half of those patients, and another one-third will have a hematologic malignancy. *C. novyi* and *C. sordellii* have been associated with outbreaks among injection drug users. Table 1 shows the clostridial species most commonly seen in gas gangrene infections.

PRESENTATION

It can take as little as 6 to 8 hours for a clostridial infection to become well established, and muscle destruction can progress rapidly. It generally occurs within 2 to 5 days of the injury, although cases with longer incubation times have also been reported.

Pain is the first symptom noted. It is described as out of proportion to the degree of injury and is "sometimes so sudden as to suggest a vascular catastrophe." The pain may progress to anesthesia. Tissue changes develop rapidly and include swelling, blistering, purple skin discoloration, and then fluid drainage. Fig. 1 shows classic advanced skin changes. A musty or sweet odor may be present. Patients frequently display mental status changes, hypotension, anemia, thrombocytopenia, and acute kidney injury. A profound leukemoid reaction with a white blood cell count (WBC) of greater than 30 × 10⁹/L or leukopenia can be seen with gas gangrene. Pyrexia is usually absent, and the patient is instead hypothermic.

Tissue cultures with gram stains are vitally important to support the clinical diagnosis. Blood cultures are typically negative in gas gangrene but should be obtained in any case. In the case of post-traumatic or postoperative causes, the diagnosis may be clearly evident. In the case of nontraumatic gas gangrene, the earliest signs are nonspecific and include pain and mental confusion. In this case, imaging can be

FIG. 2 The right leg of a patient who presented with rapidly progressive pain in the leg. On transfer to a tertiary center extensive skin changes were apparent, as was proximal limb involvement. This patient died despite undergoing a hip disarticulation. Notice the necrosis to the tumor.

essential to help localize the site of infection before the advanced or classic physical findings are evident. Whenever there is clinical doubt, operative exploration is warranted to exclude the diagnosis. Figs. 1 and 2 show the classic skin changes with subcutaneous discoloration and blistering.

DIAGNOSTIC TESTS

Ancillary diagnostic imaging may not be of value in evaluating for gas gangrene. Frequently clinical symptoms are advanced enough to require no further imaging. Plain radiography or ultrasound scanning can identify air in the tissues and is probably more sensitive than physical examination; however, in cases not due to trauma or related to a procedure computed tomography scan can be useful for identifying an occult site (Fig. 3). Some describe magnetic resonance imaging as useful. Operative exploration for diagnosis may be necessary in case of clinical uncertainty. Exploration is unlikely to worsen the clinical condition.

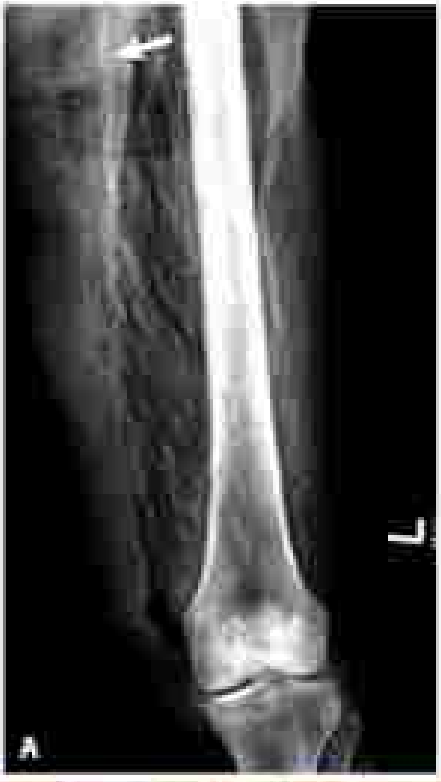
TREATMENT

Resuscitation occurs simultaneously with evaluation. Broad-spectrum antibiotics should be given at the outset (Table 2). *C. perfringens* is very penicillin sensitive; however, it may be present alone or in combination with gram-positive, gram-negative, or other anaerobes. *C. septicum* has some penicillin resistance. Protein synthesis inhibitors are added to penicillin to limit toxin production. Standard blood work includes complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, and creatine phosphokinase, liver function tests, and possibly erythrocyte sedimentation rate and C-reactive protein. Anemia, thrombocytopenia, and coagulation abnormalities may be present and require correction with the resuscitation. Tetanus immunization should be updated and tetanus immune globulin administered to those patients not vaccinated previously.

OPERATIVE TREATMENT

Definitive treatment is surgery. Although those patients present with severe physiologic derangement and some attempt at correction must occur before surgery, it is important to recognize that the physiology will not be restored with medical therapy alone and proceeding to the operating room even with persistent physiologic abnormalities is a risk that must be taken. The resuscitation can continue into the operative phase of treatment.

The extremity must be circumferentially prepped and draped, extending to the joint above and below the involvement. When the diagnosis is in question, exploration of the extremity can be diagnostic. Historically amputation has been the only procedure recommended to treat gas gangrene. Amputation is often quick and definitive. The goal is to get ahead of the infection. The limb is removed above the level of gross involvement of infection. If amputation is planned, through joint amputation should be considered because it is frequently less time consuming and results in lower blood loss. It also spares tissue for reconstruction or closure. A tourniquet used during surgery can diminish blood loss. Tourniquet use is generally discouraged in the patient with vascular disease or diabetes undergoing an amputation. However, with a patient in an unstable condition due to coagulopathy or thrombocytopenia, use of this device may prevent further debilitation from blood loss.



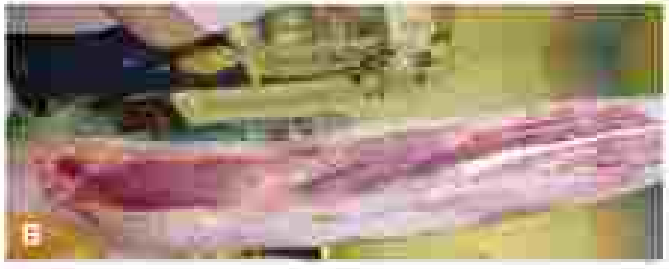


FIG. 3 (A) Computed tomography scan scout film demonstrating military appearance of air in the muscle. Also note calcified femoral artery (*arrow*). (B) Note abnormal appearance of the muscle: splendor of arm muscle with dark maroon and pale light areas with no bleeding note vertical incision that allows proximal and distal extension.

Unfortunately, gas gangrene often involves the proximal extremities, making forequarter or hindquarter amputation necessary. When hip or forequarter amputation is necessary, tourniquets are not an option (Fig. 2). There is a balance between aggressive debridement to remove compromised tissue and arrest bacterial growth with tissue preservation for further reconstruction and the possibility of recurrence of infection.

The patient's physiology usually drives decision making regarding amputation or limb salvage. In less dire cases exploration of the compartments with resection of the involved muscles is an option. When debridement is the chosen option, a vertical skin incision is made over the area of maximal skin abnormality because the skin with evidence of purpura or necrosis will be removed with the debridement. Because this infection strikes the muscle, it is therefore vital to ensure

TABLE 2 Antibiotic Choices

Clinical Circumstance	Antibiotics
Empiric antibiotics	Piperacillin-tazobactam
Gram negative	Imipenem-cilastatin
Gram positive	Meropenem
Anaerobes	Cefoxitin/ceftriaxone/cefotaxime/ceftazidime + clindamycin
With suspicion of MRSA	Add vancomycin Daptomycin Linezolid
Targeted to *Clostridium* species	High-dose penicillin (*Clostridium septicum* can be resistant) Clindamycin (inhibits toxin production)

MRSA, Methicillin-resistant *Staphylococcus aureus*.

FIG. 4 Patient from Figure 1 after subsequent amputation and extensive chest wall debridement. Negative pressure wound therapy is used to manage the wound after the active infection is controlled.

exploration of the muscle compartments because the more superficial tissue may appear unaffected. The dissection must continue through the deep fascia for thorough muscle inspection. Debridement must extend to viable muscle. It is imperative that all devitalized muscle be removed. Evaluate the muscle for color, consistency, contractility, and perfusion. Nonviable muscle is friable and pulls away easily, offering little resistance to removal. Involved muscle has a characteristic dark, maroon, or pale appearance, does not contract when stimulated with the cautery, and does not bleed when cut. (Fig. 3B shows abnormal muscle appearance.) Knowledge of the distribution of the neurovascular bundles in the muscle compartment is essential because the functional outcome can be impaired through inadvertent or unnecessary transection of blood vessels or nerves. When multiple muscle groups are involved, or the patient is hemodynamically compromised, amputation may be the best treatment option. Cultures of fluid and tissue from the wound should be obtained in the operating room. Gut gram stains can indicate the types of bacteria present and influence antibiotic choice. Pathologic evaluation can be requested as well if there is a question regarding the diagnosis.

Wound care with simple gauze dressing is the best option for immediate wound management. Gauze is inexpensive and can frequently be changed to allow the evaluation of the wound at the bedside to assess for advancing infection. Planned reevaluation of the wound in the operating room is imperative. Return is planned for 12- to 24-hour intervals until the infection is entirely controlled. Advanced wound care using negative pressure wound therapy (Fig. 4), alginates, foam, and antimicrobial impregnated dressings can be considered once the infection is controlled. These infections result in large wounds that are disfiguring and require multiple operative procedures. Caring for these patients is resource intense. Hospital and intensive care unit stays are extensive. Sepsis and the large surface area of the wound continue to increase the basal metabolic rate and increase nutritional requirements. Wound coverage ultimately requires skin grafts and or skin flaps (Fig. 5).

HYPERBARIC OXYGEN THERAPY

The use of hyperbaric oxygen for the treatment of gas gangrene is controversial. The controversy lies mostly in the lack of randomized controlled trial data supporting its routine use as an adjunct to management in the infection. Theoretically, enhanced delivery of oxygen through the tissue can be lethal to the clostridial bacteria. Because clostridia lack superoxide dismutase, they cannot survive in an oxygen-rich environment. High oxygen tensions stop α-toxin production. However, dormant spores of *Clostridium* species are unaffected by the high arterial Po_2 of 800 to 1000 mm Hg. Although

FIG. 5 Patient from Figure 4 after skin graft. Patient grew *Clostridium septicum* and was subsequently diagnosed with advanced colon cancer.

in vitro studies demonstrated hyperbaric oxygen therapy (HBOT) to be effective, clinical findings have been mixed. Small retrospective studies using a variety of protocols have yielded both positive and negative effects on outcome measures. HBOT should not delay resuscitation, antibiotic administration, or surgical debridement.

OUTCOMES

Clostridial gas gangrene infections are life changing for patients. They often affect previously healthy people, rapidly progress, and may result in sepsis and death. In a retrospective review, Ellis and colleagues identified death correlating with the presence of organ failure at admission and delay in the first debridement. Aniya and

associates found death to occur more commonly in patients who had a WBC higher than 30 × 10⁹/L, serum creatinine greater than 2 mg/dL, or preexisting heart disease. Others have found that mortality increased with the presence of premorbid conditions. The mortality rate was more than 50% in patients who had three or more of the following risk factors: age older than 50 years, malnutrition or obesity, diabetes, injection drug use, and hypertension. In short, clostridial gas gangrene infections are rapidly progressing infections that necessitate equally rapid and early diagnosis and treatment. Although novel therapies are currently under investigation as adjuncts to the treatment, surgical debridement remains the cornerstone of treatment.

Suggested Readings

Anaya DA, McMahon K, Nathens AB, et al. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg 2005;140:151–157.

Brazier JS, Hawkey PM, Hall V, et al. Isolation and identification of *Clostridium* spp. from infections associated with the injection of drugs. *J Med Microbiol* 2002;51:927–930.

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Necrotizing Skin and Soft Tissue Infections

Patrick B. O'Neal, MD, and Carl P.E. Hart, MD

OVERVIEW

Necrotizing skin and soft tissue infections (NSTIs) represent a range of infectious conditions causing deep tissue necrosis, with nomenclature based on location of infection, pathogen, and depth of necrosis. The most frequently used names include necrotizing fasciitis, Fournier's gangrene, clostridial myonecrosis, synergistic necrotizing cellulitis, and gas gangrene. Necrotizing fasciitis represents infection extending through the deep fascia below the subcutaneous layers. Fournier's gangrene is a similar condition that originates in the perineum, whereas clostridial myonecrosis and synergistic necrotizing cellulitis extend into the deep muscle compartments, causing muscular necrosis. These diseases have received extensive media attention and have been lumped under the catchy rubric of "flesh-eating" bacterial disease. Hippocrates (400 BC) acknowledged necrotizing fasciitis as "diffuse erysipelas caused by trivial accidents, where flesh, sinews, and bones fall away in large quantities, leading to death in many cases." The elaborate categorization of these conditions has caused confusion regarding this disease. Put simply, the pathophysiology of these infections in all categories is the same and is the result of bacterial penetration of skin defenses, causing widespread necrosis and leading to rapid systemic deterioration and death. Any patient who presents with signs or symptoms concerning for NSTI should raise a sense of urgency for the clinician to achieve rapid diagnosis and deliver early treatment. Unfortunately, the diagnosis of NSTI can be difficult, tempting the clinician to postpone his eating treatment while obtaining time consuming diagnostic studies. This should be absolutely avoided in favor of urgent operative management.

PATHOPHYSIOLOGY

NSTI occurs when bacteria gain entry into the subcutaneous layers of the body where areas of relatively poor blood flow and relative hypoxia exist. Such conditions allow for poor immune response to infection and rapid overgrowth and spread of bacteria. Often, these microorganisms elaborate toxins that lead to both direct necrosis and indirect necrosis through thrombosis of perforating vessels and vasoconstriction increasing tissue hypoxia. Furthermore, these bacteria elaborate exotoxins that can lead to shock and multiorgan dysfunction.

DIAGNOSIS

Necrotizing fasciitis is a rare disease with an incidence estimated at 0.4 cases per 100,000 individuals by the United States Centers for Disease Control and Prevention. Because delay in adequate treatment can have tremendous deleterious effects on outcome with increased morbidity and mortality, early diagnosis is paramount in dealing with necrotizing soft tissue infections. Surgical consultation should be immediate, and surgeon judgment should dictate management when diagnostic ambiguity exists. A thorough history and physical examination should be performed because this diagnosis relies more on clinical judgment rather than diagnostic testing. Certain comorbidities may predispose patients to this disease. Such conditions include advanced age, obesity, diabetes mellitus, alcoholism, cirrhosis, chronic debilitation, encephalopathy, intravenous drug use, immunosuppression, malignancy, chemotherapy, hypertension, chronic obstructive pulmonary disease, congestive heart failure (conditions that impair oxygen delivery), end stage renal disease, peripheral ulcers, perforated viscus, and recent surgery. A thorough history to assess patient comorbidities and risk factors may help raise suspicion of this problem. Despite this extensive list of predisposing conditions, as many as 20% of NSTIs occur in patients with no apparent predisposing factor. Although NSTI may seem to occur spontaneously without any clear injury or portal of entry, NSTI often originates in the perineum, diabetic foot ulcers, decubitus ulcers, necrotic ulcers, puncture and traumatic wounds, and as a result of perforated viscus with subsequent soiling of soft tissues.

Initial physical examination findings may range from minimal to quite dramatic (Table 1). Some of the findings can include swelling, induration, mild to exquisite tenderness, crescendo pain, mild to violaceous erythema, tenderness beyond areas of erythema, cutaneous anesthesia, necrotic tissue in skin with a blue or purplish hue, and wounds exuding purulent, gray, or foul smelling drainage (Fig. 1). The skin may blister or slough, and crepitus may be present, indicating gas formation in the tissues. Crepitus, however, is present in only a fraction of patients and should not be relied on for diagnosis. One must keep in mind that obvious signs of NSTI may be subtle. Any patient with soft tissue exhibiting pain out of proportion to examination findings should be considered to be potentially harboring an elusive deep NSTI that has yet to make itself obvious because early skin changes may be minimal despite extensive subcutaneous fat, fascia, or muscle destruction. Tenderness beyond areas of erythema may be particularly ominous because it is indicative of rapidly progressive infection in the deep layers beneath the skin.

The hallmark of NSTI is its rapidly virulent and destructive behavior. Tracking within the fascial planes beneath the skin, a place with

associates found death to occur more commonly in patients who had a WBC higher than 30 × 10⁹/L, serum creatinine greater than 2 mg/dL, or preexisting heart disease. Others have found that mortality increased with the presence of premorbid conditions. The mortality rate was more than 50% in patients who had three or more of the following risk factors: age older than 50 years, malnutrition or obesity, diabetes, injection drug use, and hypertension. In short, clostridial gas gangrene infections are rapidly progressing infections that necessitate equally rapid and early diagnosis and treatment. Although novel therapies are currently under investigation as adjuncts to the treatment, surgical debridement remains the cornerstone of treatment.

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The hallmark of NSTI is its rapidly virulent and destructive behavior. Tracking within the fascial planes beneath the skin, a place with

TABLE 1 Necrotizing Fasciitis Signs and Symptoms

Early	Late
LOCAL	
Skin puncture or injury	Hemorrhagic bullae
Erythema	Necrosis
Warmth	Purple/blue skin color
Tenderness	Crepitus
Myalgia	Hypesthesia
Hypersensitive skin	Sensorimotor deficit
SYSTEMIC	
Pain out of proportion	Fever (sometimes hypothermia)
Swelling	Hypotension
Fever	Mental confusion
	Multiorgan failure

From Wang YS, Wang CH, Tay YK. Staging of necrotizing fasciitis based on the evolving cutaneous features. *Int J Dermatol*. 2007;46:1036–1041.

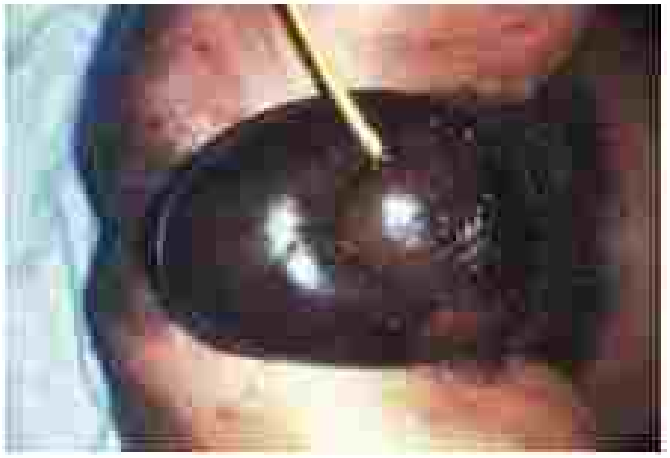

FIG. 1 Black discoloration of penile, scrotal, and perineal skin in a patient with necrotizing infection of the perineum. There is also erythema, edema, and serous exudation over the lower abdomen. (From Quiñones D, Kuo AMK. Necrotizing soft tissue infections. In: Stevens D, Bisno A, eds. *2009 IDSA Clinical Practice Guidelines for Clinical Diagnosis and Management of Infectious Diseases*. London: Future Medicine Ltd; 2009:49–67.)

poor vascularity and thin host defenses, allows for the rapid spread of bacteria and overwhelming infection. Most patients quickly develop signs of systemic toxicity, including high fever, nausea, vomiting, malaise, tachycardia, hypotension, shock, mental status changes, and oliguric renal failure.

Laboratory values are nonspecific. White blood cell counts may reveal extreme leukocytosis, leukopenia, and high bandemia. Other common laboratory abnormalities include those indicating dehydration/fluid sequestration, such as low bicarbonate levels, elevated blood urea nitrogen, creatinine, and lactate levels. Additionally, patients may present with hyponatremia, elevated creatine phosphokinase, hyperamylasemia, and coagulopathy. The Laboratory Risk Indicator for Necrotizing Fasciitis Score System (Table 2) can be used as an adjunct to assess the probability of necrotizing fasciitis. It is important to remember, however, that this scoring system is meant to assist in risk stratification but is not meant to supersede sound surgical judgment. Those patients with low risk scores may still have NSTI, whereas those with high risk scores may not have NSTI. Thus this scoring system should not discourage operative debridement when clinical suspicion is high.

TABLE 2 LRINEC Score System

LRINEC Variable	Values	Score Points
C-reactive protein (mg/L)	<150	0
	≥150	4
WBC (cells/mm³)	<15	0
	15–25	1
	>25	2
Hemoglobin (g/dL)	>13.5	0
	11–13.5	1
	<11	2
Sodium (mmol/L)	≥135	0
	<135	2
Creatinine (mg/dL)	≤1.6	0
	>1.6	2
Glucose (mg/dL)	≤180	0
	>180	1
Sum of Points	**Risk Category**	**Necrotizing Fasciitis Probability**
≤5	Low	<50%
6–7	Intermediate	50%–75%
≥8	High	>75%

For intermediate and high risk patients, the model has positive predictive value of 92.3 and negative predictive value of 96.

LRINEC, Laboratory risk indicator for necrotizing fasciitis; WBC, white blood cells.

From Wong CH, Khin LW, Heng KS, et al. The LRINEC (laboratory risk indicator for necrotizing fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32:1535–1541.

Because of the rapid lethality of necrotizing soft tissue infection, one should be cautious about obtaining advanced radiographic evidence of disease because this can delay lifesaving operative treatment. If obtained quickly in relatively stable patients, plain films may reveal air tracking in the soft tissues. Computed tomography and magnetic resonance imaging may show air tracking in soft tissues, fascial separation, and abscess formation, but often these studies do not add much because they may only reveal edema and nonspecific fat stranding. In unstable patients, these studies should be avoided in favor of rapid transfer to the operating room.

Biopsy of involved tissue typically reveals liquefaction necrosis of subcutaneous tissues and fascial layers with polymorphonuclear infiltrates and thrombosis of the perforating vessels to the skin. The fascial planes may weep a dishwater appearing or hemorrhagic fluid; fixation of soft tissues and digital probing may reveal separation of subcutaneous tissue from underlying fascia with minimal effort.

MICROBIOLOGY

Necrotizing fasciitis is well suited to a classification system based on the pathogen of origin. Type I represents polymicrobial infections, type II represents monomicrobial infections, type III represents

TABLE 3 Organisms Recovered From 198 Consecutive Patients With Necrotizing Soft Tissue Infections

Organism	No. of Cultures	No. of Isolates (% of Cultures)
Aerobic:		
Streptococci	182	83 (45.6)
Enterococci	182	61 (33.5)
Staphylococci	182	64 (35.2)
Escherichia coli	182	57 (31.3)
Proteus spp.	182	38 (20.9)
Other gram-negative bacilli*	182	76 (41.8)
Anaerobic:		
Peptostreptococci	151	45 (30.4)
Bacteroides spp.	128	29 (56.7)
Clostridium perfringens	129	13 (10.3)
Other clostridia	128	17 (13.3)
Other anaerobic species	128	27 (21.1)
Fungal species	171	9 (5.3)

*No information provided: Klebsiella spp., Enterobacter spp., Pseudomonas, Acinetobacter spp., Hemophilus influenzae, Citrobacter freundii.

From Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg. 1996;224:672–683.

marine organisms, and type IV represents fungal organisms. In all classifications, the organisms gain entry to the subcutaneous space multiplying in areas of relative hypoxia and low blood flow, allowing for rapid proliferation.

As many as 75% of necrotizing soft tissue infections are polymicrobial, with an average of four organisms in a single infection (Table 3). For this reason, initial antibiotic treatment should be broad in spectrum. Polymicrobial infections often cause extensive local damage but on the whole are less lethal than other highly virulent monomicrobial infections. The most commonly isolated gram-positive organisms in polymicrobial infections include *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Enterococcus* species. *Escherichia coli* is the most common gram-negative organism isolated, whereas *Bacteroides* species and *Peptostreptococcus* species are the most common anaerobes isolated from polymicrobial infections.

The patient's history and physical examination may provide clues regarding which organisms may be the culprit of the soft tissue infection. Soft tissue infections located in the perineum, those secondary to perforated viscus, and those secondary to decubitus ulcers in diabetics, foot ulcerations tend to be polymicrobial in nature. These infections may contain all three, gram positive, gram negative, and anaerobic organisms.

Monomicrobial infections tend to be more aggressive, commonly presenting with acute onset and rapid progression to fulminant infection. Highly virulent pathogens include *Streptococcus pyogenes* (group A, β-hemolytic *Streptococci*), *Clostridium* species, community-acquired methicillin resistant *Staphylococcus aureus* (MRSA), *Vibrio vulnificus*, and *Pseudomonas aeruginosa*.

Group A, β-hemolytic *Streptococci*, by far the most common monomicrobial isolate, can result in a rapidly progressive NSTI with systemic toxicity and high mortality rates. These bacteria produce exotoxins that independently cause systemic toxicity resulting in multisystem organ failure. Additionally, exotoxins released include powerful proteolytic enzymes such as hemolysins, fibrinolysins, hyaluronidases, streptokinases, M proteins, leukocidins, and streptolysin O and S. These allow for rapid tracking through otherwise healthy tissue.

Clostridium species such as *Clostridium perfringens* are of particular concern in puncture and traumatic wounds, as well as in intravenous drug users. *Clostridium* also produces exotoxins that are responsible for its rapid destructive spread, systemic toxicity, and high mortality rate. *Clostridium* reproduces every 8 minutes and produces a toxin (phospholipase C) and 8 toxin (perfringolysin). These toxins cause direct tissue injury, kill neutrophils, as well as impede migration, and lead to hemolysis, microvascular thrombosis, and increase vascular permeability leading to rapid destruction of soft tissues including muscle tissue. Additionally, α toxin directly inhibits myocardial contractility resulting in shock.

NSTI resulting from community-acquired MRSA is on the rise. Community-acquired MRSA is able to produce exotoxins that lead to direct tissue invasion and necrosis. In addition, this bacterium has the ability to produce Panton Valentine leukocidin, which is a potent white blood cell and dermonecrotic toxin. Common populations affected with this disease include contact sports teams, prisoners, military recruits, injection drug users, institutionalized residents, and those who attend child and adult day care centers.

Bite wounds and water borne infections are unique subdivisions of polymicrobial infections that, in addition to the more common bacteria species, tend to harbor unusual organisms including *Pasteurella multocida* in cat and dog bites and *Capnocytophaga canimorsus* from dog bites. In human bite wounds, *Eikenella corrodens* is common. Water borne infections often contain *Vibrio* and *Aeromonas* species.

TREATMENT

Support

On identifying patients with necrotizing soft tissue infection, rapid operative management should be made top priority and not be delayed for any other therapeutic or monitoring interventions so as not to increase risk of morbidity and mortality. Nonetheless, supportive measures should be initiated as soon as possible in an intensive care unit. Appropriate antibiotic therapy should be immediately delivered. Invasive monitoring should be implemented including arterial lines for blood pressure monitoring and central venous lines for the delivery of medications and central venous pressure monitoring. Patients should receive aggressive fluid resuscitation as well as vasopressor and inotropic support when needed. Aggressive glycemic control can improve outcomes; thus an insulin drip may be appropriate. Serial laboratory values should be obtained because these patients can have rapid fluid and electrolyte shifts. Foley catheter placement and lactic acid measurements can be used to direct fluid resuscitation. Urine myoglobin and creatine kinase levels should be obtained when rhabdomyolysis is suspected. Blood products should be made available because it is not unusual for these patients to develop coagulopathy or have excessive operative blood loss. Early parenteral or enteral support should be initiated on a patient dependent basis. These patients exhibit high protein and caloric requirements due to their highly catabolic state.

ANTIBIOTIC THERAPY

Antibiotic therapy should be initiated immediately on presentation and continued until there is no further evidence of infection in the involved tissues or signs of systemic toxicity. Antibiotic choice should initially be broad spectrum and then tailored to microbiologic obtained from specimens retrieved at the time of surgery (Table 3). One should acknowledge the likely origin of infection in choosing antibiotics. For example, infections from perineal and intraabdominal sources or from diabetic foot ulcers and pressure sores are more

TABLE 4 Suggested Antimicrobial Therapy for Necrotizing Infections Based on Suspected Causative Organisms

Agent	Dose	Comment
EMPIRIC THERAPY		
Vancomycin*	15 mg/kg IV q12h	
Plus one of the Following		
Piperacillin/tazobactam (Zosyn)	3.375 g IV q6h	Use aminoglycoside or fluoroquinolone with anaerobic coverage, i.e., metronidazole in patients with penicillin allergy
Ertapenem (Invanz)	1 g IV q24h	
Meropenem (Merrem IV)	1 g IV q8h	
Imipenem/cilastatin (Primaxin)	1 g IV q6–8h	
Ciprofloxacin (Cipro)	400 mg IV q12h	Require added anaerobic coverage, i.e. metronidazole
Cefotaxime (Claforan)	2 g IV q4h	
Or		
Cefoxitin	2 g IV q12h	Broad spectrum coverage including MRSA, requires added anaerobic coverage, i.e., metronidazole
Tigecycline (Tygacil)	100 mg IV, then 50 mg IV q12h	
Consider Adding to Any of These Regimens		
Clindamycin*	600–900 mg IV q8h	Provides anaerobic coverage and inhibits bacterial ribosomal exotoxin synthesis
When Newer Agents Are Unavailable, Consider		
Vancomycin*	15 mg/kg IV q12h	Provides broad spectrum coverage including MRSA and anaerobes, excellent streptococcal and clostridial coverage, clindamycin inhibits bacterial ribosomal exotoxin production, may be a lower cost regimen with improved availability in some areas
Plus		
Penicillin	2–4 MU IV q4–6h	
Plus		
Gentamicin (Gram negative coverage)	2–2.5 mg/kg IV q24h	
Plus		
Clindamycin*	600–900 mg IV q8h	
INFECTIONS DUE TO STREPTOCOCCI		
Penicillin	2–4 MU IV q4–6h	Use vancomycin, linezolid (Zyvox), or daptomycin (Cubicin) in patients with severe penicillin allergy
Plus		
Clindamycin	600–900 mg IV q8h	Inhibits bacterial exotoxin production by streptococci
INFECTIONS DUE TO MRSA		
Vancomycin	15 mg/kg IV q12h	Does not inhibit toxin production
Linezolid	600 mg IV q12h	Bacteriostatic, inhibits toxin production
Daptomycin	6 mg/kg IV q24h	Bactericidal, excellent tissue penetration, risk myopathy
Ceftaroline	600 mg IV q12h	Bactericidal
Quinupristin/Dalfopristin (Synercid)	7.5 mg/kg IV q8h	Bactericidal, inhibits toxin production
INFECTIONS DUE TO CLOSTRIDIUM SPECIES		
Penicillin	2–4 MU IV q4–6h	
Plus		
Clindamycin	600–900 mg IV q8h	
INFECTIONS DUE TO ANIMAL AND HUMAN BITES		
Ampicillin/sulbactam	1.5–3 g IV q6–8h	Good activity against *Pasteurella multocida* and *Eikenella corrodens*
Cefuroxime (Ceftin, Zinacef)	1 g IV q24h	
Cefoxitin	1 g IV q6–8h	
Ciprofloxacin	400 mg IV q12h	

Continued

TABLE 4 Suggested Antimicrobial Therapy for Necrotizing Infections Based on Suspected Causative Organisms—cont'd

Agent	Dose	Comment
INFECTIONS DUE TO WATER-BORNE BACTERIA (E.G., SHELLFISH WORKERS)		
***Aeromonas* Species**		
Doxycycline	100 mg IV q12h	
Plus		
Ciprofloxacin	400 mg IV q12h	
Or		
Ceftriaxone	1–2 g IV q24h	
***Vibrio* Species**		
Doxycycline	100 mg IV q12h	
Plus		
Ceftriaxone	1 g IV q24	
Or		
Cefotaxime	2 g IV qid	

IV, Intravenously; MRSA, methicillin-resistant *Staphylococcus aureus*; mU, million units; q, every; qid, four times daily; tid, three times daily.
*The combination of vancomycin and clindamycin can be substituted with linezolid alone in patients requiring >2 weeks of MRSA coverage and who are receiving an serotonin reuptake inhibitors.

likely to be polymicrobial, whereas necrotizing infections are more likely to be monomicrobial. Extremity infections, infections related to intravenous drug use, and infections in patients from certain backgrounds including prison inmates, Alaska natives, institutionalized individuals, and athletes are more likely to harbor community-acquired MRSA.

Infections that are likely polymicrobial can be treated empirically with broad-spectrum agents such as piperacillin-tazobactam, imipenem-cilastatin, meropenem, ticarcillin-clavulanate, and tigecycline. Vancomycin and metronidazole should be included as part of empiric therapy if MRSA and anaerobes are not covered by other agents. Evidence suggests that clindamycin's ribosomal inhibitory properties may reduce toxin production responsible for widespread organ dysfunction. As such clindamycin should be considered as an adjunct to other antimicrobial regimens. Like clindamycin, linezolid also has ribosomal blocking properties that may reduce toxin production. Combination therapy with both vancomycin and clindamycin can be substituted with linezolid alone, which covers MRSA and has ribosomal inhibitory activities. The combination of vancomycin, penicillin, and clindamycin along with a gram-negative agent such as an aminoglycoside can be used for empiric therapy if newer antimicrobials are unavailable. This combination exhibits broad-spectrum coverage including MRSA and anaerobes with a strong effectiveness against *Streptococcus* and *Clostridium*, has excellent tissue penetration, provides reduction of bacterial toxin production by clindamycin, tends to be readily available, and may have a lower cost. This combination will, however, not cover for penicillinase-producing organisms in areas where these organisms are prevalent. Antimicrobials should be de-escalated as soon as culture results and sensitivities are available. Antibiotics should be continued until the patient's clinical condition has stabilized, fever has subsided, and white blood cell count is normal.

SURGERY

Surgery should focus on rapid identification of affected tissue, with complete excision of all devitalized skin and soft tissue (Fig. 2). Reports show a seven- to nine-fold increased risk of death with inadequate or delayed initial debridement. Incision should be made with dissection through all soft tissue layers until the deep muscle

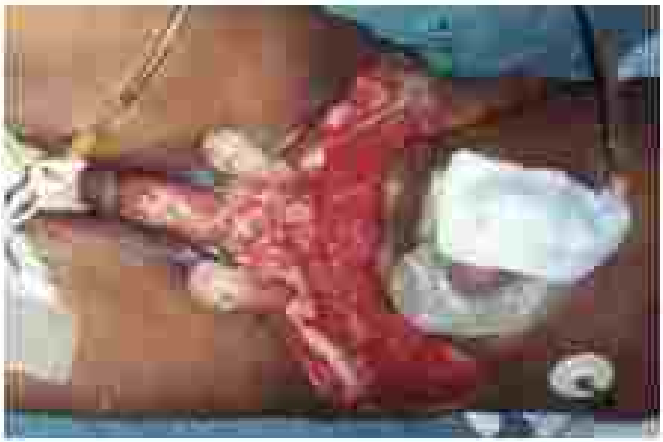

FIG. 2 Extensive debridement of the scrotum, penis, perineum, and lower abdomen was performed. A sigmoid loop colostomy was also created. (From Daigle CJ, Kuru AM: Necrotizing infection of the perineum. *Emerg Physician*. 2008;6:37.e5.)

layers are encountered. A thorough probing of all tissue and fascial planes to assess for tracking should be made to direct further dissection. Typical findings indicating devitalized tissue include murky dishwater appearing fluid in the subcutaneous fat and fascial layers, tissue that dissects from deeper tissue with minimal resistance, nonbleeding tissue, and vascular thrombosis. Non-contractile muscle indicates devitalized muscle tissue. All tissue overlying involved fascial planes should be immediately debrided along with the affected fascia. Easy separation of fascia from underlying tissue using the "finger test" indicates active infection and indicates tissue that should be debrided. All fluid collections should be drained. Debridement should extend back to viable soft tissue and muscle that exhibit brisk bleeding. Tissue (including fascia) should be sent to microbiology for Gram stain and culture for aerobic, anaerobic, fungal organisms to help tailor antibiotic usage.

In certain patient populations and NSTI presentations, operative management should be further tailored. Amputation may be necessary for infections rapidly progressing toward the trunk, involving major joints, or if extensive myonecrosis has occurred. Guillotine amputations of lower extremities should be considered, especially in patients with peripheral vascular disease for rapid containment of infection. In patients suffering from Fournier's gangrene, all affected perineal soft tissue including the scrotum and penile skin should be debrided and colonic diversion considered. Colonic diversion may need to be delayed until a second operation, depending on patient stability. Testicles can usually be preserved because they have an independent blood supply, although removal should not be delayed if they are involved. Patients with perforated viscus will require the intraperitoneal injury to be addressed, likely with diversion if caused by perforated colon.

Return to the operating room within 24 hours or earlier for a second look should strongly be considered and debridement of any retained devitalized tissues performed. Patients may require multiple trips to the operating room before the infection is eradicated completely, with a median number of returns around four.

Wounds should be treated with serial wet-to-dry dressing changes until all infection has been cleared. Some authors prefer Dakin's or iodine soaked gauze dressings and some authors recommend the use of topical antibiotics such as silver sulfadiazine. Vacuum assisted closure of wounds can send once the infection is cleared either as a primary therapy or until reconstruction is done. *No tissue grafting* should be attempted until infection is fully treated and the patient's condition has stabilized.

Adjunct Treatments

Although urgent surgical debridement is the most important therapeutic maneuver for NSTI and should never be postponed in favor of other treatment modalities, it is worth mentioning a number of mostly theoretical adjunct treatments. These include hyperbaric oxygen therapy, intravenous immunoglobulin, and plasmapheresis. Hyperbaric oxygen therapy works on the premise that it increases oxygen supply to infected tissues thus inhibiting bacterial growth and improving host response to infection. Evidence supporting hyperbaric oxygen therapy is limited, and many authors refute effectiveness. Furthermore, as urgent surgical debridement is the most lifesaving therapy, no patient should be transferred to a facility housing a hyperbaric oxygen chamber without first performing adequate surgical debridement. Intravenous immunoglobulin works by binding exotoxins and potentially decreasing systemic toxicity. Plasmapheresis filters bacterial exotoxins that result in shock and multiorgan dysfunction. By reducing circulating toxin, intravenous immunoglobulin and plasmapheresis may hasten recovery from systemic shock. Again, evidence for these treatment modalities is controversial.

RECONSTRUCTION

Reconstruction should be initiated as soon as possible once all infection has been eradicated and systemic toxicity has subsided. This will aid in ensuring hemostasis, speed healing, decrease fluid losses, and improve final cosmetic outcome. Split thickness skin grafts are favored. Staging reconstructions are used for complex reconstructions. The assistance of a plastic surgeon or urologist may be beneficial for difficult areas such as the hands, face, and perineum particularly if flaps are needed or pockets need to be made for uncovered testicles.

COMPLICATIONS

Multiple complications can occur with NSTI. Despite attempts at improving recognition and speed in surgical management of necrotizing fasciitis, improvement in mortality has been plagued with death rates remaining around 25%. Obviously, with the extent of debridement necessary, disfigurement and disability are considerable. Contractures can occur in involved limbs. Secondary infections in the critically ill are common including line infections, pneumonias, urinary tract infections, and secondary soft tissue infections. For those with Fournier's gangrene, impotence and decreased sperm count or motility are common. In addition, debridement of the perineal muscles may result in fecal incontinence and the need for a permanent colostomy.

CONCLUSION

Necrotizing soft tissue infections should be promptly recognized to expedite surgical treatment and minimize morbidity, long-term disability, and death. Diagnosis can be difficult, and there are no firm diagnostic criteria. The clinician must recognize the clues and have a low threshold for exploring areas of concern.

Suggested Readings

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MANAGEMENT OF PRIMARY CHEST WALL TUMORS

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Malcolm V. Brock, MD, FACS

P[illegible]

[illegible]

[illegible]

[illegible] by physical exam. Contrast enhanced magnetic resonance imaging is an essential tool for the evaluation of soft tissue masses and will additionally offer improved appreciation of nerve involvement and degree of bony invasion for analytic lesions. There are some general imaging findings that may be useful in assessing malignant versus benign lesions. For soft tissue masses, increased size is associated with a higher risk of malignancy, while superficially located tumors are more likely to be benign. Concerning bony abnormalities, benign lesions are usually smaller and with concrete well defined borders, while bony destruction is more characteristic of malignancies. [illegible] emission tomography (PET) scanning is appropriate for evaluating distant spread, but given the potential for benign disease, it may be prudent to wait for biopsy results before proceeding (Fig. 1).

The intention of biopsy depends on several factors, most prominently the size of the tumor and its location. Classically, tumors smaller than 5 cm in size should undergo excisional biopsy, but in practice, location and anatomic position must be considered. When an excisional biopsy is performed, the surgeon and patient should both be aware that re-resection for margins may be necessary if the diagnosis reveals malignancy. If an excisional biopsy is not feasible, an incisional biopsy offers superior diagnostic accuracy over a core needle biopsy. Some tumor types may be inconclusively identified after a core needle biopsy, as the possibility of diagnostic confusion exists with a small sample. Repeat biopsy is indicated for inconclusive samples. Once the pathologic diagnosis is obtained, a surgical plan can be appropriately and accurately devised (Box 1).

BENIGN SOFT TISSUE

Lipoma

Lipomas remain the most common soft tissue tumor in adults and are more prevalent in obese patients. On imaging, they possess attenuation common with fatty deposits, with mild enhancement of their septations. Lipomas do not enhance with contrast. Deep chest wall lesions are generally less well circumscribed than superficial lesions and may be difficult to differentiate from surrounding fat. Preoperative tagging is sometimes necessary. The principles of surgical excision involve complete removal of the capsule to prevent recurrence. Surgical removal is usually limited to symptomatic lesions, to those that are cosmetically troublesome, or where the etiology is uncertain.

Desmoid Tumor

Desmoid tumors, aggressive fibromatosis, or desmoid type fibromatosis, are soft tissue tumors that develop from deep tendons and connective tissue. While officially benign without metastatic potential, they behave clinically like low grade sarcomas with high rates of local recurrence. The tumors are slow growing and usually diagnosed incidentally but may be a source of pain or compressive symptoms. Desmoid tumors are associated with subtypes of familial adenomatous

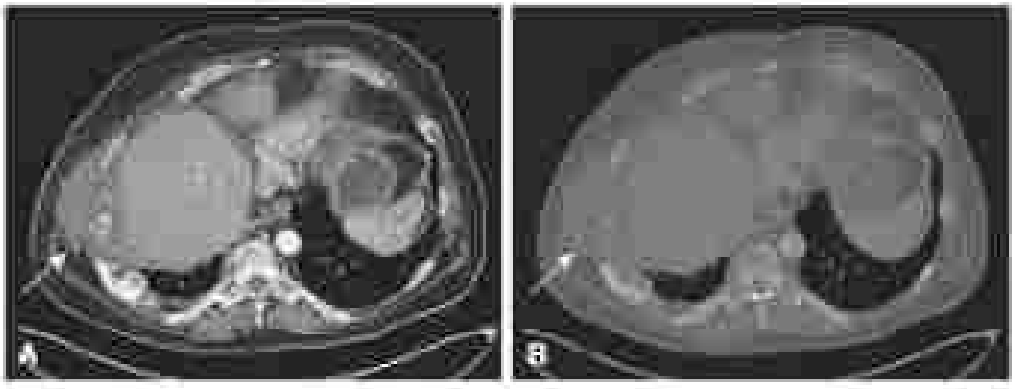

FIG. 1 Computed tomographic scans of a [illegible] malignant tumor in the chest. (A) The [illegible] the chest wall. (B) [illegible] (C) [illegible] (D) [illegible]

BOX | Common Primary Chest Wall Tumors

Soft Tissue

Benign
Lipoma
Fibromatosis coli
Lipoma
Desmoid tumor

Malignant
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Liposarcoma
Leiomyosarcoma
Primary pleuropulmonary synovial sarcoma

Bone and cartilage

Benign
Fibrous dysplasia
Osteochondroma
Chondroma
Aneurysmal bone cyst

Malignant
Osteosarcoma
Chondrosarcoma
Ewing's sarcoma

Neural tissue

Benign
Benign localized solitary fibrous tumor

Malignant
Malignant localized solitary fibrous tumor
Mesothelioma

Hematologic

Benign
Neurofibroma
Schwannoma
Paraganglioma

Malignant
Malignant schwannoma
Neurofibrosarcoma
Lymphovascular

Vascular

Benign
Cavernous hemangioma
Glomus tumor
Lymphangioma

Malignant
Angiosarcoma
Hematologic
Lymphoma
Solitary myeloma

pathogens such as Gardner's syndrome, in which case patients present with multiple lesions. Desmoids are more common in younger adults.

Desmoid tumors can be difficult to assess radiographically. On computed tomographic (CT) scan, they will appear as soft tissue masses of variable appearance, usually without distinct markings or calcifications. Low enhancement may be more common with chest wall lesions, but this is not a reliable feature. These lesions are usually well vascularized. Magnetic resonance imaging (MRI) is clearer than CT scanning, with the desmoids most commonly appearing as isointense lesions with a rim of fat. These lesions may also travel along fascial planes some distance from the main body of the tumor, and MRI is most effective at evaluating the extent of this spread. On pathology, these tumors have a solid scar-like appearance, which may be tough enough to make needle biopsy very challenging.[14] While the biologic mechanism of tumor development may vary, a central theme is β-catenin overexpression throughout the lesion, which can be immunohistochemically stained for diagnosis. These lesions appear on microscopy as poorly organized mesenchymal myofibroblasts without classic signs of malignancy.

The treatment of symptomatic desmoid tumors is primarily surgical resection. Without intervention, they usually continue to grow and become more severely symptomatic. While they are benign lesions that almost never metastasize, local recurrence is common and can be as high as 50%. Great care should be taken to obtain microscopically negative operative margins. Desmoid tumors are infiltrative and may involve themselves in critical structures, especially blood vessels, which can complicate resection. Especially complex presentations may benefit from referral to a tertiary care center, as the challenges of these resections should not be underestimated. There is still some debate on adjuvant approaches after obtaining microscopically positive margins, but re-resection should be attempted if feasible.

As an alternative to surgery, observation or systemic therapy is sometimes pursued. Observation is appropriate for lesions that are asymptomatic or multifocal, as these lesions are slow growing. For systemic therapy, tyrosine kinase inhibitors, nonsteroidal anti-inflammatory drugs and hormonal therapy have all shown efficacy in disease control and treatment usually begins with these agents. Cytotoxic chemotherapy is reserved for those patients that fail this management or present with severe disease. Due to slow response times, neoadjuvant therapy is not typically offered. The role of radiotherapy in management is currently unclear. Due to the rates of local recurrence and slow growth of the tumor, extended follow-up is recommended. When recurrence occurs, re-resection remains the treatment of choice.

MALIGNANT SOFT TISSUE

Rhabdomyosarcoma

Rhabdomyosarcoma is known for being the most common pediatric soft tissue tumor but can also present in adults with severe consequences. They uncommonly arise in the chest wall, but the course is usually a fast growing lesion with the patient seeking medical care due to pain at the site or compression of other structures. The tumor originates in skeletal muscle but can quickly invade nearby tissue.

Lesion imaging begins with CT, which will usually describe the location of the tumor, but MRI is superior for diagnosis and determining degree of involvement of other structures. The tumor usually presents with ring-like regions of contrast enhancement on MRI, which correlate with areas of vascularity versus necrosis. Biopsy is often required to obtain a diagnosis and an open biopsy is usually superior for providing an adequate sample. Rhabdomyosarcoma has several named subtypes, correlating to different macroscopic and histologic appearances, although they all develop from skeletal muscle. Adults with this disease are more likely to present with less favorable subtypes than pediatric patients.

Surgical resection represents the best chance for durable cure, but even with negative margins, the chance of recurrence remains high. Radiation and chemotherapy are routinely used, with regimens inspired by pediatric therapies, as there is a paucity of data in adult patients. Chemotherapy is typically vincristine, actinomycin

and cyclophosphamide, interposed with ifosfamide and etoposide. Median radiation dose is roughly 45 Gy. If resection compromises the chest wall or breathing mechanics, reconstruction should be done immediately. Follow up should be frequent after surgery given the likelihood of recurrence.

Malignant Fibrous Histiocytoma/Undifferentiated Pleomorphic Sarcoma

Malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma (UPS) is a sarcoma of uncertain etiology. It can arise from either soft tissue or bone and represents one of the most common soft tissue sarcomas. It often presents in the extremities but can be found in the retroperitoneum and in the chest wall. Pain is usually the presenting complaint, though asymptomatic swelling and incidentally found lesions are not uncommon. The rate of diagnosis has been decreasing over recent decades as improved diagnostic techniques label fewer tumors as UPS. As diagnostic criteria narrow, the disease is trending toward being more common in older males. Additionally, like many sarcomas, there may be risk to prior radiation.

UPS is difficult to characterize radiographically, as it has myriad appearances. Centrally, these lesions are indeterminate heterogeneous masses, with the heterogeneity more pronounced as the lesions grow. There is no imaging modality that is explicitly more advantageous, as most suspicious lesions may require imaging with CT, PET and MRI. Pathologic results are similarly varied; however, $T^{53}C$ expression and deletion mutations of $p16^{INK4A}$ have been implicated in this disease. Pleomorphic spindle cells are usually seen as infiltrative tumor on histology.

Management is surgical resection. Outcomes are poor, underscoring the importance of negative margins. When this tumor is present on the extremities, 2 cm resection margins are usually required, but this may be challenging to accomplish in the chest wall. Chemotherapy is exploratory, with new treatments seeking to explore treating this previously diverse tumor group by targeting conserved mutations. Currently, cytotoxic chemotherapy is reserved for disseminated disease for which the prognosis is extremely poor. Radiation has some efficacy and merits consideration, especially for patients for whom wide margins are not feasible. Close follow up is warranted as rates of recurrence are quite high.

Liposarcoma

Liposarcomas are responsible for a minority of chest wall soft tissue sarcomas. As understanding of their biology has progressed, the tumor is now divided into three main subtypes, well differentiated liposarcoma, myxoid round cell liposarcoma and pleomorphic liposarcoma. Well differentiated liposarcoma (referred to as atypical lipomatous tumor when localized to the extremities) is the most common subtype of liposarcoma and lacks metastatic potential. However, it can degenerate into dedifferentiated liposarcoma, which is clinically similar to high grade disease and may metastasize. Myxoid round cell liposarcoma is a mid grade tumor, while pleomorphic liposarcoma reflects high grade disease.

The diagnostic value of imaging varies by tumor subtype. For well differentiated liposarcomas, it is difficult to differentiate them from benign lesions. Myxoid round cell usually appears as multilobular lesions within muscle and with a high water content that is visible on MRI. CT scans of pleomorphic liposarcoma reveal a well circumscribed lesion, notable for the absence of fat. Necrosis, infarction and hemorrhage may all be visible on MRI.

Surgical resection affords the best opportunity for durable cure. Multiple studies have demonstrated the therapeutic benefit of appropriate surgical margins and the standard of care for malignant liposarcoma is a 2 cm margin. Liposarcomas are difficult to detect early and often present where obtaining 2 cm margins is technically demanding or infeasible. In these cases, resection even with limited margins provides a survival benefit and should be pursued, with the understanding that the goals of primary resection must be balanced against surgical feasibility on a patient to patient basis.

The role of radiotherapy in treatment of liposarcoma varies depending on tumor subtype. Well differentiated liposarcoma has no malignant potential by itself, so radiotherapy only reduces the risk of local recurrence. Myxoid round cell liposarcomas is usually highly radiosensitive, and radiation is both effective at preventing local recurrence and for shrinking the tumor preoperatively. Chemotherapy remains exploratory and patients should be considered for clinical trials if they present with disseminated disease. Neoadjuvant chemotherapy is similarly limited, and is attempted for patients who present with initially unresectable disease.

Close follow up is critical for expectant management as recurrence rates can be high. Of particular note, the myxoid round cell variant appears to have a metastatic preference for high fat locations.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare tumor derived from uncontrolled proliferation and subsequent migration of Langerhans cells. The etiology of this disease is unclear, but a viral vector has been suggested. This disease develops as a single site approximately 75% of the time, with the remainder representing as a more diffuse process. Patients may present with a growing mass or with a variety of systemic symptoms including chills, weight loss, lymphadenopathy, or bone pain. In chest wall cases, LCH predominantly affects the ribs.

Chest radiographs may be useful for identifying lytic lesions. Chest CT is more sensitive and may demonstrate a beveled edge along areas of lytic destruction, due to variable destruction of inner and outer bone cortex. MRI will show contrast enhancement and any soft tissue component of this tumor should appear hyperintense on T2 imaging. Biopsy is usually needed for diagnosis and microscopic evaluation should reveal round cells with a "coffee bean" nucleus. This tumor should be clonal, expressing CD1a, CD207, S100 and potentially BRAF^{V600E}.

While surgical excision is occasionally necessary for diagnosis or for impingement on other structures, the mainstay of treatment for diffuse disease is chemotherapy, traditionally with vinblastine and prednisone. There is also a role for curettage and irrigation of bone lesions, which has demonstrated success with small solitary lesions, but should only be attempted by experienced surgeons. Microscopically negative margins should be sufficient if formal resection is required.

Primary Pleuropulmonary Synovial Sarcoma

Primary pleuropulmonary synovial sarcoma is a synovial sarcoma that affects the chest wall, pleural, lung, heart or mediastinum and is a subtype of spindle cell sarcoma. It is alternatively referred to as primary mediastinal synovial sarcoma if affecting the heart or the mediastinum. The most common clinical presentation is consistent with obstructive symptoms, cough, dyspnea, hemoptysis or chest pain. Incidental discovery on routine imaging is also common.

CT is usually the initial diagnostic choice; the lesion is typically well defined, with areas of fluid heterogeneously present within. The CT image alone may be sufficient, depending on the tumor's size and location. A "triple sign" representing tumor, hemorrhage and necrosis is sometimes noted. Ipsilateral pleural effusion may be present as well as pleural thickening. MRI may also assist in delineation when this disease spreads into adjacent structures. Pulmonary and mediastinal lymphadenopathy is less common than with traditional lung cancer.

The vast majority of primary pleuropulmonary synovial sarcomas occur as a result of a gene translocation mutation between chromosome "X and chromosome X, leading to the common

fusion gene *SYT-SSX*. Microscopically, the spindle cells classically possess elongated nuclei and irregular borders, while the cytoplasm may stain basophilic. The extracellular membranes can be variable. Well differentiated tumor is associated with improved prognosis.

Although most tumors are diagnosed late, complete resection is the factor most associated with favorable long term outcomes. Negative margins should be pursued whenever possible. If the tumor is confined to the lung, lobectomy is appropriate. Since the diagnosis is usually made postoperatively, experience with neoadjuvant therapy is limited but could be pursued in select patients. Radiotherapy may be used for positive margins, though its efficacy is unclear. Chemotherapy agents used most often are ifosfamide and doxorubicin, which can be efficacious in up to 50% of patients. Close follow up is indicated due to the likelihood of recurrence.

BENIGN BONE AND CARTILAGE

Fibrous Dysplasia

Fibrous dysplasia is the most common benign lesion in the rib. It is characterized by progressive replacement of calcified bone and marrow with fibrous tissue due to abnormal proliferation of bone marrow stromal cells. Patients are most commonly identified either incidentally on imaging, due to chest wall swelling or complaints of bone pain at the lesion site.

Chest radiographs should classically demonstrate a well circumscribed ground glass lesion in the bone. Chest CT provides the most diagnostic value and the lesion should enhance with contrast due to its high vascularity. MRI may incrementally provide additional detail about the size and depth of the tumor, but it is difficult by MRI scan to differentiate between other bony lesions and fibrous dysplasia. A bone scan is useful for detecting multifocal disease. If radiographic diagnosis is inconclusive, biopsy may be performed for histologic evaluation.

Management of this condition is guided by the presence of symptoms. Pain may be refractory to medical management or the lesion may mechanically obstruct movement or compress structures. Rarely, the lesion may be growing sufficiently quickly to merit resection prior to the onset of probable complications.

Osteochondroma

Osteochondroma is a benign tumor that presents as an exostotic growth with a cartilaginous cap on the affected bone. While it is perhaps the most common benign bone lesion, it is relatively rare in the chest wall, responsible for fewer than 10% of bony chest wall abnormalities. These lesions are usually diagnosed either incidentally on imaging, due to a pathologic fracture or chronic pain.

Osteochondromas can extend cartilaginously, which may be appreciated on routine chest radiographs. The growth of the lesion is often complex, and CT scans better appreciate the depth of the cartilaginous cap. An MRI may have additional utility in evaluating how deeply the lesion involves the affected bone.

Malignant transformation to sure and surgical resection is typically reserved for chronic pain, impingement, or cosmesis. The one notable exception to the use of surgery for rapidly growing tumors, since these are highly suspicious for malignancy. During the procedure, the entire cartilaginous cap should be removed to prevent recurrence. The presence of more than one osteochondroma suggests a hereditary cause.

Chondroma

Chondroma is a classically benign cartilaginous cyst that can arise completely within or on the surface of bone. These hyaline cartilage producing tumors are the second most frequent cause of a benign rib lesion after fibrous dysplasia. Like most other benign bony lesions, this is usually an incidental finding as patients usually lack symptoms.

When symptoms are present, pathologic fracture or physical deformity from growth are the most common presentations. Pain may also be a referring symptom, which is classically worrisome for malignancy though retrospective studies have failed to find this link. A subset of patients will present with multiple lesions, which is often the sign of a genetic condition. Having multiple lesions also increases the risk of malignant degeneration.

Chest radiographs should show lytic lesions, while a CT scan will allow for visualization of endosteal scalloping of the tumor, which helps to differentiate chondromas from other lesions. An MRI may be useful for observation, as it is more sensitive for detecting malignant degeneration.

Resection is typically reserved for pathologic fractures or a concern for secondary chondrosarcoma. Resection of the entire cyst will minimize the risk of recurrence and eliminate the possibility of malignant degeneration. If the lesion is easily accessible and solitary, empirical resection can be considered to eliminate the possibility of any future malignancy.

Aneurysmal Bone Cyst

An aneurysmal bone cyst (A, C), despite the name, is not truly a cyst, but a benign skeletal tumor. It most commonly presents with pain, but when localized to the chest, may present with a palpable mass or atelectasis and pneumonitis from pulmonary compression. The majority of these tumors are small in size, but if undiagnosed or untreated can grow in excess of 10 cm in diameter.

This tumor appears classically on a radiograph as a "blow out" appearance in bone. CT affords better visualization, as the cortical thinning of the involved bone may lead to a soap bubble like appearance. An MRI often reveals multiple bony cysts with a thin septum, containing blood products. A biopsy usually results in blood products and most often is inconclusive. Despite this, radiographic and biopsy results can be very suggestive of this disease process even if a formal diagnosis is elusive.

Curative treatment is resection of the lesion, with complete removal of the aneurysmal bone cyst. There is no unusual urgency for resection, but if left untreated, the cyst can compromise the structure of the bone, and may cause secondary symptoms as it continues to grow.

MALIGNANT BONE AND CARTILAGE

Chondrosarcoma

Chondrosarcoma is the most common primary malignancy of the sternum, although primary chest wall malignancies represent a heterogeneous group of tumors. Pain and swelling are the most common symptoms leading to the diagnosis of chondrosarcoma, though incidental diagnosis is not unusual. Chondrosarcoma can present throughout adulthood and about 1 % of cases occur from degeneration of benign lesions, most commonly osteochondromas.

CT is the initial imaging tool of choice both for its convenience and because of its sensitivity to distinguishing the pattern of mineralization that is classic for chondrosarcoma. MRI may also be necessary to determine the degree of invasion throughout the affected bone. Histologically, these tumors have a multinodular architecture found in the myxoid stroma that is usually distinct enough to provide an accurate diagnosis after biopsy or resection. It is not unheard of, however, for additional cells or debris to be present that can cloud the diagnosis. An excisional biopsy is sometimes necessary to obtain sufficient tissue for accurate diagnosis.

Complete surgical resection is deemed for initial therapy as there are limited adjuvant treatments available. Appropriate margins vary depending on grade, but at least 1 cm margins should be obtained whenever possible. Small tumors in the chest wall should be completely resected. Limitations due to chest stability may influence totality of resection with larger lesions, but this worsens prognosis. There is some indication for curettage and cryosurgery for grade

chondrosarcoma, but this had been historically used in the long bones for limb salvage. These techniques are also associated with an increased rate of local recurrence.

Efficacy of chemotherapy depends on histologic subtype, but offers only limited benefit. Chondrosarcomas are usually also radiation resistant and require doses above 60 Gy for local control. Local recurrence may be treated with re-resection, while treatment of the unresected disease is essentially palliative.

Osteosarcoma

Osteosarcoma is most commonly thought of as a tumor of the long bones in children and adolescents. Its presentation in the chest wall is uncommon, but when it occurs, it most commonly affects adults. It usually presents as an intramuscular tumor but may extend extraskeletally. In adults, pain and swelling with a growing mass are the most common symptoms. Classically, this pain is substantial enough to wake a patient from sleep. There is some evidence of increased risk of osteosarcoma of the chest wall with prior radiation exposure to the region.

Radiographic diagnosis is made primarily through CT scanning, which allows both tumor identification and evaluation of distant spread. Radiographs are more beneficial in identifying peripheral osteosarcoma and have limited utility in the chest. MRI scanning helps delineate degree of local invasion. Core needle biopsy should be used with caution, as it may provide insufficient sample for accurate diagnosis. Pathologically, the origin of osteosarcoma is mesenchymal and the tumor classically appears as spindle cells within an immature osteoid matrix. Biopsy methods that disrupt this organization may hinder the ability to make a diagnosis. The grade of the tumor is usually high and this is unfortunately associated with worse clinical outcomes.

While local resection is the mainstay of treatment and the resection is usually straightforward, if the tumor is located in the sternum ideally some of the sternum should be salvaged to use as an anchoring point for prosthetic support. Reconstruction can safely be undertaken immediately.

Unlike many other common cancers, neoadjuvant chemotherapy has been shown to be effective, both at preventing recurrence and at limiting the scope of initial resection. Standard chemotherapy is methotrexate, Adriamycin, and cisplatin, but experimental studies are exploring tailoring this further for specific subtypes. Complete resection of affected tissue is necessary for optimal outcomes following therapy. Depending on the adequacy of response, chemotherapy may continue after resection. Radiation is typically reserved for cases that are unresectable or failed resection.

Recurrence can be either local or metastatic, and thorough physical exam as well as high clinical suspicion are essential when monitoring during follow up.

Ewing's Sarcoma

Ewing's sarcoma represents one of the most common chest wall tumors in young adults, and it is the most common chest wall tumor in the pediatric population. Ewing's sarcoma of the chest wall may present with pathologic fracture, pain, swelling or fever and systemic complaints. Pathologic fracture associated with chest wall tumors is less common than with the extremities, but there is more incidental diagnosis due to the increased frequency of routine chest imaging.

Characteristically, Ewing's sarcoma presents on radiograph as a mass with bony destruction. CT imaging affords greater visualization of the extent of disease process and can identify those instances where the bony involvement of the tumor is rather small. As the tumor grows, appearance on CT should mature from homogeneous to heterogeneous. Classically, the tumor also has an onion skin appearance, though the absence of this does not rule out Ewing's sarcoma as a diagnosis. MRI may help with evaluating for further local spread or identifying small metastasis.

Ewing's sarcoma is a result of a chromosome 22 translocation. Histologically, the small round cells of this tumor will stain for cytoplasmic glycogen, which can be used to differentiate this appearance from other tumors. Open biopsy provides superior results to core needle, but imaging may be descriptive enough to proceed with resection without a formal diagnosis if the lesion is easily accessible.

Margin-free resection is critical for favorable clinical outcomes. Chemotherapy is usually indicated after surgery, with a typical drug regimen of vincristine, actinomycin and cyclophosphamide, interspersed with ifosfamide and etoposide. Radiation is usually offered if surgical resection is not feasible or to irradiate residual tumor. Resection should be reconsidered if nonsurgical therapy shrinks a tumor to the extent it is resectable, assuming there is no growth of the disease epidemically. Reconstruction, if required, should be conducted at time of resection. Even with adequate resection and adjuvant therapy, recurrences are not unusual, so close follow up is required.

OTHER TISSUES OF ORIGIN

Benign Localized Solitary Fibrous Tumor

Solitary fibrous tumors are rare, usually benign tumors that arise from the mesenchymal layer of the parietal pleural. These localized tumors derive from the submesothelial layer. They differ from diffuse pleural neoplasms (mesothelioma), which originate from the mesothelial layer and are associated with asbestos exposure. The majority of patients with solitary fibrous tumors are asymptomatic and diagnosed incidentally on pulmonary imaging. Patients may rarely present with a paraneoplastic syndrome, most commonly hypoglycemia from tumor production of insulin-like growth factor II.

Radiologically guided biopsy may be inaccurate, as the tumor is poorly organized with spindle cells of indistinct borders interminglely situated throughout collagen and extracellular matrix, with mixed hypo- and hypercellular regions. Necrosis is most common in larger tumors and increasing tumor size is associated with the rare malignancy. An MRI may provide additional information about invasion into surrounding structures but will not usually aid with diagnosis. There are several promising diagnostic biomarkers, and presence of CD34 on staining is the most widely accepted.

Complete surgical resection is the mainstay of treatment. Lobectomy should be performed for pulmonary involvement since preoperative determination of malignancy may be imprecise. Adequate surgical resection is the most important prognostic factor, and all involved surrounding tissues should be removed. If complete resection is impossible, partial resection may be indicated for symptom management. Nonsurgical approaches should be reserved only for patients who cannot tolerate resection.

Schwannoma

Chest wall schwannomas typically arise from intercostal nerves and are most prevalent in the mediastinum. Specifically, schwannomas originate in Schwann cells, perineural cells, important for peripheral nerve support. This benign lesion is rarely encountered but can easily be misconstrued for a malignant lesion. Patients are usually asymptomatic but may develop paresthesia or other compressive symptoms as the lesion grows.

Schwannomas can be appreciated on CT imaging, but evaluating the tumor on CT images alone can be quite challenging. MRI affords superior diagnostic accuracy and can show heterogeneity, with a multicolor hyperintense appearance as the nerve tissue stands out from surrounding muscle, bone, and soft tissue. Ultrasound also has a role in diagnosis as sonographic characteristics can be used to differentiate between nerve sheath tumors. Grossly, these tumors are encapsulated and present as lobular growths along the nerve. On histology, schwannomas are divided into type 1 and type 2, with type 1 presenting with typical high cellularity and abutting Verocay bodies, while type 2 represents a degeneration of these typical features.

Surgical resection is indicated for all symptomatic lesions, but degeneration into malignant disease is exceedingly rare. If resection is complete, local recurrence is unusual, but follow up is warranted for those with underlying genetic disorder like neurofibromatosis.

Cavernous Hemangioma

Cavernous hemangiomas are benign lesions that rarely present in the chest wall. These congenital vascular malformations develop over the first decades of life and are sometimes confused as malignancies. The location of cavernous hemangiomas may vary from superficial to deep and some may invade muscles or bony structures of the chest wall, presenting as lytic lesions.

The radiographic test of choice for evaluating these lesions is an MRI scan. Characteristically there are internal T1 foci of hyperintensity with T2 shortening around the periphery with a heterogeneous appearance. The lesion should be without mass effect, unless there is surrounding hemorrhage. CT scans may help identify the presence of a lesion, but it is inferior to MRI when assessing the lesion's impact on surrounding structures. Excisional biopsy is superior as incisional or needle biopsy can carry the risk of severe bleeding due to the vascular nature of the lesion.

Surgical excision is usually performed when the diagnosis is unclear or the lesion is invading into adjacent structures. Total resection is indicated to eliminate recurrence and prevent bleeding.

Alternatives to surgical excision include observation and vascular embolization. Growth of the vascular malformation can occur after embolization, close follow up is required if this modality is used, especially if the cavernous hemangioma presents with osteolytic damage as this process can progress.

Lymphoma

Primary lymphoma of the chest wall is relatively rare. However, there is an increased incidence in patients with chronic pyothorax, resulting in pyothorax associated lymphoma (PAL). When PAL presents, they are most commonly Hodgkin's or large B cell lymphoma.

Diagnosis is preferably accomplished with a tissue biopsy as complete excision is usually unnecessary. The rare instances where resection would be indicated are in cases where a mass effect of the tumor caused a life threatening complication.

Chemotherapy is the first line therapy for lymphoma regardless of whether they are chest wall primary or metastatic. CyCOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most common regimen, though targeted immunotherapies are increasingly being used. Radiation may be indicated depending on tumor histology of the primary lymphoma.

Solitary Myeloma (Plasmacytoma)

Solitary plasmacytoma is a rare presentation of myeloma accounting for approximately 5% of malignant plasma cell tumors. Plasmacytomas of the bone preferentially occur in the vertebrae, while soft tissue plasmacytomas are most commonly localized to the head or neck. The hallmark of this disease is that unlike multiple myeloma, which may present with multiple lytic lesions, there is an absence of disseminated disease. Resection should be considered, as conversion to multiple myeloma can occur in up to 70% of cases. Plasma cytomas of the bone are more likely to progress than plasmacytomas of soft tissue and should be treated more aggressively.

SURGICAL APPROACH

There is great variety in the pathology and treatment of chest wall tumors, which makes summarizing an operative approach challenging (Box 2). However, there remain some universal guidelines that can be used to approach these patients in a safe and systematic manner.

BOX 2 Operative Chest Wall Localization Techniques

Preoperative Techniques

Correct patient positioning
Interventional radiology guided coil or wire
Methylene blue
Radiolabeled marker

Intraoperative Techniques

Manual rib counting
Angiocath placement and intraoperative imaging
Thoracoscopic entry and chest wall evaluation

Like all operative candidates, the patient must be able to safely tolerate the surgery. This threshold is understandably lower for malignant tumors, but in many cases, there is sufficient time to optimize a patient prior to surgery and a delay of even several months can be clinically appropriate.

Preoperative planning is the key to success. Complex patients or rare presentations should be ideally discussed at a multidisciplinary board and images should be reviewed with a radiologist if the surgeon does not frequently read chest wall masses. Preoperative interventional radiology guided tumor marking should be strongly considered, and while there are no specific guidelines, coils, wire localization, methylene blue, and radiographic marking with fiducial markers are all appropriate modalities to use. If a physical marker like coils or wire is used, care should be taken to position the patient identically to how they will be positioned in the operating room, as there are reports of wires moving after placement due to patient positioning.

Operative approach is most appropriately done following the experience of the surgeon, as there is no empirically superior method. The primary challenge operatively is usually identification of the lesion. Some lesions are pathologically easily identifiable, while others closely mimic surrounding tissue or are not palpable, such as lytic bone lesions. Preoperative imaging should be easily available in the operating room for reference. If any doubt exists to the location of the lesion, positioning should be reviewed. Manual counting of the ribs is the simplest means of approaching this problem, but surgeons interested in a more thorough approach may wish to place an angiocatheter needle in the suspected lesion and perform an intraoperative radiograph to confirm that the operative site matches the site on preoperative imaging. Additionally, a thoracoscopic approach may be used to verify the location of resection, either through rib counting or direct visualization. The key point is despite the apparent simplicity of removing the correct rib, medical errors do occur. A wise surgeon will be vigilant against this possibility (Box 2; Fig. 1).

The degree of resection can vary dramatically by tumor type. In some cases, diagnosis is unclear at the time of surgery, so an overly wide resection would be inappropriate. In these cases, marking the location of the lesion is important so it may be necessary to return to obtain appropriate margins or guide adjuvant treatment.

Complex or recurrent disease should be referred to a specialist if possible. While chemotherapy and radiation are usually of secondary importance when compared to primary surgical resection, for recurrent disease additional modalities need to be considered. Metastatic disease will obviously require systemic therapy, but even locally recurrent disease merits the consideration of additional therapies. Given the limitations of available data on primary chest wall tumors, these treatments may be experimental in nature and should be considered with the help of a specialist or tertiary care center.

If a large resection is required, reconstruction may be required with either tissue flap, prosthetic or both. If the complexity of the

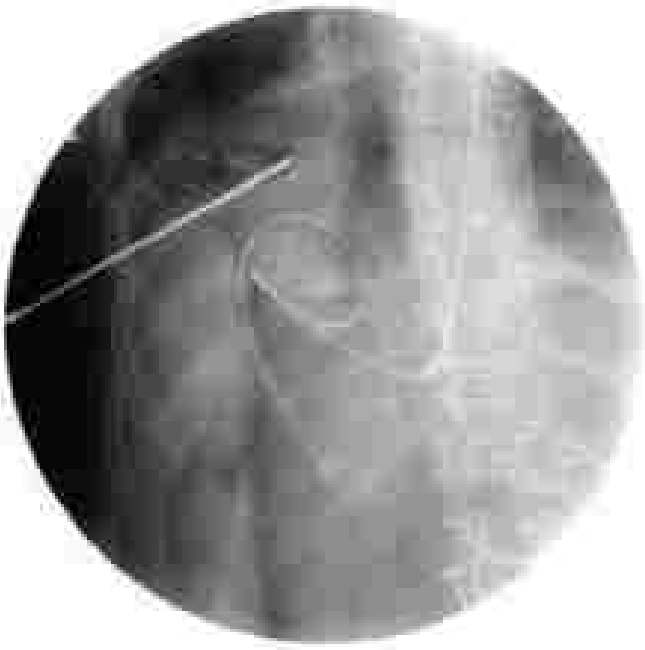

FIG. 2 Intraoperative imaging can reduce the risk of wrong site and other surgical errors. Imaging with a radiopaque overlay such as a *star* ripe or sophisticated can confirm that the suspicious lesion is located in the correct anatomic position based on preoperative imaging and exam. This is especially relevant for tumors with similar appearance to the surrounding tissue.

reconstruction is significant, a co-operative case with a reconstructive specialist is advisable. Given the nature of the chest wall as mechanically essential for respiration, immediate reconstruction is warranted even in the face of malignancy. Fortunately, the safety of this approach has also been demonstrated, as tumor seeding of these reconstructions is relatively rare. While an in-depth discussion of reconstruction goes beyond this chapter, commonly used muscle flaps are pectoralis major, latissimus dorsi, serratus anterior, rectus abdominis, and the external oblique. Choice depends on degree and location of resection, as all flaps are limited to the anatomic area they can safely cover. Prosthetics are usually mesh or titanium overlays, with some supporting that titanium may afford better chest wall mechanics for larger defects.

CONCLUSION

Primary chest wall tumors owe much of their clinical challenge to their rarity and heterogeneous nature. Despite this, with appropriate resection and use of adjuvant therapies, outcomes can be favorable. This chapter provides guidance to the general approach to these patients and how to safely manage their care. A surgeon treating these tumors will need to be familiar with both diagnosis and therapy to navigate this complex and evolving field.

SUGGESTED READINGS

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MEDIASTINAL MASSES

Hugh G. Auchincloss, MD, MPH, and Elon Jan J. Mathisen, MD

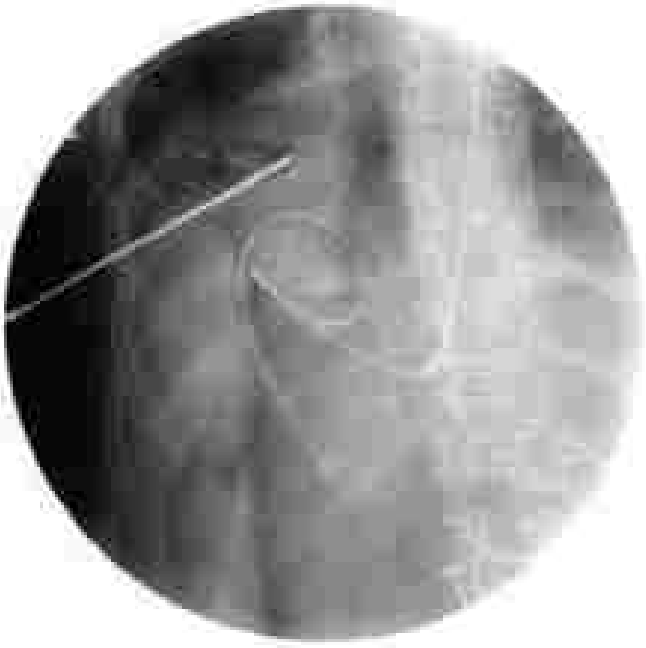
The mediastinum refers to the compartment bounded by the thoracic inlet superiorly, the diaphragm inferiorly, the paravertebral sulci posteriorly, and the pleura laterally. Historically it has been subdivided into an anterior, middle or visceral, and posterior compartment. These divisions remain useful for surgeons. The differential diagnosis for a mass arising within the mediastinum is largely a function of its location. The anterior compartment—located between the pericardium and the sternum and below the innominate vessels—contains thymic, lymphoid, and residual embryonic tissue and is a common site for an ectopic parathyroid or hyperplastic thyroid gland. Primary tumors may arise from any of these structures. The visceral compartment includes all the structures of the pericardium, heart, great vessels, airway, and esophagus. Masses in this compartment are often lymphoid in origin or may represent a cyst arising from one of the native structures. The paravertebral sulci makes up the posterior compartment and includes the sympathetic chain and roots of the intercostal nerves. Neurogenic tumors dominate the differential diagnosis within this compartment.

Mediastinal masses are uncommon. They make up only 3% of thoracic tumors. The age distribution is bimodal; however, the differential diagnosis differs between the adult and pediatric populations. Over 50% of masses arising in adults are thymic or lymphatic in origin, whereas most masses in children are neurogenic. Accordingly, three-quarters of tumors in adults are in the anterior mediastinum, whereas more than half of masses in children are in the posterior mediastinum. The origin of a mediastinal mass may therefore be suspected on the basis of its location and the age of the patient. Imaging characteristics alone are often diagnostic, and serologic study is helpful for certain tumors. Tissue biopsy remains the gold standard. Most masses are treated with surgical resection or chemotherapy.

DIAGNOSIS

Clinical Presentation

Most mediastinal masses grow slowly and are asymptomatic. They appear as incidental findings on imaging studies. Over 30% or so of masses that cause symptoms do so by compression or invasion of surrounding structures. Rarely, they present with a paraneoplastic phenomenon such as myasthenia gravis, Cushing syndrome, multiphasic hypercalcemia, or hypercalcitriolism. The most common symptoms are respiratory: nonproductive cough, dyspnea, and pleuritic pain. Compression of the superior vena cava (SVC) may result in the classic syndrome of facial edema and orthopnea (Fig. 1). Compression of



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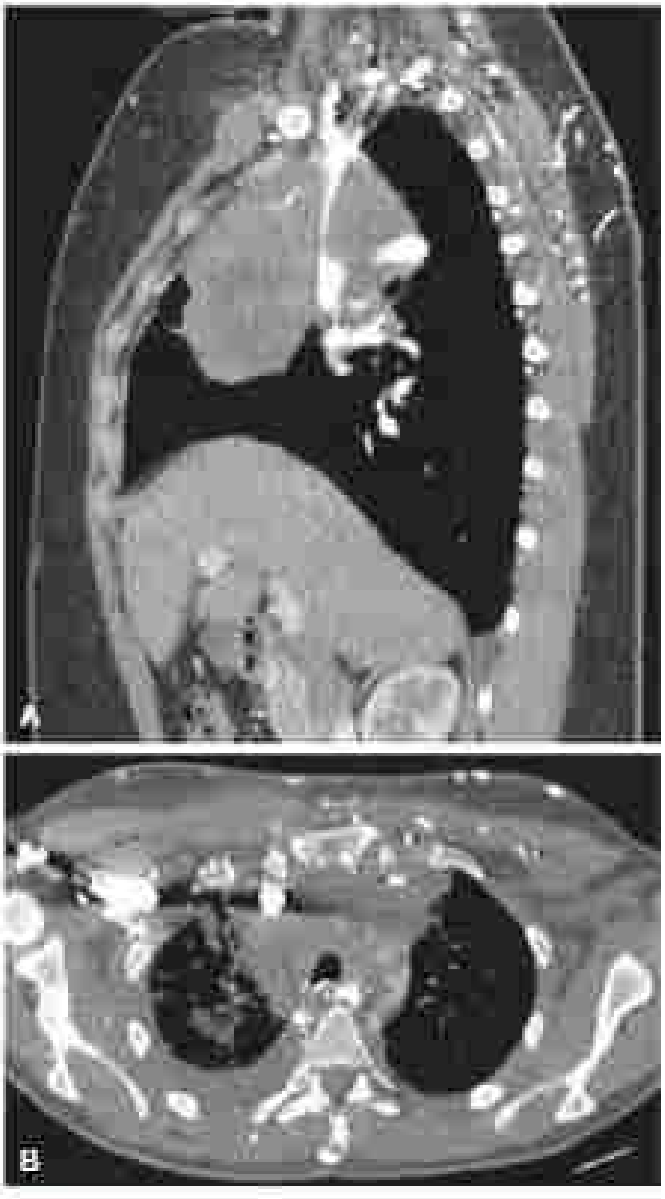

FIG. 1 Two patients with mediastinal lymphoma and superior vena cava syndrome. There are extensive venous collateral vessels in the chest wall.

the cardiac chambers is unusual, but a sympathetic pericardial effusion may produce tamponade physiology. Direct invasion of critical thoracic nerves such as the phrenic nerve, recurrent laryngeal nerve, or sympathetic trunk may result in diaphragm paralysis, hoarseness, or Horner syndrome, respectively. Duplication cysts can become superinfected and cause the patient to present with fever and malaise. Rarely these infections may present with systemic sepsis.

Imaging

Most mediastinal masses have a characteristic radiographic appearance that strongly suggests the diagnosis. Computed tomography (CT) is the primary modality for evaluating a mediastinal mass. CT demonstrates the location, size, density, and architecture of the mass. The addition of intravenous contrast helps determine the relationship between a mass and surrounding structures. Masses with neovascularity such as Castleman disease, paragangliomas, or thyroid neoplasms may demonstrate enhancement on contrast CT. Magnetic resonance imaging (MRI) is an essential adjunct to CT and has become a standard part of the workup for a mediastinal mass. MRI excels at differentiating soft tissue subtypes. A well-protocolled MRI should be able to determine whether a mass is cystic or solid and whether it invades rather than displaces surrounding soft tissue. MRI is also critical in determining whether a posterior neurogenic mass involves the spinal foramen.

Additional radiologic studies are indicated when a specific type of tumor is suspected. Positron emission tomography (PET) should be performed when thymic carcinoma is on the differential (Fig. 2). PET is also valuable when the mass is believed to be lymphoma or other lymph node disease, because it provides the best assessment of extrathoracic involvement. Other nuclear imaging studies can help localize specific tumors, including gallium citrate for neuroendocrine tumors and technetium sestamibi for parathyroid adenomas. Endobronchial ultrasonography (EBUS) and endoesophageal ultrasonography (EUS) are typically thought of in terms of their role in guiding biopsy; however, the ultrasound images from these studies may be thereafter for diagnostic, as with mediastinal cysts.

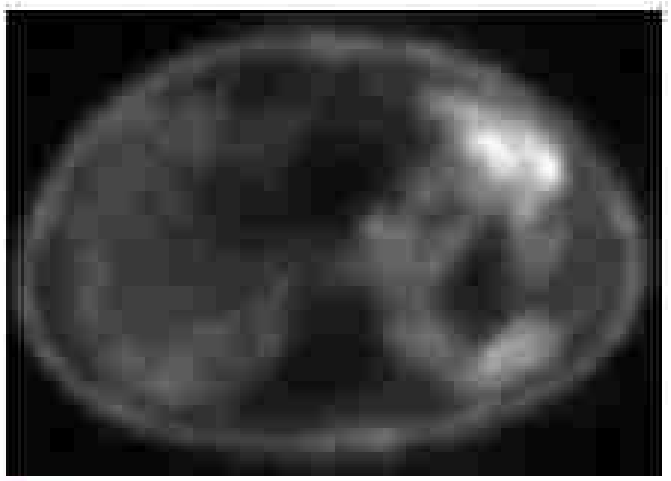

FIG. 2 A positron emission tomography scan of a patient with thymic carcinoma and extensive involvement of the left pleural space.

Serology

Certain laboratory findings provide essential diagnostic and prognostic information about a mediastinal mass, but an unfocused barrage of tests is costly and unnecessary. α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are critical to the diagnosis and management of suspected germ cell tumors. Lactate dehydrogenase (LDH), uric acid, and phosphate should be checked in patients with probable lymphoma, because treatment may induce tumor lysis syndrome. Catecholamine metabolites, adrenocorticotropic hormone levels, vasoactive intestinal polypeptide, and countless other tests are indicated only when concordant symptoms are present.

Biopsy

The role of tissue biopsy for mediastinal masses is controversial. Because many masses can be diagnosed on the basis of imaging alone and treatment is typically surgical extirpation, older thinking held that a biopsy—and the concomitant risk of seeding other structures—ought to be avoided. This is still true for small, encapsulated anterior mediastinal masses that have the classic appearance of thymoma or mature teratoma. However, a growing awareness of the benefits of induction therapy for invasive thymoma, coupled with the expanded repertoire of biopsy techniques and improved pathologic

assessment has led many surgeons to reconsider the role of biopsy for otherwise resectable mediastinal masses. At minimum, biopsy should always be performed when thymic carcinoma or lymphoma are suspected. Biopsy should be avoided for mediastinal duplication cysts, where the risk of superinfection is high. All biopsies should be undertaken with the future surgical approach in mind, especially for suspected thymoma and sarcoma where seeding is a real and costly possibility.

If a biopsy is needed, the choice is between fine needle aspiration (FNA), core needle biopsy, and surgical biopsy. The first two options can be performed via a transthoracic image guided fashion or via EBUS or EUS. FNA is sensitive for carcinoma but provides no information about the architecture of a lesion. For diagnoses where architecture is important—thymoma and lymphoma in particular—a core needle biopsy may provide that information; alternatively, a surgical biopsy may be necessary.

The choice of surgical biopsy approach depends on the location of the lesion. Cervical mediastinoscopy provides excellent access to middle mediastinal nodes and structures. For masses in the anterior mediastinum, an anterior mediastinotomy—or Chamberlain procedure—may be performed. The original description of an anterior mediastinotomy assumed the indication of staging ipsilateral pulmonary window lymph nodes for lung cancer and therefore watched sided. In practice the approach—which involves accessing the second intercostal space lateral to the sternal border while sparing the internal mammary structures, sometimes removing the third costal cartilage—can be performed on either side. It is particularly useful for patients with bulky anterior mediastinal masses and SVC syndrome who may present an anesthetic challenge. Finally, a video assisted thoracoscopic surgery (VATS) approach can be undertaken from either side and provides access to all parts of the mediastinum.

SURGICAL APPROACHES

The treatment of many mediastinal masses is complete surgical resection. The choice of surgical approach is determined by location, size, and malignant potential of the mass, and by surgeon preference.

Transcervical

A minority of anterior mediastinal masses can be approached through a transcervical approach. These include parathyroid adenomas, thyroid goiters, and benign thymic lesions like thymic hyperplasia. A collar incision is used. The platysma is divided and the strap muscles separated in the midline. A specially designed retractor is placed under the sternal notch and used to elevate the sternum. A plane is then developed above the great vessels, and the mass is removed with a combination of blunt dissection and occasional cautery. This technique spares the morbidity of a thoracic incision but has generally fallen out of favor, given the difficulty in clearing all of the anterior mediastinal contents. It has been described as an adjunct to the thoracoscopic approach to thymic tumors because of its efficacy in clearing the superior pole of the thymus.

Median Sternotomy

A median sternotomy provides access to all the structures in the anterior mediastinum and is the gold standard for resection of large or invasive anterior mediastinal tumors. An upper sternal split can be used instead of a complete sternotomy if access to only the superior anterior mediastinum is needed; alternatively, a complete sternotomy may be supplemented with an anterior thoracotomy to provide enhanced exposure to one of the pleural spaces. The chief advantage of a median sternotomy is that all of the critical structures typically involved with invasive anterior mediastinal tumors are accessible for resection and reconstruction. This includes the anterior pericardium, arch vessels, phrenic and recurrent laryngeal nerves, and SVC. Many approaches to resection and reconstruction of the SVC for mediastinal tumors have been described, including reconstruction using cardiopulmonary bypass with or without deep hypothermic circulatory arrest, placement of an extramediastinal graft of reinforced synthetic material followed by resection of the native SVC, and venoplasty with or without a shunting procedure (Fig. 2). If such a procedure is anticipated, the patient should have intravenous access established in the lower extremities, the blood pressure should be elevated, and the head of the bed should remain elevated during SVC clamping to minimize cerebral edema.

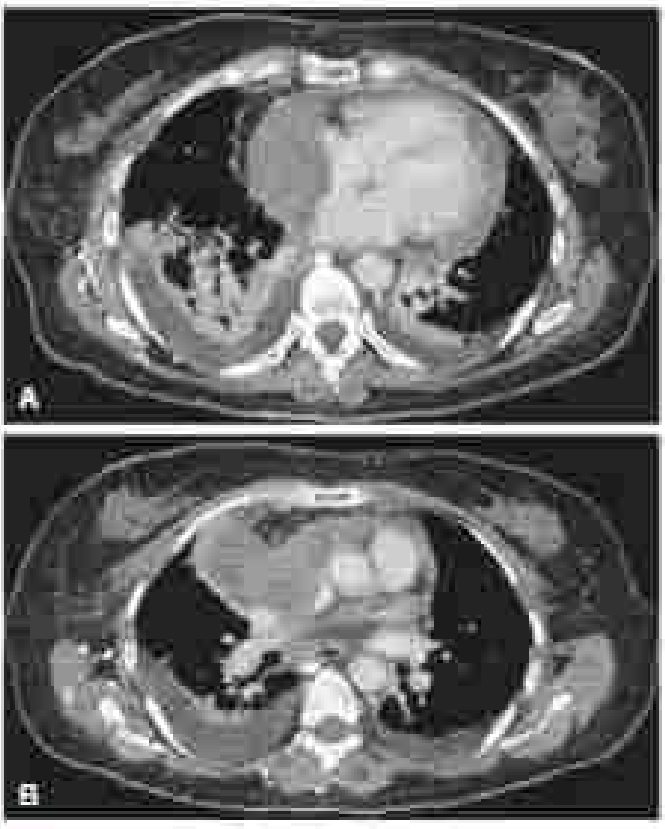

FIG. 2 A mediastinal liposarcoma with invasion into the (A) superior vena cava and (B) right atrium requiring resection and reconstruction under deep hypothermic circulatory arrest.

Thoracotomy

Mass in the middle and posterior mediastinum are amenable to a transthoracic approach. A posterolateral thoracotomy offers exposure to all the relevant hilar and posterior structures. Occasionally a partial anterior thoracosternotomy is chosen when an anterior mediastinal mass extends into the hilum. A full bilateral thoracosternotomy—clamshell incision—is required only for bulky mediastinal tumors with extension into both pleural spaces.

Minimally Invasive Approaches

Selected mediastinal tumors lend themselves well to minimally invasive surgical approaches, including transthoracic or subxiphoid VATS and robot assisted surgery. Resection of small thymomas, mediastinal cysts, and benign posterior mediastinal tumors can be performed with less morbidity than with an open approach. In many cases the improved visualization that these modalities offer leads to a more satisfying technical operation. Large, invasive, and highly malignant tumors should not be approached with these techniques because a risks compromising the oncologic outcome of the operation.

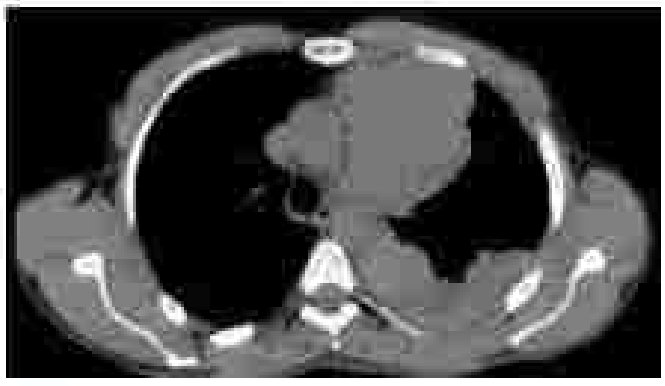

FIG. 4 Aggressive World Health Organization type B2 thymoma with involvement of the left pleural space, requiring left extrapleural pneumonectomy.

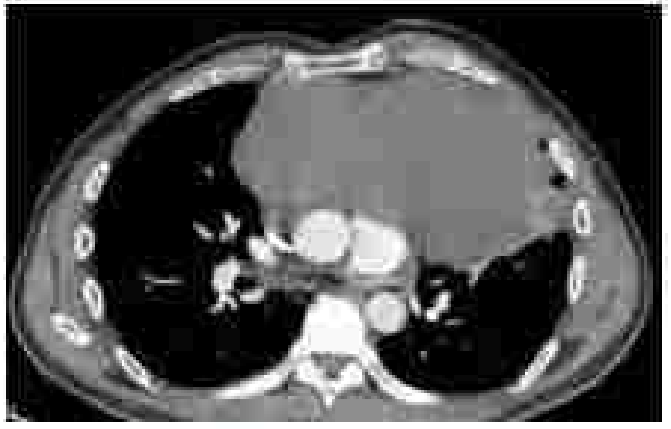

FIG. 5 Mediastinal seminoma.

ANTERIOR MEDIASTINAL MASSES

Primary Thymic Tumors

Primary tumors of the thymus include the full spectrum of thymomas, as well as neuroendocrine tumors of the thymus (sometimes called thymic carcinoids). Together these are the most common masses of the anterior mediastinum. Thymomas are classified according to either their histology using the World Health Organization (WHO) designations, or by their locoregional behavior using the Masaoka-Koga staging system. In 2016 a traditional TNM staging system was introduced that borrows heavily from Masaoka-Koga but indirectly incorporates the WHO classification system because only histologically aggressive thymomas have the propensity for nodal metastases.

Half of thymomas present with a paraneoplastic syndrome, of which myasthenia gravis is by far the most common. Red cell aplasia and hypogammaglobulinemia are also seen. The remainder present with cough or other local compressive symptoms or are discovered incidentally during routine imaging. The appearance on CT of well-defined solid or cystic soft tissue mass within the anterior mediastinum is highly suggestive of thymoma and may obviate the need for a biopsy. MRI adds clarity to the diagnosis and assesses for invasion of surrounding structures. An invasive mass should invite consideration of thymic carcinoma—WHO type C thymoma—which in turn should prompt additional workup, including PET scan, biopsy, and neoadjuvant chemoradiotherapy.

Complete surgical resection is the mainstay of treatment for thymoma and is associated with excellent long-term outcomes. Ninety percent of patients with a thymoma resected completely at an early stage are alive at 10 years. Thymic carcinomas are more aggressive and follow a course that is similar to invasive lung cancer. Complete surgical resection for thymoma may entail extensive resection of the pericardium, great vessels, and thoracic nerves, or thymoma with extensive pleural or pulmonary involvement, extrapleural pneumonectomy is sometimes performed (Fig. 4). Surgery has a role in recurrent thymoma as well. Pleural metastases are frequently managed with a combination of surgical resection and radiation.

Germ-Cell Tumors

Extragonadal germ cell tumors are comprised of three entities: mature teratomas, primary mediastinal nonseminomatous germ cell tumors (PMNSGCT) and primary mediastinal seminomatous germ cell tumors (PMSGCT). PMNSGCTs are commonly called teratomas. All arise from embryonic cells. Seminomas and PMNSGCT occur only in young men, whereas mature teratomas are seen in men and women of varying ages. Imaging and serologic studies provide initial diagnostic and prognostic information, but biopsy is usually obtained as well.

Mature teratomas are the most common germ cell tumor. They contain tissue from mesodermal, ectodermal, and endodermal cell lines. The radiographic appearance is of a heterogeneous mass often containing fluid, fat, and calcifications. AFP and β-HCG are normal. Mature teratomas are resected to prevent local compression and because there is a small incidence of immature, malignant elements being contained within otherwise mature tumors. Once resected, these tumors seldom recur.

Seminomas are slow growing tumors that rarely cause symptoms. As a result, 70% have metastasized to lymph nodes, bone, or lung at the time of presentation. Seminoma may be suspected on the basis of imaging showing a large, lobulated homogeneous lesion within the anterior mediastinum (Fig. 5). Diagnostic evaluation includes investigation for a gonadal primary, biopsy of the mediastinal lesion, and comprehensive imaging looking for other sites of disease. Laboratory studies indicate normal or mildly elevated β-HCG and normal AFP. Treatment is with systemic chemotherapy including bleomycin, etoposide, and cisplatin. Adjuvant radiation is sometimes used. Surgery has a limited role in the management of this disease. Outcomes are typically good, with survival reported to be greater than 85% at 5 years.

PMNSGCT is a more complex and varied disease than either seminoma or mature teratoma. A multimodality approach is essential to successful management. The typical presentation is of a man in the second to fourth decade life with a heterogenous anterior mediastinal mass demonstrating local invasion of surrounding structures (Fig. 6) coupled with elevation in serum β-HCG and AFP. This presentation is pathognomonic for PMNSGCT and may preclude the need for biopsy before initiation of therapy. Many patients do not have significant AFP or β-HCG elevation, though, and a biopsy is essential to differentiate seminoma from PMNSGCT. Histology shows yolk sac carcinoma, embryonal carcinoma, or choriocarcinoma. Approximately 20% of patients have metastatic disease at the time of presentation. Once the diagnosis is made, treatment begins with chemotherapy typically using bleomycin, etoposide, and cisplatin but with the availability of bleomycin sparing regimens when pulmonary toxicity is a concern. Ideally, induction chemotherapy results in normalization of serum tumor markers and decrease in the size of the mediastinal mass. Chemotherapy is followed by surgical extirpation of the residual mass. Unlike with seminoma—where a residual mass after chemotherapy is presumed to be benign—residual viable tumor is present in 60% of postinduction resected PMNSGCT. Because residual mass may not contain viable tumor, careful judgment must be used at the time of surgery to determine whether a critical mediastinal structure ought to be resected en bloc with the mass. Pericardium is frequently resected, as are lung parenchyma, phrenic nerve, and brachiocephalic vessels. Long-term outcome is determined in large part by the presence and grade of viable tumor within the resected specimen; patients with

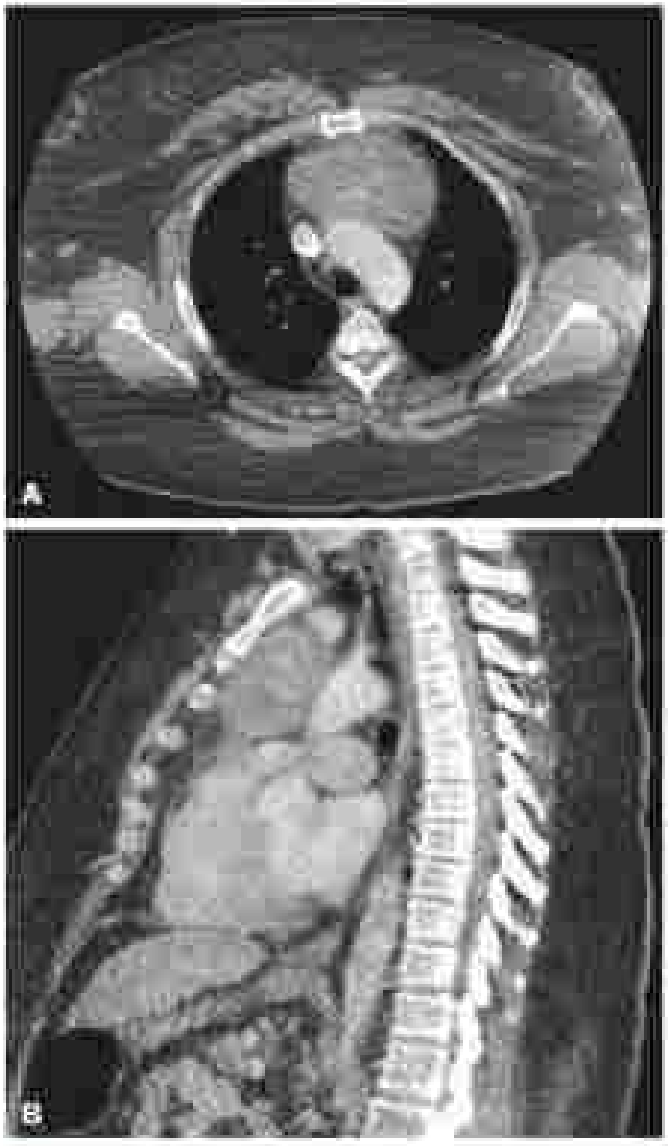

FIG. 6 Mediastinal pole tic tumor

no visible tumor can expect excellent long-term survival, whereas patients with persistent germ cell tumor elements have a poor prognosis. Patients with residual mature teratoma have intermediate outcomes. Surgery plays an important role in recurrent PMNSGCT as well. Rising serum markers and a new mass in a patient after successful resection for PMNSGCT should prompt consideration for resection.

Lymphoma

Lymphomas comprise 20% of anterior mediastinal masses and represent a heterogeneous collection of malignancies derived from lymphocytes. Broadly, they are divided into Hodgkin's and non-Hodgkin's lymphomas and staged according to degree of extranodal involvement and presence of disease on one or both sides of the diaphragm. The role of the surgeon in diagnostic surgical resection has no role in the management of lymphoma. Response to chemotherapy can initially be dramatic resulting in destruction of tumor architecture and tumor lysis syndrome. It is therefore important to obtain a biopsy before initiating treatment and to monitor uric acid, LDH, and renal function subsequently. Surgical biopsy is sometimes required when tumor architecture is crucial to a diagnosis; however, core needle biopsy targeted to PET/CT avid areas of the tumor is often sufficient.

Thyroid and Parathyroid Lesions

The thyroid and parathyroid glands coincident to the anterior cervical trachea despite distinct embryologic origins. Both can be found within the anterior mediastinum. For the thyroid gland this typically means direct extension of a thyroid goiter into the superior anterior mediastinum. Such goiters are no more likely to contain malignant cells than cervical goiters. Surgical extirpation can usually be accomplished through a low collar incision. An upper sternal split may facilitate approach to deeper lesions. A full sternotomy is unnecessary. Rarely, purely ectopic thyroid tissue can be found within the anterior mediastinum. As with a lingular thyroid, this may represent the patient's only source of thyroid function.

Parathyroid glands share an embryological origin with the thymus and therefore are frequently found in an ectopic location within the anterior mediastinum. These ectopic—or occasionally supernumerary—parathyroid glands may become hyperfunctioning adenomas resulting in symptomatic hypercalcemia. Treatment is surgical resection. Sestamibi scanning should be performed on all patients before exploration for parathyroid adenoma, given the relative frequency of a mediastinal location. Intraoperative confirmation of a 50% drop in parathyroid hormone ensures successful resection.

MIDDLE MEDIASTINAL MASSES

Mediastinal Lymphadenopathy

A mass arising in the middle mediastinum is most commonly lymphadenopathy arising from the paratracheal and subcarinal lymph nodes. The differential diagnosis for mediastinal lymphadenopathy includes infectious, inflammatory, or neoplastic lesions. Infectious lesions include bacterial, mycobacterial, and fungal diseases. The most common inflammatory lesion is sarcoidosis. Regionally advanced lung cancer, other metastatic cancer, and lymphoma may all be seen within mediastinal lymph nodes. All of these entities may demonstrate FDG uptake on PET scan. The diagnosis is made with biopsy. Cervical mediastinoscopy remains a safe and effective technique for taking large samples of mediastinal lymph nodes for culture, fungal and gram stain, flow cytometry, and pathology. EBUS or EUS with FNA or core biopsy may be sufficient to make a diagnosis—particularly when metastatic lung cancer is suspected—and is less invasive than mediastinoscopy.

Mediastinal Cysts

Cysts of bronchogenic, esophageal, or pericardial origin may arise within the mediastinum. Bronchogenic cysts are the most common—accounting for 60% of mediastinal cysts—followed by esophageal cysts. Together, these two entities may be called foregut duplication cysts. CT demonstrates a smooth-walled soft tissue density with non-enhancing—and contrast. MRI is more sensitive and specific for making the diagnosis. Increasingly, EBUS and EUS can be used to make a diagnosis. Needle biopsy is discouraged because of the risk of superinfection. These cysts are often incidental findings but may come to attention because of local compressive symptoms. Symptoms are a clear indication for surgical resection. Otherwise, the theoretical risk of malignant transformation justifies resection in patients for whom operative risk is low. Minimally invasive approaches are often used with good effect. Pericardial cysts are not believed to have any risk of malignant transformation and are resected when they are symptomatic or enlarging (Fig. 7).

Castleman's disease

Castleman's disease—or angiofollicular hyperplasia—is a rare lymphoproliferative disease that can occur anywhere in the body but favors locations adjacent to the central airways in the middle mediastinum. The classic appearance is of a solitary mass with or without associated lymphadenopathy that demonstrates intense enhancement on CT with the addition of intravenous contrast. Most patients are

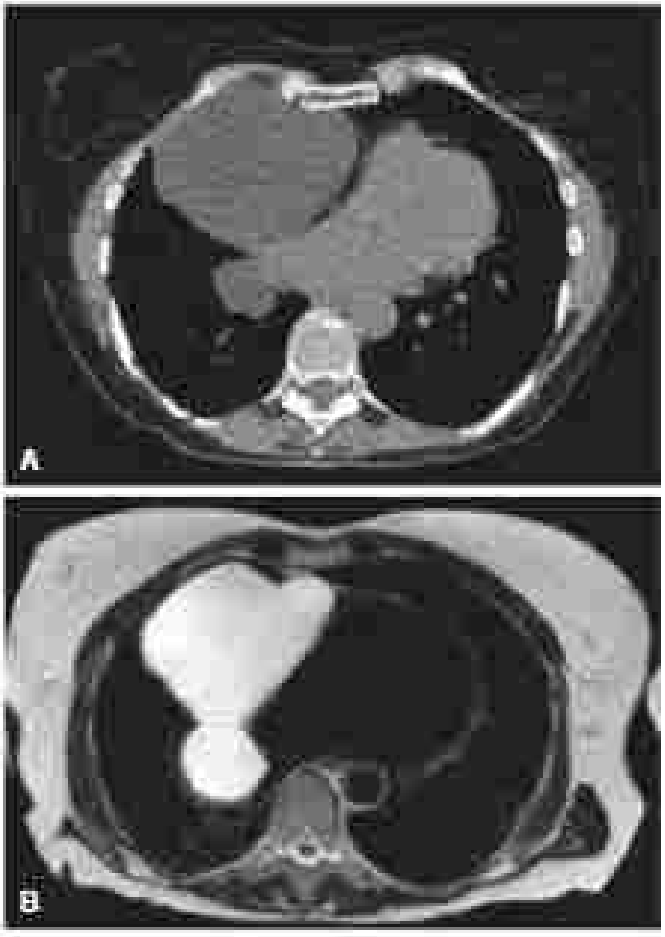

FIG. 7 Paraaortal cyst in the classic location in the right paravertebrum sulcus.

young adults and are symptom free. Immunocompromised patients are at increased risk. Treatment of unicentric disease is surgical resection. Multicentric disease is treated with a combination of B cell targeted immunotherapy and radiation.

POSTERIOR MEDIASTINAL MASSES

Most tumors in the posterior mediastinum are neurogenic in origin. This includes tumors arising from nerve sheath elements, ganglion cells, and paraganglion cells. In adults these tumors are frequently asymptomatic and benign. This is not true for children, in whom posterior mediastinal tumors are both more common and more likely to demonstrate malignant behavior. In addition to CT, MRI is indicated to determine whether the mass involves the neural foramen. In the case of dumbbell tumors, this involvement may be quite extensive and mandate the involvement of a neurosurgeon during surgical resection (Fig. 8). Biopsy is not needed before resection for most posterior masses.

Schwannomas and Neurofibromas

Tumors of nerve sheath origin make up 90% of adult neurogenic tumors. They are commonly benign, but resection is indicated to exclude malignant schwannoma or neurofibrosarcoma, both of which are highly aggressive.

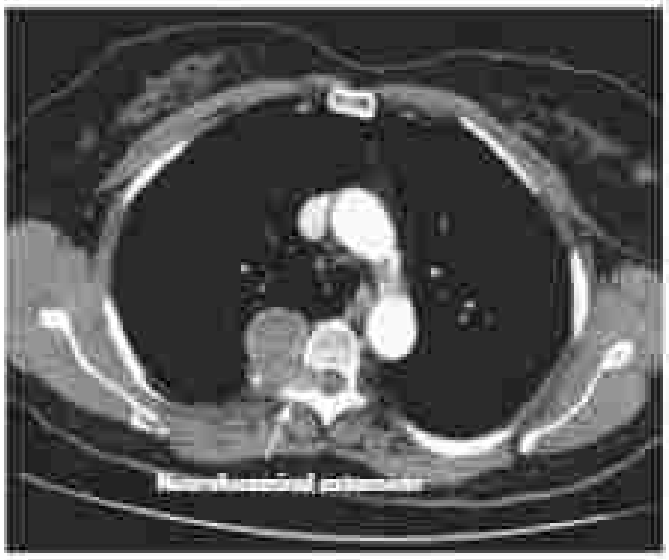

FIG. 8 Posterior mediastinal schwannoma with invasion into the neural foramen (i.e., "dumbbell" tumor).

Ganglion Cell Tumors

Ganglion cell tumors arise from the sympathetic ganglia. Ganglioneuromas are three common in adults and are benign. Ganglioneuroblastomas and neuroblastomas both arise in young children and follow an aggressive, malignant course. Any of these lesions may secrete vasoactive intestinal peptide or catecholamines. Cushing's syndrome is described. The treatment of all ganglion cell tumors is resection with adjuvant therapy reserved for those with malignant properties.

Paraganglion Cell Tumors

Mediastinal pheochromocytomas may arise from paraganglion cells and produce the classic symptoms of malignant hypertension. This symptomatology, coupled with elevated urine catecholamine metabolites and a posterior mediastinal mass that brightly enhances on contrast CT, makes the diagnosis. Biopsy should be avoided. Surgical resection is preceded by alpha and beta blockade to prevent sympathetic crisis.

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Primary Tumors of the Thymus

Cameron D. Wright, MD

Thymic tumors are rare, with an estimated incidence of 0.15 cases per 100,000 person years. They are, however, the most common tumor of the anterior mediastinum seen in adults. Usually the diagnosis can be made by careful review of a contrast enhanced chest computed tomography (CT) scan. The differential diagnosis includes more importantly lymphomas, as well as germ cell tumors such as teratomas, seminomas, and nonseminomatous germ cell cancers, retrosternal goiters, thymic cysts, thymic hyperplasia, and other uncommon tumors. Most thymomas are asymptomatic. Thymomas can be associated with several autoimmune syndromes, most importantly myasthenia gravis but also red cell aplasia, hypogammaglobulinemia and other neurologic paraneoplastic syndromes. Symptoms referable to a thymoma may include substernal chest discomfort, dyspnea, cough, and the superior vena cava syndrome. If germ cell tumors are thought to be in the differential diagnosis, then an α-fetoprotein and β-human chorionic gonadotropin level should be sent. If myasthenia gravis is present, typically a myasthenia antibody panel that includes acetylcholine receptor antibodies is obtained.

IMAGING

Obtaining a CT scan with intravenous (IV) contrast is the most important step in initial decision making in assessing a possible thymic tumor. IV contrast is necessary to highlight the mediastinum and great vessels and to look for enhancement in the lesion. Thymic tumors almost always occur in the distribution of the normal thymus in the upper substernal area, but as they enlarge they often will point to one of the pleural spaces. Thymomas are typically relatively rounded masses, are often relatively homogeneous, and, although they may abut important structures, typically the edges are relatively sharp if they are not invasive (Figs. 1 and 2). Invasive thymomas or thymic carcinomas typically look different and have many characteristics, suggesting a more advanced tumor. Invasive thymic tumors typically have fuzzy edge characteristics suggesting invasion of adjacent structures such as the lung. Other features that would suggest invasion are encasement or intravascular extension into a great vessel, areas of hemorrhage or necrosis within the tumor itself, evidence of phrenic nerve invasion with an elevated hemidiaphragm, and pleural implants (Fig. 3). Although thymomas rarely metastasize to lymph nodes, thymic carcinomas not uncommonly have lymph node metastases (Fig. 4).

Thymic cysts are typically very rounded or teardrop shaped, quite homogeneous, and sharply demarcated. They have low attenuation when Hounsfield units are measured. Thymic cysts are often difficult to differentiate from small thymomas. A mediastinal magnetic resonance (MR) examination protocoled for the thymus can be very helpful to make a definitive diagnosis of a benign thymic cyst that exhibits thin walls with no internal septation and no mural nodularity.

Thymic hyperplasia is often confused by inexperienced observers as representing a possible anterior mediastinal mass, most likely a thymoma. Typically thymic hyperplasia presents as a bilobed enlargement of the normal thymus with a homogeneous appearance and sharp demarcation with normal structures (Fig. 5). Mediastinal MR examination again can be quite helpful with a thymic protocol.

Lymphomas are typically multilobular with surrounding lymphadenopathy and obvious invasive edge characteristics (Fig. 6). There are often areas of necrosis or hemorrhage within the tumor mass. There may be an associated pleural effusion or pericardial effusion. There is often encasement or primary phenomenon of the great vessels and tracheobronchial tree with lymphoma.

PATHOLOGY

A simple pathologic classification of thymic tumors defines three types of thymic tumors: thymomas that have no atypia or mitotic activity, atypical thymomas or well differentiated thymic carcinomas, which have atypical thymic epithelial cells, and thymic carcinomas with clearly malignant cytologic features and aggressive behavior. The World Health Organization classification is used by most pathology departments and is seen in Table 1. In general type A and AB tumors tend to be early stage tumors, are more commonly associated with myasthenia gravis, and generally have an excellent prognosis. Type B tumors are typically more invasive and have an intermediate prognosis. Type C tumors are locally quite aggressive, can metastasize to lymph nodes, as well as distant sites, and have a guarded prognosis. There is independent prognostic value in the World Health Organization (WHO) classification system, but the most important factors in determining prognosis are a complete resection and the stage of the tumor. Core needle biopsy is often not informative of the exact WHO type of thymoma. A rare thymic malignancy is a thymic carcinoid tumor also known as a neuroendocrine tumor of the thymus. These tend to be very locally aggressive and have a poor prognosis.

STAGING OF THYMIC TUMORS

For many years the Masaoka Koga staging system was used for thymomas (Table 2). The basis of the staging system was the degree of invasion of the tumor into adjacent structures and whether there were any metastases. The advantages of this system are that it is relatively intuitive and simple, and there is a long history with its use. More recently the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual was published and defines a tumor, node, metastasis staging system for thymomas and thymic carcinomas (Tables 3 and 4). This system at first glance is more complex, but most patients are either stage I or stage II, so it is not unduly cumbersome. Survival for early stage thymomas is excellent. The 5-year survival rate using the Masaoka staging system is as follows: stage I, 96%; stage II, 80%; stage III, 65%; stage IVa, 50%; and stage IVb, less than 50%.

TREATMENT PRINCIPLES

The optimal treatment for all thymic tumors is a complete R0 surgical resection. A complete resection is the most important independent predictor of disease free recurrence after resection, followed by stage and WHO histology. In general the entire thymus should be resected in continuity with the tumor along with attached mediastinal fat (typically from phrenic nerve to phrenic nerve and from diaphragm to just above the innominate vein). Resection of local invasion of attached structures such as the pericardium, pleura, ipsilateral phrenic nerve, innominate vein, and superior vena cava is typically performed to accomplish R0 resection. Areas where the surgeon knows there is a close margin should be identified with a metal clip to aid in postoperative adjuvant radiation therapy.

Patients who present with clearly encapsulated tumors or tumors that have apparent minimal invasion of easily resectable structures generally have immediate resection without an attempt at preoperative tissue diagnosis or any form of induction therapy. Patients with clear cut, locally advanced, difficult to resect disease are most commonly referred for CT guided core needle biopsy, to be followed by induction chemotherapy. Resection is then performed after restaging confirms the absence of progressive disease. Patients who

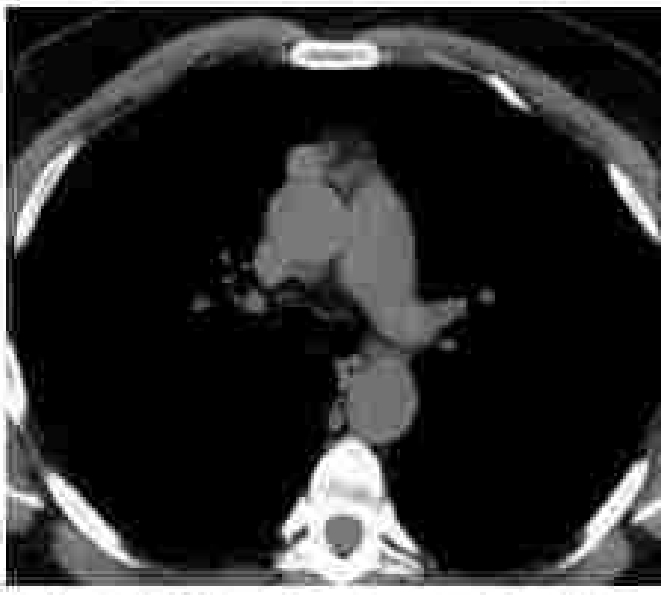

FIG. 1. Small 1.5-cm encapsulated early-stage thymoma adjacent to the aorta amenable to video-assisted thoracic surgery resection.

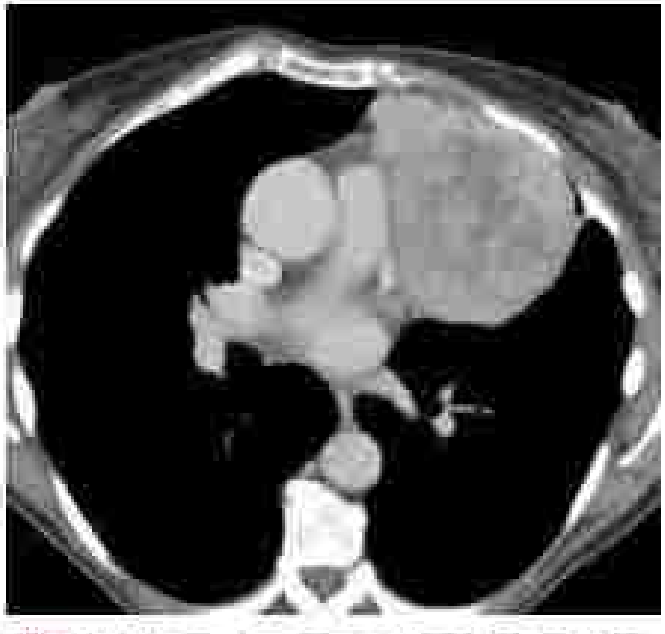

FIG. 2. A 10-cm thymoma, heterogeneous with murky borders and extensive lung abutment. This was removed by sternotomy and was a Masaoka stage II thymoma.

present with de novo pleural metastases are problematic, and there is no uniform approach. Upfront resection of both the tumor and pleural implants is acceptable, as well as induction chemotherapy first, followed by a resection. Lymph node dissection is unnecessary in patients with thymomas but is important and should be performed in patients with thymic carcinomas and nonmyasthenic thymic tumors. When patients have myasthenia gravis, it is important to work closely with a neurologist to optimally manage their myasthenia before proceeding to a resection. Patients should be very well controlled on their medical program and often need either plasmapheresis or intravenous immunoglobulin therapy for optimization before surgery.

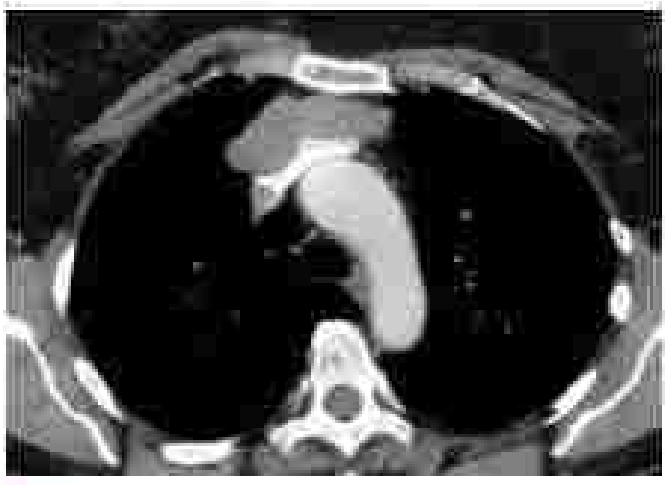

FIG. 3. Locally advanced thymoma invading the innominate vein requiring venous resection. This was a World Health Organization B3, Masaoka stage III thymoma.

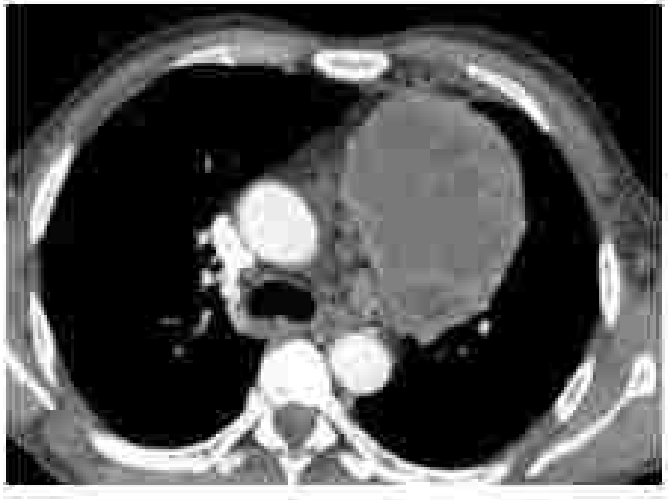

FIG. 4. Large thymic carcinoma with low-density central area (necrosis) with adjacent lymphadenopathy.

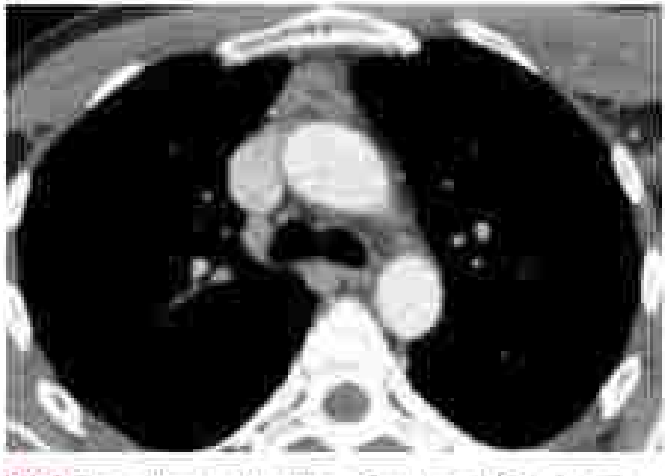

FIG. 5. Thymic hyperplasia in a symptom-free man with bilobed pleural thymus with sharp borders and no appreciable mass. The mediastinal mass mimics the normal shape of the thymus.

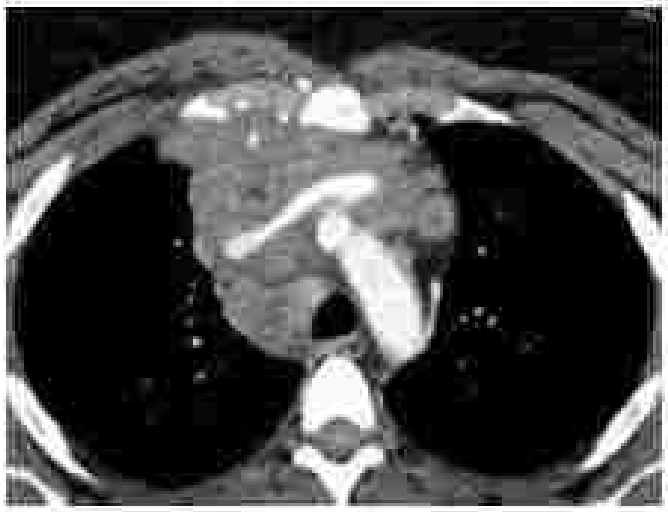

FIG. 1 Anterior Hodgkin's lymphoma with surrounding pathologic lymphadenopathy and encasement of the superior vena cava and brachiocephalic vein.

Table 1 Pathology of Thymic Tumors—World Health Organization Histologic Classification

Tumor Type	Diagnostic Criteria
Type A	Occurrence of bland, spindle shaped epithelial cells, paucity or absence of T cells
Type AB	Occurrence of bland, spindle shaped epithelial cells, abundance of immature T cells focally or throughout tumor
Type B	Thymus-like architecture and cytology, abundance of immature T cells, areas of medullary differentiation, paucity of polygonal or dendritic epithelial cells without clustering
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of inter mingled T cells
Micronodular thymoma	Nodules of bland spindle shaped or oval epithelial cells surrounded by an epithelial cell free lymphoid stroma
Type C	Thymic carcinoma; squamous cell carcinoma, non cornified carcinoma, clear cell carcinoma, basaloid carcinoma, sarcomatoid carcinoma, anaplastic carcinoma

OPERATIVE MANAGEMENT

Thymic tumors can be removed by standard open surgery and also by minimally invasive approaches with either video assisted thoracic surgery (VATS) or robotic techniques. In general minimally invasive approaches should be reserved for small, easily removable tumors. It is very important not to violate the capsule of the thymic tumor during its removal because these tumors have a unfortunate reputation for

Table 2 Masaoka-Koga Staging System

Masaoka Stage	Diagnostic Criteria
Stage I	Macroscopically encapsulated, no microscopic invasion of the capsule
Stage II	A: Microscopic transcapsular invasion B: Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs—pericardium, great vessels, lung A: Without invasion of great vessels B: With invasion of great vessels
Stage IV	A: Pleural or pericardial dissemination B: Lymphogenous or hematogenous metastases

Table 3 TNM Staging

Primary Tumor	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura T1a: Tumor with no mediastinal pleura involvement T1b: Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium
T3	Tumor with direct invasion into any of the following: Lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any that following: Aorta, intrapericardial pulmonary artery, myocardium, trachea, esophagus
REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases to anterior lymph nodes
N2	Metastasis to deep intrathoracic or cervical lymph nodes
DISTANT METASTASIS	
M0	No pleural, pericardial, or distant metastases
M1	Pleural, pericardial, or distant metastases M1a: Separate pleural or pericardial nodule M1b: Pulmonary intraparenchymal nodule or distant organ metastases

From Amin MB, Greene FL, Edge SB, et al. AJCC Cancer Staging Manual, ed 8. Springer International; 2017. Used with the permission of the American College of Surgeons.

TNM, Tumor, node, metastasis.

Table 4 AJCC Prognostic Groups

	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
	Any T	N0, 1	M1a
Stage IVB	Any T	N2	M0, M1a
	Any T	Any N	M1b

AJCC, American Joint Committee on Cancer.

From Amin MB, Greene FL, Edge SB, et al. AJCC Cancer Staging Manual, ed 8, Springer International; 2017. Used with the permission of the American College of Surgeons.

developing pleural implants. Transcervical thymectomy is not appropriate for removal of a thymic tumor but is useful for selected patients with myasthenia gravis alone.

TRANSSTERNAL THYMECTOMY

The standard approach to most thymic tumors is by a sternotomy. Sternotomy provides excellent access to the anterior mediastinum and lower neck, and it provides reasonable access to either pleural space. Tumors that are very large and are suspected of significant involvement of lung are sometimes best approached with a hemi clamshell approach with a combination of a sternotomy and lateral thoracotomy. Except for the smallest resting thymomas, it is usually best to have the anesthesiologist place a double-lumen endotracheal tube to allow one-lung ventilation during surgery to facilitate dissection of the thymic tumor away from the pericardium, phrenic nerve, and lung. It is often helpful to use a table-mounted internal thoracic artery retractor to elevate the sternum away from the mediastinum and the thymic tumor to allow dissection away from the anterior chest wall with a safe margin. If the thymic tumor appears to involve the mediastinal pleura on preoperative imaging, opening of that pleural space is recommended both to ensure wide resection of any possible involvement of mediastinal pleura and also to inspect the pleural space for a possible drop metastasis. If pleural implants are found, they should be resected. Thymectomy should be performed in addition to resection of the thymic tumor, as well as all surrounding readily removable mediastinal fat.

The dissection can be started in the neck, with each cervical tongue being isolated, separated from the inferior portion of the thyroid, and brought down to the manubrium with level. Alternatively one may start at the diaphragm level and dissect the mediastinal fat superiorly until the area of the tumor is reached. Once the area of the tumor is isolated, it is important to ascertain to what the tumor might be adherent and plan on resecting all easily removable adherent marginal tissues. One should not hesitate to resect the underlying pericardium from the tumor to ensure that the deep margin is negative. Wedge resection of a portion of the upper lobe of the lung is frequently required. Very careful dissection around the phrenic nerve is important. If cautery must be used in this area, bipolar cautery can minimize any transmission injury to the phrenic nerve itself. Sacrifice of one phrenic nerve in an otherwise healthy person is acceptable and often necessary. Bilateral phrenic nerve resection should of course never be done. There is frequently a close margin at the phrenic nerve level, and, if there is any concern for tension to this area, it should be marked with clips to aid in postoperative adjuvant radiation therapy. Typically there are two or three veins that drain directly to the innominate vein, and these can be controlled with ties, the harmonic scalpel, or clips. If the pleural space is entered, it is typically deemed with a small suction drain. The anterior mediastinum is typically drained with a standard chest tube. The sternum is reapproximated with six parasternal wires, and then the incision is closed in layers. The specimen should be marked with sutures to orient the pathologist because these resected specimens can be quite confusing, which can lead to difficulties in making a determination about the need for postoperative radiation therapy and where any possible close margins are. Patients are extubated in the operating room and typically do not require an intensive care unit environment unless they have myasthenia gravis. Drains can usually be removed on the first postoperative day, and patients can be discharged when pain is satisfactorily controlled and the patients are independently mobile. Patients are typically followed up long term after thymoma resection with periodic contrast-enhanced CT scans, yearly for low-grade tumors and more frequently for higher-grade tumors.

MINIMALLY INVASIVE RESECTION

VATS and robotic-assisted thoracic surgery have been used for many years now for resection of thymic tumors. There are no randomized studies comparing these approaches to the open approach. Early results suggest equivalent outcomes. Retrospective studies suggest a shorter hospital stay, reduced blood loss, decreased postoperative pain, and an improved cosmetic result compared with open approaches. Although there are small series and case reports of resection of advanced thymic tumors with a minimally invasive approach, most surgeons reserve a minimally invasive approach for a clinical stage I lesion.

VATS for resection of thymic tumors can be performed on either side of the chest, and typically the laterality is chosen based on the tumor projecting into that ipsilateral pleural space. For tumors that are small and midline, most surgeons choose a right-sided approach because the confluence of the superior vena cava and innominate vein is easy to approach from the right side. A double-lumen endotracheal tube is placed, and the patient is placed in a lateral decubitus position for the typical unilateral midline thymic tumor. For larger tumors it can be helpful to place a bump underneath the operative side and prep out the contralateral side as well, which allows one to put a separate camera port on the other side to facilitate dissection on the opposite side and most importantly to avoid injury to the opposite phrenic nerve. A complete port-based approach is usually performed because that allows carbon dioxide insufflation and thus opening up the mediastinum and dissection planes for ease of dissection and resection. Typically 3 ports are placed, one for the camera and two to triangulate a grasping instrument and a harmonic scalpel superior to the camera port.

Typically the dissection is started inferiorly with dissecting the mediastinal fat and eventually the thymus off the pericardium to where the tumor is present. Dissection is then done laterally around the phrenic nerve, carefully preserving it and then skeletonizing the anterior surface of the superior vena cava, which leads one to the innominate vein. Small thymic vein branches are sealed with the energy device, and the two cervical tongues of the thymus can be easily dissected into the neck and then their attachments to the thyroid divided again with the energy device. The pericardium should be entered electively if the tumor extensively abuts the pericardium at its deep margin. The specimen should be placed in a bag and then removed through an enlarged access port to prevent spillage of any thymic tumor cells. A small silicone drain is typically left in the pleural space and removed usually the next morning. Most patients can be discharged the morning after surgery, and recovery is typically quick.

ADJUVANT RADIATION

Thymic tumors are generally radiosensitive, and radiation may help reduce local recurrence after resection of advanced thymic tumors. All patients who have incomplete resections should have adjuvant radiation therapy, and close consultation with the radiation

oncologist is important to inform them of the sites of greatest risk for recurrence. Typically all patients with thymic carcinomas are referred for postoperative radiation therapy, given their very high chance for local recurrence. Completely resected Masaoka stage I tumors do not require radiation therapy. Adjuvant radiation in Masaoka stage II or III tumors that are completely resected is controversial, and there is substantial institutional variation in referral of such patients. The recurrence pattern of thymomas is that more than 75% of all recurrences occur in the pleural space such that mediastinal radiation has a questionable role in preventing most recurrences.

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Management of Tracheal Stenosis

Shahrzad Oyetunji, MD, MPH, and Douglas E. Wood, MD, FRCSEd

Disorders involving the airway are relatively uncommon, and most thoracic surgeons will see only the occasional patient with tracheal disease. However, both benign and malignant obstructions of the central airway cause significant morbidity and mortality. Successful management may correct or palliate impending suffocation, dyspnea, and obstructive pneumonitis. Tracheal resection and reconstruction may preclude the need for a lifelong tracheostomy and allow preservation of laryngeal function in patients with benign strictures and provide treatment with curative intent for airway tumors.

INDICATIONS FOR TRACHEAL RESECTION

The most common indication for tracheal resection and reconstruction is prolonged intubation or post tracheostomy stenosis. Cuff injuries occur because of prolonged pressure with resultant full-thickness necrosis of the tracheal cartilage. This produces circumferential scar contracture, with symptoms typically developing 3 to 6 weeks after extubation. Stomal stenosis after tracheostomy occurs when there is a large anterior tracheal defect from the tracheostomy stoma with subsequent anterior scar contracture when the patient is decannulated. This cause of tracheal stenosis typically results in an A frame appearance, with anterior narrowing and relatively normal posterior membranous wall.

Other causes of benign tracheal stenosis are trauma, inflammatory, or idiopathic. Neck or chest injury or operative trauma to the airway may sometimes be undetected at the time of injury but present later because of secondary tracheal narrowing. Severe tracheal infections and a number of collagen vascular diseases may result in acute and chronic inflammation with secondary tracheal stenosis. Idiopathic tracheal stenosis occurs most commonly in women from the third to sixth decade of life, most commonly located at the level of the cricoid cartilage with varying degrees of subglottic involvement.

Primary tracheal tumors are another indication for tracheal resection. Tumors of the trachea are extremely uncommon and represent only 0.2% of all malignancies of the respiratory tract. Squamous cell carcinoma and adenoid cystic carcinoma are the two most common tracheal tumors and account for more than two-thirds of all primary tumors of the upper airway. After squamous cell carcinoma and adenoid cystic carcinoma, the most common tracheal tumors are carcinoid and mucoepidermoid tumors. However, there is a wide variety of rare tumors with varying degrees of malignancy from both epithelial and mesenchymal origins. The prognosis for untreated tracheal tumors is poor even with benign tumors, because of the risk of airway obstruction. Tumors of the trachea should be considered for resection if they can be resected with less than half of the longitudinal length of the trachea and do not have unresectable local extension into surrounding structures. Although adjacent tumors with airway invasion are almost never considered for tracheal resection, one exception is locally advanced thyroid cancer. Progression of disease in the trachea can produce significant symptoms and be life limiting. These patients should be considered for tracheal resection, even in the presence of metastatic disease, because of the long natural history, and the severe impact of tracheal progression.

Tracheal reconstructive procedures are frequently regarded as complex operations with high morbidity and mortality rates. However, excellent results can be obtained in appropriately selected patients with a combination of well planned anesthetic airway management, meticulous operative technique, and careful postoperative care.

PREOPERATIVE ASSESSMENT

Symptoms of central airway obstruction can be surprisingly insidious and may often go undiagnosed for a long period of time. Dyspnea on exertion is the primary symptom in patients with a significant tracheal stenosis, but these patients may also present with wheezing, stridor, cough, difficulty clearing secretions, recurrent respiratory infections, or hemoptysis. Patients with tracheal or bronchial tumors may also present with any of the previous symptoms, but in addition may have hemoptysis. An assessment of the severity of symptoms and their time course is useful for establishing the cause and the acuity of the airway pathology. A 50% reduction in the cross-sectional area of the trachea usually results in dyspnea only with significant exertion, whereas narrowing of the lumen to less than 25% of the cross-sectional area usually produces dyspnea and stridor at rest. Patients

oncologist is important to inform them of the sites of greatest risk for recurrence. Typically all patients with thymic carcinomas are referred for postoperative radiation therapy, given their very high chance for local recurrence. Completely resected Masaoka stage I tumors do not require radiation therapy. Adjuvant radiation in Masaoka stage II or III tumors that are completely resected is controversial, and there is substantial institutional variation in referral of such patients. The recurrence pattern of thymomas is that more than 75% of all recurrences occur in the pleural space such that mediastinal radiation has a questionable role in preventing most recurrences.

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Tracheal reconstructive procedures are frequently regarded as complex operations with high morbidity and mortality rates. However, excellent results can be obtained in appropriately selected patients with a combination of well planned anesthetic airway management, meticulous operative technique, and careful postoperative care.

PREOPERATIVE ASSESSMENT

Symptoms of central airway obstruction can be surprisingly insidious and may often go undiagnosed for a long period of time. Dyspnea on exertion is the primary symptom in patients with a significant tracheal stenosis, but these patients may also present with wheezing, stridor, cough, difficulty clearing secretions, recurrent respiratory infections, or hemoptysis. Patients with tracheal or bronchial tumors may also present with any of the previous symptoms, but in addition may have hemoptysis. An assessment of the severity of symptoms and their time course is useful for establishing the cause and the acuity of the airway pathology. A 50% reduction in the cross-sectional area of the trachea usually results in dyspnea only with significant exertion, whereas narrowing of the lumen to less than 25% of the cross-sectional area usually produces dyspnea and stridor at rest. Patients

may be reasonably compensated in spite of significant stenosis but can have acute life threatening deterioration with a minor amount of airway edema or secretions. A high index of suspicion in the presence of these symptoms is critical to the diagnosis of central airway pathology.

A careful history and physical examination is performed with a focus on prior trauma, respiratory illness with prolonged intubation, or prior tracheostomy. On physical examination patients will usually have wheezing or stridor if they have significant airflow obstruction. Other signs that may be present include prolonged inspiration or expiration, use of accessory muscles, or signs of retained secretions or obstructive pneumonia.

Spirometry and flow volume loops are neither sensitive nor specific when diagnosing central airway disease. They yield little in the decision making management of these patients and should not sway a practitioner to delay or proceed with treatment.

Further radiologic evaluation of the patient should be performed for patients who do not present in respiratory distress. Plain posteroanterior and lateral chest radiography often will provide evidence of proximal airway narrowing. Thin-cut computed tomography (CT) scans also provide more anatomic definition of the location, degree, and extent of airway stenosis, which is sometimes easily portrayed in a three dimensional reconstruction. CT also provides information on relation of pathology to surrounding structures that can be important for the management of both benign and malignant lesions.

Bronchoscopic evaluation is the modality for establishing the diagnosis and defining the anatomy for subsequent therapeutic decisions. Bronchoscopy should be done by the primary surgeon, and observations of others is inadequate to assess the suitability of a patient for a possible tracheal reconstruction. Although flexible bronchoscopy is generally effective for defining the airway anatomy and performing initial endoscopic palliation, surgeons evaluating tracheal stenosis should be facile with rigid bronchoscopy, and the rigid bronchoscopes should be available as needed for all bronchoscopy procedures. Rigid bronchoscopy provides the best means for airway control and emergency airway palliation and should be available as a routine management option for physicians evaluating airway obstruction. In cases of critical tracheal obstruction or bronchial obstruction, rigid bronchoscopy with dilation, core out of tumor, laser, or stenting provides effective temporary palliation, allowing completion of the medical workup and elective timing of surgical intervention. The anatomic location, proximal and distal extent, and diameter of the stenosis is carefully examined and measured to plan the surgical approach, as well as the quality of the airway and the presence of any ongoing associated inflammation.

ANESTHESIA AND AIRWAY MANAGEMENT

The surgeon should be available during induction of anesthesia to help ensure control of the airway. Postintubation tracheal stenoses are typically amenable to dilation if needed for successful passage of an endotracheal tube. This can be accomplished with a rigid bronchoscope or a balloontipped catheter, and a variety of sizes should be available in anticipation of this. Post tracheostomy stomal stenoses are not amenable to dilation because of the normal structure of the membranous wall, although the airway easily expands with the dilation, it just as readily recoils back to the preexistent diameter when the dilating force is removed. However, this also means that a symptomatic stomal stenosis can nearly always be intubated without difficulty, even with a normal size endotracheal tube.

Anesthesia for tracheal resection is best administered as mixed inhalational and intravenous anesthetic while maintaining spontaneous ventilation until the airway is established. Short acting anesthetic agents are preferred with the goal of extubating the patient in the operating room at the end of the operative procedure.

It is important to discuss the ventilation strategy and coordination of endotracheal tube exchange with the anesthesiologist in advance of the operation and again during the preoperative briefing. Before the division of the trachea, the endotracheal tube is withdrawn into the proximal trachea and once the trachea is divided, the distal trachea is intubated across the surgical field with a sterile endobronchial tube and circuit. The endobronchial tube can be safely removed intermittently for brief periods of apnea to permit precise placement of sutures during reconstruction. Once the anastomotic sutures are placed, the oral endotracheal tube is then advanced under direct vision past the incomplete anastomosis and secured. Then the anastomotic sutures are tied, and the procedure is completed.

The goal of extubating the patient in the operating room at the conclusion of the case allows for assessment of the adequacy and stability of the reconstructed airway in a controlled environment with the surgeon and anesthesiologist present thereby avoiding unnecessary prolongation of ventilation, as well as endotracheal tube trauma to the reconstructed airway. A "protective tracheostomy" should be avoided in most cases because it is rarely needed, creates a point of airway fixation that may increase tension on the anastomosis, and provides a source of wound contamination that may increase the risk of anastomotic dehiscence. For patients with a very high laryngotracheal anastomosis and postoperative vocal cord edema that threatens airway stability, a tracheostomy may be useful, placed well below the anastomosis, or an alternative is to consider a short period of oral intubation until the edema partially resolves.

SURGICAL TECHNIQUE FOR TRACHEAL RESECTION

Tracheal resection techniques have evolved over the past four decades. Initially, safe length of tracheal resection was limited to 2 cm. Pioneered by Grillo and others, tracheal resection and reconstruction was shown to be safe up to lengths of 3 to 4 cm. This is due to experience with tracheal resection technique, and development of proximal and distal tracheal mobilization to allow for tension free reconstruction. Furthermore, sulpluth- and carinal resection techniques have been developed for more proximal and distal tumors, respectively.

For benign tracheal lesions, most can be resected and primarily reconstructed if they involve less than half of the tracheal length. The primary contraindications for tracheal reconstruction include the need for continued mechanical ventilation, a lesion that cannot be completely excised and primarily reconstructed (approximately half of the trachea), active infection or inflammatory lesion, or stenosis from an uncontrolled systemic disorder such as Wegener's granulomatosis or sarcoidosis.

Despite being a major operation, tracheal resection and reconstruction are usually physiologically trivial, with minimal pain, minor fluid shifts, little blood loss, and stable hemodynamics, so that even significant comorbidities are not usually contraindications for surgery. Tracheal resection and reconstruction is a major undertaking, however, requiring experience with complex perioperative airway management, judgment regarding the extent of resection, and meticulous attention to the technical details of airway reconstruction. It is obvious that technical or judgment failures are potentially life threatening. Success with the primary attempt at reconstruction is critical because there are no prosthetic substitutes for the trachea, which limits the extent of airway resection.

Most benign stenoses are approached through a neck incision and rarely require thoracotomy. Principals of reconstruction include resection to normal airway, minimal dissection beyond the segment to be resected to avoid devascularization, and primary reconstruction without anastomotic tension, using a variety of standard and extended mobilization techniques. In some cases, proximal tracheal stenosis may extend into the subglottis, larynx, requiring resection of the anterior cricoid cartilage and laryngotracheal reconstruction. Management of tracheal stenosis by tracheal resection and

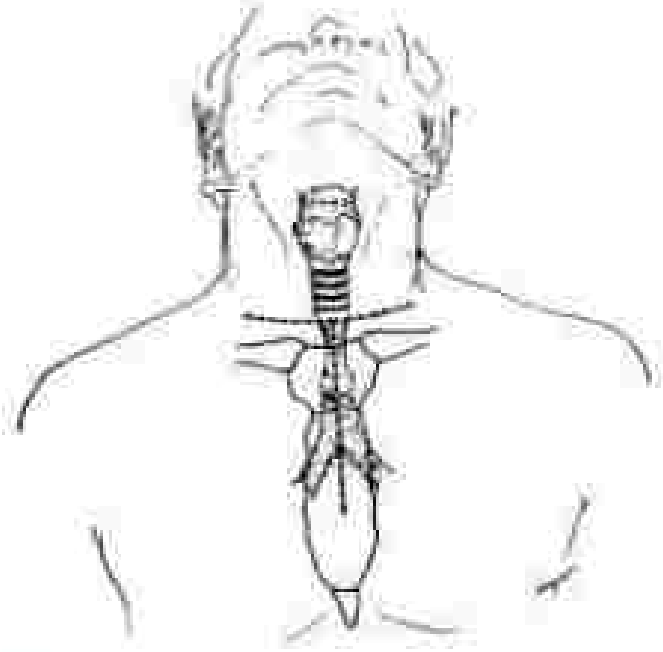

FIG. 1 Collar incision with T extension if needed for additional exposure. [This is described in] Ogura JH, Fuller DB, Calcaterra TC, Hyde GL. Management of the larynx and hypopharynx. 2nd ed. Philadelphia: WB Saunders; 1983.

reconstruction produces reliable and durable results with low morbidity and mortality rates.

For lesions in the upper two thirds of the trachea, the patient is placed supine on the operating table with a roll underneath the shoulders to extend the neck. The head is then moved to a beach chair position, with the feet flexed at the hips and the torso raised 30 degrees. A collar incision is typically used, however, for lesions that extend too caudal to be accessible through a collar incision, the exposure can be significantly increased by making a T incision in which the vertical arm extends caudal to a point 2 cm below the sternal angle (Fig. 1).

For the most common cervical approach, subplatysmal flaps are raised to the thyroid cartilage superiorly and the sternal notch inferiorly. The strap muscles are not divided but are reflected laterally to expose the anterior trachea from the cricoid to the thoracic inlet, dividing the isthmus of the thyroid gland if needed.

Tracheal reconstruction requires a clear understanding of tracheal blood supply to perform adequate airway mobilization without unnecessary devascularization of the trachea. Tracheal blood supply is segmental, and the lateral tracheal blood supply must be preserved to avoid anastomotic complications or the potential for downstream ischemic necrosis of the residual trachea. Mobilization of the trachea should be limited to the involved area and the proximal and distal tracheal margins skeletonized to the extent needed to complete the anastomosis, usually 5 to 7 mm. The lateral dissection is performed directly on the trachea wall to avoid injury to the recurrent laryngeal nerves, esophagus, and innominate artery. In general, it is safest to follow this technique rather than identifying the recurrent laryngeal nerves individually, although this may be necessary when doing more extensive radial dissections in cases of airway tumor.

To achieve a tension free anastomosis, tracheal release maneuvers are critically important. Dissection of the avascular pretracheal plane as described above and neck flexion are two tracheal release maneuvers that are simple and effective and should be performed routinely for all tracheal resections.

Dissection of the avascular pretracheal plane should be performed routinely early in the dissection because it also helps with surgical exposure. From a cervical approach, this is similar to development of the plane for mediastinoscopy; the pretracheal fascia is incised, and blunt digital dissection over the anterior surface of the trachea is performed down to the carina and mainstem bronchi. The smallest zoscope and mediastinoscope dissector can be used to ensure complete dissection of this plane and allow an extension of the dissection over each mainstem bronchi beyond what can be reached with digital dissection alone. Neck flexion up to 30 degrees is simple and effective in further decreasing anastomotic tension and is usually well tolerated by the patient. If needed, further neck flexion beyond 30 degrees may permit resection of an additional 1 to 1.5 cm of trachea, however, this degree of flexion will likely be uncomfortable for the patient to maintain in the postoperative period. These two maneuvers (pretracheal dissection and neck flexion) provide assurance of a tension-free anastomosis in nearly all short-segment tracheal resections and are the only airway release maneuvers required in more than 90% of patients.

Once the tracheal mobilization and dissection is completed, the endotracheal tube is withdrawn into the proximal trachea and the trachea is divided. The division of the trachea should be performed sharply and perpendicular to the axis of the airway. The distal trachea is then intubated across the surgical field with a sterile endobronchial tube and circuit. The endobronchial tube can be safely removed intermittently for brief periods of apnea to permit precise placement of sutures during reconstruction.

The anastomosis is performed and is end first by placing traction sutures using 2-0 absorbable braided suture in the mid-lateral portion of each airway approximately one or two tracheal rings back from the cut edge of the trachea; a total of four traction stitches are placed, two in the proximal trachea and two in the distal trachea. If the tracheal circumference is considered as a clock face, with the mid anterior trachea at 12 o'clock, these full thickness lateral traction sutures are placed at 3 and 9 o'clock, respectively. The first stitch for anastomosis is placed at the midline posteriorly (6 o'clock) using 4-0 absorbable braided interrupted stitches. The sutures are placed in a manner such that the knots will be on the outside. Subsequent sutures are placed approximately 4 mm from the cut ends, generally ignoring the tracheal rings, but ensuring a healthy, full thickness bite that incorporates the tracheal mucosa. Posteriorly, it is important to hold the placed sutures out for each subsequent suture placement to prevent suture entrapment when these are tied in reverse order. Using an open anastomotic technique, placing all sutures before pulling the anastomosis together provides several advantages. First, it allows very accurate suture placement and progressive correction of any size discrepancy. Second, it avoids tension on the anastomosis during suture placement and allows maximum exposure because the neck can stay extended during suture placement. The sutures are placed circumferentially, from posterior to anterior in four quadrants: 6 to 3 o'clock, 6 to 9 o'clock, and then 3 to 12 o'clock and 9 to 12 o'clock, respectively. Meticulous attention is necessary, and systematic approach is needed to keep all the stitches in order on the surgical field; this can be achieved by individually placing each suture on a separate clamp and lining the clamps up in order. Once all of the sutures are placed, the oral endotracheal tube is advanced through the anastomosis under direct vision. The shoulder roll is removed and the neck flexed forward by the anesthesiologist, approximating the proximal and distal tracheal ends to allow a tension free anastomosis. The head flexion is not simply an elevation of the head, as for intubation, but rather an actual rotation of the head forward, bringing the chin down toward the manubrium. The lateral traction sutures are tied, and each anastomotic suture is then tied in the reverse order of placement to avoid entanglement of the sutures (Fig. 2).

The neck is maintained in gentle flexion during the initial postoperative period to prevent tension on the anastomosis. This is achieved by use of a guardian suture placed just posterior to the tip of the chin and deep within the presternal soft tissue at the level of the sternal manubrial junction. This suture is typically left in place for 7 days after operation, and it is an effective reminder for the patient during sleep or other unconscious movement to prevent neck extension beyond the degree determined at time of surgery.

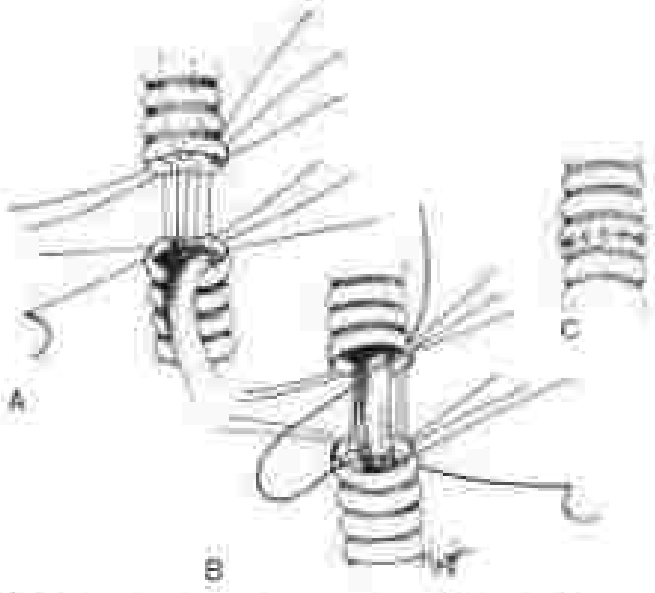

FIG. 2 Tracheal resection and reconstruction. (A) Endotracheal tube withdrawn into the proximal airway and sterile ventilatory tubing placed in distal airway; (B) placement of laryngeal anastomic sutures and replacement of endotracheal tube; (C) completed tracheal anastomosis. [From Mathisen DJ: Surgery of the trachea. In Iglesias Cort Pedro S (ed): ... p. 215.]

The goal of tracheal resection and reconstruction is for the patient to be extubated in the operating room. If the patient requires mechanical ventilation after surgery, usually due to postoperative laryngeal edema, a small, uncuffed endotracheal tube is placed with the plan to return to the operating room after 24 to 48 hours for an attempt at extubation. Failure to extubate should prompt a small tracheostomy placed two tracheal rings distal to the anastomosis. Alternatively, if the surgeon judges that timely extubation is unlikely, a tracheostomy may be placed in this location at the time of initial surgery.

SPECIAL CONSIDERATIONS

If the innominate artery is adjacent to the completed tracheal anastomosis, a strap muscle flap should be interposed between the artery and the tracheal anastomosis at the completion of reconstruction. For lesions that are too far below the sternum to be accessible through a collar incision, the exposure can be increased by making a T incision to which the vertical arm extends downward to a point 4 cm below the sternal angle. The manubrium is divided at the sternomanubrial junction and separated with a pediatric chest spreader. The upper sternal division provides access to the lower trachea; exposure is not further augmented by a complete sternotomy because of the tracheal extension behind the great vessels and heart. However, in certain circumstances for exposure of the distal tracheal or carina, a sternotomy can be performed and the distal airway exposed through a transpericardial approach, reflecting the ascending aorta to the left, the superior vena cava to the right, and opening the posterior pericardium just above the right main pulmonary artery. However, in general, the distal trachea and carina are best exposed by a right posterolateral thoracotomy, entering in the fourth or fifth interspace.

Laryngeal and hilar release maneuvers can be performed if additional mobilization is required to achieve a tension-free anastomosis. As discussed above, pretracheal dissection and neck flexion should be a routine part of every tracheal resection and provide adequate mobilization in the vast majority of cases. When mobilization is required to the proximal trachea, a suprahyoid laryngeal release can produce 1.5 to 2 cm of additional tracheal length. For distal tracheal and carinal lesions, a hilar release provides the same degree of mobility to the distal airway. The suprahyoid release involves division of the suprahyoid laryngeal respiratory attachments: the stylohyoid, mylohyoid, geniohyoid, genioglossus muscles and division of the hyoid bone anterior to the digastric muscle attachments bilaterally. The major complication of both maneuvers is a common occurrence of postoperative dysphagia and aspiration, and thus they should only be performed when routine mobilization techniques are inadequate to provide a low-tension anastomosis. Hilar release maneuvers are not often used for proximal tracheal resections as they provide little mobility to the upper cervical trachea. However, they allow for significant cephalad mobilization of the distal trachea, carina, and mainstem bronchi. This entails division of the pulmonary ligament, division of the pericardium around the inferior aspect of the inferior pulmonary vein, and division of the raphe attachment of the pericardium to the left atrium below the vein.

POSTOPERATIVE MANAGEMENT

During emergence from anesthesia, it is critical to manually support the flexed position because the guarding nature is an effective reminder when the patient is awake and alert, but before this time they may inadvertently pull against the guarding suture without recognizing painful feedback. Dry heaving and emesis are potentially catastrophic events in a patient with a fresh tracheal anastomosis given the association with sudden neck hyperextension and the potential for aspiration of gastric contents. Prevention and management of postoperative nausea, both by encouraging minimization pain management and with liberal use of antiemetics, is an important component of the postoperative management.

COMPLICATIONS OF TRACHEAL SURGERY

Meticulous operative technique in avoiding devascularization and ensuring a low-tension anastomosis are the key to minimizing complications. One of the most common complications in the immediate postoperative period is laryngeal edema which manifests within 24 to 72 hours and typically resolves without any intervention. If subcutaneous emphysema develops after surgery, this is likely an indication of anastomotic dehiscence and should be treated as a surgical emergency. The patient should be returned to the operating room immediately and the airway secured. A bronchoscopic evaluation is performed to evaluate the anastomosis. If an anastomotic dehiscence is confirmed, the patient should undergo surgical exploration with repair attempted if it is a small area of dehiscence. If the anastomotic dehiscence is not amenable to repair, the mainstay of management is a tracheostomy or a T tube, although an endobronchial stent is occasionally useful for a small dehiscence later in the postoperative course. A local muscle flap should be used to buttress the repair, tracheostomy or T tube.

RESULTS

The most in-depth analysis of patient outcomes after tracheal surgery in patients with postintubation stenosis was reported by Grillo and colleagues in a series of 503 patients who underwent tracheal resection and reconstruction from 1965 to 1992. A total of 521 resections were done, 19 for restenosis after initial repair. Lengths of resection averaged 3.5 cm and extended up to 7.5 cm. Laryngeal release maneuvers were only performed in 46 patients. Results were good to 87.5% and satisfactory in 6%; failure occurred in 6% and deaths in 2.4%. Failures were treated with tracheostomy in 31 patients, with T tubes in 7 patients, and with dilations in 3 patients. Prior resection

increased the failure rate from 2.1% to 9.7% and the mortality rate from 2.1% to 3.8%. The extent of airway resection is also a predictor of failure. A subsequent publication identified the risk factors for anastomotic failure: length greater than 4 cm, diabetes, age younger than 17 years, preoperative tracheostomy, reoperation, and laryngeal anastomosis.

Airway surgery experience, meticulous surgical technique, and attention to the limits of tracheal surgery—resect to normal airway, maintain tracheal blood supply, and use of progressive maneuvers for achieving a low-tension anastomosis—are critical for optimal results after a trachea resection and reconstruction.

Suggested Readings

Grillo HC, Donahue DM, Mathisen DJ, Wain JC, Wright CD. Post-intubation tracheal stenosis: treatment and results. J Thorac Cardiovasc Surg 1995;109:486–93.

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Management of Acquired Esophageal Respiratory Tract Fistula

Abhi Pandia, MD, Travis Hall, MD, PhD, and Christo Ilan Morse, MD

OVERVIEW

A tracheoesophageal fistula (TEF) is defined as any communication between the respiratory tract and esophagus. In adults, benign fistulas are most commonly acquired as a result of prolonged endotracheal intubation in mechanically ventilated patients and are typically managed with surgery. Malignant fistulas are challenging to manage, and a conservative approach directed at patient palliation remains the mainstay of therapy. This chapter reviews the cause, clinical manifestation, diagnosis, approach, and surgical management of acquired TEF.

PATHOGENESIS

An acquired TEF is caused by tissue necrosis and breakdown of the respiratory tract and esophagus, resulting in an extraluminal communication most commonly located in the upper one-third of the esophagus where the membranous wall of the trachea lies adjacent to the esophagus. The cause of TEF can be broadly classified as benign or malignant. The latter is the most common cause of acquired TEF, and esophageal carcinoma, particularly squamous cell carcinoma, is responsible for approximately 70% of cases. However, direct invasion secondary to bronchogenic or thyroid carcinoma is also a possible cause, as is mediastinal lymphoma. In addition, radiation therapy itself, often necessitated by these malignancies, poses an increased risk for TEF. Benign TEF can be subclassified as iatrogenic, infectious, or traumatic based on the cause.

Iatrogenic

The most common cause of benign TEF is long-term mechanical ventilation whereby an endotracheal tube leads to pressure-mediated ischemic necrosis of the posterior membranous tracheal wall and anterior esophagus. This often leads to circumferential necrosis of the trachea and is potentiated by a rigid tube, such as a nasogastric tube or temporary probe, in the esophagus, or in patients with impaired wound healing, such as the immunocompromised, long-term steroid users, or those with poorly controlled diabetes. Because this is usually a long-term process, gross contamination of the mediastinum is less likely.

Other iatrogenic causes of TEF include injuries from intubation, tracheostomy tube placement, and esophageal or laryngeal resection. Perisurgical anastomotic leak or devascularization of the trachea from close bilateral paratracheal dissection potentiates the risk for TEF, as does dilation of benign esophageal strictures or surgical anastomoses of the trachea or esophagus. Moreover, stenting of the trachea or esophagus can result in erosion or injury, especially if placement or extraction of the stent is difficult or traumatic.

Infectious

Infectious TEF is most commonly seen with pathogens that cause granulomatous inflammation, including histoplasmosis and tuberculosis, which is both more common and severe in patients with immunodeficiency syndromes, including human immunodeficiency virus.

Traumatic

TEF acquired as a result of a traumatic process such as foreign body impaction and erosion, ingestion of caustic agents, batteries, or poisons and penetrating or blunt trauma to the neck often lead to extensive gross contamination of the mediastinum because of their acute nature. It is important to recognize that, in cases of polytrauma, the diagnosis of TEF may be delayed during the treatment of other life-threatening injuries. As is discussed in this chapter, the surgical management of traumatic TEF may therefore follow an alternate algorithm.

CLINICAL FEATURES

Despite the broad spectrum of causes, the clinical features of acquired TEF in adults are similar and represent the sequelae of an abnormal connection between the upper respiratory and gastrointestinal tracts. Patients generally present with chronic cough, often exacerbated by oral intake, and with expectoration of food. Secondary to recurrent aspiration across the TEF, they often develop recurrent bronchopulmonary infections, which may manifest as hemoptysis, fevers, or frank and life-threatening pneumonia or mediastinitis, the latter is more likely in an acutely acquired TEF. Notably, TEF caused by malignancy often becomes apparent after chemotherapy or radiotherapy treatment of the primary tumor.

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Nikhil Panda, MD, Travis Hall, MD, PhD, and Christopher R. Morse, MD

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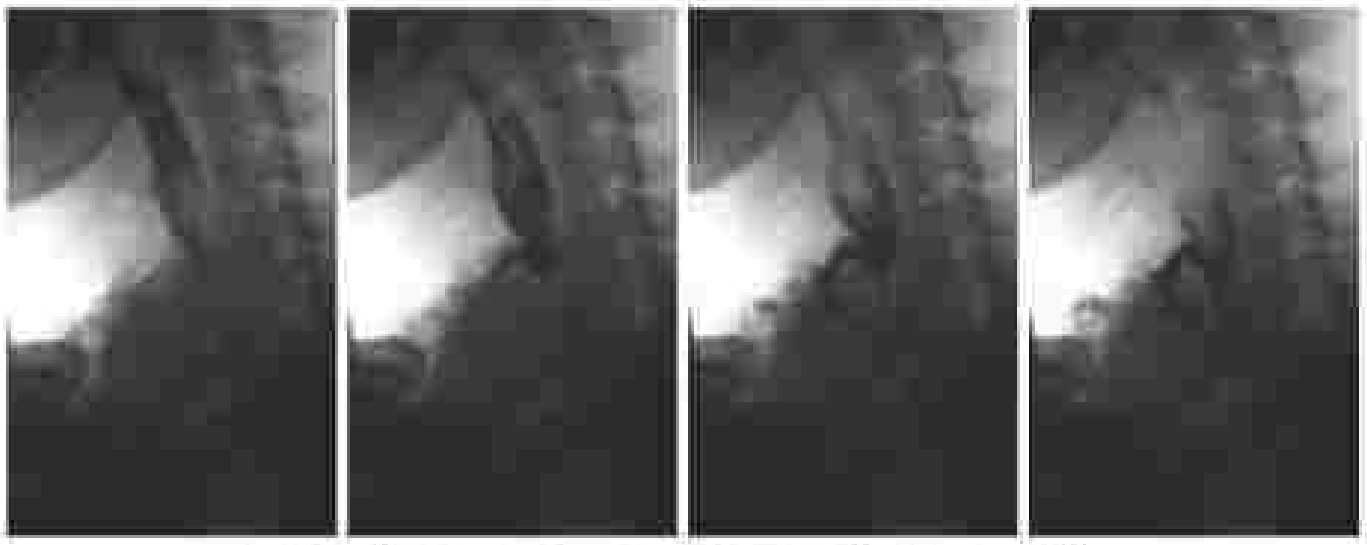

FIG. 1 Barium contrast esophagram showing fistulous communication between esophagus and airway.

In the mechanically ventilated patient, signs suggestive of TEF include inadequate return of tidal volumes, often in the setting of gastric abdominal distension on physical examination or a large gastric bubble on abdominal imaging. Additional clues include increased secretions, aspiration of tube feeds from the airway on manual suction, difficulty maintaining seal with the cuff of the endotracheal tube, or persistent sepsis, pneumonia, or pulmonary infiltrates not attributable to other causes.

DIAGNOSIS

In patients with a symptom complex suspicious for TEF, diagnostic workup begins with chest radiographs, which may reveal sequelae of a TEF, including aspiration pneumonitis or a dilated stomach and distal esophagus in patients on gastric pressure ventilation. In patients with recurrent aspiration pneumonitis, swallow evaluation may be beneficial to rule out oropharyngeal dysphagia as a cause. Small fistulas (<1 cm) are difficult to diagnose and are best detected with barium swallow using dilute barium (Fig. 1). Large fistulas are best diagnosed with bronchoscopy and esophagoscopy. Bronchoscopy is essential to locate the fistula and to perform a mucosal survey. Rigid bronchoscopy allows for complete inspection of the airway, including careful measurements such as fistula size and distance between the fistula and the vocal cords proximally, as well as the carina distally. Bronchoscopy also provides the opportunity for biopsy if malignancy is suspected and cultures to guide antibiotic therapy if necessary. Although esophagoscopy is less reliable in the diagnosis of TEF, it can be used in conjunction with bronchoscopy to instill air and methylene blue to define the anatomy, particularly for small fistulas. Further imaging with modalities such as computed tomography scanning is not necessary or helpful in benign disease, but it is useful in TEF secondary to a suspected or confirmed malignant process.

TREATMENT

Preoperative Care

The treatment of acquired TEF begins with preoperative planning and patient optimization. Preoperative chest radiography, barium swallow, bronchoscopy, and esophagoscopy must be reviewed to determine the anatomy of the fistula, which will guide surgical exposure. Patients with pulmonary sepsis as a result of chronic airway contamination from aspiration of enteric contents should be adequately treated with antibiotics and stabilized before surgery. In situations where mechanical ventilation can be weaned, it is paramount to delay surgery until ventilation can be definitively ceased to minimize postoperative manipulation and positive pressure within the reconstructed trachea. In patients who are intubated, it is important to advance the endotracheal tube below the level of the fistula and inflate the cuff to prevent further contamination. Nutrition should be optimized with nasoenteral or transmural feeding tubes to minimize further esophageal trauma. Lastly, preoperative coordination with an experienced team of anesthesiologists familiar with the challenges of induction and intraoperative ventilation during tracheal resections is paramount.

Operative Management of Benign Acquired Tracheoesophageal Fistulas

Benign TEF are managed primarily with surgery. Exposure is achieved via an anterior collar incision, which may include a tracheostomy if necessary (Fig. 2). Alternatively, a left cervical incision along the anterior border of the sternocleidomastoid can be used. Importantly, both approaches may be extended to include a sternotomy for exposure of the distal trachea and for proximal control of the great vessels. For more distal TEF or bronchoesophageal fistulas, a right posterolateral thoracotomy through the fourth or fifth interspace provides adequate exposure.

Conservative surgical management includes two stages: initial tracheal resection and reconstruction with esophageal diversion via cervical esophagostomy, followed by subsequent interval primary esophageal reconstruction. Such an approach may be appropriate for patients with traumatic TEF, where the degree of local contamination, loss of viable tissue, or other traumatic injuries may preclude a single stage repair. When feasible, a single stage repair is advisable because it avoids stoma reoperation, as well as loss of esophageal length during the takedown of the cervical esophagostomy.

Principles of single stage surgical repair as originally described by Herbert Griffin include complete dissection and division of the fistula with tracheal transection to expose the esophagus, two layer esophageal closure, mansentimento of the trachea, and buttressing the repair with a pedicled tissue flap. There are several technical considerations in each of these steps. First, during the exposure and dissection of the fistula, where in most cases the fistula is acquired from long-term mechanical ventilation, the trachea often requires segmental resection with distal tracheal intubation given the circumferential damage from the endotracheal or tracheostomy tube cuff. This provides adequate exposure to the esophagus (Fig. 3). During this dissection, care must be taken to avoid damage to the recurrent laryngeal nerves that

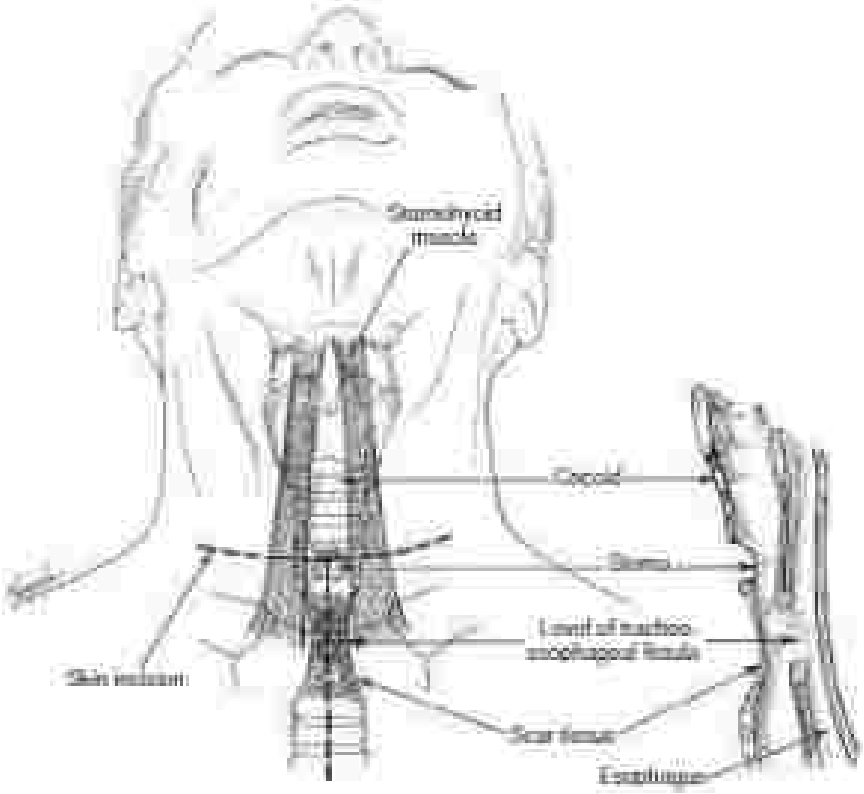

FIG. 3 Surgical exposure for repair of tracheoesophageal fistula. Both a transverse anterior collar incision incorporating a tracheostomy or left cervical incision provides necessary exposure. Additional exposure for distal fistulae can be obtained with division of the manubrium.

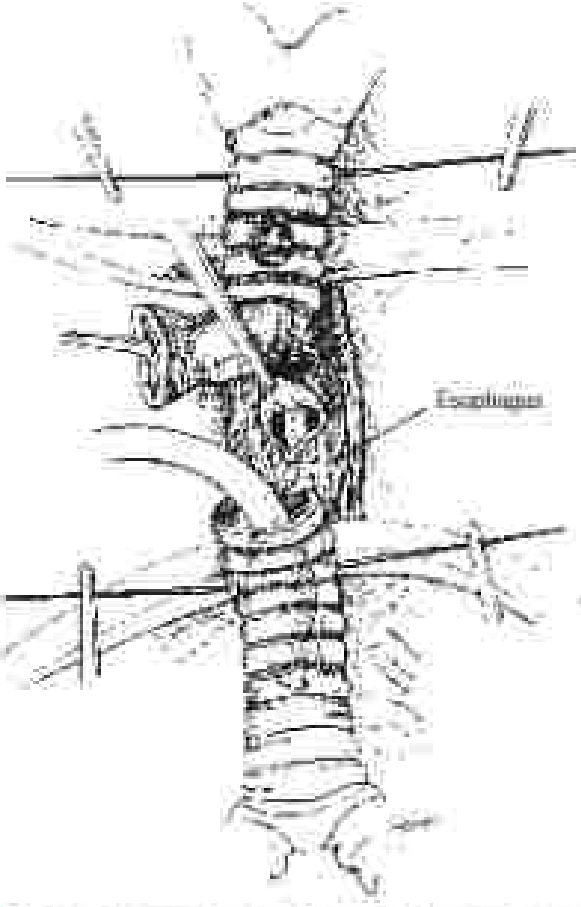

FIG. 4 Tracheal resection. Esophageal exposure after segmental tracheal resection in cases of isolated proximal tracheoesophageal fistula.

lie within the tracheoesophageal groove on either side. The nerves may be identified cranially or caudally from the location of the fistula, where identification can be challenging from local inflammation and scarring.

Second, once identified and divided, the esophagus is closed over a nasogastric tube to avoid narrowing the lumen. We advocate for a two-layer closure with interrupted nonabsorbable sutures in the inner layer to approximate and invert the esophageal mucosa, with an outer layer of approximated esophageal musculature to cover the inner repair (Fig. 4). It is important to debride the esophageal defect to healthy tissue to ensure the integrity of this primary repair.

Third, during tracheal repair, we recommend the use of interrupted absorbable sutures with the knots outside the lumen of the trachea. This minimizes the formation of postoperative granulomas at the suture line (Fig. 5). Fourth, in cases of long segment tracheal damage and resection where simple neck flexion does not allow for primary repair, the trachea may be repaired over a T tube. Alternatively, experienced surgeons may perform a variety of release maneuvers, including a suprahyoid laryngeal release, right pulmonary hilar mobilization, or pericardial release.

Last, the use of a pedicled muscle flap to buttress both the esophageal repair and tracheal reconstruction is paramount to prevent recurrence of the TEF from the abutting suture lines. An available neck muscle, typically the sternohyoid, is of adequate length and size to be secured to the repair with interrupted nonabsorbable sutures (Fig. 6).

At the conclusion of the repair, a subcutaneous drain is placed before the incision is closed. The nasogastric tube is gently removed from the esophagus and a "guardian suture" is placed from the chin to the sternal angle to maintain neck flexion at approximately 30 degrees. The patient is extubated to prevent prolonged positive pressure ventilation within the reconstructed trachea. In situations where mechanical ventilation is necessary after surgery, a tracheostomy tube may be placed at least two tracheal rings below the level of the repair.

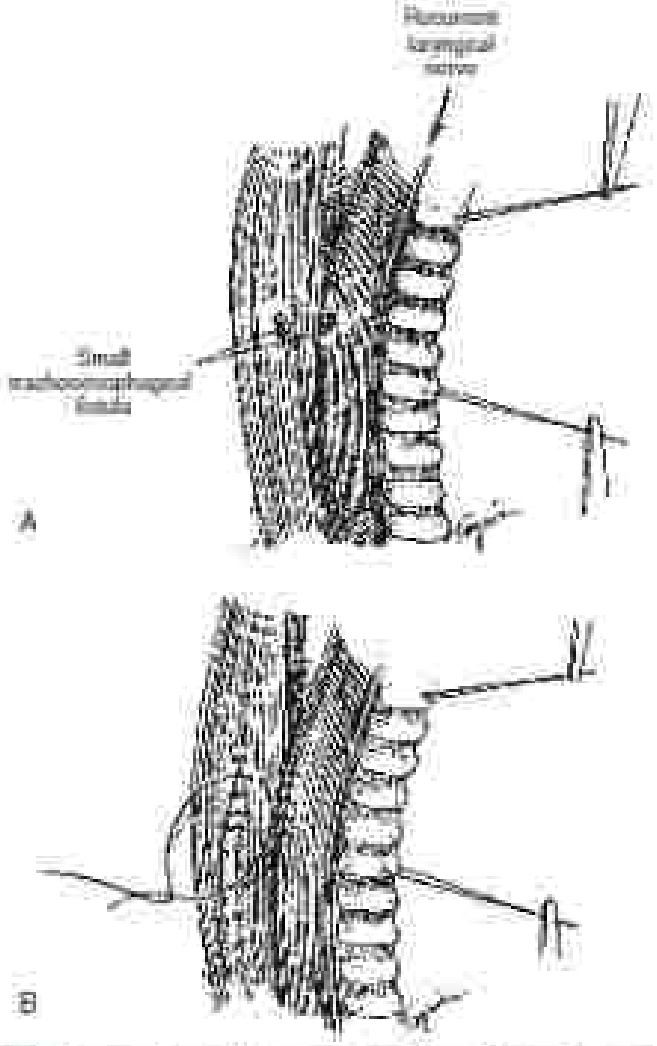

FIG. 4 Esophageal repair. (A) Lateral cervical approach to a small proximal tracheoesophageal fistula. (B) The esophageal defect is repaired in a two-layer fashion with interrupted sutures. The defect in the membranous wall of the trachea is repaired with a single layer of interrupted sutures.

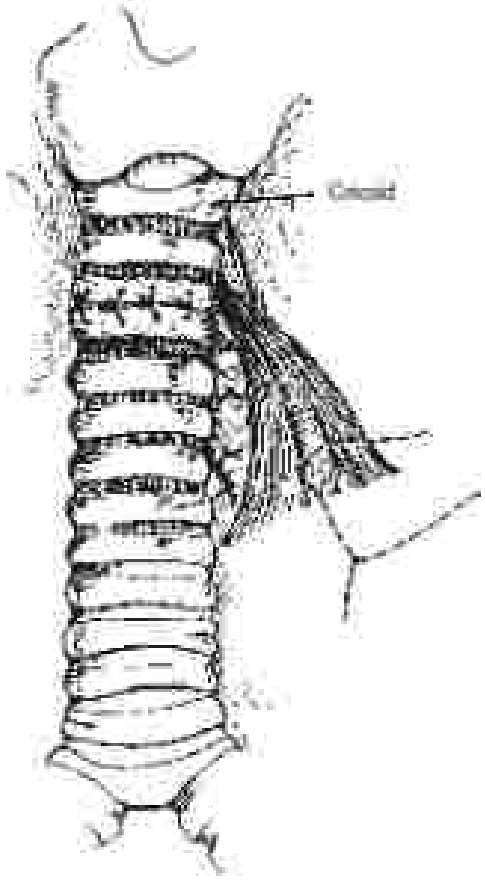

FIG. 5 Tracheal reconstruction. Placement of interrupted nonabsorbable sutures for tracheal reconstruction.

Postoperative Management

Postoperative care is focused on pain and nausea control to prevent cough or emesis. The patient is maintained nil per os; nutrition is provided via preoperative enteral access or parenteral nutrition. The patient returns to the operating theater 7 days after surgery for bronchoscopic surveillance of the tracheal reconstruction, at which time the guardian suture is removed. A barium swallow is also performed to confirm the integrity of the esophageal repair before initiating a liquid diet.

Management of Malignant Tracheoesophageal Fistulas

The management of malignant TEF is aimed at palliation. As opposed to benign TEF, where surgical interventions restore the integrity and continuity of the airway and intestine, malignant fistulas represent the sequelae of advanced metastatic esophageal or bronchogenic carcinomas. Surgery, in many of these cases, is not within the initial oncologic principles of management. Furthermore, these patients are often significantly deconditioned and malnourished as a result of their disease burden, systemic chemotherapy, and local radiation. For these reasons, outcomes from radical and palliative surgery to address malignant TEF result in significant rates of morbidity and mortality.

In cases of incurable disease, airway and esophageal stenting has emerged as a viable option to achieve palliation. Either individual or a combination of stents across the fistula is placed to prevent further spillage of enteric contents across the fistula, thus minimizing pulmonary contamination and alleviating the symptoms of chronic aspiration and pulmonary sepsis.

The principals of preoperative planning in benign TEF also apply to patients with malignant disease. Preoperative imaging, including barium swallow, should be obtained to determine the anatomy and level of the fistula. Pulmonary sepsis should be treated with antibiotics, mechanical ventilation should be weaned as allowed, and nutrition should be optimized.

Most malignant TEF may be sealed using a self-expanding covered or partially covered metal or plastic esophageal stents. These stents are typically placed under direct endoscopic guidance with the assistance of bedside fluoroscopy. In some cases, tracheal stents may also be needed and should be placed under bronchoscopic vision before the esophageal stent. This technique decreases the incidence of tracheal narrowing from initial esophageal stenting.

For fistulas located at or above the cricopharyngeus, the placement of a stent is not recommended because a foreign body in the pharynx or larynx results in significant patient discomfort and the inability to swallow. In such cases, a definitive tracheostomy tube with inflatable cuff to protect the distal airways may be placed. Likewise, fistulas to the lobar or segmental bronchi are difficult to seal via bronchial stenting because there is a lack of healthy tissue proximally and distally. Typically treated with an esophageal stent alone, these peripheral fistulae may also be managed with the addition of a tracheobronchial stent.

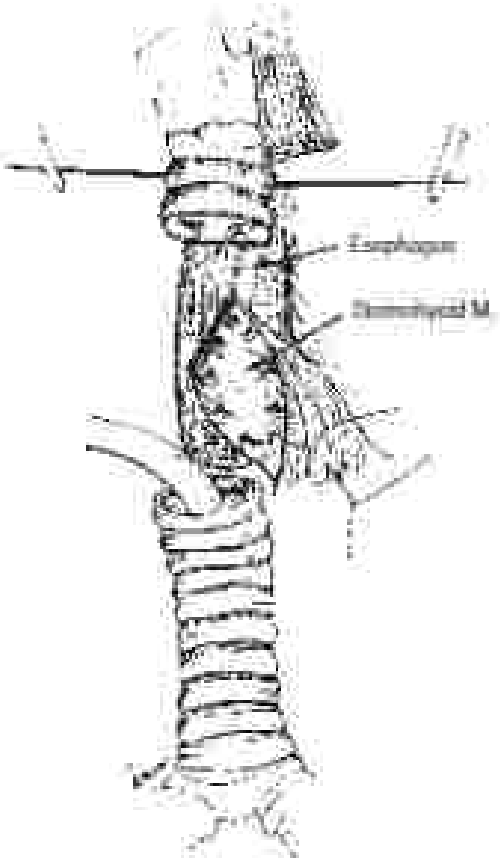

FIG. 6 Placement of partially retrograde stent inserts in between tracheal and esophageal tissues does to buttress repair and prevent fistula recurrence.

The placement of self expanding stents, whether in the esophagus or airway, can be safely accomplished with minimal intravenous sedation and the use of topical or nebulized anesthetic. Although well tolerated, patients should be counseled on the complications of esophageal and airway stenting, from minor to devastating. This includes bleeding, migration, erosion, and further progression of the fistula, leak, and occlusion.

OUTCOMES

Surgical treatment of benign TEF is successful in fistula closure and is associated with minimal morbidity and mortality. In the largest recent series reporting the outcomes of a cervical approach to primarily postintubation TEF repair, successful fistula closure occurred in 95% of patients. Approximately 83% of patients resume alimentation, and 72% are free from a tracheostomy or T tube. Other sources of postoperative morbidity include fistula recurrence, pneumonia, wound infection, and postoperative tracheal stenosis. Death after TEF repair is rare.

Patient survival in malignant TEF is poor regardless of supportive care, stent placement, or aggressive surgical treatment. Life expectancy is on the order of weeks to months. Symptomatically, however, self expanding stents have successfully palliated and provided relief of dysphagia for a majority of patients with malignant TEF.

SUMMARY

Most benign acquired TEF are amenable to surgical repair. We emphasize the importance of a comprehensive preoperative evaluation to determine the anatomy of the fistula and optimize respiratory status and nutrition. A single stage repair with division of the fistula, two layer esophageal closure, tracheal resection and reconstruction, and buttressing the repair with a pedicled intercostal muscle flap has demonstrated excellent results. Malignant TEF remain a challenging clinical entity and are primarily managed nonsurgically with the use of self expanding stents to maximize patient palliation.

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Repair of Pectus Excavatum

Paul D. Danielson, MD, FACS, FAAP,
and Paul M. Colombani, MD, MBA, FACS, FAAP

Pectus excavatum (PE), historically known as "funnel chest," is the most common chest wall deformity. It occurs in approximately 1 in 500 live births, with a male predominance of 2:1 to 5:1 in various series. The sternum is depressed toward the vertebral column, with the greatest depression typically at the level of the xiphoid process. The implications of PE may range from cosmetic deformity with psychologic distress to significant cardiopulmonary impairment from decreased thoracic cavity capacity and compression of the heart. Although the exact cause of PE is unclear, the condition is believed to result from abnormal development of the costal cartilages. Overgrowth or increased flexibility of the costal cartilages, especially cartilages 4 through 7, leads to progressive dorsal displacement of the sternum. PE is associated with connective tissue disorders such as Marfan syndrome. PE often runs in families, but no specific genetic cause has been identified.

EVALUATION OF THE PATIENT WITH PECTUS EXCAVATUM

Initial evaluation of the patient with PE requires a careful history and physical examination. One third of patients with PE have a defect evident from early childhood, and the remainder first appreciate the problem during the adolescent growth spurt. A history of worsening

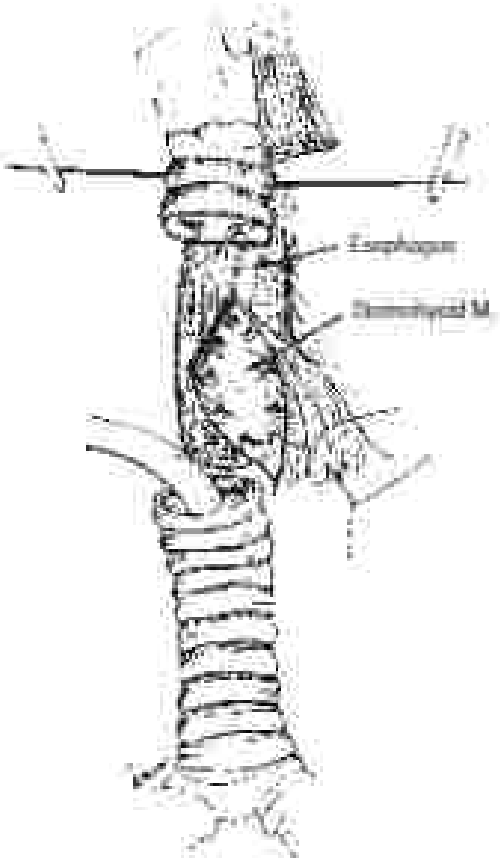

FIG. 6 Placement of positive extrapleural strap muscle in between tracheal and esophageal suture lines to buttress repair and prevent fistula recurrence.

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Most benign acquired TEF are amenable to surgical repair. We emphasize the importance of a comprehensive preoperative evaluation to determine the anatomy of the fistula and optimize respiratory status and nutrition. A single stage repair with division of the fistula, two layer esophageal closure, tracheal resection and reconstruction, and buttressing the repair with a pedicled intercostal tissue flap has demonstrated excellent results. Malignant TEF remain a challenging clinical entity and are primarily managed nonsurgically with the use of self expanding stents to maximize patient palliation.

Suggested Readings

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Repair of Pectus Excavatum

Paul D. Danielson, MD, FACS, FAAP,
and Paul M. Colombani, MD, MBA, FACS, FAAP

Pectus excavatum (PE), historically known as *funnel chest*, is the most common chest wall deformity. It occurs in approximately 1 in 500 live births, with a male predominance of 2:1 to 5:1 in various series. The sternum is depressed toward the vertebral column, with the greatest depression typically at the level of the xiphoid process. The implications of PE may range from cosmetic deformity with psychologic distress to significant cardiopulmonary impairment from decreased thoracic cavity capacity and compression of the heart. Although the exact cause of PE is unclear, the condition is believed to result from abnormal development of the costal cartilages. Overgrowth or increased flexibility of the costal cartilages, especially cartilages 4 through 7, leads to progressive dorsal displacement of the sternum. PE is associated with connective tissue disorders such as Marfan syndrome. PE often runs in families, but no specific genetic cause has been identified.

EVALUATION OF THE PATIENT WITH PECTUS EXCAVATUM

Initial evaluation of the patient with PE requires a careful history and physical examination. One third of patients with PE have a defect evident from early childhood, and the remainder first appreciate the problem during the adolescent growth spurt. A history of worsening

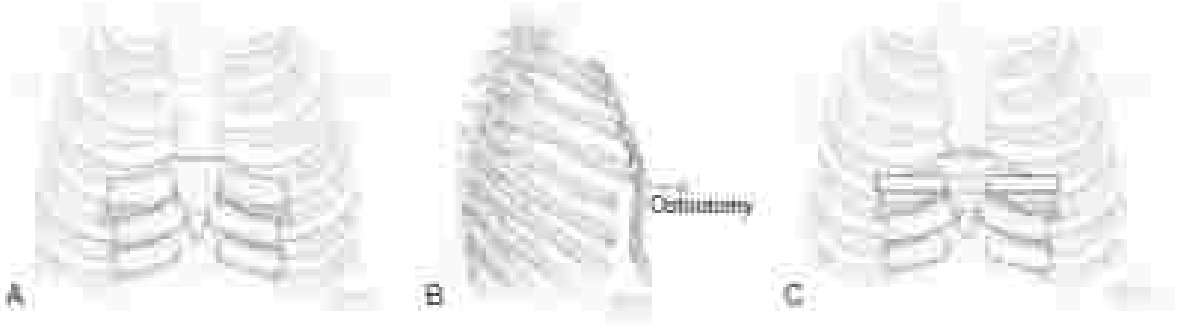

FIG. 1 *Open repair of pectus excavatum.* Following a transverse infraumbilical incision and bilateral elevation of the pectoralis major muscles, costal cartilages are freed circumferentially from the perichondrium and divided at the junctions with the sternum and with the ribs (A). A transthoracic osteotomy allows the sternum to rise to a more anterior position (B). An Adkins strut in place maintains elevation (C). (Courtesy John P. Kelly, Chicago, Illinois. Reproduced from Kelly RE Jr, Obermeyer RJ, Nuss D, et al. Pectus excavatum. In: Mattox KL, Feliciano DV, Moore EE, eds. *Trauma*. 8th ed. New York: McGraw-Hill Education; 2017.)

deformity around this time is often elected. Symptoms at rest are rare, but the patient may report impaired exercise tolerance with shortness of breath. On physical examination, the chest should be examined for symmetry and location of the deepest point of the pectus. Asymmetry is not uncommon, and the defect is often slightly skewed to the right side. Patients with PE have a typical kyphotic posture with a protuberant abdomen and flaring of the costal margin. Calipers can be used to measure the chest diameter at both the deepest point of the deformity and the lateral chest wall to get an approximate indication of the severity of the pectus. Caliper measurement demonstrating greater than 2.5 cm difference indicates a significant deformity. Stigmata of collagen vascular disease, such as long fingers and toes, myopia, and easy bruising, may be observed. Patients who have clinical signs of Marfan syndrome but do not carry this diagnosis may benefit from referral for diagnostic evaluation.

Further diagnostic examination, including chest computed tomographic (CT) scanning, pulmonary function tests (PFT), and transthoracic echocardiography, is indicated to assess the degree of cardiopulmonary impairment caused by the PE. A chest CT scan without intravenous contrast allows the calculation of the Haller index, a quantification of the severity of the PE defect. Magnetic resonance imaging can also be used to minimize radiation exposure. For determination of the Haller index, the anteroposterior (AP) diameter of the chest is measured from the inner ribcage to the spine at the greatest point of the defect. The transverse diameter of the chest is measured from the inside of the ribs at the same location. The index is the ratio of the transverse to the AP diameters of the chest. PE repair is generally recommended at a Haller index of 2.5 or greater. An exercise PFT is performed for assessment of lung volumes at rest and exercise. Typically, a mild to moderate restrictive defect is seen in these patients at rest. With exercise, a significant decrease in O_2 pulse and maximal exercise capacity (VO_2 max) may be present. This indicates decreased diastolic filling secondary to compression. Finally, echocardiography may show right ventricular compression or mitral valve prolapse. A subset of patients with PE with narrow chests exists for whom the Haller index underestimates the severity; an improved corrective index has been developed to help evaluate this cohort of patients.

The extent of cardiopulmonary involvement in PE remains a subject of debate. Increasing Haller index has been associated with worse impairments in pulmonary function, but many patients with PE have spirometry values within the normal range. Many patients report subjective improvement in exercise tolerance after repair despite having normal PFT values both before and after surgery. In many cases, third-party payers require documentation of objective measures of cardiopulmonary impairment or significant PE–related symptoms before authorization of repair. The operation is otherwise considered cosmetic in nature and is not covered.

OPEN REPAIR

The first widely adopted technique for repair of PE was the Ravitch operation. In this procedure, a fourth intercostal transverse incision is performed, and skin and muscle flaps are elevated to expose the sternum and the costal cartilages. The abnormal costal cartilages are resected to the subperichondrial plane. An anterior sternal wedge osteotomy is performed to elevate the sternum. A metal strut is placed retrosternally to provide more secure fixation. Historically, the Ravitch procedure was performed as early as age 4 years. However, a very small but significant subset of patients who underwent repair at such an early age subsequently acquired lesser syndromes (asphyxiating thoracic dystrophy) as they progressed through puberty. These patients' thoracic cavities failed to expand with growth, presumably as a result of abnormal fixation of the growth plates in the costochondral joints. Correction of acquired lesser syndrome is complex and often unsatisfying. Most authors recommend delay of open PE repair until puberty to avoid this complication (Fig. 1).

MINIMALLY INVASIVE REPAIR (NUSS PROCEDURE)

In 1987, Nuss introduced a minimally invasive approach to PE repair. This approach relies on the natural flexibility of the costal cartilages to enable repair from the inside of the chest. Advantages include a shorter operative time and less disfiguring scar. The patient is placed supine with arms extended. The site of deepest depression of the sternum is identified and traced laterally. After intravenous antibiotic prophylaxis, incisions of 4 cm in length are made bilaterally along this line at its intersection with the anterior axillary line and are deepened until the pleura are entered with direct vision. In the original description, an introducer is then passed with thoracoscopic guidance from the left chest just retrosternally into the right chest. The thoracoscope is transferred to the right chest to observe passage of the introducer. Remaining strictly in the immediate retrosternal plane and using thoracoscopic guidance minimizes the chance of cardiac perforation or other mediastinal injury. However, in the authors' practice, thoracoscopy is no longer used during passage of the introducer. With use of digitally tunneled techniques, the pericardium is seen and the bar passed from the left without difficulty. In difficult cases, sternal elevation can be used to facilitate transmediastinal passage of the introducer. An umbilical tape is tied to the introducer as the tip exits the right lateral skin incision. The introducer is then withdrawn back through the left chest so that the umbilical tape traces its transthoracic passage. A pectus bar is selected based on the patient's body habitus. Ideally, the bar should extend beyond the edge of the rib cage on each side without protruding too far beyond the ribcage, typically 2.5 cm shorter than the distance between the midaxillary lines. The exact degree of

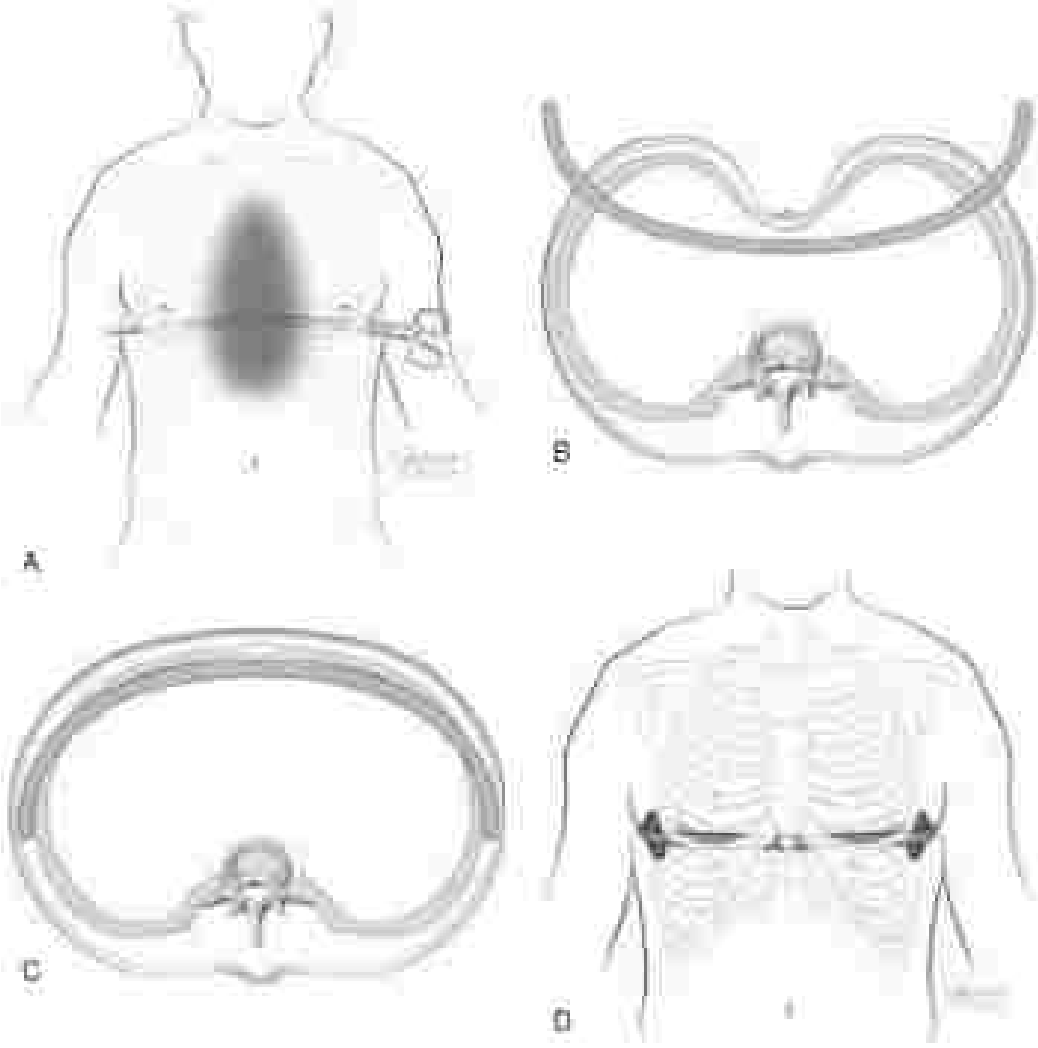

FIG. 2. Minimally invasive pectus excavatum repair. (A) Schematic of bar being passed posterior to the sternum through bilateral thoracic incisions. (B) Initial orientation of bar after passage through chest. (C) Position of bar after flipping. (D) Bar stabilizers in position. (Courtesy John Hopkins University Center for Pediatric [illegible], Baltimore, MD, 2014.)

bend that must be applied to each side of the bar is a matter of judgment, but the goal is to slightly overcorrect the sternum rather than undercorrect it. The umbilical tape is tied to one end of the bar and then withdrawn through the chest with the bar upside down (concave side up). After the bar is grasped exiting the right chest, it is flipped 180 degrees so that the convex side is elevating the sternum. Many techniques for bar fixation have been described. Stabilizers can be placed over the end of the bar on one or both sides to secure the implant above the rectus. Wire or heavy polydioxanone suture fixation of the stabilizers around the ribs can also be used bilaterally to avoid bar displacement. Patients with complex asymmetric defects, patients with Marfan syndrome, and patients with suboptimal elevation of the sternum after placement of a single bar may benefit from placement of a second bar to improve sternal elevation. Placement of a second bar follows the principles of placement of the initial bar. A chest x-ray film is obtained routinely in the recovery room. Small bilateral pneumothoraces are commonly observed as a result of air introduced during bar placement and in general may be managed expectantly without further imaging as long as the patient is clinically well (Fig. 2).

Preoperative counseling is essential before repair. Postoperative pain can be considerable during the first few postoperative weeks, and some patients continue to experience pain for the entire period while the bar is in place. In severe cases, this can require removal of the bar with likely recurrence of the PE defect. Postoperative use of ketorolac and gabapentin can limit the use of narcotic analgesics. In general, the authors limit physical activity for the first 6 weeks after bar placement. After this point, there are no specific activity restrictions.

The ideal age for minimally invasive PE repair continues to be debated. A shift has been seen over the years toward repair at an older age, especially late adolescence into early adulthood. The authors typically perform the repair at 14 years of age. Recent reports suggest that patients over 30 years of age are more likely to require placement of two bars.

The correct length of time for the bar to remain in place remains debated. At least 2 years is recommended to allow adequate time for the costal cartilages to remodel in their new position. The authors have had rare immediate recurrences with bar removal at 2 years that have led them to favor leaving the bar in position for 3 years. Patients with Marfan syndrome and other connective tissue disorders should have bars in for 5 years. At this point, the bar may be removed as an outpatient procedure. With general anesthetic, the previous incisions are reopened, and any wires or stabilizers used for fixation are removed. The bar ends on either end of the bar are removed, and the bar can then be pulled out of one side of the chest. The deep layers of the incision are closed with 2-0 polyglycolic acid suture and final while

a Valsalva maneuver is performed to evacuate any introduced air. After routine subcuticular skin closure, the patient is returned to the recovery room. A postoperative chest radiograph is obtained. Small bilateral pneumothoraces may be seen and do not require intervention in the absence of clinical symptoms. The patient is discharged home with narcotic analgesia after a suitable observation period in recovery.

COMPLICATIONS OF MINIMALLY INVASIVE REPAIR

Although asymptomatic pneumothorax is commonly observed after PE repair, symptomatic pneumothorax may rarely result from inadvertent injury to lung parenchyma during bar placement. Enlarging pneumothorax in the setting of clinical deterioration requires placement of chest tubes, often bilaterally. Urinary retention is frequently noted after surgery at a rate that exceeds that seen with other operations. The cause of this finding is uncertain, but this generally resolves within several days.

Intraoperative cardiac perforation is the most dreaded complication of minimally invasive repair. Although this is exceptionally rare, it is highly lethal. Immediate median sternotomy and cardiac repair are indicated in this setting.

Displacement of the bar can occur in as many as 5% of patients, often leading to immediate recurrence. Reoperation is required to flip the bar back into the appropriate position and reconcave the bar to the rib cage. Additional wires may be necessary to adequately secure the bar in position. Wound infection is rare, occurring in less than 2% of patients, and can often be treated with antibiotics. Surgical drainage is sometimes necessary for more extensive infections.

Most pectus bars are composed of stainless steel, although titanium bars are available by special order. Unsuspected allergy to nickel may lead to localized skin reaction at the incisions or pericarditis. Symptoms may not occur for many months after placement, and these patients can often be treated medically with corticosteroids until it is time to remove the bar. Metal salt patch testing can be used before surgery to identify patients with allergies if a history of sensitivity is present. A titanium bar is used in these individuals; however, it cannot be bent to shape as with a stainless steel bar. It must be molded to the correct shape by the manufacturer with guidance from the preoperative CT scan.

OUTCOME OF PE REPAIR

Neither the open nor the minimally invasive technique of PE has been shown to be clearly superior in the repair of PE. Both have a higher than 90% success rate in improving psychologic perceptions and subjective assessment of exercise tolerance. No difference is seen in length of stay, although the rate of pneumothorax and reoperation is higher in the minimally invasive repair. Since its introduction, the minimally invasive repair has far surpassed the open repair in popularity and is used for the majority of PE repairs. However, the open repair may still be preferable in patients with severely asymmetric defects and in patients with mixed carinatum/excavatum phenotype. Failures of open repair have been successfully corrected with the minimally invasive approach, as have previous failures of minimally invasive repairs.

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Open Repair of Abdominal Aortic Aneurysms

Bruce A. Perler, MD, MBA

A[illegible] aneurysm ... [illegible] ... are increasingly encountered by vascular specialists in the future. In fact, it has been estimated that the incidence of AAAs may be as high as [illegible]% to 15% in high risk patients. [illegible] risk factors for AAAs include advanced age, male gender, white race, positive family history of AAAs, and history of cardiovascular and peripheral arterial occlusive disease and their associated risk factors.

Rupture of an AAA, its most serious complication, occurs in roughly 15,0[illegible] individuals annually in the United States. Risk factors for rupture include chronic obstructive pulmonary disease, [illegible] hypertension, rapid increase in aneurysm size, and absolute aneurysm size. The key to minimizing mortality due to aortic aneurysm disease is early diagnosis and timely intervention in the elective setting. The introduction and in recent years significant technologic refinement of less invasive endovascular aortic aneurysm repair (EVAR) has allowed repair to be carried out in increasing numbers of individuals who formerly may have been considered to be too high risk for conventional open repair. In fact, in contemporary practice it is estimated that 70% to [illegible]% of elective and even ruptured aortic AAA repairs are undertaken with EVAR. Nevertheless, there is still a role for traditional open AAA repair in practice today and this expertise should be in the armamentarium of every vascular surgeon. This chapter will outline the key principles in safely performing open AAA repair.

[illegible]

The majority of AAAs are diagnosed by routine physical examination or are detected on radiologic studies performed in the evaluation of other conditions. While the presence of a pulsatile abdominal mass is highly suggestive of an AAA, physical examination is not consistently reliable. Specifically, the likelihood of detecting an AAA on physical examination is inversely correlated with the patient's body mass index and directly correlated with the aneurysm diameter. The simplest radiologic study to confirm the presence of an AAA is a plain lumbosacral spine radiograph using lateral technique. At least 70% of atherosclerotic AAAs contain sufficient calcium within the aneurysm walls to allow detection and fairly accurate estimation of the extent of the aneurysm, as well as its anterior–posterior diameter. Abdominal ultrasound is a noninvasive and highly reliable method to confirm the presence of an AAA and depict its diameter, although ultrasound tends to overestimate the diameter by about 20%. Nevertheless, this modality is highly reliable and very reproducible, cost effective, and therefore is the technique of choice for serial follow up of the patient with a small aneurysm being managed nonoperatively. Computed tomography (CT) is more accurate in depicting aneurysm size, although it is more time consuming, expensive, and entails radiation exposure. CT is much more accurate than ultrasound in confirming the juxtarenal or suprarenal extent of the aneurysm and can provide other key anatomic features relevant to the planning of EVAR. CT is also valuable in detecting associated anatomic features that might impact on open repair, such as an iliac aneurysmal aneurysm, evidence of a leak, retroperitoneal fibrosis, a horseshoe kidney, retroaortic renal vein or other venous anomalies, or multiple renal arteries. Magnetic resonance imaging (MRI) will also provide accurate information with respect to aneurysm size and extent, and associated vascular anomalies, although it seems inferior to CT in this clinical setting. CT angiography has largely obviated a need for contrast angiography in planning open AAA repair, unless there are specific indications for angiography such as a suspicion of significant renal or visceral artery lesions, or iliofemoral or femoral-popliteal occlusive disease for which the surgeon may elect endovascular intervention before open AAA repair.

Indications for Repair

The overwhelming majority of patients with AAAs are completely asymptomatic, and the decision to proceed with repair depends on the size (diameter) of the aneurysm and the patient's overall comorbidity and risks for surgical intervention. As noted above, in contemporary practice the less invasive EVAR option has allowed surgery to be performed on patients who might have had prohibitive risks for conventional open repair (see below).

The current clinical recommendations for elective intervention in the asymptomatic patient are based on several clinical trials. The UK Small Aneurysm Trial randomized 1090 patients between the ages of 60 and 76 years with aneurysms ranging from 4.0 to 5.5 cm in diameter to open repair versus surveillance, and the Aneurysm Detection and Management trial randomized 1136 patients between the ages of 50 and 79 at Veterans Administration medical centers with aneurysms ranging from 4.0 to 5.4 cm in diameter to open repair versus surveillance. Based on these trials and a subsequent Cochrane review, in contemporary practice the threshold for elective repair is an AAA diameter of 5.5 cm in men and 5.0 cm in women, due to

the smaller normal aortic diameter in women and the slightly higher rupture rate. Neither of these studies provided evidence to support elective repair of small AAAs, although a significant proportion of the patients in the surveillance groups ultimately underwent AAA repair due to increase in size of the AAA or the development of symptoms. There is no substantive evidence to suggest that the size threshold for intervention should be influenced by the method of repair; that is, it should not be lowered if EVAR is an option. According to the Society for Vascular Surgery (SVS) guidelines, patients with smaller aneurysms should undergo preoperative surveillance: every 3 years if 3.0 to 3.9 cm, every 12 months if 4.0 to 4.9 cm, and every 6 months if 5.0 to 5.4 cm in diameter. Ultrasound is the most cost-effective imaging modality for long-term surveillance.

Commonly, symptoms of abdominal or back pain suggestive of rapid aneurysm expansion or impending rupture or actual rupture is an indication for urgent repair irrespective of size. Less commonly, patients may present with peripheral ischemia due to distal embolization of aneurysmal mural thrombosis or aberrant flow, or acute aneurysm thrombosis, which typically occurs in smaller aneurysms, and is an indication for repair irrespective of aneurysm diameter.

INDICATIONS FOR OPEN REPAIR

In contemporary practice, it is estimated that 70% to 80% of patients undergoing AAA repair undergo EVAR. Nevertheless, while further advances in endovascular therapy, such as the availability of fenestrated endovascular aneurysm repair, and other techniques, such as so-called snorkel/chimney grafts, have allowed treatment of juxtarenal and even suprarenal AAAs that formerly would be treated endovascular repair, there are specific anatomic considerations for which open repair may be the most appropriate treatment. Therefore vascular surgeons should be trained and feel competent in performing open AAA repair. These anatomic features include a very short, excessively angulated, trapezoidal, heavily calcified, or thrombus-filled infrarenal aortic neck. In addition, severe iliac artery occlusive disease and especially iliac artery occlusions may be an indication for open repair. Finally, patient preference, especially in the relatively young patient who wishes to delay the lifelong radiographic surveillance following EVAR may be an indication for open repair.

PREOPERATIVE EVALUATION AND MEDICAL MANAGEMENT

Cardiac and pulmonary diseases remain the major etiologies of perioperative morbidity and long-term mortality in AAA patients, so a thorough history should be obtained prior to open repair. According to the most recent SVS guidelines, all patients should undergo a 12-lead electrocardiogram. Among patients who are functionally active, no further cardiac evaluation is necessary prior to open repair. An echocardiogram is indicated for patients with active symptoms of dyspnea or a history of congestive heart failure (CHF). In patients with three or more clinical risk factors such as angina pectoris, a prior myocardial infarction, compensated or history of CHF, diabetes mellitus, or renal insufficiency, noninvasive cardiac testing is indicated preoperatively. Further, for patients with active cardiac symptoms of unstable angina, a recent myocardial infarction, active arrhythmias or valve disease, formal cardiology evaluation and possible catheterization may be indicated. Pulmonary function testing is indicated for patients with active symptoms of COPD, and aggressive bronchodilator therapy should be instituted for 2 weeks prior to operation.

The most significant aspect of perioperative medical management include continuation of β-blockers, although one should not initiate β-blockade therapy preoperatively since this has been associated with an increased risk of stroke and all-cause mortality. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be held on the morning of surgery, as they can be associated with hypotension with the induction of anesthesia and dehydration in patients with preexisting renal insufficiency. Aspirin should be continued.

OPERATIVE THERAPY

Operative Exposure

AAA repair may be carried out via a midline abdominal transperitoneal incision or extended left retroperitoneal approach. Each approach has its advantages for specific anatomic considerations and potential disadvantages.

Transperitoneal Approach

The traditional midline abdominal transperitoneal incision allows excellent exposure of the distal common iliac arteries and the external, and if necessary, internal iliac arteries bilaterally. Since the patient is placed in the supine position, laparotomy can be expeditiously achieved, which is of benefit in the emergency setting. The surgeon is able to perform an exploratory laparotomy prior to aneurysm repair, identify unsuspected intra-abdominal pathology, assess bowel viability following aneurysm repair, and if necessary perform associated surgical procedures such as cholecystectomy. A drawback to this approach is it may provide limited exposure and control of a relatively short infrarenal aorta, such without excessive aneurysm manipulation, especially with a very large aneurysm or in the case of a juxtarenal aneurysm where suprarenal or supraceliac control is necessary. In this setting, medial visceral rotation may be required (see below). Further, this approach can be associated with a significant postoperative ileus and may compromise lung function in patients with limited pulmonary reserve.

Technical Details

The patient is prepped and draped from the xiphoid to the knees. A midline incision is carried out from the xiphoid to the pubis and the peritoneum entered. The small bowel and transverse colon are packed in moist towels out of harms way. The ligament of Treitz is divided and the duodenum mobilized to the right. The lymphatic tissues over the aorta are divided along the anterior surface of the aorta with care to carefully identify the inferior mesenteric artery, and the inferior mesenteric vein. The dissection should be continued to the level of the renal arteries, dictated by the crossing left renal vein (Fig. 1). The renal vein can be mobilized in a cephalad direction to facilitate exposure of the aortic neck for clamping, and the gonadal, adrenal, and lumbar branches can be divided. One should avoid dividing the left renal vein since this can lead to renal dysfunction. If absolutely necessary to divide the left renal vein for exposure, it is critical to preserve the aforementioned branches. If the left renal vein is not identified, this may reflect its retroaortic position and this must be confirmed to avoid injury during clamping, which can lead to severe bleeding.

If suprarenal exposure is made easy, the suprarenal aorta can be exposed by dividing the lesser omentum and gastrohepatic ligament. A nasogastric tube will identify the esophagus, which should be retracted to the patient's left. Although usually not necessary, the left lobe of the liver can be mobilized by dividing the left triangular and coronary ligaments and the falciform ligament.

Alternatively, a medial visceral rotation can be carried out. The left colon is mobilized to the right by incising the posterior peritoneum lateral to the line of Toldt. This incision is continued cephalad through the phrenicocolic ligament and to the aortic hiatus. A plane is developed along the posterior abdominal wall to allow mobilization of the colon, pancreas, spleen, and left kidney (Fig. 2). However, we believe that juxtarenal and suprarenal aortic exposure is most easily accomplished through the extended left retroperitoneal approach (see below).

Extended Left Retroperitoneal Approach

AAA repair may also be performed via the extended left retroperitoneal approach. There are several advantages of this approach, which

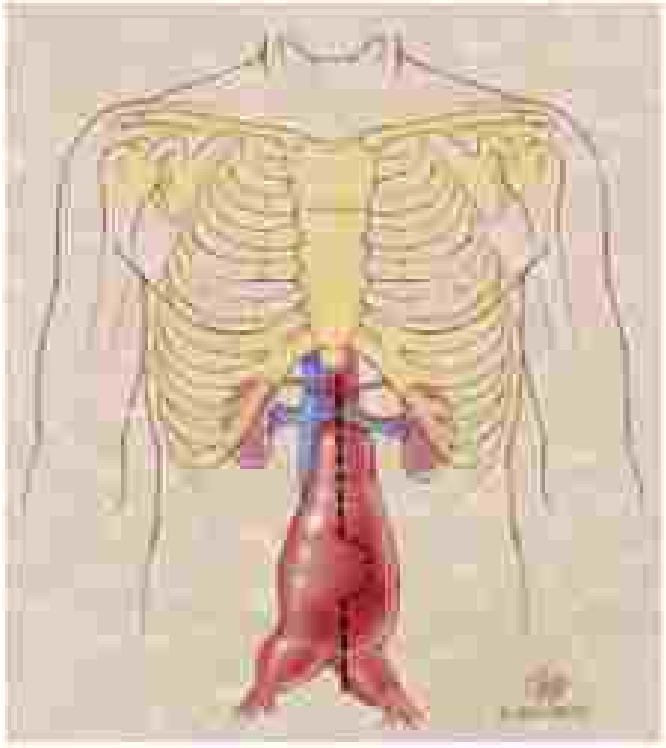

FIG. 1 The transperitoneal approach allows exposure from the ili[illegible] artery [illegible] to the renal arteries. To access the [illegible] aneurysm, the [illegible] must be mobilized to reveal the aneurysm, [illegible]. [illegible] (Reprinted courtesy Mayo Foundation.)

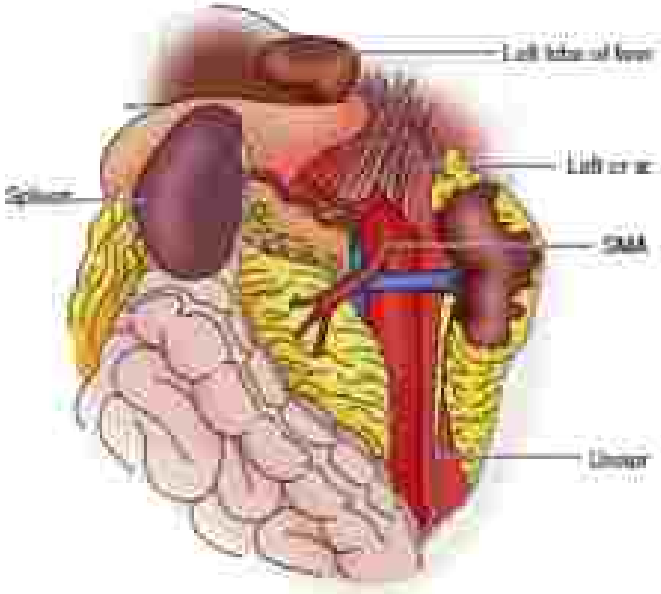

FIG. 2 Medial visceral rotation flexes the left colon and pancreas, spleen, and left kidney medialward inferiorly to allow superomedial [illegible] exposure of the [illegible] superior mesenteric artery. [illegible]

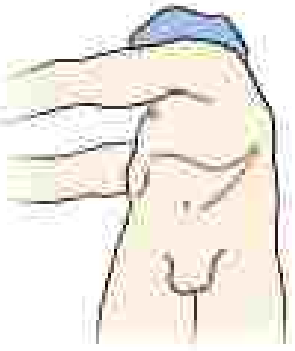

FIG. 3 The patient is placed in the lateral position with the hips swung [illegible]. [illegible]

makes it my preferred method for most patients undergoing open AAA repair. Proximal infrarenal aortic control is easily achieved without aneurysm manipulation. This is particularly useful in the patient with an inflammatory aneurysm. It also is useful in the very obese patient or if there is a colostomy or other previous abdominal surgery producing a so-called hostile abdomen. The duodenum and left renal vein are not exposed and therefore protected from injury. In the case of a juxtarenal aneurysm or if there is suprarenal extension, suprarenal or supraceliac aortic exposure and control can be easily achieved. Occlusive disease of the renal and/or mesenteric vessels can undergo transaortic endarterectomy when indicated without additional dissection. Further, the retroperitoneal approach is associated with less physiologic stress, with minimal or no postoperative ileus. There also is less respiratory compromise so that this approach is particularly appropriate for patients with COPD. One disadvantage of this approach is that exposure and control of the distal right iliac axis is difficult, especially with a large right common iliac artery aneurysm. This may require intraluminal balloon vascular control or performing the distal anastomosis to the right common femoral artery, although right groin exposure through this approach is more difficult than when aneurysm repair is carried out via a midline approach.

Technical Details

The patient is placed in the lateral position on a surgical beanbag with the left side up and the hips free with the iliac crest over the break in the table, which is extended to open the space between the left iliac crest and the lower left rib margin (Fig. 1). The incision extends from just below the umbilicus and lateral to the left rectus to the 11th intercostal space. With known suprarenal extension mandating more proximal exposure, the incision can be carried to the 10th intercostal space. The incision is deepened through the external oblique, internal oblique, and transversalis abdominis muscles, with care taken not to enter the peritoneal cavity. The peritoneal contents and left kidney are bluntly mobilized medially. The paraaortic lymphatics are ligated and divided, and a descending branch of the left renal vein should be identified and ligated to avoid troublesome bleeding. The left ureter, which courses over the left common iliac artery, should also be identified. If more proximal aortic exposure is necessary, the crus of the diaphragm can be divided with cautery to expose the suprarenal aorta. Further, if a mesenteric bypass is planned, more proximal aortic control is obtained with the left kidney mobilized anteriorly; it can be brought back posteriorly to allow exposure of the proximal celiac and superior mesenteric arteries anterior to the left kidney.

[illegible]

Irrespective of the surgical approach, the fundamental principles of operative repair are the same, and critical to the safe and effective conduct of the operation. Adequate exposure and vascular control proximal and distal to the aneurysm is essential. The aortic neck

RESULTS

Perioperative Mortality

With the introduction and growth in the performance of EVAR in contemporary practice, open AAA repair is increasingly being performed in patients with more anatomically complex aneurysms and not infrequently requiring suprarenal and supraceliac cross clamping. Despite this, and an increasingly ageing patient population with aneurysmal disease undergoing open surgery, open repair of AAAs has become increasingly safe in modern practice. Recent randomized controlled clinical trials have documented a perioperative mortality rate of 3.5%. This is paralleled by a mortality rate of approximately 3% in population-based studies. In a meta-analysis of 20 series with a minimum of 100 patients, perioperative mortality was 3.4%. In studies at Johns Hopkins as well as those done by others, it seems clear that the best results are achieved by surgeons with the highest operative volumes and in the highest volume centers, although an absolute minimum annual case volume is difficult to define. In a review of seven series of patients undergoing open AAA repair requiring suprarenal aortic cross clamping, and with at least 50 cases, perioperative mortality ranged from 1.9% to 3.6%, with mortality 3% or less in five of the seven series.

Perioperative Complications

Perioperative complications are not uncommon following open AAA repair, the incidence correlates with the complexity of the operation (Box 1). In one recent population-based registry, serious adverse events occurred in 26% cases and major adverse events in 11% of cases.

The majority of perioperative deaths result from cardiac complications. Better perioperative evaluation and perioperative medical management, including β-blocker use, have reduced the incidence of cardiac morbidity. Nevertheless, myocardial ischemia may be seen in up to 10% of patients in the early postoperative period. The incidence of respiratory complications correlates with the complexity and duration of the procedure and associated blood loss and fluid administration; patients benefit for aggressive early diuresis and extubation as soon as clinically safe in the early postoperative period to minimize pulmonary morbidity. Nevertheless, postoperative pneumonia may occur in 1–6% of patients following open AAA repair. The incidence of renal insufficiency following open AAA repair has declined significantly in recent years, but remains a potential complication, especially in cases requiring suprarenal or supraceliac aortic cross clamping. In a series of Medicare patients, the incidence of renal functional deterioration was 10%. In a meta-analysis of patients undergoing juxtarenal aortic aneurysm repair, postoperative dialysis was required in

BOX 1 Postoperative Complications

Early

Myocardial ischemia
Respiratory insufficiency
Respiratory failure
Pneumonia
Renal insufficiency
Ischemic colitis

Late

Sexual dysfunction in males
Impotence
Retrograde ejaculation
Aortoiliac/aortic fistula
Graft infection
Abdominal wall hernia

only 3.5% of patients. As noted above, administration of furosemide and mannitol to generate a brisk diuresis before aortic clamping is protective. Peripheral perfusion should be assessed before the patient leaves the operating room by palpating the peripheral pulses and performing a Doppler examination. Limb ischemia typically results from intraoperative distal embolization of aneurysmal thrombus or atherosclerotic debris. Application of the distal clamps before the aortic clamp and minimizing aortic dissection before clamping is protective. If backbleeding from the distal vessel seems inadequate, an embolectomy catheter should be passed distally before completing the distal anastomosis. The development of acute limb ischemia in the early postoperative period usually results from a technical error or clamp injury and warrants immediate exploration.

Although less commonly encountered than after repair of ruptured AAAs, ischemic colitis may complicate elective repair. Ligation of a patent IMA, occlusion of hypogastric artery flow, severe iliofemoral arterial occlusive disease, mesenteric arterial occlusive disease, and intraoperative atheroembolism are predisposing factors. The development of abdominal pain, fever, leukocytosis, and bloody gastric positive stools should warrant immediate sigmoidoscopy. This complication usually presents from 1 to 4 days postoperatively and can range pathologically from mucosal edema and hemorrhage to transmural infarction. When diagnosed early, mild to moderate colon ischemia may resolve, albeit with late stricture formation in some cases. Conservative medical therapy including cessation of oral intake, nasogastric suction, administration of broad spectrum intravenous antibiotics, and serial sigmoidoscopic examinations. Mortality with severe ischemic colitis has been reported in 25% to 50% of cases.

Sexual dysfunction in the male patient is a potential complication of open AAA repair, which should be discussed with the patient preoperatively. Difficulty with achieving or maintaining an erection may result from occlusion of internal iliac artery flow. Further, as many as 40% of male patients may experience retrograde ejaculation due to disruption of autonomic nerve fibers at the aortic bifurcation. One should minimize dissection at the aorto-bifurcation to minimize the incidence of this complication.

Less commonly, aorto-enteric fistula formation may complicate 1% to 2% of open AAA repairs and may present from a few months to several years following surgery. Closure of the residual aneurysm wall and coverage with omentum when operating through the transperitoneal approach are important to reduce the incidence of this complication. Further, it appears that the extended left retroperitoneal approach may be associated with a reduced incidence of this very serious complication. Likewise, prosthetic graft infection may complicate 1% to 2% of open AAA repairs and may present in the early postoperative period or several years postoperatively. Careful attention to intraoperative hemostasis to avoid postgraft hematoma formation, careful wound closure, and perioperative broad spectrum antibiotic administration are key to preventing this complication. These principles will also minimize the development of abdominal wall hernias following the transperitoneal approach or abdominal wall laxity following the left retroperitoneal approach.

Suggested Readings

Clark [illegible] [illegible] [illegible]

[illegible] [illegible] [illegible]

[illegible] [illegible] [illegible]

Endovascular Treatment of Abdominal Aortic Aneurysms

[illegible] [illegible] [illegible] [illegible] [illegible]

Abdominal aortic aneurysm (AAA) is defined as a 50% increase in diameter compared with the baseline diameter of a given blood vessel. There is a strong male predominance, with a male to female ratio of 6:1. AAA is fairly common, affecting 12% of men over age 65 and accounting for approximately 15,000 deaths annually in the United States. The average rate of growth of an AAA is approximately 3 mm/yr. Smoking increases the average annual growth by 20% and also increases the risk of rupture twofold. Multiple trials have established that an AAA should be repaired once it reaches a threshold of 5.5 cm in men and 5 cm in women.

Endovascular aneurysm repair (EVAR) was first performed in 1990 by Juan Parodi in Buenos Aires. The first EVAR was performed using a stainless steel bare metal stent sutured to a Dacron graft, which was then mounted on a large angioplasty balloon and crimped inside a large sheath. The graft was then inserted and deployed through an open exposure to the common femoral artery. This successful first procedure paved the way for the current era of endovascular aneurysm repair.

In the 20 years since EVAR was first introduced, the techniques and devices have been refined and improved. In 2003 EVAR surpassed open aneurysm repair as the preferred method, and currently approximately 80% of AAAs are repaired using an endovascular technique. EVAR has been shown to have a lower perioperative mortality rate, shorter hospital length of stay, and lower rates of early complications.

Several randomized controlled trials have compared endovascular and open aneurysm repair. These include the EVAR 1 trial, the DREAM trial, and the OVER trial. The results of the 3 trials are consistent and lead to similar conclusions. First, EVAR has lower perioperative and 30-day morbidity and mortality rates compared with open aneurysm repair. Second, the short-term survival advantage of EVAR diminishes with time, and there are equal mortality rates between the techniques at 2 years and beyond. Finally, EVAR is associated with higher long-term device-related complications as compared with open aneurysm repair. Therefore, the planning, accuracy of deployment, and long-term follow-up with imaging are important to achieving a good long-term result.

Preoperative Planning

Precise preoperative planning is essential for short- and long-term outcomes after EVAR. Procedural success depends on several factors. Adequate ilio-femoral access for device delivery, adequate proximal seal zone below the renal arteries, adequate distal seal between the graft limbs and the iliac arteries, and adequate length of overlap between components of the graft. To assess the patient's anatomy

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Suggested Readings

Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg 2018;67:2–77.

Cronenwett JL, Lin JW, Conglon TA, Williams GM, Taylor DA. Results of elective abdominal aortic aneurysm repair in the 1990s: a population-based analysis of 2235 cases. J Vasc Surg 1995;30:808–906.

Dossa SE, Lancaster RT, Stanl GL, Indes JE, Rybin D, Conrad MF, et al. Contemporary outcomes of open complex abdominal aortic aneurysm repair. J Vasc Surg 2016;63:1195–1200.

Heard JR, Kelly BM, Rubin BG, Thompson RW, Allen KT, et al. Transabdominal versus retroperitoneal incision for abdominal aortic surgery: report of a prospective randomized trial. J Vasc Surg 1996;23:178–185.

Endovascular Treatment of Abdominal Aortic Aneurysms

Richard P. Cambria, MD, and Scott G. Prutkin, MD

Abdominal aortic aneurysm (AAA) is defined as a 50% increase in diameter compared with the baseline diameter of a given blood vessel. There is a strong male predominance, with a male to female ratio of 6:1. AAA is fairly common, affecting 12% of men over age 65 and accounting for approximately 15,000 deaths annually in the United States. The average rate of growth of an AAA is approximately 3 mm/yr. Smoking increases the average annual growth by 20% and also increases the risk of rupture twofold. Multiple trials have established that an AAA should be repaired once it reaches a threshold of 5.5 cm in men and 5 cm in women.

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before the procedure, a computed tomography (CT) angiogram with fine cuts (~2.5 mm) is a necessity. The axial, coronal, and sagittal images should be reviewed, along with three-dimensional (3D) reconstructions to perform pre-procedural measurements. There are several commercially available third-party software programs that can be used to create these reconstructed images. These programs include Vitrea, 3mensio, Terarecon, and Intellispace. These reconstructions show detailed images of the aortic lumen, branches, and aortic wall. The software can be used to generate a centerline through the aorta into both external iliac arteries, allowing for precise measurement of the distances between branch vessels to make an accurate plan in terms of the type and size of device. The length of the main body and corresponding iliac limbs are dictated by these careful centerline measurements performed using three-dimensional reconstructions. The CT angiogram is also used to carefully inspect the aortic neck morphology in terms of calcification, mural thrombus, and diameter. It is also important to carefully assess the iliofemoral access to safely introduce and deploy the endovascular device.

Assessing Access Vessels

Current endovascular technology requires bilateral access for device delivery, with the most common site of entry being the common femoral arteries. It is important to assess the iliofemoral vessels for patency, diameter, calcification, thrombus, and tortuosity. If there is significant common femoral disease, an endarterectomy may be required to facilitate placement of the delivery sheath. Luminal diameter should be carefully measured to ensure that it is sufficient for placement of the device sheath safely. Iliac stenosis can be managed with angioplasty before device sheath placement. Patients with small external iliac vessels may require the creation of an iliac conduit through a retroperitoneal incision using a 10 mm Dacron graft on the distal common iliac artery. Alternatively, an endoconduit can be performed by placing a 10 mm covered stent graft followed by angioplasty. Tortuous iliac arteries are generally straightened with the use of a stiff guidewire; however, severe tortuosity may preclude safe delivery of the device.

Proximal Aortic Seal

Achieving appropriate proximal seal between the endovascular device and the aorta depends on adequate apposition between the graft and nonaneurysmal aorta. The minimum length required for adequate seal varies between 10 and 15 mm depending on the device (Table 1). Adequate seal is assessed by measuring the aortic diameter below the level of the lowest renal artery and in 5 mm increments cranially to assess for a conical neck. The seal zone should be assessed for angulation relative to the adjacent aorta, calcification, and mural thrombus. It is important to perform these measurements in centerline, perpendicular to the wall of the aorta to ensure adequate graft sizing. If measurements are made on axial CT angiography without taking into account the centerline, the aortic neck diameter can be overestimated, leading to oversizing of the endograft and fabric infolding, resulting in possible type Ia endoleak. The proximal endograft is then oversized approximately 10% to 20% relative to the diameter of the aorta and the seal zone.

Distal Iliac and Junctional Seal

A nonaneurysmal distal seal zone is required in the common iliac artery for adequate distal fixation. The current devices require either 10 or 15 mm of length for adequate seal. If the common iliac artery is aneurysmal and adequate seal cannot be achieved, the graft may be landed in the external iliac artery. If the graft is sealing in the external iliac artery, the internal iliac artery must be embolized either before or as part of the aneurysm repair to prevent endoleak. In patients for whom it is important to preserve blood flow to one or both of the internal iliac arteries, there is a commercially available iliac branch endograft that places a second bifurcated component into the external and internal iliac arteries to preserve pelvic flow. Iliac artery diameter measurements should be taken perpendicular to the wall of the artery, again taking advantage of the 3D reconstruction software and using the centerline measurement. Iliac limbs should be oversized between 10% and 20% just as in the proximal aortic fixation. Junctional seal should be maintained between components, generally about 3 cm of overlap, depending on the device. Once the device is placed, angioplasty should be performed on the overlap zone to prevent type III endoleak.

Patient Selection

As mentioned previously, the major selection criteria for endovascular aneurysm repair are anatomic factors that can be used to predict outcomes. These include the diameter of the aortic neck, the length of the neck, angulation, and the distal iliac seal zone. There are currently 6 commercially available endovascular aneurysm devices that are approved by the Food and Drug Administration in the United States (Table 1). These current devices recommend a neck length between 10 and 15 mm and angulation between 0° and 60 degrees. One exception is the neck angulation in the Anaconda device, which allows for neck angulation up to 90 degrees. Generally, neck diameters up to 32 mm can be accommodated by current grafts.

Adherence to the instructions for use is vital to good short- and long-term outcomes. In general, vascular surgeons have had low rates of adherence to the instructions for use. It has been shown that nonadherence leads to a higher rate of endoleak and corresponding AAA sac diameter growth at 5 years. This puts patients at risk for rupture and requires a higher intervention rate. Therefore patients who have anatomy that is not suitable for endovascular repair should be offered open surgical repair or fenestrated EVAR.

PROCEDURAL STEPS

Arterial Access

Open Femoral Access

Either a vertical or oblique skin incision is made overlying the common femoral pulse just below the inguinal ligament. The vertical incision includes the advantage of getting additional exposure to the iliac and femoral vessels if necessary; however, the oblique incision is favored by many surgeons due to a lower incidence of wound complications. The common femoral artery is dissected distal to the inguinal ligament and controlled with vessel loops. An 18 gauge access needle is then inserted into a distinct free portion of the artery, and a 0.035" starter wire is advanced into the proximal aorta. A short sheath is placed over the wire and into the common femoral artery. A stiff wire, either an Amplatz or Lunderquist wire, is inserted into the descending thoracic aorta. A pigtail catheter with multiple 1 cm markers is introduced on the contralateral side in place just above the renal arteries. The patient is then systemically heparinized.

Percutaneous Femoral Access

Percutaneous access for EVAR has increased in popularity over the past 10 years. This approach has the advantage of shorter procedure times, less postoperative pain, and decreased risk of wound complications. Disadvantages of this approach include increased hospital costs and occasional urgent conversion to open access and arterial repair. We recommend routine use of ultrasound guidance with percutaneous access to help identify an area on the anterior wall of the common femoral artery that is free of atherosclerotic plaque. A small transverse stab incision is made with an 11 blade just below the probe. The tract is then dilated above the artery using blunt dissection with a hemostat. A micropuncture needle is then inserted into the common femoral artery under ultrasound guidance, followed by the micropuncture wire and sheath. At this point arteriography is performed to ensure adequate positioning of the arterial access in the common femoral artery before ejecting the sheath. If satisfied with the access

TABLE 1 Characteristics of Currently Available Endovascular Devices

Device	Graft/Stent Material	Treatable Aortic Neck Diameter (mm)	Main Body Diameter (mm)	Delivery System and Main Body Size (Fr)	Proximal Neck Angulation and Length	Distal Fixation Length (mm)	Fixation	Design Features
Endurant	ePTFE stent	19–32	23–36	14–16/22–25	>15 mm and ≤60 degrees	8–25	10	Infrarenal	Repositionable proximal delivery system to achieve accurate proximal landing zone
Zenith Flex	4 mm polyester stainless steel	18–32	22–36	21/14–16	≥15 mm and ≤60 degrees	7.5–20	>10	Suprarenal	Partial proximal repositioning; shortened Z-stents inhibit kinking
Endurant II	4 mm polyester stent	19–32	23–36	18/14–16	>10 mm and ≤60 degrees or ≥15 mm and ≤75 degrees	8–25	≥15	Suprarenal	Approved for treatment of 10 mm proximal aortic neck
AFX	ePTFE cobalt chromium alloy	18–32	25–38	1–39	≥15 mm and ≤60 degrees	10–20	≥10	Infrarenal or Suprarenal	Unibody device provides anatomic fixation on aortic bifurcation
Ovation	ePTFE stent	16–30	20–34	14–15/22–25	>10 mm and ≤60 degrees or ≤10 mm and ≤45 degrees	8–25	>10	Suprarenal	Smallest delivery sheath; proximal sealing ring with Polymer
Aorfix	4 mm polyester stent	19–29	24–36	22/26	≥15 mm and ≤90 degrees	—1,	≥15	Infrarenal	Ability to treat aortic necks with severe angulation

ePTFE, Expanded polytetrafluoroethylene.

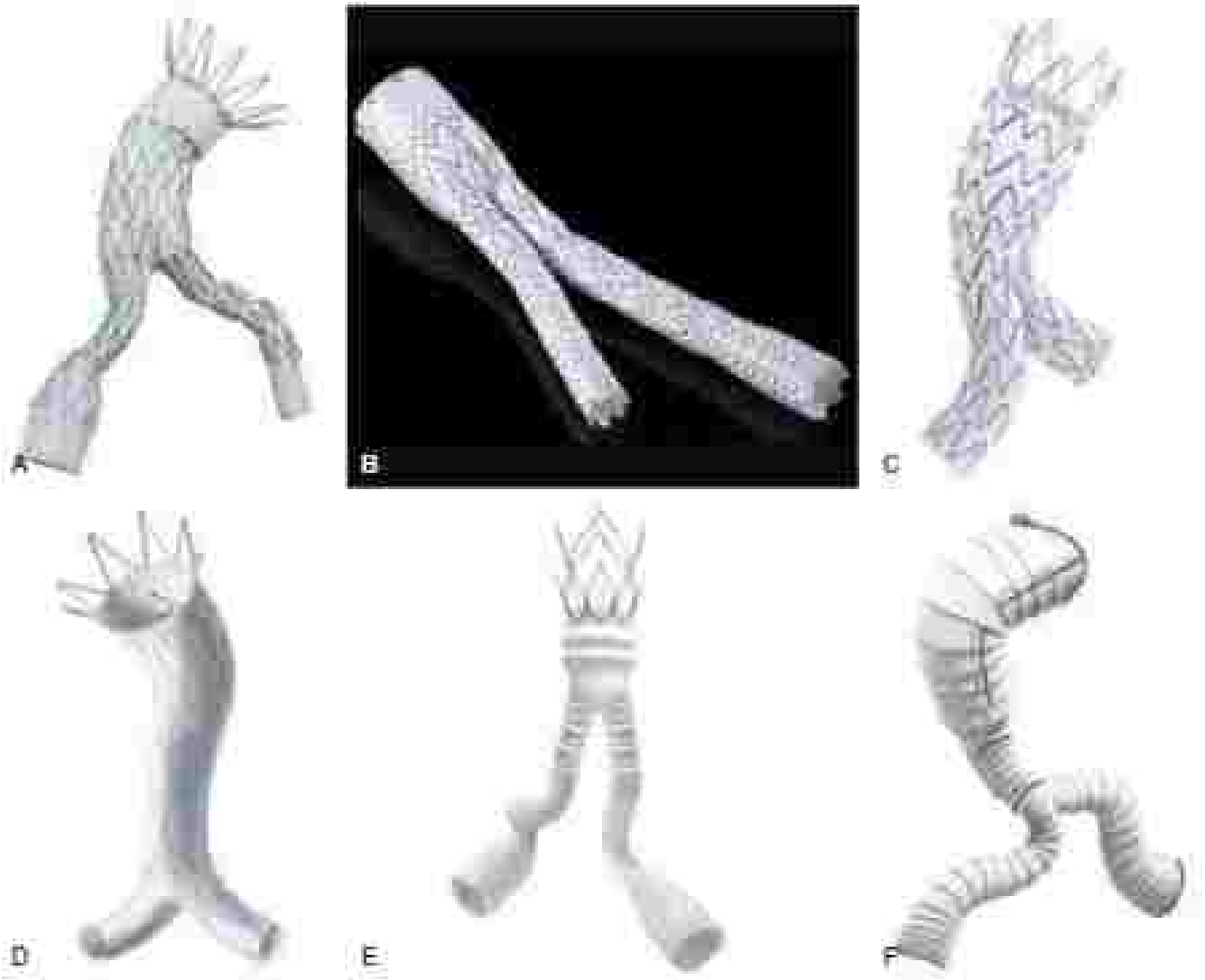

FIG. 1 Commercially available aortic grafts. (A) Cook Zenith Flex. (B) Gore Excluder C3 IBE endoprosthesis. (C) Medtronic Valiant Captivia thoracic endoprosthesis. (D) Endologix Powerlink. (E) Jotec E-vita abdominal. (F) Cook Zenith TX2 TAA endovascular graft. (Courtesy WL Gore & Associates, Flagstaff, AZ; Medtronic, Minneapolis, MN; Endologix, Irvine, CA; and Cook Medical, Bloomington, IN.)

this, a 0.035 guidewire is placed, followed by a sheath. Next, the sheath is removed, the Proglide is placed over the wire, and the wire is removed. The first Proglide is deployed in the 10 o'clock position, and the sutures are clamped with a straight snap. The 0.035 wire is replaced, the Proglide is removed, and manual pressure is held while the next Proglide device is placed over the wire. The wire is again removed, and the sutures are deployed in the 2 o'clock position. The sutures are then clamped with a curved snap and the wire is again replaced. After the Proglide is removed, manual pressure is held, and an 8Fr sheath is placed for hemostasis. This is repeated on the contralateral side. The patient is then systemically heparinized. On the ipsilateral side the wire is exchanged for either an Amplatz or a Lunderquist wire to facilitate the placement of a large sheath. A marker pigtail catheter is placed just above the renal arteries on the contralateral side.

Device Deployment

We will describe the steps here for the deployment of a bifurcated modular graft because this is the most commonly used device. After bilateral open or percutaneous femoral access is performed, a floppy Glidewire is placed into the proximal thoracic aorta and exchanged over a catheter for a stiff wire, either Amplatz or Lunderquist. It is important always to visualize the tip of the stiff wire in the aortic arch to minimize inadvertent placement in the arch vessels, increasing the risk of stroke. A pigtail catheter is then placed through the contralateral side and placed just above the level of the renal arteries generally at about the T1 vertebral body. If there is a question about iliac occlusive disease or about the length of main body needed, an angiogram can be obtained now to make length measurements. However, usually the main body is inserted through the ipsilateral side in the undeployed position, and angiography is performed to confirm the position of the renal arteries.

To properly deploy the main body, the contralateral gate should be oriented under fluoroscopy before insertion. The orientation should be confirmed as the device is being advanced to avoid the gate spinning to a difficult position to cannulate. Once the undeployed graft is placed in the paravisceral aorta, angiography is performed to confirm the position of the lowest renal artery, which is then marked on the screen. Initial deployment should begin about 1 cm above the renal arteries, and, as the graft is deployed it is slowly pulled down below the lowest renal artery. After the proximal landing zone is established, the deployment continues until the contralateral gate is open. At this point, the bare metal suprarenal stent is deployed for the devices that have it.

The next step is cannulation of the contralateral gate. This is generally performed using a Glidewire and catheter. It is important to confirm that the wire tracked has passed through the contralateral gate. This can be done by either placing a pigtail into the main body to ensure that it goes easily because it will be constrained behind the graft if not through the gate or by inflating an angioplasty balloon at the level of the contralateral gate and spinning the gantry to confirm its position within the gate. Once this is done a stiff wire is placed, and the gantry is moved to 20-degree left anterior oblique for the right common iliac artery or right anterior oblique for the left common iliac artery. Angiography is then performed using the marker catheter to measure the length from the distal graft to the iliac bifurcation. The appropriate limb is then inserted with the least minimal overlap between device components and landed just above the takeoff of the internal iliac artery. At this point the ipsilateral limb is fully deployed, and, if necessary and depending on the device, an ipsilateral iliac limb extension is advanced and deployed in a similar manner to the contralateral limb.

Once the graft is fully deployed, a compliant balloon may be used for gentle angioplasty of the aortic neck, device overlap zones, and distal seal. It is important not to be overly aggressive with angioplasty so as not to cause proximal aortic or iliac artery rupture. After this, completion angiography is performed. The angiographic catheter is placed in the proximal aorta, and the following should be carefully inspected on the angiogram: patency of the renal and internal iliac arteries, position of the proximal seal zone, flow through the graft and iliac arteries bilaterally, and inspection for endoleak.

Once the surgeon is satisfied with the result, femoral closure is performed. If open access was performed, the wires and sheaths are removed, the arteries are clamped, and repair is performed, transversely with 5-0 Prolene suture. If percutaneous access was used, the sheath is removed, while leaving the wires in place to maintain access, and the ProGlide device sutures are cinched down. Once adequate hemostasis is obtained, the wires can be safely removed.

Follow-up

Patients return to the office for follow up at 1 month after surgery, at which time a CT angiography of the abdomen and pelvis is performed, which serves as the baseline study. Repeat CT angiography is performed at 1 year after surgery. Presence or absence of endoleak and aortic sac regression are determined by CT angiography, and follow up is performed annually. Patients with shrinking aneurysm sacs and no evidence of endoleak can be safely managed with yearly duplex ultrasound scanning. Patients with enlarging sacs or endoleaks are best monitored with yearly CT angiography.

COMPLICATIONS

Endoleak

Endoleak is defined as persistent blood flow to the aneurysm sac after endovascular aneurysm repair. This results in continued pressurization of the aneurysm sac, which places the patient at continued risk of aneurysm growth and ultimately rupture. Endoleaks can be classified in to one of five categories (Fig. 1), which help to determine the best course of treatment.

Type I Endoleak

Type I endoleak (Fig. 2) occurs as a result of an incomplete seal at either the proximal aortic sealing zone (Type Ia) or the distal iliac seal zone (Type Ib). This results in continued pressurization of the aneurysm sac, leading to sac growth. Type I endoleak is generally encountered at the time of stent graft placement or shortly thereafter, although it can be encountered at any time. Because this pressurization and aneurysm growth leads to continued risk of rupture, treatment of type I endoleak is mandatory. Proximal, Type Ia endoleak can be treated with angioplasty with a compliant balloon, proximal extension cuff if there is adequate length below the renal arteries, placement of a Palmaz stent, or with the use of the Aptus Endovascular

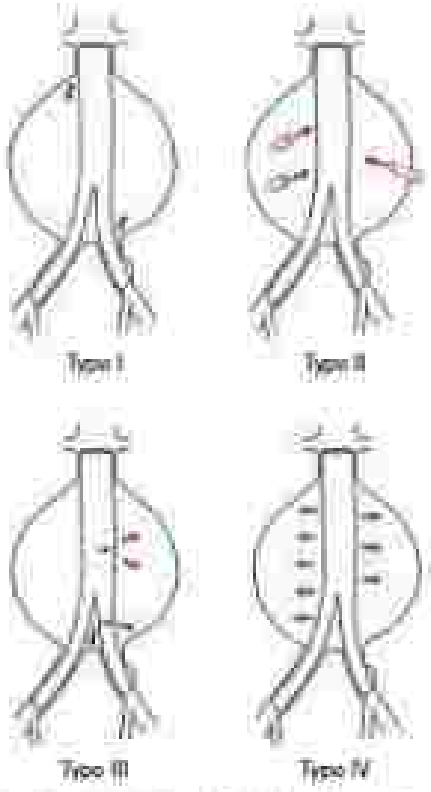

FIG. 2 Type I to IV endoleaks. Type I endoleak originates from an incomplete seal at the proximal (type Ia) and distal (type Ib) seal zone of the endograft. Type II endoleak, the site most commonly treated, results from retrograde flow of blood into the aneurysm sac from a patent branch vessel, such as the inferior mesenteric artery and lumbar arteries. Type III endoleak originates from a defect in the graft fabric and from junctional tears between graft components. Type IV endoleak results from porosity in the graft fabric.

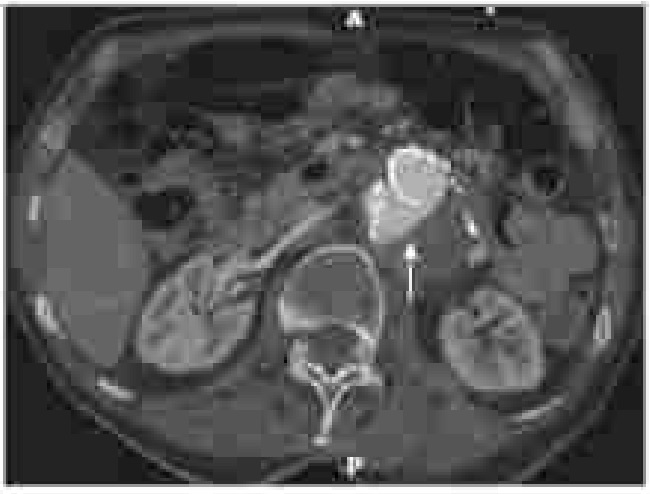

FIG. 3 Type Ia (proximal) endoleak originating from the superior seal zone of an endograft.

Repair Systems. Treatment of type Ib endoleak can be done by deploying an iliac limb extension with embolization of the proximal iliac artery as necessary.

Type II Endoleak

Type II endoleak (Fig. 4) is defined as persistent sac filling from back bleeding side branches such as the inferior mesenteric artery, lumbar arteries, or middle sacral artery. Type II endoleak is relatively

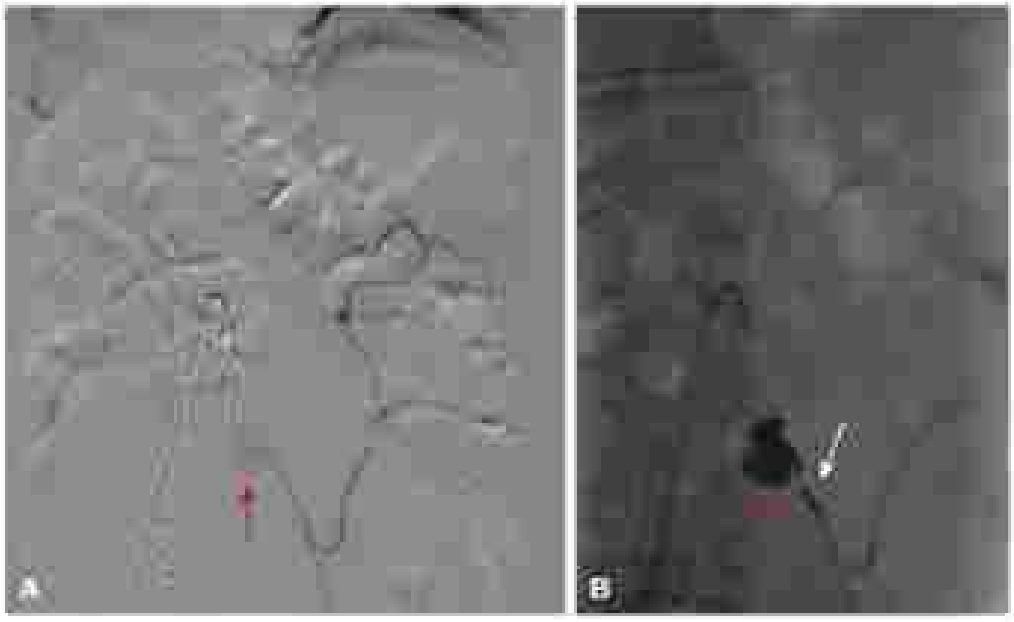

FIG. 4 Type II endoleak from the inferior mesenteric artery. (A) Angiography performed via retrograde catheter placement in the superior mesenteric artery demonstrates a filling defect at the origin of the inferior mesenteric artery feeding an enlarging abdominal aortic aneurysm sac. (B) Coil embolization of the endoleak with Onyx glue (red arrow) and coil embolization (white arrow) of the inferior mesenteric artery.

common and seen in between 10% and 20% of patients on CT angiograms after EVAR. Generally, there is a benign course with as many as 80% spontaneously resolving within 6 to 12 months of stent graft placement. It has been shown in multiple studies that the risk of aneurysm rupture due to type II endoleak is small. Therefore treatment is only performed if there is documented sac enlargement. Treatment is generally performed through endovascular means using coil embolization or Onyx Liquid Embolic System (ethylene vinyl alcohol copolymer). This embolization can be performed through a transarterial approach via the superior mesenteric artery or internal iliac arteries. It can also be performed from the iliac arteries and directly accessing the aneurysm sac from behind the iliac limb. If transarterial embolization is unsuccessful, embolization can be attempted via either a translumbar or transcaval approach. If embolization is unsuccessful by all means and the sac continues to grow, open sac intervention can be performed by explant of the graft and open repair or distal ligation of back bleeding vessels.

Type III Endoleak

A type III endoleak (Fig. 5) occurs when there is a tear in the fabric of the graft or flow between separate components of the graft. This leads to continued pressurization and sac enlargement increasing the risk of rupture as in type I endoleak. Therefore treatment of type III endoleak is again mandatory. Treatment involves placement of a cuff or a new limb to bridge the gap between separated components. Treatment may require relining the graft with a new stent graft, which is generally performed using an aorto-uni-iliac device along with a femoral-femoral bypass and coil embolization of the contralateral common iliac artery.

Type IV Endoleak

Type IV endoleak is related to flow through the graft due to the porosity of the fabric. It is rare to encounter this type of endoleak with the current generation of stent grafts. Typically, no treatment is necessary, and the endoleak resolves as the graft interstices thrombose.

Type V Endoleak

This type of endoleak is referred to as endotension and is defined as sac enlargement without an identifiable endoleak on imaging studies.

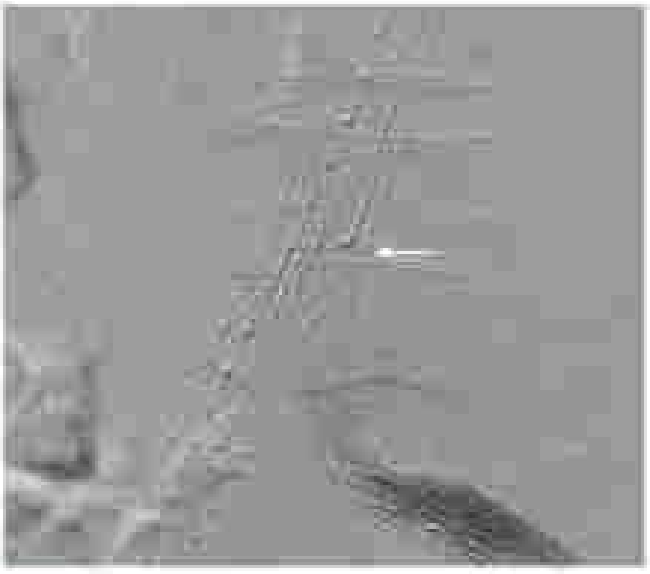

FIG. 5 Type III endoleak from separation of the limb from the main body of the graft (arrow).

There are several proposed theories behind type V endoleak. One theory is that the flow into the aneurysm sac is so slow that it cannot be detected with current imaging techniques. Another theory postulates that pressure is transmitted across thrombus in the aneurysm sac maintaining sac pressure. Regardless of the mechanism, continued sac pressurization leads to ongoing risk of rupture. Close follow-up is recommended to determine the rate of growth and the necessity of repair. Repair is performed through relining with a new graft or with explant and open repair.

Graft Limb Occlusion

Occlusion of one graft limb occurs in about 3% of patients and usually occurs in the first 6 months after EVAR. It is more common with

aortoiliac occlusive disease, a small distal aorta, or tortuous iliac arteries. It was more common in stent grafts with unsupported limbs; however, in the current generation of stent grafts, with supported limbs, lower limb occlusion rates have been noted. Most patients with limb occlusions present with buttock, thigh, or calf claudication. Rest pain or acute limb ischemia occur but are less common. Several approaches have been used to treat limb thrombosis including thrombolysis, angioplasty, and stent placement to straighten out kinks. Open surgical approaches include femoral-femoral bypass, axillary-femoral bypass, axillary-bifemoral bypass, or surgical thrombectomy.

Ischemic Complications

Ischemic complications after EVAR stem from one of several mechanisms, including direct vessel occlusion, atheroembolization during manipulation and device deployment, and inadequate collateralization of the mesenteric and pelvic circulations. Pelvic ischemia can present as buttock claudication, buttock necrosis, spinal cord ischemia, colon ischemia, and erectile dysfunction. Pelvic ischemia can occur frequently after EVAR, especially sexual dysfunction and buttock claudication, which should be discussed with the patient during the consent process. It generally occurs after embolization of one or both internal iliac arteries for the treatment of common iliac artery aneurysm. Buttock claudication can occur in more than 50% of patients with unilateral internal iliac artery embolization and more than 60% with bilateral internal iliac artery embolization. Erectile dysfunction occurs in 17% of patients with unilateral internal iliac artery embolization and 24% with bilateral embolization. Although the incidence of buttock claudication is relatively high, approximately two thirds of patients report resolution of symptoms within 1 year of EVAR. Although mesenteric ischemia has a high mortality rate after aneurysm repair, it is seen in less than 2% of endovascular procedures. Spinal cord ischemia is an extremely rare event after endovascular AAA repair and has been reported in less than 0.5% of cases.

Renal Artery Occlusion

Renal artery occlusion either occurs from coverage of the origin of the artery by the graft or through embolization. Upward movement of the graft after deployment is uncommon. Usually renal artery coverage is a complication that occurs as a result of deploying the graft too high, either from misjudging the location of the fabric relative to the radiopaque markers on the graft or due to parallax if there is improper gantry position. If coverage is detected on the completion angiogram, attempts should be made to salvage the kidney. If there is some flow identified over the top of the graft, this can usually be accomplished by placing a stent into the renal artery ostium, which is easiest from a left brachial approach. If the renal artery cannot be visualized and a wire cannot pass, it is sometimes possible to pull the graft down slightly to make a small channel for the wire. This can be accomplished with gentle traction downward with a compliant ball loon inflated to the main body or with a wire snared up and over, "flossing" the graft to allow for traction. If all of these techniques fail, open splenorenal or hepatorenal bypass may be necessary. Embolization to the renal arteries can present with early or delayed renal insufficiency. This is especially true when there is thrombus in the aorta neck and a graft with suprarenal fixation is used.

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Management of Ruptured Abdominal Aortic Aneurysms

Andrew R. Ramaiah, MD, Sean P. Roche, MD, and Ross A. Clouse, Jr., MD

Delays in the diagnosis and treatment of patients presenting with a ruptured abdominal aortic aneurysm (rAAA) directly increase the risk of death and long-term morbidity. The establishment of aortic centers using a multidisciplinary team approach, established protocols for transfer, and expeditious treatment of acute aortic emergencies has improved patient care. For 50 years, the mortality rate of rAAA reaching a hospital has remained unchanged at 40% to 50%. However, in the last 2 decades, with a shift toward endovascular aneurysm repair (EVAR) for rAAA, this figure has decreased to around 20% to 30% in many studies. In 1991, the first use of endovascular methods for repair was reported and sparked interest in a resolution of a minimally invasive modality for rupture repair. Many hospitals have adopted preferential endovascular repair of ruptured abdominal aortic aneurysms (rEVAR), with only select individuals undergoing an attempt at open repair. Despite this, there have been four randomized studies that demonstrated no proven mortality benefit of rEVAR over open repair.

The best treatment is preventative or early detection. In the United States, The Centers for Medicare and Medicaid Services cover a one-time ultrasound screening for men aged 65 to 75 years who have smoked at least 100 cigarettes or anyone with a family history of abdominal aortic aneurysm (AAA). This highlights the fact that smoking is the strongest risk factor for aneurysm formation. Additional risk factors for rupture include size, rapid growth, tenderness over the aneurysm, chronic obstructive pulmonary disease, familial predisposition, and female sex.

PRESENTATION AND DIAGNOSIS

The classical triad defining the presentation of an rAAA is acute abdominal or back pain, hypotension, and a palpable abdominal

aortoiliac occlusive disease, a small distal aorta, or tortuous iliac arteries. It was more common in stent grafts with unsupported limbs; however, in the current generation of stent grafts, with supported limbs, lower limb occlusion rates have been noted. Most patients with limb occlusions present with buttock, thigh, or calf claudication. Rest pain or acute limb ischemia occur but are less common. Several approaches have been used to treat limb thrombosis including thrombolysis, angioplasty, and stent placement to straighten out kinks. Open surgical approaches include femoral-femoral bypass, axillary-femoral bypass, axillary-bifemoral bypass, or surgical thrombectomy.

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Management of Ruptured Abdominal Aortic Aneurysms

Andrea R. Ramdass, MD, Sean P. Roddy, MD, and R. Clement Darling III, MD

Delays to the diagnosis and treatment of patients presenting with a ruptured abdominal aortic aneurysm (rAAA) directly increase the risk of death and long-term morbidity. The establishment of aortic centers using a multidisciplinary team approach, established protocols for transfer, and expeditious treatment of acute aortic emergencies has improved patient care. For 50 years, the mortality rate of rAAA reaching a hospital has remained unchanged at 40% to 50%. However, in the last 2 decades, with a shift toward endovascular aneurysm repair (EVAR) for rAAA, this figure has decreased to around 20% in many studies. In 1991, the first use of endovascular methods for repair was reported and sparked interest in a resolution of a minimally invasive modality for rupture repair. Many hospitals have adopted preferential endovascular repair of ruptured abdominal aortic aneurysms (rEVAR), with only select individuals undergoing an attempt at open repair. Despite this, there have been four randomized studies that demonstrated no proven mortality benefit of rEVAR over open repair.

The best treatment is preventative or early detection. In the United States, The Centers for Medicare and Medicaid Services cover a one-time ultrasound screening for men aged 65 to 75 years who have smoked at least 100 cigarettes or anyone with a family history of abdominal aortic aneurysm (AAA). This highlights the fact that smoking is the strongest risk factor for aneurysm formation. Additional risk factors for rupture include size, rapid growth, tenderness over the aneurysm, chronic obstructive pulmonary disease, familial predisposition, and female sex.

PRESENTATION AND DIAGNOSIS

The classical triad defining the presentation of an rAAA is acute abdominal or back pain, hypotension, and a palpable abdominal

mum. This full complement continues to infrequent, and there are many disorders that can be concomitant with an asymptomatic AAA or even mask the presentation. A perforated viscus, peptic ulcer disease, cholecystitis, cholecystitis, myocardial infarction, pericarditis, pancreatitis, and kidney stones are some of the differential diagnoses that should always be entertained. The converse is also true, because one always should have a high index of suspicion for rupture in any individual with an AAA. rAAAs can mimic other causes by presenting with pain radiating to the groin, dysuria, syncope, gastrointestinal bleeding, and bowel obstruction.

Initial evaluation follows airway, breathing, and circulation protocol. Depending on the acuity of the presentation, this may make the diagnosis challenging. Large bore intravenous access should be commenced with a full physical examination. Although many patients present with hypotension, we strongly believe in hypotensive hemostasis and do not give vigorous fluid resuscitation until the patient is in the operating room, where proximal arterial control can be expeditiously obtained. Abdominal ultrasonography, although sensitive enough for AAA, does not have the specificity to diagnose rupture. Upright chest radiography may be useful to rule out a perforated viscus and may show calcifications in the abdominal aorta. The best imaging to detect an rAAA is computed tomography (CT) with intravenous contrast of the abdomen and pelvis. CT scans give a definitive diagnosis and objective measurements on whether the rAAA is amenable to endovascular repair. (See Fig. 1 showing CT scans of a computerized AAA rupture, which is amenable to rEVAR.) In most emergency departments, CT scanning is readily available without delay. However, if the patient is unstable and there is suitable clinical evidence that the patient has an rAAA, then they should be transported directly to the operating room for expeditious treatment.

ENDOVASCULAR VERSUS OPEN REPAIR

As mentioned earlier, the NOTTINGHAM, IMPROVE, ECAR, and AJAX randomized rAAA trials compared open to endovascular repair for rAAAs and did not show any survival advantage for the rEVAR group. Reported results using EVAR for rAAA have been similar in most large single center series with around a 20% mortality rate, even to the series by Mayer et al where all consecutive rAAA were treated by an all EVAR approach. Most institutions have adopted an EVAR first approach, but any center taking on rAAA should be comfortable with both procedures. There may be some distinct advantage for EVAR. For example, rEVAR patients are more likely to be discharged home, with a lower incidence of blood loss and cardiac complications but a higher incidence of abdominal compartment syndrome. Limitations, to be amenable to endovascular repair, include several anatomic features:

- Aortic neck diameter less than 32 mm
- Aortic neck angulation less than 60 degrees
- Limited aortic neck thrombus/calcification (relative)
- Parallel wall and undilated neck length (1 cm or more) below low renal artery
- Iliac arteries usable and without excessive tortuosity to accommodate device delivery and a 10 mm end zone

However, many take a more liberal approach in evaluating suitability and one needs to acknowledge that these may be outside the official instructions for use and not universally accepted or approved by the United States Food and Drug Administration (FDA). There are currently six FDA approved infrarenal devices that are available for elective repair in the United States, all of which have various forms of data on their use with ruptured aneurysms. However, it is estimated that between one half to three quarters of rAAA are amenable to rEVAR. As the technology grows, adjuncts such as snorkel, chimney, stapled or even fenestrated or branch devices may broaden the choices for repair.

RUPTURE PROTOCOL

Time to aortic occlusion, or cessation of hemorrhage, is key and of the utmost importance. However, it is also important to transport the patient to the appropriate facility for definitive care. Warner et al demonstrated that transfer of patients to an aortic center from smaller regional hospitals with rAAA did not increase and maybe even decreased mortality rates. The caveat to this study was that there was an "all accept" policy and one number to call to facilitate transfer. Hinchliffe et al showed that CT does not delay time to operating room versus the French randomized trial, which suggested that EVAR delayed timing to surgery greater than twofold. The author's own institution has an average time to operation of 10 to 35 minutes. No other vascular surgery pathology has a more devastating consequence with delays. Lloyd et al showed that greater than 80% of patients died within 2 hours after diagnosis of a ruptured aneurysm. As a result, benefits of a contrast CT in the stable patient can be rewarding to determine the possibility of rEVAR inclusive of accessible neck and sizing, as well as ruling out other pertinent disease.

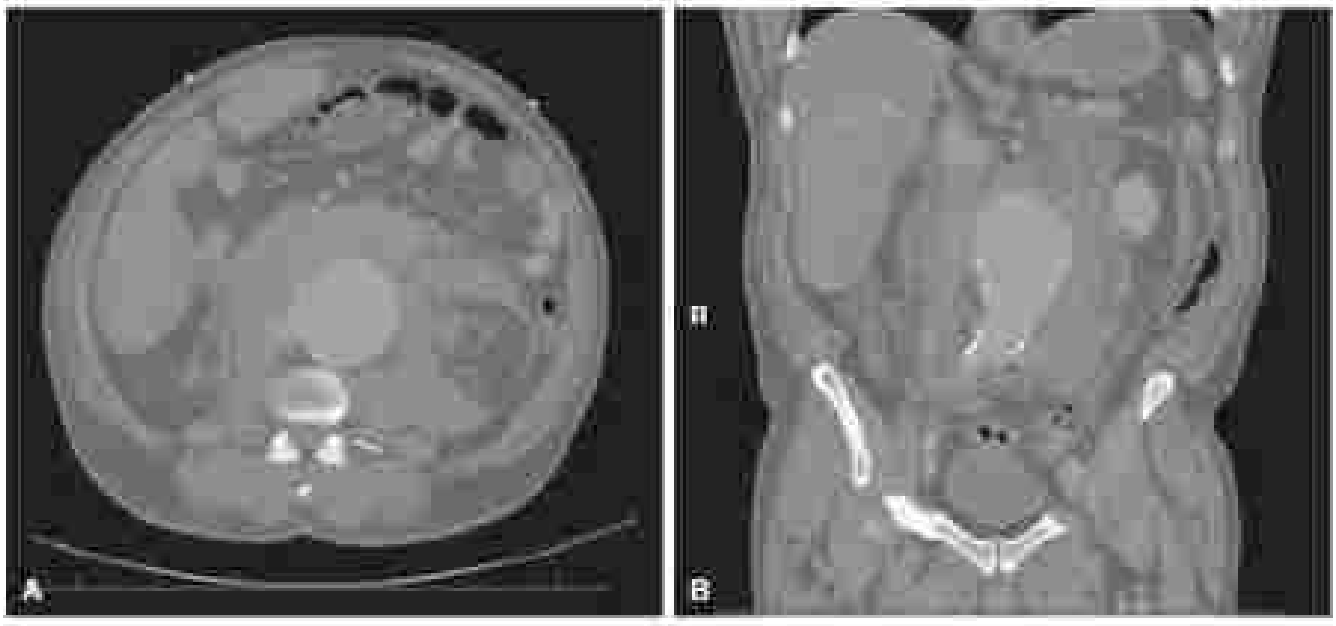

FIG. 1 (A) Transaxial imaging showing the large retroperitoneal hematoma (hematoma) draping over the vertebral body (B) Coronal image showing the extent of the hematoma

Unstable patients can be taken directly to the operating room. The concept of "hypotensive hemostasis" or permissive hypotension is contrary to the thought process of most physicians and health care employees, but the concept must be enforced to limit blood loss, rerupture, and further aortic tearing. On presentation, we are more concerned about end organ perfusion than strict blood pressure. If the patient is hemodynamically unstable with systolic pressures around 80 mm Hg, we complete the workup and preparations expeditiously on the way to the operating room. The endovascular first approach allows for aortic control with a percutaneously placed occlusion balloon in the descending thoracic aorta similar to the REBOA technique recently adopted in the trauma literature. The amenability to rEVAR is then based on the initial aortogram. If the anatomy is not amenable to endovascular repair, the endovascular aortic control proves to be invaluable as an "aortic cross clamp" similar to supraceliac aortic control or thoracic aortic control without the added morbidity of a thoracotomy. See Fig. 2 with an aortogram showing amenability to rEVAR with the aortic occlusion balloon inflated.

TECHNIQUE OF REPAIR

A multidisciplinary team consisting of vascular surgeons, anesthesiologist, emergency department physicians, radiology technicians, and operating room staff knowledgeable of endovascular techniques and a standardized protocol to the treatment are essential to the performance of the procedure and therefore survival of the patient. The operating room should be capable of both open and endovascular techniques. Over the past 40 years we have managed more than 1000 rAAA. We have evolved from initially performing them via the transabdominal approach to the open extended paramedian retroperitoneal approach as described by Mel Williams, and now to EVAR in more than 75% of the cases. As previously reported by Wanhainen et al, we have set up a network for transfer of aortic emergencies. In that article, we demonstrated that transfer was feasible and lowered mortality rates for rAAA. This corroborated other reports that show that low volume hospitals had a higher mortality rate even if the same board certified vascular surgeons performed the repair in the low volume hospitals. Most patients have had preoperative imaging and, if transferred from other hospitals, can have CT scan images transferred electronically well before the patient arrives at the aortic center. This provides the receiving institution the ability to assess the suitability for EVAR and prepare the hybrid room. If deemed unsuitable for EVAR, the staff can prepare for an open procedure. In those instances when the patient is unstable and no images are available, one has to approach the procedure in the way the surgeon and staff are most comfortable. Historically, 50% of intraoperative deaths were from venous injuries obtaining aortic control. Thus, as surgeons become less familiar with open aortic exposure, most feel more comfortable obtaining femoral access, placing an occlusion balloon, and then proceeding with either EVAR or open repair depending on the interpretation of the angiogram obtained after aortic occlusion. Remember that this has to be done quickly, and progress made without delay to definitive treatment, thus reinforcing the need for institutional and surgeon experience in rAAA.

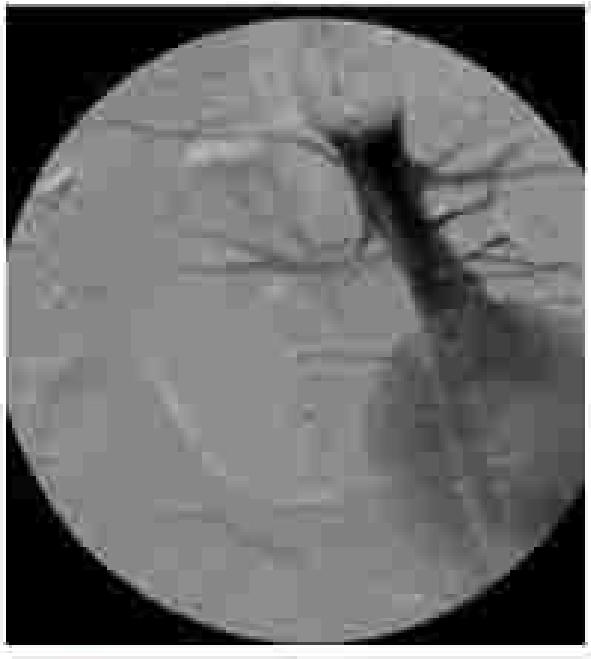

FIG. 2 Aortogram with aortic occlusion balloon inflated.

Technique of Repair: Endovascular Repair

The endovascular approach should have a variety of off the shelf devices with possible endograft already lined up in the room to allow for easy and rapid deployment. Adjuncts, such as sheaths, wires, and catheters, should be readily available, and an aortic occlusion balloon should be opened and on the operating room table. The contralateral setup for possible open repair must be in the actual operating room.

Local anesthesia should be used, as was shown with the mortality benefit from the IMPROVE trial. At minimum, the patient should be prepped and draped for rapid aortic occlusion balloon for control before induction of anesthesia. Percutaneous femoral access under ultrasound or fluoroscopic guidance is followed by the placement of a stiff wire into the descending thoracic aorta, closed with a 12Fr introducer sheath and an occlusion balloon. Place the supporting sheath as far as possible to prevent the distal migration of the aortic balloon when circulation is restored. In an unstable patient, there may not be time for placement of closure devices before sheath placement, and the femoral arteries can be exposed and primarily repaired at the end of the case. It is not uncommon for the access vessel anatomy to be challenging. The arteries can be navigated with a guidewire that is chased with a flush- or angle-tipped catheter and then exchanged for stiffer wire. The key is to get through the iliac arteries without creating a dissection flap or tearing the artery. The next step is creating a stable platform for sheath placement. A stiff wire can be used to straighten tortuous iliac arteries, which may need to be relined with covered stent grafts (crack and pave technique). This will allow the endograft to seal within the covered stent. Often access vessel injury is not identified until after the endograft is in place and the sheaths are being removed. If an injury occurs, the large sheath usually tears the external iliac artery off of the common iliac artery at the origin of hypogastric artery while going in but seals the defect when repositioned. The key is to maintain wire access so that an occlusion balloon can be placed while a stent graft is used to bridge the gap and seal the bleeding temporarily in preparation for a covered stent. The use of an exchange length wire such as Lunderquist wire (Cook Medical) is invaluable because it will support the balloon in the descending aorta and limit the need for wire exchanges.

Once the occlusion balloon is in the appropriate position, make sure the anesthesia team is aware to allow for aggressive resuscitation. Images can then be gathered to determine whether the AAA is amenable to rEVAR through contralateral groin access using percutaneous methods with a preclose technique. The contralateral access can be used for a second stiff wire and introduction of the stent graft main body. We have found that crossing of the limbs offers the best configuration for cannulation of the contralateral gate. Once the device is in the appropriate position, the occlusion balloon must be retracted into the sac to prevent impinging and entrapment with deployment of the main body. Anesthesia must be prepared to treat some degree of resultant hypotension. Communication is important during the conduct of the case to maximize outcomes. Two approaches exist with respect to deployment of the main body. One method is to fully deploy the main body and retract the occlusion balloon into the aortic neck from the main body side. A second option is to continue cannulating the gate and proceed in the traditional fashion. Gate cannulation is the most time consuming and in 10% will require greater than 30 minutes for cannulation. It is important to have a variety of

cadaveric shapes and tip conformation to assist with cannulation. If all else fails, the bifurcated device can be converted to aortomonoiliac configuration, with the contralateral common iliac artery then embolized and a cryogenic bypass performed.

Another important clinical issue is whether bifurcated or aortomonoiliac endografts are better. The ARAS randomized trial used only aortomonoiliac endovascular grafts with the advantage of an easy learning curve and rapid control of abdominal hemorrhage, but it added time for the femoral-femoral crossover and increased risk of infection. In the acute setting, aortomonoiliac grafts may require general anesthesia as do the bilateral groin cutdown and tunneling of the femoral-femoral crossover bypass.

Once the graft of choice is deployed and the proximal, distal and connecting segments are ballooned, a completion aortogram is performed. See Fig. 3, a final aortogram showing complete sealing. Specifically, attention must be paid to ensure that there are no type I endoleaks (leaks at the area of fixation of the graft). Other useful adjuncts such as aortic coils, staples, stented chimney grafts, or a giant Palmaz stent may be used for type Ia endoleaks. For type Ib endoleak, sacrificing the hypogastric artery may be necessary for cessation of a distal seal. As the technology improves, newer devices off the shelf, such as the branch and fenestrated devices, may offer more advanced options for repair. Conversion to open ranges from 1% to 2% in most series and also has a mortality disadvantage.

Technique of Repair: Open Repair

Open repair has the option of a transperitoneal (TP) versus retroperitoneal (RP) approach. The TP approach uses a generous midline incision from the xiphoid bone to the symphysis pubis. If the aortic occlusion balloon is not used, supraaortic control can be obtained rapidly by mobilizing the left lateral lobe of the liver and retracting it to the right. The gastrohepatic ligament is incised and placed under tension, retracting the stomach to the left and downward with care taken to protect the left gastric or a replaced left hepatic. The esophagus (identified with nasogastric or orogastric tube) is identified and retracted away to the left. The right crura that is in full view is then divided with electrocautery to expose the supraaortic aorta. Attention is then shifted to the distal control at the level of the common iliac arteries and the distinction of the type of repair necessary. The more expedient repair is preferred, even with extensive iliac disease. Once the supraaortic clamp is applied, expeditious efforts should be made to move the clamp distally to perfuse the viscera. The infrarenal aorta is exposed by retracting the transverse colon cephalad and sweeping the small bowel to the right. Incision of the peritoneum by release of the ligament of Treitz allows the mobilization of the duodenum to the right and the anterior wall surface of the aorta. In a ruptured state with a clamp in situ, this can be challenging and care is needed to prevent further injuries. The goal at this point is to locate the renal arteries and find a suitable clamping site. After proximal and distal control is established, the sac is opened and repair is conducted in the standard fashion. Aortic arterial fistula presents a challenge wherein the sac open is met with robust bleeding from the right side of the aneurysm sac. Large bites of a nonabsorbable suture from inside the aneurysm sac along with aggressive suctioning with sponge sticks applied proximal and distally to attempt control is the best strategy to offer a chance of survival in this situation.

The RP approach is feasible in the acute setting with a bump or small bag to allow the left chest to be elevated at 60 degrees with the pelvis at 45 degrees. It is the standard for the authors to manage ruptures in this fashion because we have performed more than 600 rAAA repairs using this technique. Incision is made from the margin of the rectus (mid distance between the pubis and umbilicus to the tenth intercostal space). Dissection is performed through the three muscle layers with gentle care taken to prevent entry into the peritoneum. As the retroperitoneum is entered, the hematoma has usually done the dissection for you, and the bowel and ureter are swept toward the right, and the kidney is retracted toward the left shoulder. The surgeon's left hand can be slipped into the lateral gutter as the kidney and peritoneum can be retracted medial and cephalad. When moving each hand along the diaphragm, one will encounter the left crus. This allows excellent digital control of the supraaortic aorta. Once digital control is obtained and the patient is stabilized, one can incise the left crus and place an aortic clamp supraaortic, above or below the renal arteries.

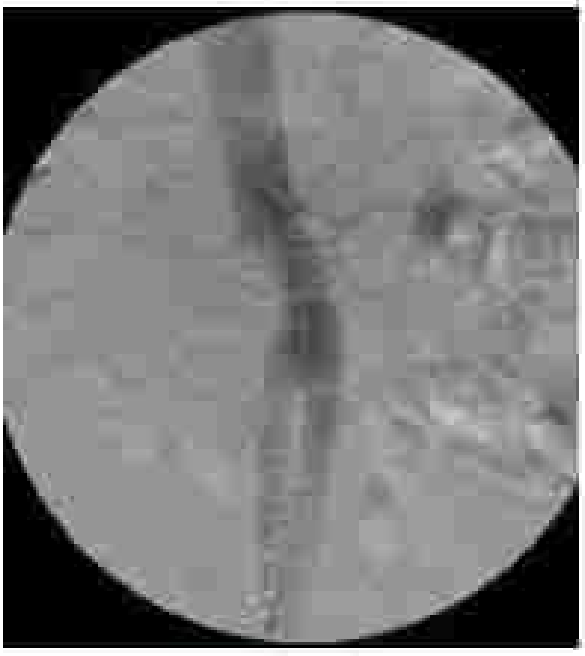

FIG. 3 Final aortogram.

COMPLICATIONS

Ruptured aneurysms exponentially inflate the rate of complications compared with elective aneurysm repair. Keen attention to details to minimize preventable measures while limiting obstacles as much as possible is the key to survival. The postoperative period poses a significant challenge. Complications can generally be divided into systemic or specific organ systems. The generalized state of shock impacts on the all the tissues and is the major obstacle of the postoperative period. Myocardial infarction is reported to be as high as 25%, respiratory failure 40%, acute renal failure 40%, and sepsis 15%.

Bowel ischemia or infarction, colitis increases fivefold after ruptured aneurysm surgery. The risk factor for this is in part due to age and coverage of the inferior mesenteric artery, which are not controllable risk factors. Systemic hypotension alone is enough to cause colonic ischemia, coupled with the occasional need for coverage of one or both internal iliac arteries. The watershed area of the inferior mesenteric artery (i.e., the sigmoid colon) is logically affected first. The impact of bowel ischemia not only adds to the morbidity of the disease, but significantly increases mortality rates. Bowel movements during surgery, or even in the immediate perioperative time, should raise suspicions for colonic ischemia. Additionally, worsening of pain, bloody bowel movements, or both are important symptoms. A rapid rise in white blood cell count after surgery should also increase suspicion. It is routine practice at many centers that all ruptured aneurysms undergo sigmoidoscopy within the first 24 hours after repair. This can be performed with a bowel preparation enema and bedside sigmoidoscopy. Treatment for colonic ischemia is based on the degree of ischemic colon. Mild ischemia is usually treated with intravenous antibiotics, bowel rest, and close monitoring. Severe forms of colonic ischemia need rapid bowel resections.

Abdominal compartment syndrome in rAAA ranges up to 20%. A large retroperitoneal hematoma presents a space-occupying lesion coupled with large fluid volumes for resuscitation, leading to intestinal edema with resultant increased pressure on the renal vein and inferior vena cava, subsequently impeding venous drainage leading to

renal dysfunction and hypovolemic shock. Pressure on the diaphragm reduces lung volumes. Massive transfusion, coagulopathy, and use of aortic occlusion balloons have all been linked to abdominal compartment syndrome. Open transperitoneal repair offers removal of a large portion of retroperitoneal hematoma, direct assessment of abdominal wall laxity, and the opportunity to leave the fascia open as damage control. The retroperitoneal approach is unique in that it must be closed primarily. In that situation, a transperitoneal laparotomy is necessary, leaving the fascia open. Usually this diagnosis is based on clinical suspicion, because overt signs of compartment syndrome signify a delayed diagnosis, which exponentially increases mortality risk. Adjuncts such as bladder pressure and peak airway pressure monitoring can be used to detect early rising toward compartment syndrome.

Access-related complications are frequent and mitigated with an armamentarium of endovascular and open techniques. Chronically occluded iliac arteries can be difficult to navigate, but the more worrisome and dreaded is the ruptured external iliac artery as the previously placed sheath, which tamponaded the tear, is removed from the patient. Having several sized covered stent grafts and maintaining wire access usually solves this issue. An occlusion balloon is inflated, followed by rapid deployment of a covered conduit, which can typically treat the tear. Thrombosis and acute occlusion of the stent graft limbs or native iliac arteries is not unusual. This is effectively treated by use of an embolectomy catheter after cutdown on the femoral artery or arteries or, in the worst case, by femorofemoral crossover bypass. Always be suspicious of a kinked or stenotic stent graft limb in acute occlusion. Distal ischemia from emboli is also treated with embolectomy in the standard fashion. The use of heparin is based on individual practice patterns. There exists a combination of practices, ranging from heparin after aortic control, to half dosing, to no anticoagulation due to the inherent hypercoagulable state induced by shock.

Acute renal failure may occur due to a combination of hypotension and any form of aortic clamping/manipulation. Additionally, the contrast agent used in rEVAR is additive to the renal impairment.

CONCLUSION

rAAA is one of the most devastating disorders treated by surgeons. Despite many advances in the field since the endovascular revolution, survival remains poor. Active screening programs, multidisciplinary aortic care centers, and smoking cessation programs have shown a reduction of the rupture repairs. Nevertheless, it must be entertained in the differential diagnosis with abdominal pain and considered in unusual presentations. Once a diagnosis is made, transfer the patient to a center equipped to care for acute aortic emergence with capabilities for rapid delivery of endovascular and open repair. These centers must have specialized capabilities to handle the complications to enhance the possible outcomes.

Suggested Readings

Hinchliffe R, Kolvekar H, Kalodiki S, Brady M, Cleary P, et al. Editor's choice: UCAN (Endovascular or Chirurgie dans les Anévrysmes aortiques Rompus) a french randomized controlled trial of endovascular versus open surgical repair of ruptured aorta iliac aneurysms. Eur J Vasc Endovasc Surg. 2013;45(6):563–569.

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Abdominal Aortic Aneurysm and Unexpected Abdominal Pathology

Aarona M. P[illegible], D, and Natal a "Ra [illegible] a, , D, ,h D

Abdominal aortic aneurysm (AAA) is a typically asymptomatic condition with potentially life-threatening complications if ruptured. The management of ruptured AAAs is an emergent setting is well understood, but the management of concomitant intraabdominal pathologies at the time of elective aneurysm surgery, a rarely encountered situation, is less well documented. Although endovascular aneurysm repair (EVAR) or retroperitoneal open approaches may be encouraged with concomitant intraabdominal pathology, these may not always be possible. This chapter aims to organize the two pathologies along two axes of decision-making, based on these axes, we propose management recommendations and raise questions that warrant further inquiry.

GENERAL MANAGEMENT OF AAA AND CONCOMITANT PATHOLOGY

We believe that AAA management with concomitant pathology should be organized along two axes. The first axis concerns whether the AAA repair is emergent. Along these lines, the concomitant pathology should be evaluated. Is it emergent, urgent, or nonurgent? This helps to clearly delineate the prioritization of pathologies present and direct management of each. The second important axis of management concerns the degree of contamination involved with the concomitant pathology organ system. For instance, biopsy of a retroperitoneal lesion may be considered a sterile concomitant procedure, whereas biopsy of an intestinal lesion would expose an aortic graft to contaminated flora.

EMERGENT AAA REPAIR AND COEXISTING PATHOLOGY

If emergent AAA repair is being attempted and resources allow for an endovascular repair, this should be attempted; however, certain

renal dysfunction and hypovolemic shock. Pressure on the diaphragm reduces lung volumes. Massive transfusion, coagulopathy, and use of aortic occlusion balloons have all been linked to abdominal compartment syndrome. Open transperitoneal repair offers removal of a large portion of retroperitoneal hematoma, direct assessment of abdominal wall laxity, and the opportunity to leave the fascia open as damage control. The retroperitoneal approach is unique in that it must be closed primarily. In that situation, a transperitoneal laparotomy is necessary, leaving the fascia open. Usually this diagnosis is based on clinical suspicion, because overt signs of compartment syndrome signify a delayed diagnosis, which exponentially increases mortality risk. Adjuncts such as bladder pressure and peak airway pressure monitoring can be used to detect the early trending toward compartment syndrome.

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Abdominal Aortic Aneurysm and Unexpected Abdominal Pathology

Aarona M. Ali, MD, and Natalia Glebova, MD, PhD

Abdominal aortic aneurysm (AAA) is a typically asymptomatic condition with potentially life-threatening complications if ruptured. The management of ruptured AAAs is an emergent setting is well understood, but the management of concomitant intraabdominal pathologies at the time of elective aneurysm surgery, a rarely encountered situation, is less well documented. Although endovascular aneurysm repair (EVAR) or retroperitoneal open approaches may be encouraged with concomitant intraabdominal pathology, these may not always be possible. This chapter aims to organize the two pathologies along two axes of decision-making, based on these axes, we propose management recommendations and raise questions that warrant further inquiry.

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EMERGENT AAA REPAIR AND COEXISTING PATHOLOGY

If emergent AAA repair is being attempted and resources allow for an endovascular repair, this should be attempted; however, certain

aneurysm anatomy require open repair. In this circumstance, the following pathologies are explored.

EMERGENT COEXISTING INTRAABDOMINAL PATHOLOGY

Appendicitis

Acute appendicitis is considered an intraabdominal general surgical emergency. Although data regarding the use of antibiotics alone for treatment are controversial, especially in the setting of an appendicolith, there have been reports of post-EVAR appendiceal rupture causing erosion into aorta, endograft, and subsequent life-threatening infections. The potential risk of appendiceal rupture in acute non-perforated appendicitis, with subsequent intraperitoneal contamination and biofilm creation, in our opinion warrants concomitant laparoscopic appendectomy or open appendicectomy with meticulous attempts at control of intraperitoneal contamination. Stenting the AAA Dacron graft in rifampin should be considered. Additionally, closure of the aortic sac and retroperitoneum over the graft should be performed. Irrigation of any pus should be avoided because it may spread the contamination.

Ruptured Tubo-ovarian Abscess

Ruptured tubo-ovarian abscess can be a true emergency. Contamination may involve the entire pelvis and bilateral lower abdominal quadrants. This may present problems especially regarding the distal limbs of a tube graft placed for an emergent AAA repair. Once again, consideration for EVAR or retroperitoneal AAA repair should be given if possible. Frequently, a laparotomy for emergent AAA repair is performed and thus the previously mentioned alternatives are not possible. Laparoscopic suction, consideration of a pelvic drain, long-term antibiotics, and meticulous graft coverage should be undertaken. Though this circumstance has been reported rarely, it is even more uncommon than appendicitis given that it generally occurs in women of childbearing age, and ruptured AAA is more likely to present in an older population.

URGENT COEXISTING INTRA-ABDOMINAL PATHOLOGY

Cholecystitis

Although cholecystitis is not generally considered an emergency, it is a surgical urgency and can lead to gangrene or perforation, sepsis, or cholangitis if left untreated, especially in the diabetic population. The earliest signs of an infection should be investigated and antibiotics started to cover gram-negative flora; in addition, antibiotics such as a cholecystostomy tube should be considered in the immediate postoperative circumstance of cholecystitis arising after an open AAA repair. If cholecystitis is present at the time of open AAA repair, a large series of more than 600 patients from the Veterans Affairs experience has demonstrated that concomitant repair can be fraught with more complications than staged repair, and the authors recommended staged repair. In a much smaller series of mixed abdominal pathology including symptomatic cholelithiasis with AAA repair, the authors described concomitant repair with the cholecystectomy performed after the AAA repair had been done and the retroperitoneum closed tightly, with no subsequent complications. However, an argument may be made about bacterial contamination to acute cholecystitis that may preclude concomitant surgery if a cholecystostomy tube is possible.

Pancreatitis

Coexisting pancreatitis is rare, but clearly poses a dilemma because it can be both a peritoneal and retroperitoneal process causing significant inflammation, with the potential for pancreatic necrosis, further infection, and making dissection around the mesenteric plate difficult. As far as we know, there have been no reports of AAA repair with concomitant pancreatitis, but coexisting pathology would certainly make the operation more difficult and, if possible, endovascular repair should be attempted.

NONURGENT COEXISTING INTRA-ABDOMINAL PATHOLOGY

Diverticular Disease

Though there is a paucity of evidence-based support, we advise against resection of an incidentally found Meckel's diverticulum. An elective bowel operation should be avoided if possible in the face of an open AAA repair because of contamination; however, large bowel symptomatic diverticulitis is a different pathology. In one study, a combined retroperitoneal approach for AAA repair and laparotomy for diverticular disease was not associated with increased mortality nor did it increase incisional hernias. Moreover, in symptomatic disease, staging a colectomy and open AAA repair did not appear to increase aneurysm-related mortality. Notably, two colonic anastomotic leaks were managed nonoperatively in this study with paracutaneous drains, with no graft infection noted; however, the risks of possible graft infection should be seriously considered, with a low threshold for extraanatomic bypass because infected graft erosion and subsequent herald bleeds or rupture can be catastrophic.

URGENT AAA REPAIR AND URGENT/EMERGENT CONCOMITANT PATHOLOGY

Appendicitis

Although unusual, reports of a large symptomatic AAA causing acute back pain with concomitant appendicitis have been case described. In this case, the authors proceeded with appendicectomy followed by a second-stage AAA repair. We agree with the initial management of appendicitis, but intraoperative vascular surgical consultation for consideration of concomitant EVAR or retroperitoneal repair may be warranted because of evidence in the surgical literature of laparotomy-associated AAA rupture. The hemodynamic changes associated with sepsis from a coexisting intraabdominal pathology, which are usually supplemented with large volume resuscitation per most sepsis protocols, can lead to increased intraluminal pressure precipitating AAA rupture and has even been reported in elective colectomies. Although it may seem reasonable to undertake robotic or laparoscopic colectomy in this circumstance to prevent gross contamination and avoid violation of fascial planes, any prolonged anesthetic times associated with hemodynamic instability should be avoided with large AAA.

Colitis

Infectious colitis at the time of concomitant urgent AAA repair should be addressed. Although most diverticulitis will respond to antibiotic therapy, Hinchey III or IV diverticulitis should be expeditiously washed out, drains placed to discourage erosion and abscess formation around aortic grafts, and stentification should be given to an ostomy to prevent anastomotic leak associated complications, which would then be a significant threat to the aortic graft.

ASSOCIATION OF CONCOMITANT CONDITIONS

Inflammatory Bowel Disease

Lately, a link between Lynch/Peto syndrome and ulcerative colitis has been proposed; what has been known for some time is that up to one half of these patients do have associated colitis and inflammatory bowel disease manifestations. The idea that these patients could present a scenario with both pathologies in active disease state is not impossible, although the disease itself is rare. If there is no clinical suspicion for active infectious colitis, however, the colitis should be left for medical management and the vascular pathology should be addressed

to a prioritized fashion if the AAA meets size criteria for repair or is causing symptoms. Additionally, there is some evidence that a retroperitoneal approach to open AAA repair may be associated with less inflammatory markers and an earlier resolution to inflammation postoperatively. These data suggest that if there is known concomitant inflammatory bowel disease, preferential consideration should be given to retroperitoneal AAA repair over transperitoneal approach.

NONEMERGENT AAA REPAIR AND CONCOMITANT NONEMERGENT DISEASE

Colorectal Cancer and AAA

Multiple studies have examined concomitant management versus staged management of AAA and colorectal adenocarcinoma. A meta-analysis pooling several studies examined concomitant open AAA repair (or EVAR) with colectomy versus staged repair. Except for a few patients (n < 5) with graft-related complications (thrombosis) associated with EVAR, the long-term outcomes favored EVAR over open AAA repair. Only one graft infection was reported in more than 200 cases; most deaths were attributable to either cancer or cardiac complications and no deaths were attributed to aneurysm rehabilitation. This is a change from the traditional findings in the 1980s regarding risk of rupture of larger AAA after unrelated laparotomy for elective colorectal cases. This improvement in outcomes may be attributable to improved anesthesia, better understanding of hemodynamics associated with AAA, or shorter operative times for colorectal cases. It is important to be aware of the complication of sigmoid ischemia after EVAR following a prior colectomy resulting in inferior mesenteric artery coverage, and the dangers it could pose to a colorectal anastomosis.

Renal Neoplasm and AAA

Although renal neoplasms are not a type of malignancy that general surgeons routinely treat, the concomitant renal mass found during an elective, urgent, or emergent AAA repair poses questions regarding the prognosis, renal ischemia regarding juxtarenal repair, tumor staging, and the safety of any biopsies in case of a renal or perinephric mass that is suspicious. The largest series to date examining the question examined 27 patients undergoing either simultaneous or staged repair and found that the group undergoing simultaneous repair had better long-term survival. A smaller series concurred with this result, but also observed that concomitant open AAA repair and radical nephrectomy was associated with higher postoperative acute kidney injury, although it appeared to resolve without any long-term affect on renal function.

Other Solid Organ Systems and AAA

Other solid organ tumors such as gastric cancer, liver tumors, and peritoneal implants have been rarely described, but there is no clear precedent for their management with concomitant incidental AAA. The considerations once again center around the emergency or urgency of associated pathology, and the more life threatening of the two should take priority. Another important consideration, however, is regarding contamination. Most genitourinary masses or other solid organ masses can at least be safely biopsied since these systems are normally sterile by nature; gastrointestinal masses should not be routinely biopsied due to contamination risk. Additionally, in any situation of elective AAA repair and incidental intraabdominal pathology, consideration should be given to the benefit of AAA repair (namely, prevention of rupture and mortality) in the setting of a possible malignancy that may be the rate-limiting condition affecting the patient's life span. If obvious metastatic cancer is present during laparotomy for AAA repair, one should consider aborting the repair as its benefit for the patient's life span may not outweigh the risks of the operation.

CONTAMINATION AND ITS EFFECT ON INTRAOPERATIVE DECISIONS

An interesting question arises regarding existing stomas during open AAA repair. Historically, large bowel and even urinary stomas were considered a contraindication to elective open AAA repair. However, open transperitoneal AAA repair in presence of permanent ostomies has been described, without any graft infection or adverse outcomes on long-term follow-up. We encourage proceeding with the operation if necessary, especially with long-standing stomas that have not had any associated hernias, infection, or uncontrolled output. If open AAA repair is indicated, retroperitoneal approach should be considered to avoid the stoma if possible.

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Management of Descending Thoracic and Thoracoabdominal Aortic Aneurysms

Roland Assi, MD, MHS, Toby Steinberg, MD, and Prashanth Vallabhajosyula, MD, MS

Descending thoracic aortic aneurysms (DTAAs) involve the thoracic aorta from the left subclavian artery (LSA) to the diaphragmatic hiatus. Thoracoabdominal aortic aneurysms (TAAAs) involve varying lengths of both the descending thoracic and the abdominal aorta. It is not uncommon for these aneurysms to be associated with aneurysms of the aortic root, ascending aorta, and aortic arch. The management of DTAA and TAAA is rather complex and historically has been plagued by significant morbidity and mortality. This has improved with better understanding of the disease natural history, improved technical skills and available technology, and the use of organ protection methods.

INDICATIONS FOR SURGERY

Different disease processes can lead to DTAAs and TAAAs. Atherosclerotic disease is the hallmark of the aneurysms of the abdominal aorta, whereas aortic dissection, degenerative disease, connective tissue disorders, inflammatory disease, and trauma are more commonly involved in thoracic aortic aneurysms. Clinical presentation is also variable, ranging from incidental findings on cross-sectional imaging

to a prioritized fashion if the AAA meets size criteria for repair or is causing symptoms. Additionally, there is some evidence that a retroperitoneal approach to open AAA repair may be associated with less inflammatory markers and an earlier resolution to inflammation postoperatively. These data suggest that if there is known concomitant inflammatory bowel disease, preferential consideration should be given to retroperitoneal AAA repair over transperitoneal approach.

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for other reasons, to compressive syndromes causing pain or obstruction, to embolization, and, not uncommonly, rupture.

The most common indication for surgery is the absolute size of the aneurysm or the growth rate per 6 months or 1 year. In general, aneurysms larger than 6 cm should be repaired as long as the operative risk is not prohibitive. In patients with connective tissue disorders or chronic dissections, it is reasonable to intervene at 5 or 5.5 cm. A growth rate more than 5 mm per 6 months or 10 mm per year is also considered an indication for repair. The patient's age, comorbidities, and symptoms should be taken into consideration. In particular, we tend to intervene at an earlier stage in patients with pain or compressive syndromes, women more urgently, and in patients with family history of aneurysm rupture.

PREOPERATIVE CONSIDERATIONS

Anatomy

Knowledge of the anatomy of the entire aorta and major branches is critical for surgical planning. This is best done using high resolution computed tomography angiography with three-dimensional reconstruction. The anatomy of the aneurysm will dictate the extent of the repair and the extent of the operative risk. The Crawford classification remains the most commonly used for these purposes (Fig. 1). In addition, exact knowledge of the aortic anatomy is critical for the use of endovascular stent grafts. This includes identification of proximal and distal landing zones, the degree of tortuosity, and the use of access vessels.

Risk Assessment

A comprehensive workup is mandatory to evaluate the physiologic reserve. All patients undergo cardiac echocardiography and exercise testing. This is crucial because of the significant hemodynamic stresses and fluctuations that result from repeated aortic clamping and blood loss intraoperatively. Cases requiring circulatory arrest mandate knowledge of the left ventricular and aortic valve function. Those patients with abnormal tests undergo left and right heart catheterization. Pulmonary function testing is used to determine whether single lung ventilation would be tolerated and to identify the presence of chronic lung disease, which is associated with significant perioperative morbidity. Smoking cessation is mandatory for at least 6 to 8 weeks preoperatively to optimize pulmonary function and clearance. Renal function is evaluated with a baseline serum creatinine level. An elevated creatinine level should be investigated, and any systemic vascular causes should be intervened on. Preoperative chronic kidney disease is a factor for postoperative acute renal failure, and dialysis imposes a significant increase in operative mortality and might constitute a relative contraindication to elective TAAA repair. Frailty in elderly patients is an important risk factor for poor outcomes; in general, patients older than 75 years with poor functional status should not be offered open surgery.

OPERATIVE STRATEGY

Anesthesia

General endotracheal anesthesia is used in all patients. Double lumen intubation used to allow for single lung ventilation, which is required in the majority of cases. A right jugular venous sheath is inserted and a pulmonary artery catheter is placed. Unless there is an anatomic esophagogastric contraindication, a transesophageal echocardiography (TEE) probe is placed and continuous imaging is used throughout the case. The information gathered from the pulmonary artery catheter and the TEE is highly valuable in the hemodynamic management intraoperatively. A urinary catheter with temperature probe is used for the monitoring of urine output and core temperature. Right radial and left femoral arterial lines are placed and allow for monitoring of blood pressure to the brain and to the lower body, respectively. In patients requiring cardiopulmonary bypass via left thoracotomy cannulation, a right femoral arterial line is mandatory. Prophylactic antibiotics are administered and redosed as indicated.

Neurologic Monitoring

Near infrared spectroscopy, somatosensory evoked potentials (SSEPs), and motor evoked potentials (MEPs) are used for neurologic monitoring. Near infrared spectroscopy is useful for monitoring brain oxygen consumption, particularly in extent 1, in which the distal aortic arch is clamped or when circulatory arrest is used. When circulatory arrest is planned, electroencephalogram leads are placed for monitoring. SSEPs and MEPs are very sensitive in detecting spinal cord injury, but MEPs alter the anesthetic management but may be more sensitive for spinal cord injury detection than SSEP. A lumbar drain is placed in all cases in which a significant portion of the thoracoabdominal aorta is replaced (i.e., extents I, II, III, and V) because it has been shown that lowering cerebrospinal fluid (CSF) pressure is the most important intervention to prevent spinal cord injury (SCI). Other factors to consider to decrease risk of SCI include maintaining a high perfusion pressure (mean arterial pressure [MAP] >80 mm Hg), a patent LSA, short

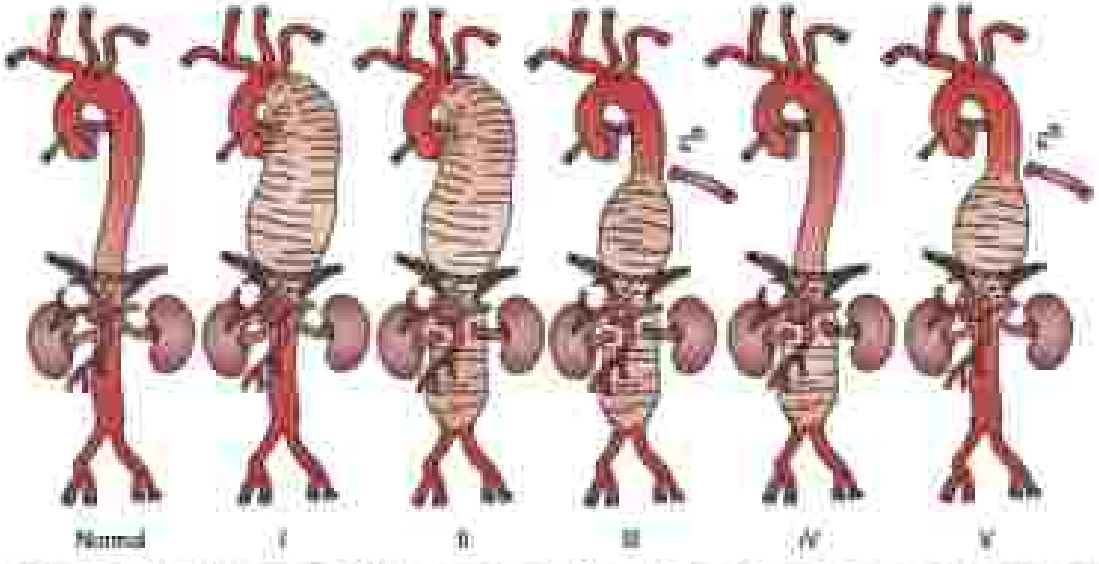

FIG. 1 Crawford classification of thoracoabdominal aortic aneurysms. Type I: distal from origin of left subclavian artery to above renal arteries. Type II: distal from the left subclavian artery to the infrarenal aorta. Type III: from the sixth intercostal space to the infrarenal aorta. Type IV: from the 12th intercostal space to the aortic bifurcation. Type V: below the sixth intercostal space to the renal arteries. (From Cronenwett JT, Johnston [illegible]. Rutherford's Vascular Surgery. 7th ed. Philadelphia: Saunders; 2007. Fig. 120.8.)

cross-clamp time, patent internal iliac arteries, and reimplantation of large intercostals with no back bleeding.

Positioning, Incision, and Exposure

The patient is positioned in a right lateral decubitus position over a beanbag with careful padding of all pressure points. The left arm is supported over an arm rest and the hips are rotated slightly to the left to allow for left groin access. The table is flexed at the hips about 40 to 45 degrees, allowing for complete exposure of the left chest and flank. The skin is prepped from the base of the skull to the mid thighs, from the spine to the sternum and from the spine to the right of the umbilicus (Fig. 2).

For DTAAs, a fourth intercostal space thoracotomy is used and allows an excellent exposure of the distal aortic arch. The fifth intercostal space is used for TAAAs extent I or II, and sixth or seventh intercostal spaces are used for extent III/IV (Fig. 2). The incision can be extended posteriorly and superiorly to improve exposure of the proximal descending thoracic aorta. In addition, the posterior ribs at the level of the incision are notched, which improves exposure significantly. The incision is then extended to the abdomen in a left paramedian fashion and the retroperitoneal space is exposed, avoiding violation of the peritoneum (Fig. 3). In retracting the peritoneal contents, extreme caution must be taken to avoid recoil or overt splenic injury.

In the chest, the left lung is isolated and the inferior pulmonary ligament is divided up to the level of the left inferior pulmonary vein. The lung is then retracted medially and anteriorly, allowing for excellent exposure of the thoracic aorta (Fig. 4). It is not uncommon to encounter some adhesions between the lung and the aorta or the chest wall; this is reflective of the inflammatory nature of the aortic disease. During dissection of the lung tissue off the aorta, care must be taken to visualize and preserve the vagus nerve that runs posteriorly to the pulmonary hilum, the phrenic nerve that runs anteriorly to the pulmonary hilum, and the left recurrent laryngeal nerve that drapes around the isthmus and is usually concealed by lymphatic tissue. It can usually be bluntly dissected and gently pushed out of the way to the right to allow aortic cross clamping or anastomosis. The diaphragm is divided circularly off the chest wall leaving a 3- to 4-cm rim to allow for reapproximation at the end. We typically place sutures of alternating color on either side of the diaphragm to help approximation during closure. The left crus of the diaphragm is then bluntly divided, exposing the aorta. In the abdomen, the incision is extended along a left paramedian line and the peritoneum is swept to the right, exposing the left psoas muscle and the left iliac artery. A table-mounted retractor system is deployed, allowing a complete exposure of the thoracoabdominal aorta as dictated by aneurysm anatomy.

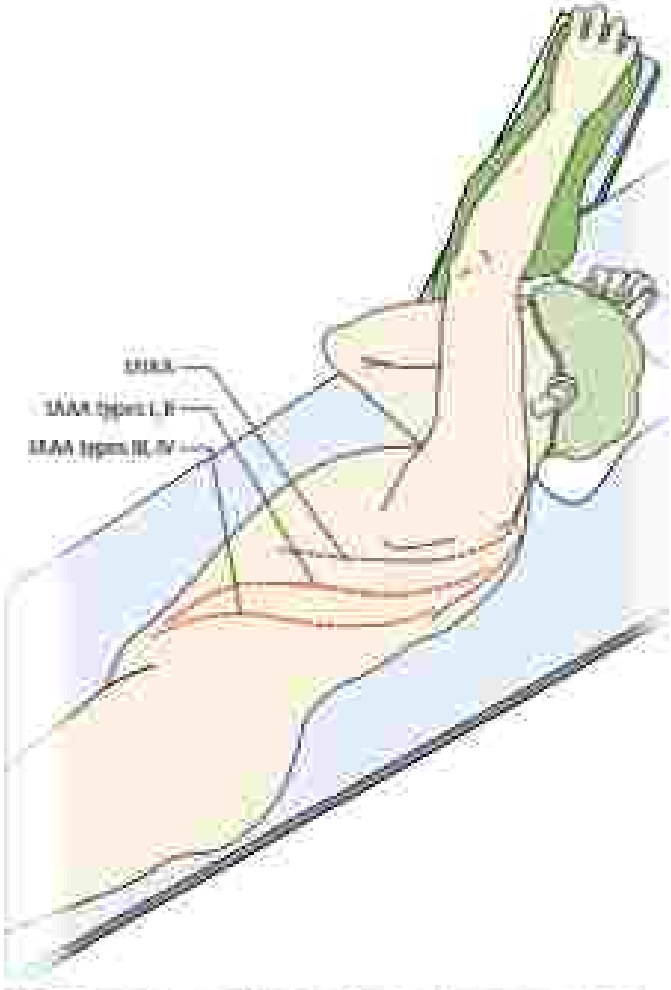

FIG. 2 Patient positioning in the right lateral decubitus position with hip rotation to the left to facilitate access to the femoral vessels. The level of the skin incision varies with the extent type of the aneurysm. DTA, Descending thoracic aortic aneurysm; TAA, thoracoabdominal aortic aneurysm.

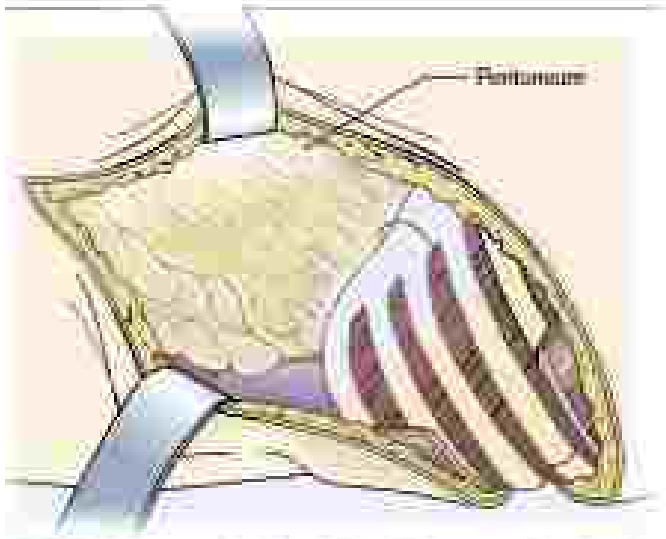

FIG. 3 Surgical exposure. Division of the cartilaginous costal margin and notching of the posterior aspect of the exposed ribs improve surgical exposure. Chest tube was removed during the peritoneal entry.

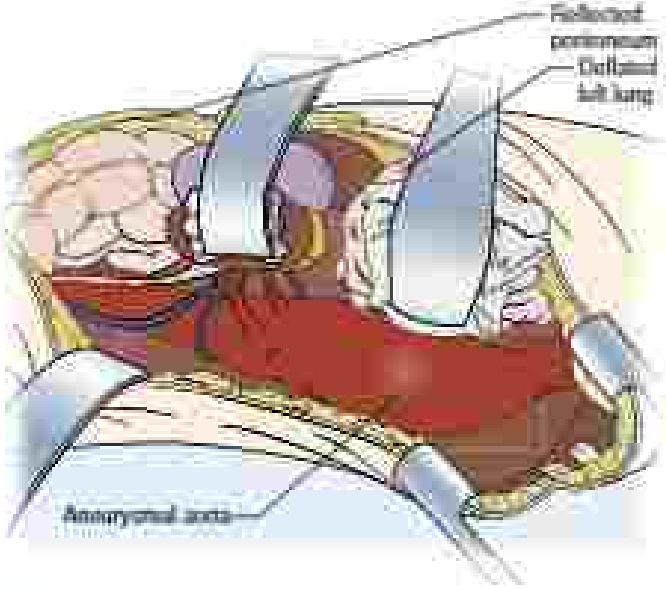

FIG. 4 Exposure of the aorta. The peritoneum is reflected medially to expose the abdominal aorta. The left lung is deflated to allow complete mobilization of the left lung.

P ...f ... Strategy

...

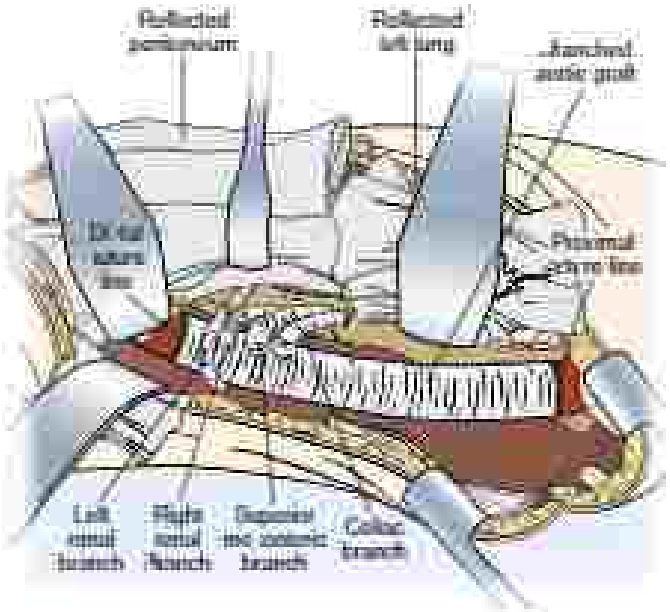

FIG. 1. ...

Organ Protection Strategy

During cross-clamp and visceral ischemic time, the renal, celiac, and superior mesenteric arteries are selectively cannulated with flexible balloon tip cannulas and perfused with cold blood at 8°C, but other groups have shown excellent results with cold crystalloid perfusate to the renal arteries. We usually ligate the inferior mesenteric artery.

For spinal cord protection, ischemic time is minimized as much as possible, MAP to the spine is maintained at 70 mm Hg or higher, SCP is drained to maintain a pressure of 8 to 10 mm Hg, hemoglobin is maintained at a physiologic level, and intercostal arteries are selectively reimplanted. It is our practice to reimplant only large intercostals that do not backbleed when the aorta is open. Other intercostals with good backbleeding are ligated to achieve hemostasis and prevent shunting of the spinal blood away from the spinal cord.

...hoice of Grafts and Technical Aspects

We use Dacron grafts that are sized based on the preoperative imaging and intraoperative findings. Graft diameters will fall between 28 and 32 mm for the thoracic aorta. For the abdominal aorta, we most commonly use 24-mm multibranched Dacron grafts. For reimplantation of the visceral vessels in extent type I, the distal aspect of the graft is beveled to create a patch that includes the celiac, SMA, and renal arteries. For extents II, III, IV, and V, we prefer to use branched aortic grafts instead of reimplantation in a patch configuration. This allows for complete resection of all aortic tissue around the visceral ostia and eliminates the risk of enlargement of residual aortic tissue. In many instances in which there is significant size discrepancy between the proximal and distal aorta, and when bifurcated grafts to the iliac arteries are used, we prefer to use separate grafts for the proximal and distal anastomosis. A graft to graft anastomosis is then completed after tailoring of the length and lay of the grafts. Aortic anastomoses are usually completed with 3-0 polypropylene and visceral branches with 4-0 or 5-0 polypropylene, depending on the vessel size and quality.

Closure and Transition to the Intensive Care Unit

After all reconstruction is completed, heparin is reversed with protamine, meticulous hemostasis is achieved, the surgical field is copiously

tonguard, and the peritoneal cavity is allowed to rest back in position with careful attention to [illegible]

[illegible]

[illegible]

ENDOVASCULAR REPAIR

[illegible] ... SSEP and/or MEP monitoring ... [illegible]

[illegible]

circumferential calcifications, usually accommodates most device sheaths. Rarely, when femoral access is not adequate, iliac or distal aortic access can be achieved through a retroperitoneal incision. An aortogram is performed and measurements are confirmed against the preoperative computed tomography scan. For aneurysms, we use covered stents with 10% to 20% oversizing at the landing zones. For chronic dissecting aneurysms, we aim to cover the whole length of the DTA from the LSA to just above the celiac artery. This extent of coverage is associated with the best chances of aortic remodeling and obliteration of the false lumen. Besides anatomic considerations (access, tortuosity, length of landing zones), we avoid endovascular repair in patients with connective tissue disorders unless the landing zones are in graft material or as part of a staged hybrid procedure.

For TAAAs, we reserve endovascular repair for patients who have a prohibitive open surgical risk or as part of a hybrid staged procedure. Access to the visceral arteries is obtained through a sheath placed in the left brachial artery. Multiple variations in techniques and devices are available, but in general fenestrated grafts, snorkel, chimney and "sandwich" TEVAR techniques are used. Currently, clinical trials are under way for the use of endovascular branched stent grafts.

OUTCOMES

Risk factors for poor outcomes include advanced age, acute aortic syndrome, extensive repair, and history of stroke, cardiac, or pulmonary diseases. The expected operative mortality for DTAAs and TAAAs in experienced centers ranges between 2% and 10%, renal failure in 3% and 8%, and paraplegia in 1% and 8%. These numbers vary significantly depending on the extent of the repair, with extents II and III being the most morbid. Although in general the stroke risk is low, it has been reported around 2%, but up to 7% when circulatory arrest for arch reconstruction is used. Pulmonary complications remain the most common operative morbidity (up to 50% of patients) related to single volume ventilation, the retraction of a heparinized lung, the long duration of the surgery and mechanical ventilation, and adult respiratory distress-like syndrome related to acute blood loss, massive transfusion, fluid shifts, and ischemic and hypothermic injuries.

TEVAR for DTAAs is associated with significantly better operative mortality and adverse outcomes including SCI when compared with open repair at the cost of increased secondary reintervention rates to seal endoleaks.

Paraplegia resulting from SCI is probably the most devastating complication specific to aortic repair. Risk factors for SCI include advanced age, renal dysfunction, emergency surgery, aortic dissection or rupture, prior abdominal surgery, occluded internal iliac arteries, and the extent of repair. Many strategies have been proposed to mitigate this risk, including routine reimplantation of the intercostal arteries and intrathecal infusion of cold perfusate, but the most significant intervention to date remains the insertion of lumbar drain for CSF drainage, which we use on all DTAA and TAAA repairs. CSF drainage can also be used as a salvage strategy for patients who develop signs of SCI in the perioperative setting.

SUGGESTED READINGS

[illegible]

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Management of Acute Aortic Dissection

Robert J. Bu[illegible] M.D., M[illegible] H. [illegible] M.D., F.A.C.C.

Acute aortic dissection is a distinct entity within the group of aortic pathologies known as acute aortic syndromes. It represents a true medical emergency that should prompt the early involvement of the surgical team. Its incidence is estimated to account for 400... to 1000... hospital admissions within the United States annually, though this likely is an underrepresentation that does not account for aortic dissection causing death before reaching the hospital. Because of its varied presentations and potential for rapid clinical deterioration, early diagnosis and treatment requires a high index of suspicion and a thorough understanding of pathophysiology and associated treatments. Even with this, aortic dissection can prove a challenging clinical entity even to practiced physicians. As Sir William Osler quipped, no disease is more "conducive to clinical humility."

PATHOPHYSIOLOGY AND RISK FACTORS

Aortic dissection results from a tear in the intimal layer of the aortic wall. Following this disruption, blood will quickly infiltrate the layer between the intima and the media, resulting in a "false lumen." It is the extent of this false lumen, including initial location within the ascending or descending aorta, direction of propagation (retrograde or antegrade), and involvement of branch vessels, that will ultimately determine the clinical manifestations of aortic dissection. The causative event resulting in the initial tear that initiates the aortic dissection pathway is an area of ongoing research, but likely represents a mechanical failure in a diseased aorta. This hypothesis is supported by biomechanical testing demonstrating that the intima of normal aortas is able to tolerate pressures well beyond those experienced physiologically. As such, an understanding of the risk factors that may precondition an aorta to dissection warrant discussion.

Hypertension is present in over two-thirds of all patients with acute aortic dissection. The effect of hypertension is twofold. First, the increased wall shear stress caused by increased systolic blood pressure directly increases the mechanical stress on the intima. Additionally, aortic ectasia or aneurysm results in medial thinning and increased risk of dissection, and hypertension is a risk factor for both these conditions. Smoking, dyslipidemia, and drug (crack, cocaine or amphetamine) use are among the highly prevalent modifiable risk factors for patients with aortic dissection. Genetic risk factors, including mutations in genes controlling connective tissue expression such as *FBN1* (Marfan syndrome), *TGFBR1/2* (Loeys-Dietz syndrome), *COL3A1* (Ehlers-Danlos vascular type IV), and *MYH11* or *ACTA2* (familial thoracic aortic aneurysm syndrome), result in increased risk of aortic dissection. Further, a family history of aortic dissection, even without an identifiable genetic predisposition, places a patient at increased risk.

PRESENTATION AND DIAGNOSIS

The diagnosis of aortic dissection relies on a high index of clinical suspicion early in the patient's clinical presentation. Symptoms are often vague and varied, and the historical symptom of "tearing" chest pain is present in less than 50% of individuals with aortic dissection. The consequences of an aortic dissection in the ascending aorta include acute myocardial infarction, cardiac tamponade, and hemothorax rupture, with associated mortality of 1% per hour. Dissections in the descending aorta can be more extensive and therefore affect nearly any body system through disruption of the arterial blood supply. These so called "malperfusion" symptoms can include acute mesenteric ischemia, stroke, acute renal failure, and acute limb (both upper and lower) ischemia. Especially in the case of limb ischemia, absence of pulses or pulse deficits can help raise the suspicion of dissection. Therefore, the diagnosis of aortic dissection should be considered in any patients with a history of hypertension presenting with these symptoms.

Risk score calculators help to delineate important elements of the clinical presentation that can aid in the rapid diagnosis. In 2010, the American Heart Association/American College of Cardiology (AHA/ACC) released guidelines for the diagnosis of acute aortic dissection, outlining a three point scoring system, which has subsequently been validated, to assess the risk of aortic dissection. Within the Aortic Dissection Detection (ADD) risk calculation, there are three categories, for which the presence of any factor within a category earns the patient a point. These categories include high-risk predisposing conditions, high-risk pain features and high-risk clinical manifestations (including pulse deficit and systolic blood pressure differential). The ADD risk score has sensitivity rates up to 97.7% and has been recently coupled with a D-dimer test to effectively rule out patients who do not have aortic dissection.

In patients with ADD risk scores of 2 to 3, expedited aortic imaging is warranted with transesophageal echocardiography, computed tomographic angiography (CTA) and or magnetic resonance angiography (MRA). Among these, CTA has emerged as the gold standard due to its widespread availability and rapid diagnosis. The use of contrast aids in the identification of the true and false lumens, with the false lumen being larger than the true lumen in 80% of cases. Absent contrast cessation or asymmetric kidney enhancement are evidence of malperfusion and can help to dictate the need for revascularization. Additionally, CTA may reveal the presence of an intramural hematoma, though the clinical implications of this entity are unclear.

CLASSIFICATION

Traditionally, aortic dissection has been classified using the DeBakey or Stanford classification systems, according to the segment of aortic involvement (Fig. 1). Within this system, DeBakey I and II (Stanford A) dissections involve the ascending aorta and DeBakey III (Stanford B) dissections extend to the descending aorta only. This classification system has been used historically to dictate clinical management, though with the advent of improved endovascular repair, additional detail is often required to guide more contemporary management. To this end, the DISSECT classification system was developed to more accurately communicate specific details regarding the dissection between providers. The DISSECT classification consists of the following elements: duration (Acute: <2 weeks; Subacute: 2 weeks to 3 months; >3 months), intimal tear location (ascending, arch, or descending), size of the aorta, segmental extent of aortic involvement, clinical complications, and thrombosis of the false lumen. Through a more accurate description of both the dissection location and clinical features, the intent of the DISSECT mnemonic is to convey all the information of interest that could help drive disposition to medical or surgical management.

MANAGEMENT STRATEGIES

Through most of the history of aortic dissection, treatment has been largely relegated to medical management. However, with their report of surgical repair of six aortic dissections in 1955, DeBakey, Cooley, and Creech helped to establish the efficacy of surgical treatment for acute aortic dissection. Their reported perioperative mortality of 33% (two of the six) was a dramatic reduction from the estimated 75% to 90% mortality of nonsurgical management reported at the time.

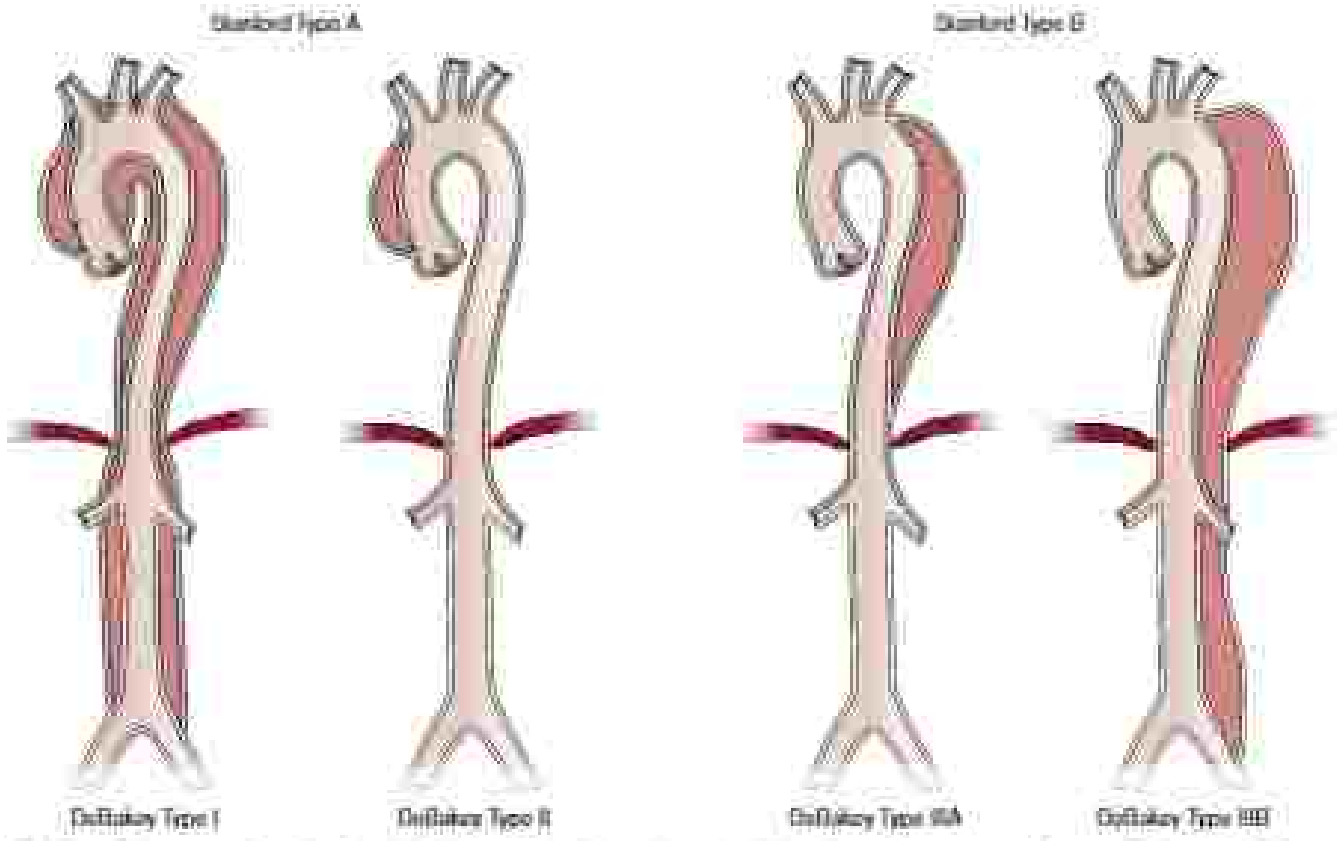

FIG. 1 Classification systems for aortic dissection. DeBakey I dissections involve a combination of ascending aortic, aortic arch, and descending aortic segments (Stanford type A). DeBakey II dissections are limited to the ascending aorta only (Stanford type A). DeBakey IIIA dissections involve the descending aorta only (Stanford type B). (Modified from Cooper MA, Ikonomidis JS, Hawkins AT, et al. Ann Thorac Surg. 2007;83(4):1546–1553; with permission.)

Through examination of the International Registry of Acute Aortic Dissection (IRAD), we have further delineated which patients will benefit from operative management. Initial management of patients with acute aortic dissection includes aggressive heart rate and blood pressure control, except in situations of hypotension and rupture. An important early distinction is the presence of a type A aortic dissection (TAAD) or type B aortic dissection (TBAD). Indeed, it is important to recognize that TAAD has high mortality that mandates early surgical therapy as opposed to TBAD, which are often treated medically.

SURGICAL MANAGEMENT OF TYPE A AORTIC DISSECTION

Surgical management is the mainstay of therapy for treatment of acute TAAD. The rate of early mortality in this population has been cited as greater than 1% per hour. The majority of patients in initial report of the IRAD data in 2000 by Hagan et al. involved the ascending aorta, and in these patients, the operative mortality was only 16% compared to ~3% for medical management. These results are recapitulated in a recent Society of Thoracic Surgery database, in which operative mortality in the United States for TAAD was approximately 17% compared to contemporary estimates of greater than 50% in nonoperative management. These patients are at high risk for early postoperative complications including acute myocardial infarction, renal failure, stroke, and new visceral/limb malperfusion syndromes.

Approximately 80% of patients with TAAD progress to the operating room within 24 hours to an emergent fashion, the majority of which will require circulatory arrest. Strategies for cannulation for cardiopulmonary bypass are varied and include axillary, femoral, aortic, and combinations thereof, dependent on patient location. The femoral cannulation site has the longest history in ascending dissections and may facilitate the most rapid initiation of cardiopulmonary bypass, though evidence is emerging to suggest better outcomes with axillary cannulation. Approximately 50% of patients require a concomitant aortic valve procedure, with aortic valve resuspension being the most common valve procedure performed. In situations in which both the valve and the coronary stems can be spared, ascending aortic replacement can be completed with an interposition Dacron graft (Fig. 2). Postoperatively, TAAD patients are at high risk for continued bleeding, requiring ongoing transfusions, or possible reexploration.

MANAGEMENT OF TYPE B AORTIC DISSECTION

Early management of all acute TBAD should be directed at aggressive heart rate control to reduce the oscillatory shear stress exerted on the aortic wall. Patients should be closely monitored in an intensive care setting. The ACCF/AHA recommend a target heart rate of <60 beats/min, to be achieved with the use of intravenous beta blockers, with esmolol commonly being the agent of choice due to its rapid on/off profile and ease of titration. For patients who are unable to tolerate β-blockade, especially those with aortic regurgitation or at risk for a chronic obstructive pulmonary disease exacerbation, calcium channel blockers may be used. Once heart rate control has been achieved, blood pressure should be targeted for a systolic pressure of 120 mm Hg to reduce the risk of flap propagation and aortic rupture. This can be accomplished through a combination of ACE inhibitors and other antihypertensive agents if β-blockade is not sufficient. Blood pressure control should not be attempted prior to heart rate control, as compensatory tachycardia can lead to increased risk of rupture. Patients with persistent or refractory pain, aortic expansion, or evidence of malperfusion are deemed "complicated." There are two dominant mechanisms for malperfusion. Malperfusion may result from either

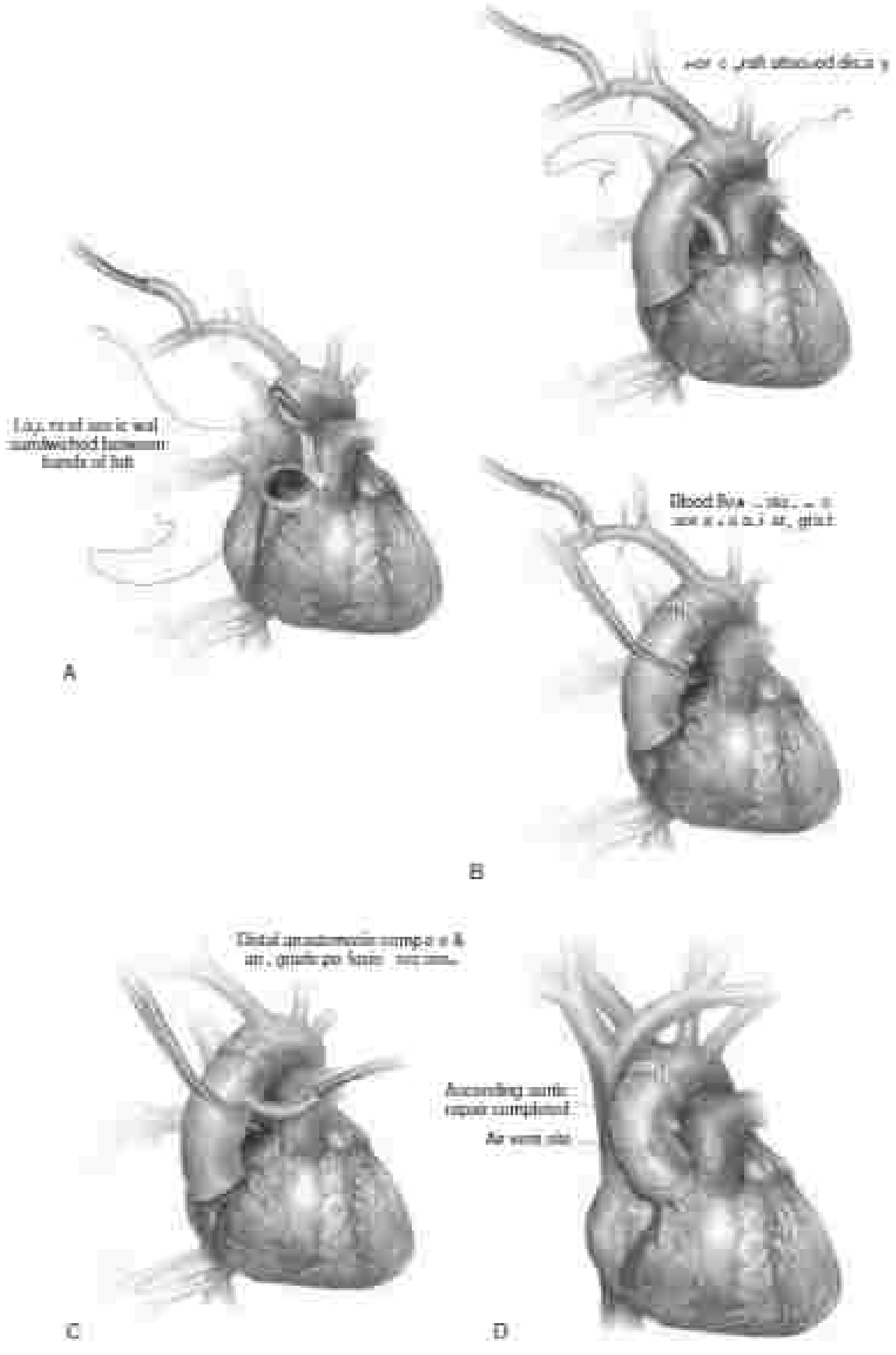
A
B
C
D

FIG. 2 Static (A) and dynamic (B) dissection flaps for aortic dissection. Static flaps result in permanent occlusion of outflow vessel with resultant thrombus. Dynamic dissection flaps result in intermittent occlusion and can lead to thrombus formation if not treated promptly.

static or dynamic dissection flap obstructions, leading to possibly intermittent malperfusion (Fig. 2). Clinical parts after dynamic flaps can be difficult to diagnose based on static images. Computed tomography (CT) angiography and magnetic resonance angiography (MRA) are the most commonly used imaging modalities in patients with aortic dissection. These studies are typically performed in patients with stable vital signs. Although these studies can be very helpful in delineating the anatomy of acute dissection, they are limited in their ability to assess dynamic flow patterns. Intraoperative transesophageal echocardiography (TEE) can be very helpful in assessing dynamic flow patterns and can be used to help guide surgical decision making.

Open Surgical Repair

The traditional open surgical approach to acute aortic dissection is to resect the intimal tear. Contemporary surgical repair is much more conservative and includes resection of the proximal intimal tear as well as the distal intimal tear and hematoma. As the proximal aorta is the most frequent site of acute dissection, most surgical repairs involve replacement of the ascending aorta with or without hemiarch replacement. Cannulation for cardiopulmonary bypass is usually performed through the right axillary artery or femoral artery. Cannulation through the left axillary or femoral artery for partial cardiopulmonary bypass if needed. Historically the results of open surgical management of TBAD are poor, with high rates of paraplegia, stroke and acute kidney failure. As such, open surgical intervention for TBAD has largely been abandoned, except in the case of rupture.

Endovascular Management

Thoracic stent graft repair of acute TBAD has become a mainstay for management of complicated dissections. Successful repair of complicated TBAD requires thorough preoperative planning. CTA of the entire aorta, from the heart to the pelvis, should be obtained, outlining the aortic anatomy to include the great vessels through the femoral vessels (Fig. 4). This allows for identification of proximal entry tear, which will need to be covered during endograft deployment, as well as ensuring adequate femoral and iliac vessel size for catheter and sheath introduction. Additionally, this may help to identify the location of the ostia of the visceral vessels in relationship to the true and false lumens.

Bilateral femoral cannulation is the preferred approach; however, in cases in which tortuosity in the thoracic aorta will likely prevent safe navigation of the thoracic endograft, brachial artery cannulation can be employed. This allows for dissection into the true lumen, using a "through and through" approach. From the femoral cannulation site, intravascular ultrasound (IVUS) is often useful to determine positioning within the true lumen and should be available prior to the start of the procedure. More typically, the true lumen is the more anterior of the two lumens, giving rise to the superior mesenteric and right renal arteries. However, preoperative assessment of the relationship between the true and false lumen can be determined based on the CT acquisition (Fig. 4). After cannulation, the anterior aorta is located using the left renal vein identification with IVUS and the location of the wire within the true lumen can then be confirmed.

Static obstructions (see Fig. 2) of visceral segments often mandate stenting, while dynamic obstructions may resolve with aortic stent grafting. In rare cases in which aortic stent grafting does not resolve visceral or renal malperfusion, fenestration of the dissection flap and stenting should be performed near the ostia of the branch vessel and should be limited to one to prevent further true propagation. It is important to note, excessive fenestration in the proximal abdominal aorta may increase the risk of subsequent visceral segment malperfusion due to unpredictable flow dynamics.

Thoracic endograft placement in complicated TBAD should be targeted to cover the primary entry tear of the dissection (Fig. 4). Coverage of additional smaller entry tears or distal entry tears may require introduction of additional stent grafts. It is possible that additional stent graft coverage may increase the risk of spinal cord ischemia, which results from coverage of thoracic lumbar arteries responsible for spinal blood supply, in distinction to degenerative aneurysms. Acute thoracic endografts should be oversized 5% to 15% larger than preoperative aortic diameter, oversizing of thoracic endografts in the setting of dissection is minimal. It is theorized that aggressive oversizing on a freshly dissected aorta may increase the risk of acute stent graft associated rupture, tearing of the dissection septum, or retrograde aortic dissection into the arch. The endograft should be positioned just distal to the left subclavian artery and a standard 2- cm proximal landing zone is advocated. In instances in which the dissection flap includes the ostium of the left subclavian or anatomic characteristics preclude adequate landing zone, the left subclavian artery can be covered. It is not necessary to perform a subclavian revascularization (most commonly through a carotid subclavian bypass or subclavian transposition) at the time of thoracic endovascular aortic repair (TEVAR), although it may be preferred if technically feasible and patient hemodynamics allow.

After the endograft has been successfully deployed, balloon dilatation should be avoided to prevent rupture or further dissection. A completion angiogram and IVUS are then performed to document coverage of the intimal defect as well as appropriate flow to the visceral vessels (Fig. 5B). If IVUS demonstrates significant true lumen compression or persistent malperfusion of the visceral or renal vessels, then additional fenestration or stenting may be required. After determination of a good angiographic result, catheters, wires, and sheaths can be removed in the standard fashion. The artery is then repaired with interrupted prolene sutures. If a conduit was used, it can be oversewn and left in situ.

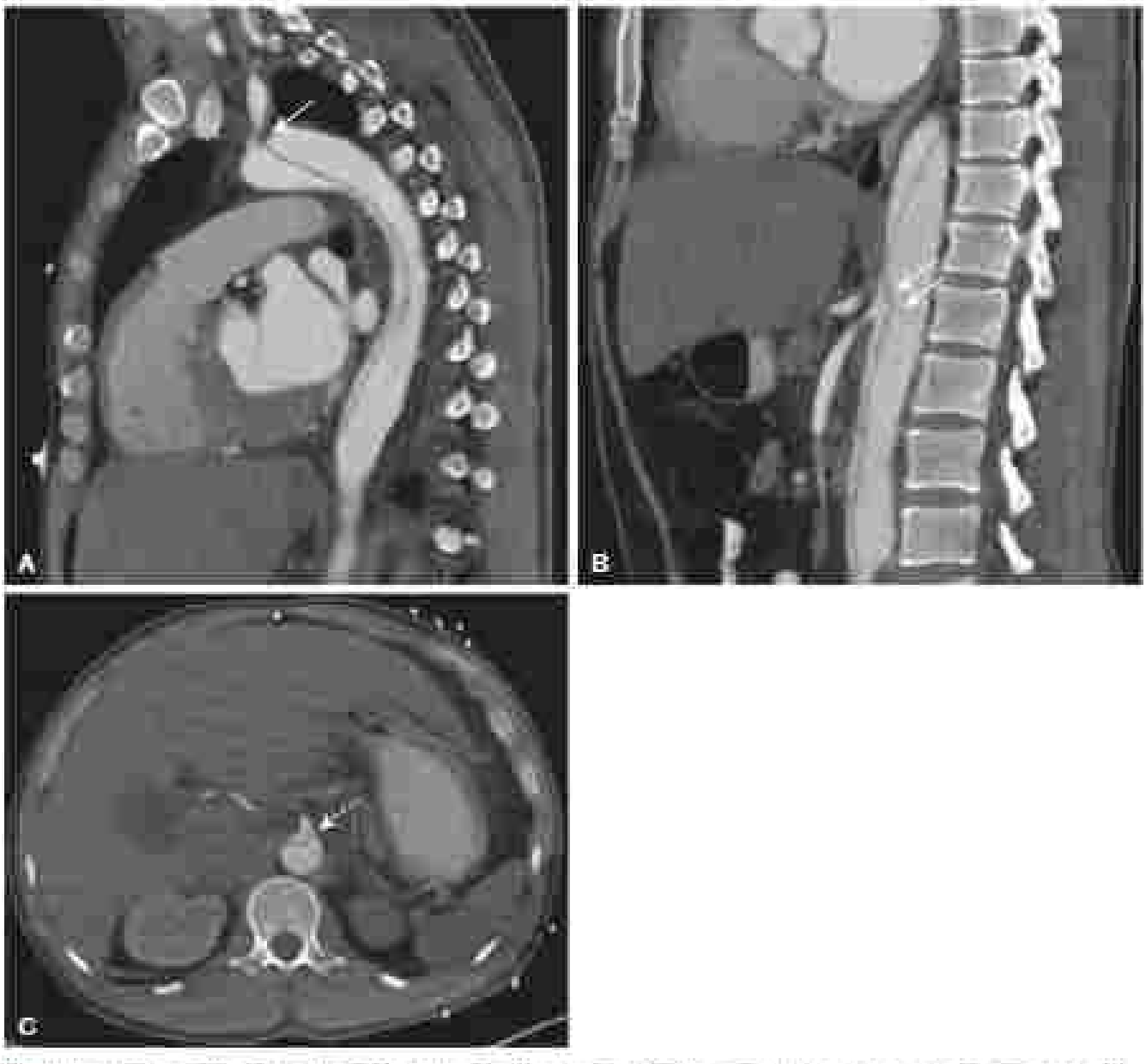

FIG. 4 (A) Preoperative sagittal computed tomography (CT) demonstrating luminal luminal starting immediately distal to left subclavian artery. (B) Sagittal CT demonstrating anterior true lumen from which the superior mesenteric artery (SMA) arises (arrow). (C) Axial CT demonstrating stable anterior true lumen with takeoff of the SMA (arrow).

The role for endovascular repair of uncomplicated TBAD is still an area of study. Investigators from the multicenter INSTEAD trial demonstrated equivalent 30 day mortality among patients undergoing endovascular repair (TEVAR) or maximal medical management. Additionally, the group undergoing surgical repair had a higher 1 year mortality. However, more recent evaluation has supported a lower "aorta related" mortality among patients undergoing early endovascular repair (6.9% vs 19.5%, $P = 0.2$), a result that is further supported by 5 year follow up studies in the IRAD database. Patients who undergo early TEVAR have higher rates of false lumen thrombosis and favorable aortic remodeling compared to maximal medical management.

COMPLICATIONS

Because of the tortuosity of the thoracic aorta, special care must be taken to limit "endoleaking" of the endograft. This occurs when the proximal edge of the graft pulls away from the tissue distortion of the aorta and provides a possible avenue through which blood may dissect between the aortic wall and the endograft. This can result in device migration and/or collapse and in rare instances, may result in aortic occlusion and subsequent cardiovascular collapse. Retrograde type A dissection has also been reported, in which the stress of the thoracic endograft cause an intimal tear that may propagate proximally and lead to stroke, myocardial infarction, or cardiac tamponade. This phenomenon is rare and is believed to be related to the noncompliant endografts, especially first generation and bare metal stent endografts. Additionally, the aneurysmal or heavily atherosclerotic thoracic vessels are also at risk for complications following device manipulation. Due to the large sheath size, these vessels may rupture on device removal. Any acute cardiovascular decompensation or loss of flow to the ipsilateral limb after device removal should immediately prompt concern for this vessel rupture or dissection. Provided the guidewire has not been removed, this can often be temporized with balloon inflation, followed by deployment of a covered stent.

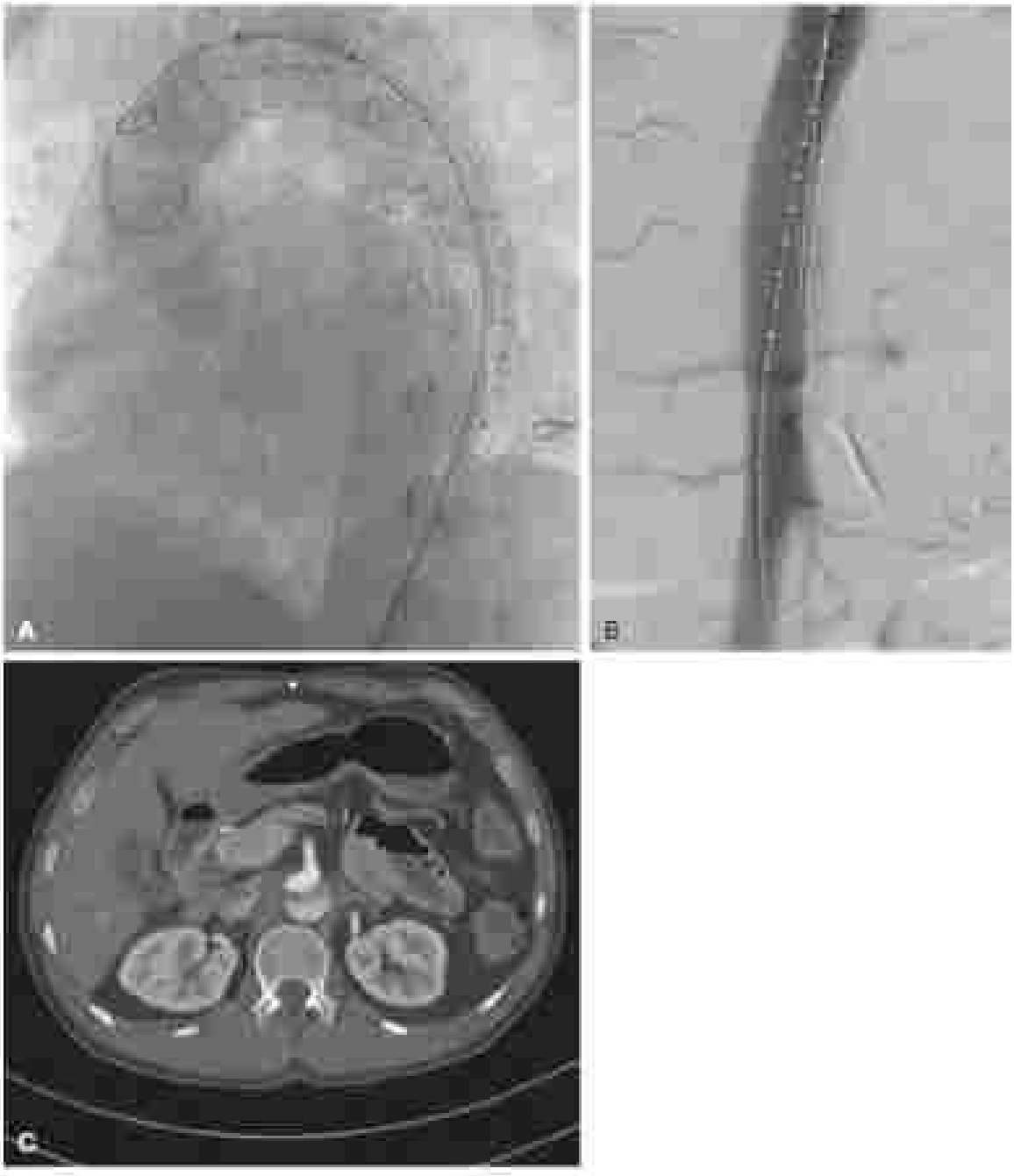

FIG 5. Operative and postoperative imaging for patient shown in Figure 4. (A) Deployment of thoracic endograft overlapping site of preoperative luminal tear. (B) Completion angiogram demonstrating adequate luminal result and visceral artery perfusion. Note enhancement of the thoracic false lumen is filling retrograde and likely resulting from a fenestration in the septum in the visceral segment of the aorta. (C) 3-month follow-up computed tomography scan demonstrating preferential filling of anterior true lumen, with continued visceral perfusion via patent superior mesenteric artery. The false lumen is appreciated to have decreased contrast density consistent with progressive thrombosis.

FOLLOW-UP

Long-term follow-up after acute aortic dissection is mandatory, as surveillance imaging may detect onset of degenerative aneurysms related to chronic aortic dissections. Patients should undergo CTA or MRA (if no indwelling thoracic stent). For surveillance of patients with chronic TBAD without indwelling stent graft, MRA may be preferred to monitor for degenerative changes and reduce the risk of repeated radiation exposure. For patients in whom an intervention has been performed, CTA surveillance should be started 1 month post procedurally (Fig 5C). In particular, the false lumen should be evaluated for luminal density appearance indicating progression to thrombosis. All dissection patients regardless of type or initial management strategy are recommended to undergo regular surveillance imaging at 1 month, 3 months, 6 months, 12 months and then annually thereafter.

For patients who underwent visceral segment angioplasty or stenting, postoperative evaluation with ultrasound may be a useful adjunct to limit overall radiation exposure. However, it should be noted that this requires a vascular lab facility to such an evaluation and

a patient with limited coronal obesity. All patients should be placed on statin and aspirin therapy and should have aggressive blood pressure control. These efforts are often best achieved through early coordination with the patient's primary care provider or cardiologist.

Suggestions Readings

[illegible]

Carotid Endarterectomy

Courtenay M. Holscher, MD, and Che[illegible]
Rafa[illegible], MD, FACS

According to more than [illegible] million adults in the United States, stroke is a leading cause of death and disability. Stroke incidence increases with age, which must be considered in the context of an aging population. Approximately 80% of strokes are ischemic; of these, approximately 40% are caused by atherosclerotic disease of the carotid bifurcation. Carotid endarterectomy (CEA), originally performed by DeBakey in 1953, has become the definitive management of carotid artery stenosis to prevent death and disability due to stroke.

PRESENTATION

Clinical presentation

The management of carotid artery disease depends on whether patients present with neurologic symptoms referable to a carotid artery event or are found to have asymptomatic carotid artery disease either incidentally or on screening studies. Patients presenting with neurologic symptoms of carotid artery disease including stroke, transient ischemic attack (TIA), or other ischemic signs in the carotid distribution should undergo carotid artery imaging. This includes patients with amaurosis fugax, retinal artery emboli on funduscopic exam, and those with asymptomatic cerebral infarction found incidentally on imaging. It is important to note that if significant carotid artery stenosis is discovered on the contralateral side of a cerebral infarction or other ischemic sign, it would be considered asymptomatic. For example, should a patient with left sided weakness secondary to a right sided cerebral infarction have significant left carotid artery stenosis and no right carotid artery stenosis, this would be considered asymptomatic left carotid artery disease. In addition to evaluating for carotid artery disease, other causes of stroke should be ruled out, including cardiac thrombus, endocarditis, and intracranial cerebrovascular disease.

Screening of select asymptomatic patients should be considered only when patients are operative candidates and are willing to undergo a carotid intervention should a significant stenosis be found. These patients may include those with clinically significant peripheral vascular disease and patients aged [illegible] years or older who have another atherosclerotic risk factor such as tobacco smoking, hypercholesterolemia, or coronary artery disease.

Routine screening is not recommended in the general population due to the low prevalence of carotid artery disease. A neck bruit without other atherosclerotic risk factors is not an indication for screening. A bruit is neither a sensitive test a specific sign of carotid artery stenosis among those with a bruit, no more than 50% to [illegible]% will be found to have significant stenosis in the internal carotid artery (ICA).

[illegible]

Among those with high grade ICA stenosis, no more than 20% to 50% will have an ipsilateral bruit.

Imaging Studies

Duplex ultrasonography (DUS) by an accredited vascular laboratory is the imaging modality of choice for evaluation of carotid artery disease. DUS provides both anatomic information (B-mode) as well as flow velocity information (spectral Doppler), which can be used to determine the degree of stenosis. Multiple studies have correlated velocities with degree of anatomic stenosis based on catheter angiography, with increasing peak systolic (PSV) and end diastolic velocity corresponding to more significant narrowing. Many accredited vascular labs rely on the internal carotid to common carotid artery PSV ratio, as this controls for altered cardiac output and localized changes to carotid vessel flow dynamics due to collateralization and/or severe contralateral disease.

Beyond determination of the degree of stenosis, DUS can characterize the morphology of a carotid plaque, including calcification, lumen irregularity, ulceration, and the pattern of echogenicity that may indicate plaque instability caused by intraplaque hemorrhage or degeneration. Findings suggestive of an unstable plaque further support timely intervention in a patient with a significant carotid artery stenosis. DUS does have limitations to the setting of carotid artery disease, shadowing from calcific plaques creates artifacts that can limit ability to measure vessel anatomy and velocity. Additionally, DUS is not able to evaluate intracranial carotid disease or more proximal vessel disease in the chest.

Computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or catheter based digital subtraction angiography (DSA) can be useful, whereas DUS is nondiagnostic or the vessels proximal or distal to the carotid bifurcation must be evaluated. It should be noted that there are several ways to measure carotid artery stenosis. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) used different measurements to describe the degree of stenosis (Fig. 1); the NASCET measurement, which is commonly used in the United States, is less likely to classify stenosis as severe compared with the ECST measurement.

While time of flight MRA tends to overestimate stenosis, it spares contrast administration needed for gadolinium-enhanced MRA or CTA. Gadolinium enhanced MRA better defines the degree of carotid artery stenosis; however, gadolinium is associated with a risk, albeit low, of nephrogenic systemic fibrosis to patients with renal impairment. Although MRA can identify lipid core plaque morphology through black blood image sequences, CTA has replaced MRA as the axial imaging technique of choice. CTA can be performed quickly and provides anatomic information about the aortic arch, degree of carotid bifurcation calcification, tortuosity of the cervical carotid, and intracranial carotid arteries. Catheter based DSA, while previously the diagnostic gold standard, is associated with a 1% to 2% stroke risk and is, therefore, reserved for those cases where noninvasive imaging is indeterminate.

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Suggestions Readings

Dake MD, Kato N, Mitchell RS, et al. Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med*. 1999;340(20):1546–1552.

Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283(7):897–903.

Nienaber CA, Rousseau H, Eggebrecht H, et al. INSTEAD trial. Randomized comparison of strategies for type B aortic dissection: the investigation of STent Grafts in Aortic Dissection (INSTEAD) trial. *Circulation*. 2009;120(23):2519–2528.

Carotid Endarterectomy

Courtenay M. Holscher, MD, and Christopher J. Abularrage, MD, FACS

Affecting more than a million adults in the United States, stroke is a leading cause of death and disability. Stroke incidence increases with age, which must be considered in the context of an aging population. Approximately 80% of strokes are ischemic; of these, approximately 40% are caused by atherosclerotic disease of the carotid bifurcation. Carotid endarterectomy (CEA), originally performed by DeBakey in 1953, has become the definitive management of carotid artery stenosis to prevent death and disability due to stroke.

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MEDICAL MANAGEMENT OF CAROTID ARTERY STENOSIS

Regardless of plans for procedural intervention, patients with carotid artery stenosis should be treated for hypertension, hypercholesterolemia, and provided counseling and resources for smoking cessation. However, aggressive treatment of hypertension is not recommended in the setting of an acute stroke. While diabetes should be medically managed, there is no evidence to support tight glucose control for reduction of stroke risk or reduction of perioperative risks of CEA. Patients should be counseled that smoking cessation both lowers their risk of stroke as well as their operative risks if CEA is indicated.

Antiplatelet and statin therapy is indicated for all patients with carotid stenosis. There is no evidence to support management with dual antiplatelet agents, nor evidence to support a particular aspirin dose. P2Y12 inhibitors, such as clopidogrel or ticagrelor, should be prescribed for patients with an aspirin allergy or sensitivity. Anticoagulation is not recommended but may be used if there is another indication, such as cardioembolic stroke. Statin therapy is associated both with decreased perioperative stroke and death risk and with decreased long-term stroke risk. Additional perioperative management is described below.

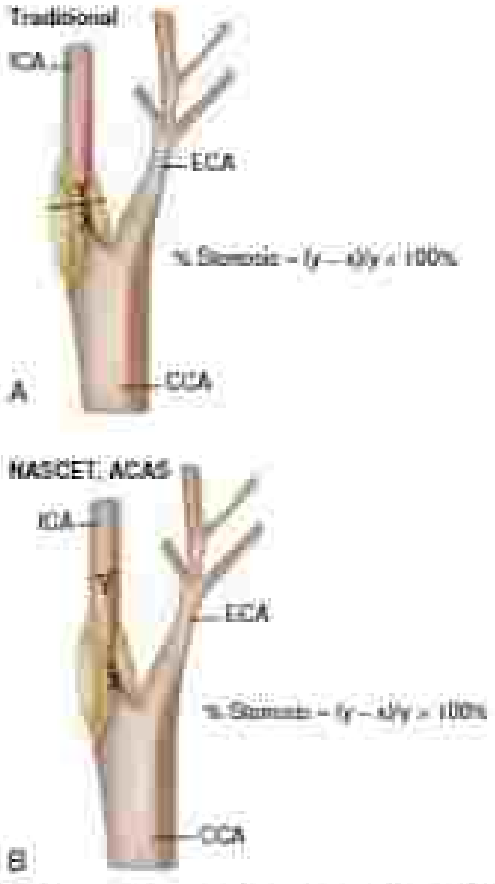

FIG. 1 Three methods of measuring carotid artery stenosis on an angiogram when the stenosis is within the bulb. CCA, Common carotid artery; ECA, external carotid artery; ICA, internal carotid artery. [illegible]

INDICATIONS FOR CAROTID ENDARTERECTOMY

Interestingly, there were five independent international guidelines with recommendations for management of carotid artery stenosis that were published in 2011: the Society for Vascular Surgery, the American College of Cardiology/American Heart Association, the European Society of Cardiology, the United Kingdom National Institute of Health and Clinical Excellence, and the Australasian guidelines. While these committees based their recommendations on the same literature, there are some differences between them. I.e report the Society for Vascular Surgery recommendations as they best follow the published evidence.

Symptomatic Disease

The Society for Vascular Surgery 2011 guidelines for management of extracranial carotid disease recommend CEA for a symptomatic carotid artery stenosis of 50% or greater. This recommendation is based on evidence from prospective randomized trials summarized in Table 1. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) collaborators, in their landmark 1991 paper, reported a 17% reduction in stroke risk over 2 years for stenosis >70% with CEA as compared to best medical treatment, which at that time was aspirin 1300 mg daily. The same year, the European Carotid Surgery Trial (ECST) collaborators reported a 13.9% risk reduction over 5 years for stenosis of 70% or greater. Subsequent analysis of NASCET participants with symptomatic 50% to 69% stenosis demonstrated a 4.5% reduction in stroke risk over 5 years.

Ideally, CEA should be performed within 2 weeks of the index event to prevent additional ischemic insult, based on the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).

TABLE 1 Randomized Trials Comparing Carotid Endarterectomy with Medical Management of Ca...rtid Ste...osis

Trial	Stenosis Indication	Medical Stroke Risk	Surgical Stroke Risk	Risk Reduction
SYMPTOMATIC				
NASCET	70%–99%	26%	9%	17% over 2 years
	50%–69%	22.2%	15.7%	6.5% over 5 years
ECST	70%–99%	20.6%	6.8%	13.8% over 5 years
ASYMPTOMATIC				
ACAS	60%–99%	11.8%	5.1%	5.9% over 5 years
ACST	60%–99%	12.8%	6.8%	6.8% over 5 years

NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial.

CEA is preferred over carotid artery stenting (CAS) for reduction of stroke and mortality risk in the majority of patients. While CEA was associated with a slightly increased risk of perioperative myocardial infarction, it was associated with both a lower risk of stroke and an improved long-term quality of life.

Asymptomatic Disease

Intervention for asymptomatic carotid artery stenosis depends both on the individual patient's life expectancy, as well as on the surgeon's perioperative stroke and death rates. If a patient has a life expectancy greater than 3 to 5 years and a surgeon's perioperative risk of stroke or death is less than 3%, the Society for Vascular Surgery 2011 guidelines recommend that asymptomatic patients with carotid artery stenosis of ≥60% or greater be considered for CEA. This is based on evidence summarized in Table 1. The Asymptomatic Carotid Atherosclerosis Study (ACAS) found a 5.9% reduction in risk of stroke over 5 years with CEA compared to medical management with aspirin 325 mg daily. Similarly, the Asymptomatic Carotid Surgery Trial (ACST) found a 5.4% risk reduction over 5 years with CEA compared to medical management.

It is important to note that alongside improved perioperative outcomes of CEA and CAS, there have been significant advances in medical treatment available including the introduction of statins in 1987. This has led to some clinical equipoise in the management of asymptomatic carotid artery stenosis, which should be addressed by the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) that began in 2014.

SPECIAL CONSIDERATIONS

Coronary Artery Bypass Grafting

Patients in need of coronary artery bypass grafting (CABG) should be screened for carotid artery stenosis prior to undergoing CABG given the high prevalence of carotid artery stenosis in this population. Patients with symptomatic carotid artery stenosis or severe bilateral asymptomatic carotid artery stenosis who are in need of CABG should undergo CEA prior to or concomitant with CABG. The surgical timing of carotid endarterectomy and CABG in patients with asymptomatic disease is controversial and may be performed based on surgeon and patient preference.

Prior Head and Neck Irradiation

Carotid screening is not recommended for asymptomatic patients who have had prior head and neck irradiation, but is recommended for patients with neurologic symptoms including stroke or TIA. For symptomatic patients with prior head and neck irradiation found to have a high grade stenosis, CAS is preferred over CEA.

OPERATIVE TECHNIQUE

Preoperative Medical Management

Perioperative management of patients undergoing CEA should include control of hypertension targeting a blood pressure less than 140/90 mmHg, β-blockade targeting a heart rate of 60 to 80 beats/min, and statin therapy targeting a low density lipoprotein level less than 100 mg/dL. Statin use decreases perioperative stroke risk and mortality as well as recurrent carotid stenosis; the evidence favors all patients undergoing CEA to be treated perioperatively and long-term with statins. Antiplatelet therapy with aspirin or P2Y12 inhibitors is also indicated.

Some surgeons use a dextran infusion for its antiplatelet effects intraoperatively and while the patient recovers in hospital. While previous studies have shown a reduction in embolic transcranial Doppler signals and perioperative stroke, more recent population based evidence suggests that it does not decrease perioperative stroke risk and may increase the risk of perioperative myocardial infarction and congestive heart failure.

Anesthesia

CEA can be performed under local anesthesia, regional anesthesia with a cervical block, or general anesthesia. Comparable lengths of hospital stay are seen with each anesthetic modality. The advantage of local or regional anesthesia, as compared to general anesthesia, is improved perioperative cardiac stability; however, this must be weighed against patient discomfort and anxiety. Our institutional practice is to perform CEA with general anesthesia unless the patient has prohibitive cardiac risks.

Positioning

Appropriate patient positioning is the first step in gaining adequate operative exposure, and is critical to preventing hyperextension injury to the patient. The patient is positioned supine and a roll is placed behind the scapula to extend the neck. The patient's head is turned to the contralateral side and a padded ring is placed to prevent extreme neck hyperextension (Fig. 2). The endotracheal tube and electroencephalogram electrodes and wires should be directed away from the operative field. The operating table should be adjusted to a beach chair with reverse Trendelenburg position to decompress the venous system. The field should be prepped from the base of the earlobe and mastoid to the sternal notch. If local or regional anesthesia is used, drapes should be suspended away from the patient's face for comfort and to prevent claustrophobia.

Incision

The standard incision for CEA is a longitudinal incision along the medial border of the sternocleidomastoid (Fig. 3). The upper portion of the incision can be angled posteriorly toward the earlobe to avoid the parotid gland if exposure above the angle of the mandible is needed. Alternatively, a transverse incision or an existing skin crease can provide excellent cosmesis, but there may be difficulty with exposure if the transverse incision is not directly superficial to the carotid bifurcation. A transverse incision does not easily allow cephalic or caudal extension. As such, intraoperative US can be helpful to guide placement of a transverse incision.

Exposure

Meticulous surgical technique to minimize manipulation of the carotid artery is critical to avoid nerve injury and intraoperative

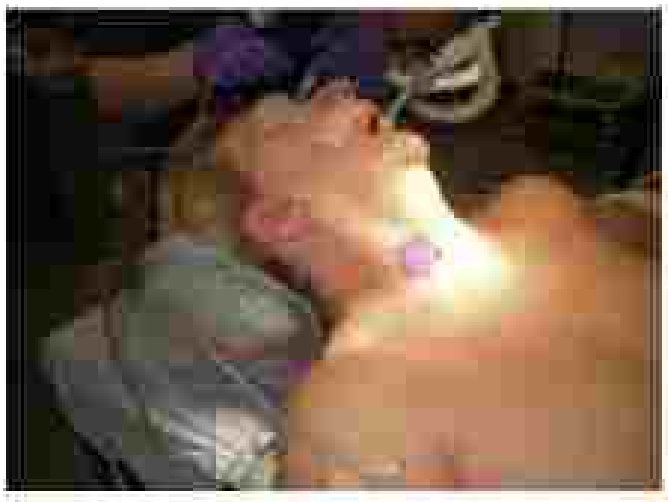

FIG. 2 Appropriate patient positioning includes a roll under the patient's scapula to extend the neck and a padded ring under the patient's head, with the endotracheal tube, electroencephalogram electrodes, and wires directed away from the operative field.

embolization. The platysma is divided and the medial border of the sternocleidomastoid muscle is mobilized. The external jugular vein and the greater auricular nerve are located deep to the platysma and should be preserved, particularly as the external jugular vein can be used as a vein patch if needed. The sternocleidomastoid is retracted laterally, exposing the carotid sheath. The carotid sheath is entered. The internal jugular vein is dissected free along its medial border, facilitated by division of the facial vein, and retracted laterally. The vagus nerve should be identified and preserved (Fig. 4). Dissection continues to free the distal CCA where the ansa cervicalis should be identified, as well as the bifurcation into the ICA and external carotid artery (ECA). The ansa cervicalis can be followed superiorly to its junction with the hypoglossal nerve, which should be preserved. The superior thyroid artery is identified at its origin from the ECA and

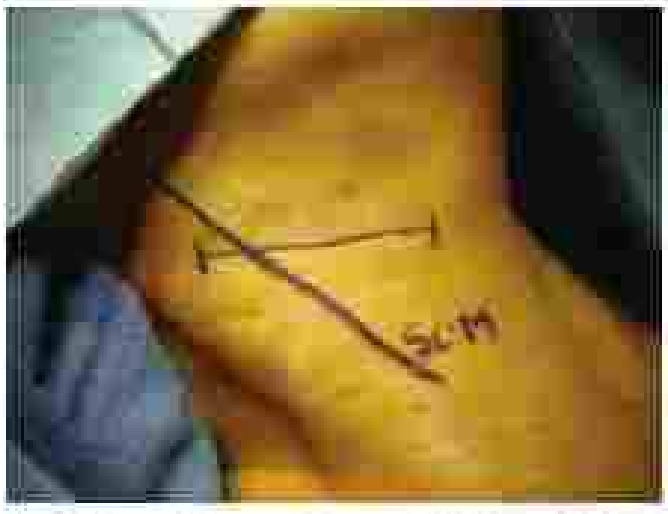

FIG. 3 Longitudinal and transverse incision options for carotid endarterectomy. A longitudinal incision is made along the medial border of the sternocleidomastoid (SCM). A transverse incision can provide improved cosmesis; however there may be difficulty with exposure of the carotid bifurcation should a transverse incision be made in a suboptimal location. (From Veith, F. et al. Rutherford's Vascular Surgery 7th ed. Elsevier, 2010.)

FIG. 4 Intraoperative exposure of the carotid bifurcation. The common carotid is encircled with an umbilical tape while the internal carotid, external carotid, and superior thyroid arteries are controlled with vessel loops. The vagus nerve (*small arrow*) and hypoglossal nerve (*big arrow*) should be identified and avoided.

controlled with a 3-0 or vessel loop. Dissection of the ICA should continue to a portion of the artery that is above the plaque and free of disease. During dissection of the carotid bifurcation, extreme care should be taken to avoid injuring the carotid body, located in the crotch of the carotid bifurcation. Injury to the carotid body can result in bleeding and hemodynamic instability. The carotid body can be injected with 0% lidocaine to prevent hemodynamic instability.

The carotid bifurcation ranges in location from the level of the second to the seventh cervical vertebrae. A bifurcation located high in the neck should ideally be noted on preoperative imaging. CTA can be useful to delineate bony anatomy in the setting of a high bifurcation. There are several methods to improve exposure for high carotid bifurcations. Nasotracheal intubation allows the patient's mouth to be closed during the operation, displacing the mandible 1 to 2 cm anteriorly. Next, the posterior belly of the digastric muscle can be divided. After the posterior belly of the digastric is divided, the muscular insertions of the styloid process can be divided and the styloid process can be resected for further exposure if necessary. Finally, if additional exposure is still needed, the mandible can be subluxed anteriorly with the assistance of an oral or plastic surgeon.

At this point, the CCA and its main branches are exposed and controlled (see Fig. 4). 70 to 100 U/kg heparin should be given and allowed to circulate for 3 minutes prior to any clamping, and a decision must be made regarding cerebral protection and monitoring.

Shunts and Cerebral Monitoring

There are three approaches to maintaining cerebral perfusion during carotid clamping: (1) performing CEA without a shunt, (2) routine use of shunts for all CEAs, and (3) selective use of shunts. In the case of CEA without a shunt, there is a small incidence of perioperative stroke and, therefore, this technique is considered outside the standard of care. Many surgeons routinely use shunts for all CEAs as it maintains antegrade perfusion of the ipsilateral cerebral hemisphere. This is especially important in those patients with contralateral disease, although technical issues related to shunt placement may rarely cause distal embolism or dissection. In the case of selective use of shunts, which aims to balance these risks, there are several techniques used to determine whether a shunt is needed. If local anesthesia or intraoperative electroencephalography is being used, a test clamp should be applied to the distal ICA for at least 3 minutes to assess for neurologic changes. If such changes occur, the ICA should be unclamped and reperfused before the bifurcation is opened and a shunt placed. If carotid stump pressure is being used, clamps are placed on the CCA and ECA and a needle connected to a pressure line is placed in the distal CCA superior to the clamp and inferior to the carotid bifurcation. A stump pressure higher than 50 mm Hg generally indicates adequate perfusion. Transcranial Doppler measurement of middle cerebral artery flow and measurement of cerebral oximetry can also be used to guide selective use of shunts following artery clamping. It must be noted that any clamping or placement of a needle into the vessels is associated with a risk of embolization.

Endarterectomy

Conventional Endarterectomy

Conventional endarterectomy uses a longitudinal arteriotomy and a patch closure. The ICA is clamped first to prevent any embolization that might result from CCA or ECA clamping. The longitudinal arteriotomy begins in the CCA with an 11 or 15 blade and continues through the carotid bifurcation into the ICA using Potts scissors. If a shunt is used, it is placed in the ICA and backbled before the proximal end is placed into the CCA. A number of commercial shunts are available including Argyle, eSAT, and Pruitt-Inahara shunts, and all have excellent results.

The endarterectomy is started mid plaque with a Freer or Penfield elevator in the plane between the media and adventitia (Fig. 5).

The plaque is freed inferiorly to an endpoint in the distal CCA where the plaque is transected. It is freed superiorly toward an endpoint in the ICA where it is either transversely pulled off the artery or transected. A smooth transition from endarterectomized surface to normal intima is critical to prevent embolization or dissection with reperfusion. Gentle saline injection into the endarterectomized surface can reveal intimal flaps that can be tacked down with 7-0 polypropylene or further endarterectomized. Tacking sutures are associated with increased perioperative stroke risk and should be avoided if possible. The plaque is then freed to the ECA where it is endarterectomized with eversion after the ECA clamp is removed. The endarterectomized surface should be carefully inspected and all residual fragments of intima and media removed.

Closure of the arteriotomy is accomplished with a patch (Fig. 4); primary closure is associated with a higher rate of restenosis. Materials used for patch closure include autologous vein, bovine pericardium, polytetrafluoroethylene, and woven polyester (Dacron), and all have excellent results. If a shunt was used, it should be removed and the ICA should be back bled to clear debris associated with shunt use. The arteriotomy is closed and the ICA clamp is briefly released to fill the vessel, then replaced. The CCA and ECA clamps are released to flush any remaining debris or air through the ECA before ICA reperfusion. The ICA clamp is removed last.

Eversion Endarterectomy

Eversion endarterectomy is an alternative technique used by many surgeons (Fig. 7). In this technique, the ICA is transected from the carotid bifurcation and the plaque is excised from the ICA. The plaque is endarterectomized from the CCA and ECA through the ICA origin transection. The ICA is then reanastomosed to the carotid bifurcation. Advantages of eversion endarterectomy include its rapid performance, lack of patch requirement, and low restenosis rate. However, eversion endarterectomy does not easily allow use of shunts and it can be difficult to visualize the endpoint of ICA endarterectomy because the artery wraps once the plaque has been endarterectomized.

Completion Studies

Perioperative thromboembolism and carotid artery thrombosis due to technical errors should be considered preventable. Technical defects that might lead to these etiologies of perioperative stroke can be assessed using intraoperative Doppler evaluation, DUS, or angiography. Doppler scan evaluation can identify areas of turbulence and

FIG. 5 Plaque within the carotid artery.

FIG. 6 Aortic pericardial patch seen with 4-0 polypropylene running sutures following endarterectomy.

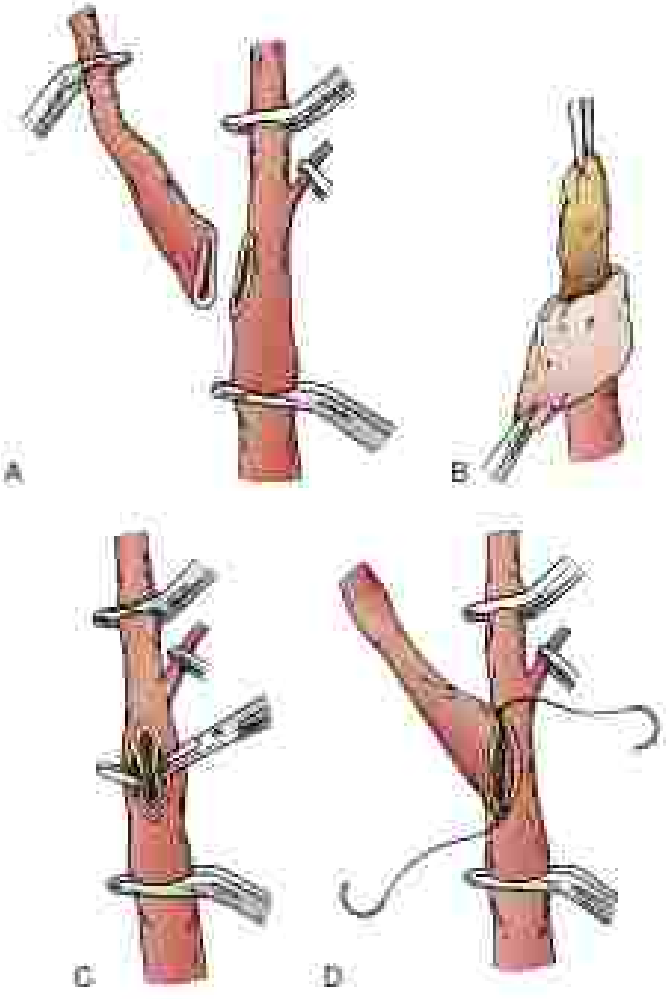

FIG. 7 Eversion endarterectomy. (A) Internal carotid artery dissected from the bifurcation. (B) Atherothrombotic plaque from the internal carotid artery plaque. (C) Plaque endarterectomized from the common carotid artery and origin of the external carotid artery. (D) Reattachment of the internal carotid artery to the bifurcation. (From Wong JK et al: Rutherford's Vascular Surgery, 9th ed. Elsevier, 2019.)

high velocity, but is highly operator dependent. Intraoperative completion DUS provides detailed anatomic information about the CEA clamp site that otherwise is difficult to assess. Catheter-based angiography has similar sensitivity in detecting major technical defects of the endarterectomy. However, there is not consensus as to which criteria merit re-exploration. Most agree that minor defects should be left alone while major technical defects should be addressed. Additionally, a postoperative DUS is indicated within 30 days to assess the status of the endarterectomized vessel.

RESULTS

Recent reported perioperative mortality after CEA ranges from 0.4% to 1.9% and is mainly due to myocardial infarction (Table 2),

TABLE 2 Perioperative Morbidity and Mortality Associated with Carotid Endarterectomy

	Reported Incidence
Death	0.4%–1.9%
Stroke	0.3%–2.9%
Myocardial infarction	0.2%–1.5%
Cranial nerve injury	
Hypoglossal	4.4%–17.5%
Recurrent laryngeal	0.3%–1.5%
Superior laryngeal	1.8%–4.5%
Marginal mandibular	1.1%–2.1%
Glossopharyngeal	0.2%–1.5%
Spinal accessory	1.0%
Cerebral hyperperfusion syndrome	0.4%–7.7%
Infection	0.09%–0.5%
Bleeding	0.7%–3.0%
Recurrent carotid stenosis	5.0%–22.0%

although mortality has declined over time. This reflects the systemic nature of atherosclerotic disease. Rates of perioperative stroke range from 0.3% to 2.9% and have also decreased over time. The most frequent complication of CEA is cranial nerve injury or dysfunction. Patients with high carotid bifurcation are at higher risk of cranial nerve injury. The majority of these nerve injuries are due to traction and resolve within a few days to weeks. While perioperative hemodynamic instability due to manipulation of the carotid sinus baroreceptors is not uncommon, it typically resolves within a few hours of CEA. A more severe loss of autoregulation in cerebral hyperperfusion syndrome, which occurs days after CEA. This is an acute neurologic deficit that is often preceded by a severe headache and is associated with hypertension. Cerebral hyperperfusion syndrome can result in intracerebral hemorrhage. Perioperative blood pressure control with a goal of less than 140/80 mm Hg to 0 might be preventive. While infection and bleeding are rare complications of CEA, recurrent carotid stenosis is seen on follow-up imaging in 5% to 22% of patients. However, only 3% of recurrent stenoses are symptomatic.

SUGGESTED READINGS

Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995;273(18):1421–1428.

Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG, CREST Investigators. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke. 2010;41(Suppl 10):S33–S34.

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MANAGEMENT OF RECURRENT CAROTID STENOSIS

Roopanshu Tiwari, MD, and Ying "Bei" Lum, MD

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) are prospective randomized trials that have established carotid endarterectomy (CEA) as the gold standard treatment for high-grade symptomatic and asymptomatic carotid stenosis respectively. CEA significantly reduces the risk of stroke and death compared to best medical therapy. It is a safe and durable procedure with minimal morbidity and mortality when performed by qualified practitioners on appropriate surgical candidates. More recently, the evolution of endovascular therapy has introduced carotid angioplasty and stenting (CAS) as an alternative to CEA in patients who are considered at high risk. However, both CEA and CAS are not full-proof procedures. Timely carotid artery surveillance imaging post CEA and CAS have shown that a minority of patients will develop a narrowing of the carotid artery at or adjacent to the site of revascularization. A luminal diameter narrowing of 50% or greater on duplex ultrasonography (DUS), which corresponds to a 75% or greater narrowing in the cross-sectional area, is the most commonly used criteria to define carotid restenosis. Restenosis after CEA and CAS has been reported to range from 5% to 20% depending on the definition used to characterize restenosis and the duration of follow-up. This chapter aims to discuss the risk factors, morbidity, pathogenesis, the timing of surveillance and management of carotid artery restenosis after both CEA and CAS.

INCIDENCE, RISK FACTORS, AND IMPLICATION OF RECURRENT CAROTID STENOSIS

Patients who develop recurrent carotid stenosis post CEA are more likely to be asymptomatic. About 8% to 23% will present with

high velocity, but is highly operator dependent. Intraoperative completion DUS provides detailed anatomic information about the CEA clamp site that otherwise is difficult to assess. Catheter-based angiography has similar sensitivity in detecting major technical defects of the endarterectomy. However, there is not consensus as to which criteria merit re-exploration. Most agree that minor defects should be left alone while major technical defects should be addressed. Additionally, a postoperative DUS is indicated within 30 days to assess the status of the endarterectomized vessel.

RESULTS

Recent reported perioperative mortality after CEA ranges from 0.4% to 1.9% and is mainly due to myocardial infarction (Table 2).

TABLE 2 Perioperative Morbidity and Mortality Associated with Carotid Endarterectomy

	Reported Incidence
Death	0.4%–1.9%
Stroke	0.3%–2.9%
Myocardial infarction	0.5%–1.5%
Cranial nerve injury	
Hypoglossal	4.4%–17.5%
Recurrent laryngeal	1.3%–15%
Superior laryngeal	1.8%–4.5%
Marginal mandibular	1.1%–3.1%
Glossopharyngeal	0.2%–1.5%
Spinal accessory	<1.0%
Cerebral hyperperfusion syndrome	0.4%–2.7%
Infection	0.00%–0.5%
Bleeding	0.7%–3.0%
Recurrent carotid stenosis	5.0%–22.0%

although mortality has declined over time. This reflects the systemic nature of atherosclerotic disease. Rates of perioperative stroke range from 0.3% to 2.9% and have also decreased over time. The most frequent complication of CEA is cranial nerve injury or dysfunction. Patients with high carotid bifurcation are at higher risk of cranial nerve injury. The majority of these nerve injuries are due to traction and resolve within a few days to weeks. While perioperative hemodynamic instability due to manipulation of the carotid sinus baroreceptors is not uncommon, it typically resolves within a few hours of CEA. A more severe loss of autoregulation is cerebral hyperperfusion syndrome, which occurs days after CEA. This is an acute neurologic deficit that is often preceded by a severe headache and is associated with hypertension. Cerebral hyperperfusion syndrome can result in intracerebral hemorrhage. Perioperative blood pressure control with a goal of less than 140/80 mm Hg is thought to be preventive. While infection and bleeding are rare complications of CEA, recurrent carotid stenosis is seen on follow up imaging in 5% to 22% of patients. However, only 3% of recurrent stenoses are symptomatic.

Suggested Readings

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Management of Recurrent Carotid Stenosis

Rengarajan Sooppan, MD, and Ying Wei Lum, MD

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) are prospective randomized trials that have established carotid endarterectomy (CEA) as the gold standard treatment for high-grade symptomatic and asymptomatic carotid stenosis respectively. CEA significantly reduces the risk of stroke and death compared to best medical therapy. It is a safe and durable procedure with minimal morbidity and mortality when performed by qualified practitioners on appropriate surgical candidates. More recently, the evolution of endovascular therapy has introduced carotid angioplasty and stenting (CAS) as an alternative to CEA in patients who are considered at high risk. However, both CEA and CAS are not fail-proof procedures. Timely carotid artery surveillance imaging post CEA and CAS have shown that a minority of patients will develop a narrowing of the carotid artery at or adjacent to the site of revascularization. A luminal diameter narrowing of 50% or greater on duplex ultrasonography (DUS), which corresponds to a 75% or greater decrease in the cross sectional area, is the most commonly used criteria to define carotid restenosis. Restenosis after CEA and CAS has been reported to range from 5% to 20% depending on the definition used to characterize restenosis and the duration of follow up. This chapter aims to discuss the risk factors, morbidity, pathogenesis, the timing of surveillance and management of carotid artery restenosis after both CEA and CAS.

INCIDENCE, RISK FACTORS, AND IMPLICATION OF RECURRENT CAROTID STENOSIS

Patients who develop recurrent carotid stenosis post-CEA are more likely to be asymptomatic. About 9% to 25% will present with

symptomatic neurologic events (i.e., transient ischemic attack [TIA], stroke). The incidence of recurrent carotid stenosis varies widely in the literature based on the method and time interval of surveillance. Follow-up prospective data collection from the ACAS trial using Doppler ultrasound surveillance has shown that the incidence of recurrent carotid stenosis post CEA is 4.1% in the early postoperative period (<3 months), 7.6% from 3 to 18 months and 1.9% from 18 to 60 months. Data from other studies have also shown that the average rates of recurrent carotid stenosis after CEA can be estimated to be 10% at 1 year, 3% in the second year, 2% after 3 years, and 1% after 5 years.

Several risk factors have been associated with recurrent carotid stenosis after CEA, namely continued smoking, hyperlipidemia, diabetes, hypertension, primary closure without patch angioplasty, and end-stage renal disease (Box 1). In-stent restenosis (ISR) after CAS has been attributed to similar risk factors as recurrent stenosis after CEA and to residual stenosis, use of balloon-expandable stent, stent undersizing, and deployment of multiple stents (Box 2).

Recurrent carotid stenosis post CEA increases the risk of cerebrovascular ischemia secondary to flow obstruction and thromboembolism. The risk of ipsilateral stroke after CEA is at its highest within the first 2 years after the operation and the risk decreases over time after 2 years. This can be explained by the relatively higher incidence of recurrent carotid restenosis during that time frame, which increases the risk of ipsilateral stroke. In fact, up to 50% of ipsilateral symptomatic strokes can be attributed to recurrent carotid stenosis after CEA. Not surprisingly, as the incidence of recurrent carotid stenosis decreases over time, so does the risk of developing symptomatic ipsilateral strokes after 2 years post CEA.

The real incidence of ISR after CAS is unclear, with reports ranging from 5% to 21%. The incidence of 80% or greater ISR after CAS has been reported to occur in up to 42.2% of patients and ISR of 80% or greater in as 8% at 5 years. Although ISR puts patients at increased risk of cerebrovascular events, the neointimal hyperplastic reaction seems to be associated with a reduced risk of distal embolization as compared to the initial native lesion. Several clinical trials have looked into the risk of stroke secondary to ISR. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed an increased risk of stroke at 5 years in patients who develop severe (>70%) carotid artery ISR. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) also showed similar results, with more than 70% ISR after CAS placing patients at increased risk of stroke. However, multiple other studies including the Stent Protected Angioplasty versus Carotid Endarterectomy Trial (SPACE) showed that there was no associated increased risk of cerebrovascular ischemia in patients who develop ISR at 2 years.

BOX 1 Risk Factors Associated With Recurrent Carotid Stenosis After Carotid Endarterectomy

- Smoking
- Female sex
- Diabetes
- Hypertension
- Hyperlipidemia
- [illegible] stage renal disease [illegible] dialysis
- [illegible] [illegible] [illegible] carotid artery [illegible] at [illegible] to [illegible]
- Small internal carotid artery diameter
- Prior [illegible] carotid artery injury

BOX 2 Risk Factors Associated With In-Stent Restenosis After Carotid Angioplasty and Stenting

- Female sex
- Smoking
- Diabetes
- Hypertension
- Hyperlipidemia
- End-stage renal disease
- Residual stenosis after index procedure
- Use of balloon-expandable stents
- Stent under-expansion
- Deployment of multiple stents

PATHOGENESIS OF RECURRENT CAROTID STENOSIS

Intimal hyperplasia is the primary cause of recurrent carotid stenosis in the first 2 years after CEA. The endarterectomy bed undergoes a hyperplastic reaction, which accounts for the decrease in luminal diameter in the first 2 years after carotid endarterectomy. After 2 years, luminal narrowing is secondary to atherosclerotic lesions, which are deposited throughout the artery and not necessarily confined to the endarterectomy bed. Interestingly, patients who undergo CEA for asymptomatic carotid stenosis have been observed to have a higher risk of developing carotid restenosis at 1 year compared to patients who underwent CEA for symptomatic disease (i.e., TIA). This observation can be explained by the difference in atherosclerotic plaque content in asymptomatic compared to symptomatic patients. Asymptomatic patients tend to have stable plaques that have low macrophage levels, small or absent lipid core, and low levels of matrix metalloproteinase. On the other hand, inflamed plaques with high levels of macrophages, leukocytes, and lipid rich cores have high levels of matrix metalloproteinase activity, which leads to expansive remodeling of the media and adventitia and less restenosis.

Restenosis can also be secondary to a focal reactive process such as in cases where there are iatrogenic injuries to the blood vessels (i.e., trauma from forceps, vascular clamps, and intravascular shunts). Improper surgical technique can also contribute to recurrent stenosis (i.e., residual atheroma post endarterectomy, intimal flap, patch irregularities, residual thrombus, and irregular bends and kinks in the blood vessel after reconstruction).

ISR after CAS is the likely result of neointimal hyperplasia caused by chronic inflammation secondary to endothelial dysfunction and traumatic irritation of the intima. It occurs within 2 years after the index procedure or as de novo atherosclerotic lesions after 2 years. Interestingly, patients who develop recurrent carotid stenosis after CEA have a higher risk of developing ISR if their restenosis are treated with carotid artery balloon angioplasty or stenting; thus, suggesting that some patients have an above average aggressive hyperplastic response and unfavorable biology that places them at higher risk to develop early restenosis. Carotid ISR is often detected on surveillance DUS and is categorized in a classification pattern that is similar to the one used for the coronary circulation. There are five types of ISR summarized in Table 1 and Fig. 1. Notably, type 1 lesion (focal end-mid) are the most common after CAS and type IV lesions are very often found in the diabetic population and are predictive of subsequent stent failure that will require further intervention.

METHOD OF RECONSTRUCTION AND INFLUENCE ON RESTENOSIS AFTER CAROTID ENDARTERECTOMY

The carotid artery can be reconstructed by primary closure or with patch angioplasty. Comparison of outcomes between the two has been extensively studied and there is clear and overwhelming evidence that patch angioplasty is superior to primary closure in reducing the rate of carotid artery restenosis, especially when patients continue postoperative aspirin and statin therapy. The ACAS study showed a restenosis rate of 4.6% with patch angioplasty versus 16.9% with primary closure. The CREST trial also showed a reduction in restenosis rate with patch angioplasty but no difference in stroke

TABLE 1 Different Patterns of Carotid In-Stent Restenosis

Type	Description and Characteristics of ISR Lesion
I (Focal end-stent group)	Lesions are <10 mm long and are positioned at the proximal or distal margin (but not both) of the stent. Lesions >10 mm long at both ends of the stent are defined as type I, multifocal end-stent.
II (Focal intra-stent group)	Lesions are <10 mm long and are confined to within the stent(s) without extending outside the margins. Two or more discrete lesions <10 mm long located within the stent are defined as type II, multifocal intra-stent.
III (Diffuse intra-stent group)	Lesions are >10 mm long and are confined to within the stent(s) without extending outside the margins.
IV (Diffuse proliferative group)	Lesions are >10 mm long and extend beyond the margin(s) of the stent(s).
V (Occlusion group)	Lesion have no prograde flow and no lumen is identified.

ISR, in-stent restenosis.

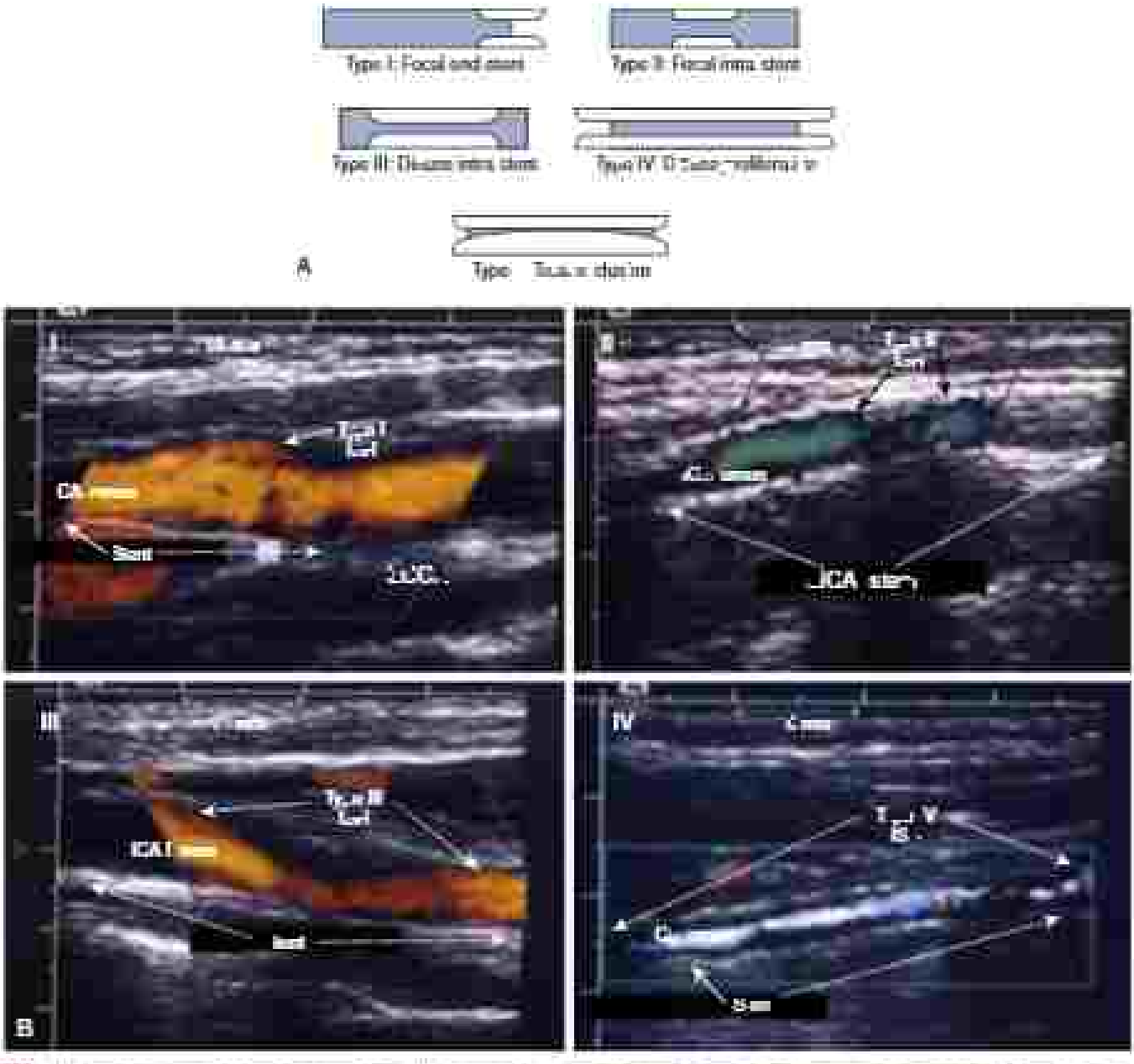

FIG. 1 (A) Type I to V carotid in-stent restenosis (ISR). (B) Representative B-mode ultrasound images of ISR corresponding to types I to IV of post-carotid angioplasty and stenting ISR. C, internal carotid artery; CCA, left common carotid artery; I, A, left internal carotid artery (Modified from [illegible] Patterns of in-stent restenosis after carotid artery stenting: classification and long-term outcomes [Chin Surg 2007;82:420–425])

rate. A Cochrane Systematic Review of the literature examined 1307 CEA operations in 1137 patients and found that patch angioplasty was superior to primary closure because there was a more than 50% reduction in occlusion and stroke rate at 1 year in the patch angioplasty group. Moreover, that study also showed that there was also a reduction in perioperative arterial occlusion and return to the operating room. Similarly, a retrospective review of 2017 CEA performed at The Massachusetts General Hospital identified primary closure as an independent risk factor for the development of restenosis. The Vascular Study Group of New England (VSGNE) review of CEA from their database from 2003 to 2008 also showed evidence that patch angioplasty significantly reduces the rate of restenosis post CEA compared to primary closure.

Some surgeons preferentially use the eversion endarterectomy technique when performing carotid endarterectomy. In this technique, the internal carotid artery is transected at the level of the carotid bulb and the distal segment of the internal carotid artery is everted and the plaque pealed away, leaving the endarterectomy bed behind. The Eversion Carotid Endarterectomy Versus the Standard Trial compared restenosis rates between standard CEA with patch angioplasty and the eversion technique. The study showed that the restenosis rates were similar in both techniques. In light of such convincing evidence from multiple studies that are in favor of conventional CEA with patch angioplasty or eversion endarterectomy over primary closure alone, the Society for Vascular Surgery (SVS) recommends patch angioplasty after conventional CEA or eversion endarterectomy in its practice management guidelines for CEA in order to decrease restenosis rate.

TYPE OF STENT AND INFLUENCE ON RESTENOSIS AFTER CAROTID ANGIOPLASTY AND STENTING

Carotid stents come in two main categories: open cell stent and closed cell stent. Open cell stents are designed to keep adjacent segments of the stent detached from one another. This design allows for better conformational change and adaptability to the vessel anatomy, but with less plaque coverage and more tissue prolapse. Closed cell stents, on the other hand, are designed with a higher density of interconnections due to more bridging of the adjacent segments. Closed cell stents offer more plaque coverage but have reduced conformability and apposition to the vessel wall. No long-term study, up to now, has shown a difference in restenosis rate between the two types of stents.

SURVEILLANCE OF RECURRENT CAROTID STENOSIS

After Carotid Endarterectomy

It is crucial to have a methodical and timely surveillance imaging schedule after CEA to assess for ipsilateral restenosis and contralateral progression of preexisting stenosis. In fact, the progression of contralateral stenosis is more common than ipsilateral recurrent stenosis. DUS is the imaging modality of choice for surveillance after CEA because it is noninvasive, cost effective, and has a sensitivity of 91% and specificity of 82% for detecting a ≥50% restenosis of the carotid artery. In its best practice guidelines, the SVS recommends surveillance imaging within 30 days postoperatively after CEA. The SVS guidelines also recommend continued surveillance in patients with 50% or greater ipsilateral restenosis or contralateral stenosis, in those who underwent primary closure of the artery after endarterectomy and in patients with high risk factors for atherosclerotic disease progression. However, there is no consensus on the timeline and the frequency of surveillance beyond the postoperative period, and this has been the subject of many debates. Since patients are more likely to develop an ipsilateral restenosis within the first 2 years after CEA, it is essential to have more frequent duplex surveillance in the early postoperative period. Most patients who develop atherosclerotic disease of the carotid artery have underlying risk factors such as smoking, diabetes, hyperlipidemia, and hypertension that inherently places them in the high risk patient category. In our practice, we surveil our patients at the 1 month, 6 month, and 1 year marks postoperatively after CEA. The subsequent surveillance schedule is then tailored to the patient's specific needs depending on their risk factors and the data from previous duplex about the progression of their disease.

After Carotid Angioplasty and Stenting

Surveillance for ISR in patients who underwent CAS is particularly important because the rate of developing restenosis after CAS is higher than after CEA, albeit most ISR are mild to moderate and require no intervention and only a minority of patients will develop high grade ISR that will require reintervention. Unlike restenosis after CEA, ISR after CAS can develop many years after the index procedure. A timely surveillance schedule is very important to identify hemodynamically significant lesions that need reintervention; however, there is no consensus on the time intervals and duration of surveillance after the procedure. As with CEA, the imaging modality of choice for surveillance after CAS is DUS. Other modalities such as computer tomographic angiography and magnetic resonance angiography can also be used to detect ISR. However, these imaging modalities tend to overestimate the degree of ISR and the results are often affected by stent artifacts. Whenever a hemodynamically significant ISR is suspected on noninvasive imaging, it is best to assess the suspected lesion with digital subtraction angiography to get a more accurate estimate of the degree of restenosis.

In our practice, patients who underwent CAS are surveilled in a similar fashion as our patients who underwent CEA. We obtain a DUS at the 1 month, 6 month and 1 year mark. Subsequent surveillance is then tailored according to DUS findings and progression of the disease. It is important to note that the velocity criteria for duplex surveillance post CAS are different from the velocity criteria used for surveillance post CEA. A summary of the velocities and corresponding degrees of restenosis post CEA versus CAS adopted by our vascular laboratory is shown in Table 2. The peak systolic velocity threshold used to correlate with the degree of restenosis is higher in CAS. The goal of duplex surveillance imaging is to identify patients who are at risk of hemodynamically significant (>70%–80%) restenosis that may result in a cerebrovascular event if not detected and intervened upon in a timely fashion. Patients found to have less than 50% stenosis do not need a rigorous surveillance schedule. Those who have 50% to 69% stenosis need closer surveillance as there are limited data available on the natural progression of such lesions. Patients with 50% to 70% restenosis need duplex surveillance every 6 months to monitor the disease progression into the severe ISR category. When 70% to 80% restenosis is identified, patients should undergo digital subtraction catheter angiography.

MANAGEMENT OF RECURRENT CAROTID STENOSIS

After Carotid Endarterectomy

In the ACAS and NASCET trials, patients who underwent CEA were concurrently treated with best medical therapy. The results established by these trials reflect the combination of CEA and best medical management. Therefore, it is imperative that all patients be placed on an antiplatelet agent (e.g., aspirin), lipid lowering therapy (e.g., statin) and their modifiable risk factors are reduced or controlled post CEA to reduce their risk of recurrent carotid stenosis. Despite best medical management post CEA, a subset of patients still develop high grade restenosis requiring surgical intervention. Reoperative CEA has a higher morbidity rate compared to primary CEA. The post procedural stroke rate is 7% and the cranial nerve injury rate is as high as 19%. Although some recent studies have shown that reoperative CEA with similar morbidity perioperative morbidity rates to primary CEA can be achieved, the risk of death, stroke, and myocardial

TABLE 2 Duplex Ultrasonography Velocity Criteria to Establish the Presence of Recurrent Carotid Stenosis in the Native Carotid Artery Post-Carotid Endarterectomy Compared With Established Velocity Criteria to Establish the Presence of In-Stent Stenosis Post-Carotid Angioplasty and Stenting

Degree of Stenosis	Native Carotid Artery	Stented Carotid Artery
0%–19%	PSV <130 cm/s	PSV <150 cm/s and ICA/CCA ratio <2.5
20%–49%	PSV 130–199 cm/s	PSV 150–219 cm/s
50%–79%	PSV 200–299 cm/s and EDV <120 cm/s	PSV 220–339 cm/s and ICA/CCA ratio >2.5
80%–99%	PSV >300 cm/s and EDV >120 cm/s, or ICA/CCA ratio >4.0	PSV >340 cm/s and ICA/CCA ratio >4.5

EDV, end-diastolic velocity; ICA/CCA, internal carotid artery/common carotid artery; PSV, peak systolic velocity.

infarction (MI) are all significantly increased in reoperative CEA compared to the primary procedure. In fact, analysis of the VISCAT registry showed a 3.9% death and stroke rate with reoperative CEA compared to 1.2% rate of stroke and death with primary CEA.

Symptomatic patients after CEA need a reoperation if their degree of restenosis is 50% or greater. The decision to operate on asymptomatic patients is more complex and requires weighing the risk of operative morbidity against the morbidity of stroke with medical management alone. To justify a reoperation in the asymptomatic population, the benefits of the operation must outweigh the risks of the operation (i.e., MI and stroke) and the risks of observation alone. The SVS and European Society for Vascular Surgery (ESVS) recommend against a reoperative intervention when the combined stroke and death rate exceeds 6% for patients with symptomatic carotid restenosis and 3% for those with asymptomatic carotid stenosis. In our practice, we initially treat asymptomatic carotid restenosis with a maximal statin and antiplatelet therapy. Surgical intervention is considered in patients who progress to high-grade restenosis despite maximal medical management.

SURGICAL TECHNIQUES FOR MANAGEMENT OF RECURRENT STENOSIS

Reoperative CEA is a high-risk operation and no specific technique has been described to offer superior results over another. Some of the techniques described include endarterectomy alone, patch angioplasty alone without endarterectomy (the patch can be saphenous vein, Dacron, or polytetrafluoroethylene [PTFE]), endarterectomy with patch angioplasty (the patch can be saphenous vein, Dacron, or PTFE), and resection of the artery with interposition graft (saphenous vein, Dacron, or PTFE; Fig. 1). In our practice, we attempt excising the previous patch, repeat an endarterectomy, and replace the old patch with Dacron or bovine pericardium. If the repeat endarterectomy is technically not feasible or leaves the artery severely compromised, our approach is to resect the artery and perform an interposition repair with translocated reversed greater saphenous vein graft preferentially. In patients who do not have suitable veins, we use PTFE for an interposition conduit. In patients who develop recurrent stenosis for the second time after a reoperation, we follow a similar algorithm to a first-time restenosis. Patients who are symptomatic with a 50% or greater restenosis and asymptomatic patients with a 70%–80% restenosis are offered an operation. However, for tertiary carotid interventions, we prefer resection of the involved segment of the artery with interposition graft with translocated reverse greater saphenous vein or PTFE.

Some surgeons prefer CAS as first-line management for secondary carotid interventions to avoid dissecting into a reoperative field hence reducing the risk of cranial nerve injury. CAS is an acceptable alternative to reoperative CEA. Both techniques have been studied retrospectively and have comparable outcomes in the endpoints of death, stroke, and MI. However, some studies have shown that CAS has a higher rate of restenosis compared to reoperative CEA. One study showed that reoperative CEA had a 50% restenosis rate of 5.9% compared to 20% for CAS, but the difference in restenosis rate was not associated with increased risk of death, stroke, or MI. A recent meta-analysis showed that patients who developed restenosis after CEA had a lower rate of tertiary restenosis when treated with CAS (4.2%) instead of repeat CEA (8.0%). Overall, current evidence appears conflicting and does not favor one technique over the other. Instead, the decision should be made on a case-by-case basis, especially taking into account the perioperative risk of MI if reoperative CEA is being considered. In anatomically suitable patients, our practice is to offer the patients CAS. However, we favor and perform reoperative CEA if the patient has a type III or severely calcified aortic arch, excessively

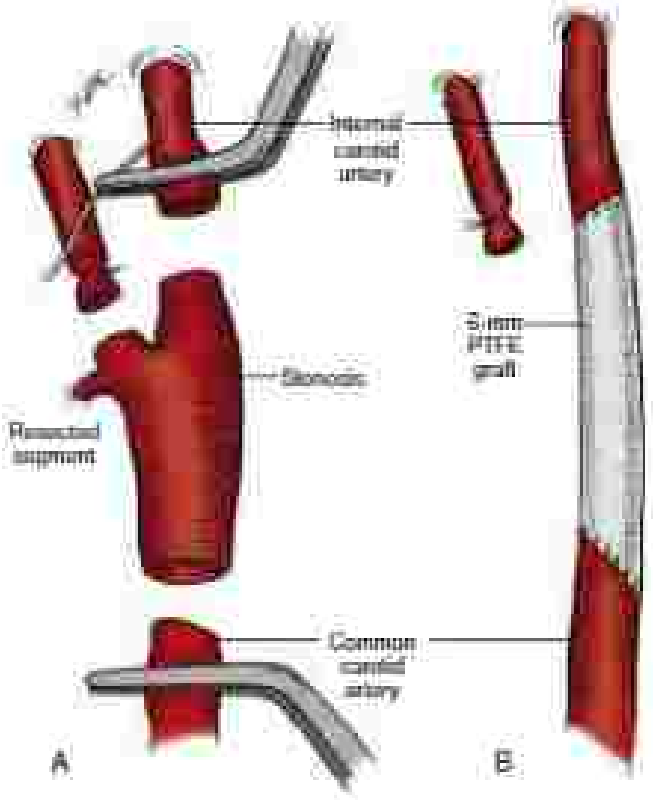

FIG. 1 (A) Resection of a diseased segment of the common and internal carotid arteries with ligation of the external carotid artery. (B) Placement of an interposition graft for reconstruction of the internal carotid artery circulation, in this case using polytetrafluoroethylene (PTFE). Reverse saphenous vein graft or Dacron additionally may be utilized. This is our preferred technique for management of tertiary recurrent carotid stenosis and for management of recurrent in-stent stenosis when endovascular options are not technically feasible.

tortuous, severely calcified and/or long segment stenosis of the internal and/or common carotid artery.

After Carotid Angioplasty and Stenting

The management of ISR after CAS is a subject of many debates, especially for the asymptomatic patient population. There are no prospective trials that have established time tested practice guidelines for the management of ISR after CAS. The consensus among most surgeons is that patients who are symptomatic and have an ISR of 50% or more require a reintervention. Patients who are asymptomatic with high-grade ISR of 70% or more on surveillance duplex should be considered on a case by case basis, taking into account the anatomy of their stenosis, lesions and their perioperative risk of stroke and death.

Endovascular techniques described to treat ISR after CAS include balloon angioplasty alone, repeat CAS alone, or a combination of repeat CAS and balloon angioplasty. Balloon angioplasty can be achieved by using a regular angioplasty balloon, a drug coated balloon, or a cutting balloon. Repeat stenting can be done with either a drug eluting or a regular stent. There are no prospective data that have established one technique to be superior to another. However, because ISR is caused by intimal hyperplasia many surgeons favor the use of balloon angioplasty with a cutting balloon over regular balloon angioplasty alone because of the reduced rate of recurrent stenosis of 4.2% with a cutting balloon as compared to 15% to 23% with a regular balloon. Fig. 3 shows an example of a type II carotid artery in-stent stenosis treated with angioplasty and stenting that showed improvement on both the completion digital subtraction angiography study and noninvasive duplex study 1 month postoperatively.

Open surgical techniques (i.e., CEA or carotid artery bypass/interposition grafting with translocated and reversed great saphenous vein or PTFE) can also be used for management of ISR after CAS, especially in cases where there are primary stent thrombosis, technical failure during stent deployment, heavily calcified lesions that precluded optimal stent apposition to the vessel wall resulting in an inadequate technical result, and pericarotid lesions that cannot be traversed using endovascular methods. In our practice, we prefer to manage ISR after CAS using angioplasty or repeat CAS if the lesion is anatomically amenable to endovascular intervention. Open repair is reserved for cases where the patient has a type III or severely calcified aortic arch, excessively tortuous, severely calcified and/or long segment stenosis of the internal and/or common carotid artery. We preferentially attempt stent removal with CEA and patch angioplasty and reverse carotid bypass or interposition graft with greater saphenous vein or PTFE for cases where an endarterectomy endpoint cannot be safely achieved without compromising the integrity of the vessel wall proximal or distal to the endarterectomy bed.

SUMMARY

Symptomatic and asymptomatic carotid artery stenosis are routinely treated with either CEA or CAS. The majority of patients have excellent long term results. However, there is a small subset of the patient population who have an aggressive disease biology and tend to develop severe intimal hyperplasia that causes recurrent stenosis of the carotid artery after both CEA and CAS. Routinely scheduled surveillance DUS is the best imaging modality to detect these lesions, such that timely intervention can be offered to the patients to prevent cerebrovascular events. Symptomatic patients who are found to have 50% or greater stenosis on duplex or asymptomatic patients with 70% or greater stenosis after both CEA and CAS are candidates for reintervention. The procedure of choice for a secondary intervention depends on the

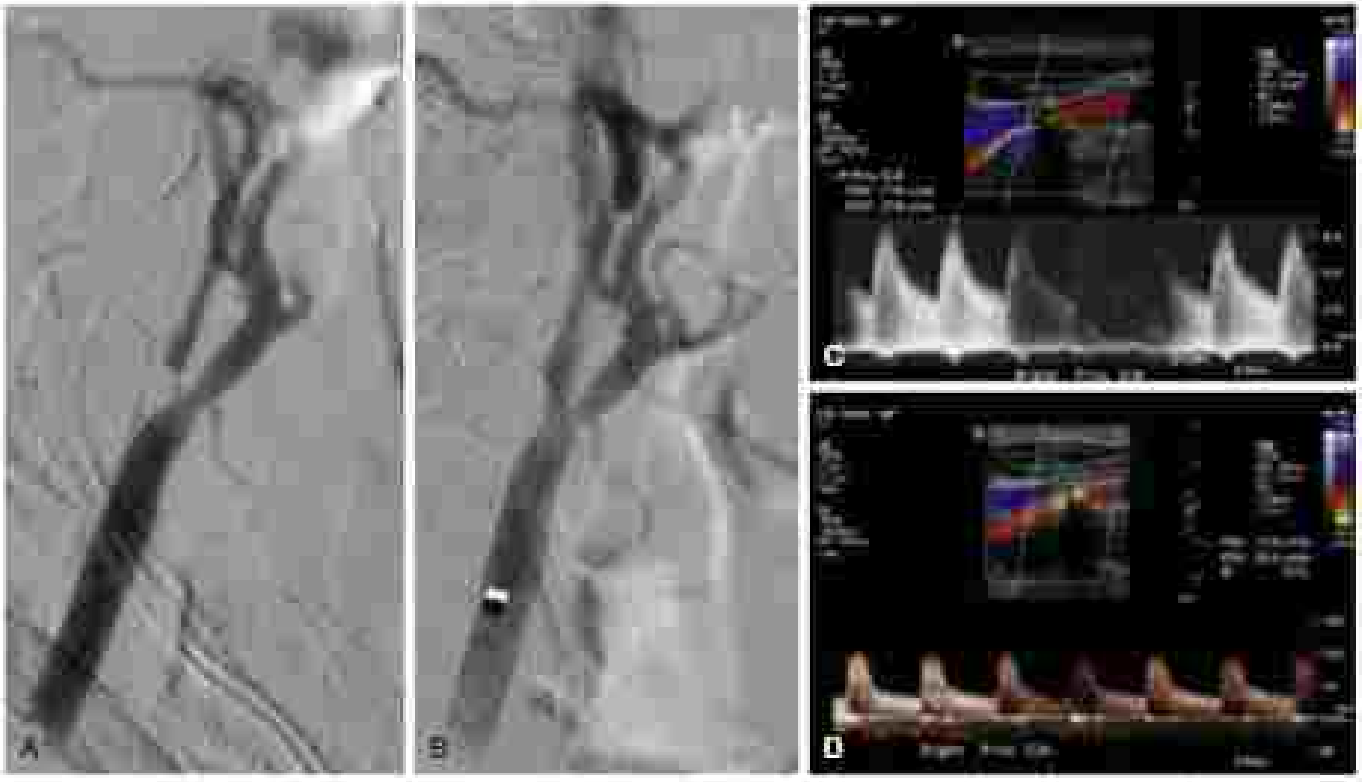

FIG. 3. Distal (type II) carotid in-stent restenosis (ISR) in a 78-year-old man with high-grade asymptomatic ISR a years after initial carotid angioplasty and stenting. (A) Carotid angiography demonstrated a string sign of the proximal internal carotid artery (ICA) with approximately 99% stenosis. (B) The restenosis was managed with carotid angioplasty with embolic protection followed by placement of a self-expanding 7 × 30 mm nitinol nonpreferential angiogram is demonstrated. (C) Preoperative duplex ultrasound demonstrated severe ISR with peak systolic velocity (PSV) of 710 and end-diastolic velocity (EDV) of 27 cm/s and ICA/common carotid artery (CCA) ratio of 12.3. (D) Duplex ultrasound obtained 1 month postoperatively demonstrated PSV of 136, EDV of 33 and ICA/CCA ratio of 2.5.

patient functional status, comorbidities, and anatomy of the tandem lesion. All patients should be on maximal medical treatment with an antiplatelet agent and a lipid lowering agent, preferably a statin.

Suggested Readings

Ronald Lee H, et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *The Lancet Neurology*. 2006;5(11):930–935.

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Lal Bhagesh K, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomized controlled trial. *Lancet Neurology*. 2013;12(10):955–963.

Ioannidis _, et al. Carotid artery endarterectomy versus carotid artery stenting for restenosis after carotid artery endarterectomy: a systematic review and meta-analysis. *World* Journal 2010.

Balloon Angioplasty and Stents in Carotid Artery Occlusive Disease

Dawn J. Garrido, MD, Daniel E. [illegible], MD, and Charles S. [illegible], MD, MCA

Nearly 800,000 people have a stroke each year in the United States, making it the third leading cause of death in people of years of age and older and the leading overall cause of serious, long-term disability. The total cost nationally for stroke-related illnesses is approximately $34 billion per year. The majority of strokes (about 87%) are ischemic in nature. Of these, an estimated 20% to 30% are related to an atherothrombotic or thrombotic event caused by carotid occlusive disease.

The first successful carotid endarterectomy (CEA) was done in 1953 by Dr. Michael DeBakey to prevent stroke. In the early 1900s, the efficacy of CEA came under intense scrutiny, largely due to highly variable perioperative stroke and mortality rates coupled with increasing frequency of the procedure being done. In response, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS) were undertaken, and they established the efficacy of carotid endarterectomy over medical management for both symptomatic and asymptomatic carotid stenosis.

With the advent of endovascular interventions for other arterial occlusive lesions, carotid artery balloon angioplasty and stenting (CAS) was advocated as an alternative to CEA for treatment of carotid atherosclerosis. The first percutaneous transluminal carotid angioplasty was performed by Kerber in 1980. Although both CAS and CEA can be performed using local anesthesia with similar operative and hospitalization times, CAS offers the advantage of percutaneous groin arterial access rather than a neck incision for carotid artery exposure, which carries risk of mechanical pain, cranial nerve injury, wound infection, and neck hematoma.

In 2010, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST 1) compared the outcomes of CAS with those of CEA for patients with symptomatic or asymptomatic extracranial carotid stenosis. The trial demonstrated the relative safety of CAS in both symptomatic and asymptomatic patients. However, the data showed a periprocedural stroke rate for CAS of 4%, with the highest risk for periprocedural stroke being among patients of advanced age (>70 years) and with recent (within 2 weeks) neurologic ischemic symptoms. In the CEA arm, the stroke rate was 2.3%. Myocardial infarction (MI) was noted to be more frequent with CEA than with patients undergoing CAS (2.3% vs 1.1%). However, these are numbers that should be interpreted in light of the fact that patients with a stroke complication were documented to have a worse quality of life than those who had MI.

Interpretation of the results of CREST 1 have been intensely debated and influenced by biases for or against CAS or CEA. Stenting enthusiasts argue that statistical similarity in the primary composite endpoint establishes equipoise for the procedures. In contrast, others question the inclusion of MI as a component of the primary endpoint for procedures that have stroke prevention as their principal objective. They argue for the use of only stroke and death as a more appropriate composite endpoint, which significantly favors endarterectomy in CREST 1.

Suffice it to say, CREST 1 has produced valuable level I data comparing CAS with CEA, but the trial did not fulfill the expectation of some of proving undeniably that CAS is better than or even equal to CEA. At the time of publication, the CREST 2 trial is in progress. Briefly, it consists of two independent multicenter, randomized controlled trials of carotid revascularization and intensive medical management versus medical management alone in patients with asymptomatic high-grade carotid stenosis. One trial randomizes patients in a 1:1 ratio to endarterectomy versus endarterectomy and another randomizes patients in a 1:1 ratio to carotid stenting with embolic protection versus no stenting. Medical management is uniform for all randomized treatment groups and is centrally directed. Results of CREST 2 are anxiously awaited.

PREPROCEDURAL CONSIDERATIONS

Preprocedural assessment includes a complete history focused on cardiovascular elements and on symptoms of neurologic or ocular ischemic events related to the carotid circulation. A thorough physical examination with an emphasis on palpation of pulses, auscultation for bruits, and complete neurologic assessment is of utmost importance. The decision about advising for or against CAS is influenced by current CMS guidelines regarding indications for the procedure. These guidelines are listed in Boxes 1 and 2.

Preprocedural imaging should include carotid duplex scan, computed tomographic angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance angiography. These imaging modalities give important information about the presence and hemodynamic significance of carotid occlusive disease, the condition of the brain parenchyma, the presence of additional intracranial or extracranial vascular anomalies (e.g., vascular aneurysms, vascular malformations), and the anatomy of the aortic arch.

Prior to CAS, patients should begin dual antiplatelet therapy. Our regimen consists of clopidogrel 75 mg daily and aspirin 81 mg daily beginning 5 to 7 days before the procedure. In emergency circumstances, when antiplatelet therapy has not been started before the procedure, we use a loading regimen of clopidogrel 600 mg and aspirin 325 mg given at the time of the intervention. In addition, for patients who have been taking antiplatelet therapy on a chronic basis,

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Suggested Readings

Brott TG, et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurology*. 2009;8(11):908–917.

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BOX 1 Indications for Carotid Stenting According to the Centers for Medicaid and Medicare Services

- Patients who are at high risk for CEA and who also have symptomatic carotid artery stenosis >70%
- Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%
- Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis >80%

Medicare coverage is limited to patients having these indications and to procedures performed using Food and Drug Administration–approved carotid artery stenting systems and cerebral protection devices.
CEA, Carotid endarterectomy.

BOX 2 Patients at High Risk for Carotid Endarterectomy According to Centers for Medicaid and Medicare Services

- Congestive heart failure class III/IV
- Left ventricular ejection fraction <30%
- Unstable angina
- Contralateral carotid occlusion
- Recent myocardial infarction
- Previous CEA with recurrent stenosis
- Prior radiation treatment to the neck
- Other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCTICR, CARESAGE, SAPPHIRE, BEACH, and MAVERIC II.

CEA, Carotid endarterectomy.

we typically give a smaller loading dose of clopidogrel (150 to 300 mg) immediately after the intervention. If oral administration is not possible, clopidogrel can be given via nasogastric tube, aspirin can be given similarly or per rectum (300 or 600 mg suppository).

There are two major decisions to consider in planning CAS. Since the procedure is traditionally performed percutaneously, the first decision is the choice of access vessel. The second decision is what cerebral protection device, if any, should be used. Of these decisions, the former must be thoroughly assessed to ensure the most suitable platform to safely deliver the interventional devices. The latter is highly dependent on operator preference, but we encourage using one of the commercially available cerebral protection devices.

Traditionally CAS is performed via a percutaneous transfemoral arterial approach. Assessment of the iliofemoral arterial system and evaluation of the arch anatomy via CTA will determine the suitability of this access as a successful platform to deliver the treatment. The presence of an easily palpable femoral pulse strongly suggests that femoral access is suitable. On the contrary, the absence of a femoral pulse should trigger exploring other access options. The presence of a type III or bovine aortic arch, or severe arch atheroma, or of prior aortic or cervical arterial procedures each complicate the use of the femoral arteries as the access vessel and can potentially increase the risk of cerebral embolization.

TRANSFEMORAL APPROACH FOR CAROTID ANGIOPLASTY

Provided that the patient has suitable iliofemoral and aortic arch anatomy, the transfemoral approach is usually chosen. The patient is placed supine on the angio table. Topographic fluoroscopic evaluation of the chest and the neck is performed prior to prepping to identify objects such as wires, leads, or other previously inserted devices that would interfere with imaging. The range of motion of the C-arm is also evaluated to make sure it will rotate freely and away from other equipment in the procedural room.

We use local anesthesia at the groin access site when performing a transfemoral approach to afford patient comfort while also being able to assess neurologic function during the procedure. At certain times during CAS, the patient is asked to intermittently squeeze a neurologic testing device held in the contralateral hand for motor function and to count verbally to assess cognitive function.

To facilitate accurate entry, the chosen femoral artery is accessed under ultrasound guidance with a micropuncture needle that is subsequently exchanged over a micro wire for a micropuncture sheath using the Seldinger technique. If this step goes smoothly, we do not perform an access arteriogram. If there is any question about the appropriateness of the vascular access, an arteriogram should be performed through the micropuncture sheath and any consequential iliofemoral lesion identified should be managed prior to continuing with the planned intervention.

Once the access is deemed satisfactory, systemic anticoagulation therapy is initiated either with intravenous heparin bolus administration at 100 U/kg wt. for those patients where heparin is contraindicated, bivalirudin (Angiomax) at 0.75 mg/kg intravenous bolus, followed by 1.75 mg/kg per hour intravenous infusion. During the procedure, activated clotting times are maintained between 250 and 300 seconds.

A standard 0.35 straight tip wire is advanced just distal to the aortic arch under fluoroscopic guidance. The micropuncture sheath is exchanged for a 90 cm 6 F sheath, and the tip is advanced to the proximal thoracic aorta. Over the same wire a 5 Fr or 6 Fr pigtail catheter is advanced retrograde through the arch into the proximal ascending aorta. The C-arm is positioned at 30 to 40 degrees in the left anterior oblique orientation and arch aortography is performed via the pigtail catheter using 15 to 20 mL of contrast by either power or hand injection. This imaging should provide sufficient anatomic detail for choosing an appropriate catheter to selectively cannulate the common carotid artery on the side of the pathology.

Typical aortic arch anatomy allows for use of a selective catheter with a simple curve, while increasingly complex and tortuous aortic arch anatomy requires the use of selective catheters that have either an intermediate curve or a complex curve. The pigtail catheter is then exchanged over a guidewire and the chosen catheter is advanced to the previously mapped area of interest. We use a floppy glide wire to select the common carotid with the aid of the catheter. The catheter is advanced to a reasonable purchase but kept proximal to the level of the carotid bulb. The guidewire is then exchanged for a stiffer wire and the 6Fr sheath is advanced either over the catheter or by exchanging the catheter for the sheath introducer to the distal common carotid artery.

If the purchase on the wire is not enough to advance the sheath, angiographic mapping and super selective cannulation of the external carotid artery (ECA) often provides the required strength to advance the sheath into the common carotid (Fig. 5). Extreme care is given to avoid introduction of microthrombi and tiny air bubbles by frequent wiping of guidewires with Telfa nonadherent strips moistened with heparinized saline and by meticulous flushing of catheters and sheaths with heparinized saline solution.

After successful cannulation of the common carotid artery, a distal filter typically is used for embolic protection. The distal filter, attached to a 0.014 inch wire, is passed through the sheath, carefully maneuvered through the carotid stenosis under fluoroscopic control, and placed in the distal cervical internal carotid artery (ICA), where it is deployed with removal of its covering sheath. Very tight carotid stenosis that cannot be safely negotiated with the tip of the embolic protection device may require use of a low profile microcatheter and steerable microwire. Occasionally, predilation of a tight stenosis with a low profile coronary angioplasty balloon may be necessary to allow subsequent crossing of the lesion with the distal filter. Also, problems imposed by vessel angulation and tortuosity can be resolved with use of a "buddy wire" to slightly straighten the anatomy and facilitate

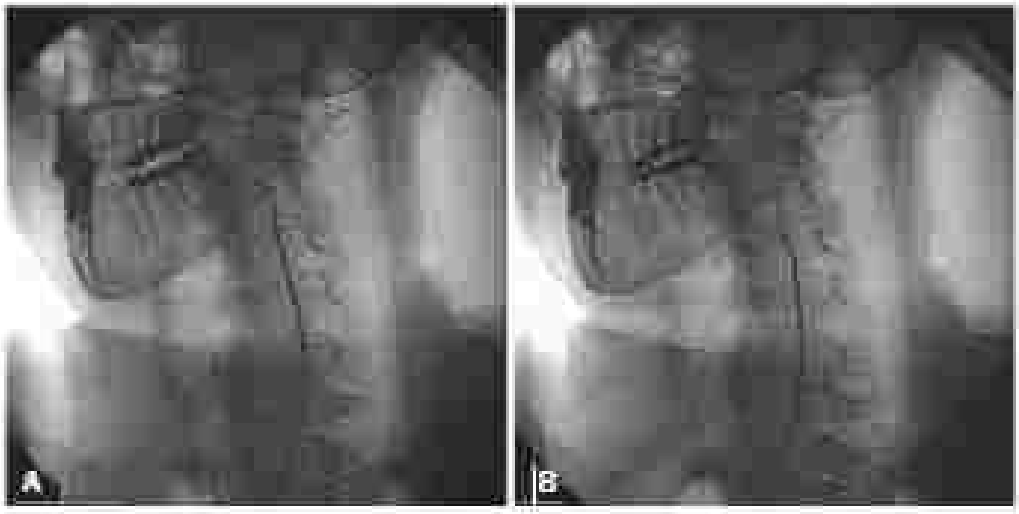

FIG. 1 (A) Selective injection to document catheter location in a posterior branch of the external carotid artery before placement of the exchange-length wire used for positioning of the long sheath into the distal common carotid artery. (B) Wire placement into the external carotid artery branch through the ascending catheter demonstrates vessel perforation by the wire; must be readily managed with manual compression against the posterior neck muscles.

crossing of a lesion by the distal filter, angioplasty catheter, or stent. Furthermore, for situations in which passage of the distal filter is difficult, maneuvers such as having the patient take deep breaths, having the patient turn the head far to one side or the other, or carotid manual pressure on the side of the patient's neck by an assistant can be helpful.

The stent is advanced over the wire to cover the carotid lesion. Because most lesions occur near the carotid bulb, tapered stents are better suited to accommodate any size mismatch of the common carotid and the internal carotid (Fig. 2). If a residual stenosis of more than 30% is present after stent placement alone, post deployment balloon angioplasty is typically done with a balloon that is 5, 5.5, or 6 mm in diameter and 20 mm in length within the confines of the stent. Post deployment balloon angioplasty is used to achieve an angiographically acceptable but not necessarily perfect result (Fig. 3).

The balloon angioplasty catheters and the carotid stent are passed into position over the wire attached to the distal filter. The same wire is used for passage of a retrieval sheath that captures the filter along with any microemboli that have been trapped during the procedure. After retrieval and removal of the filter and its wire, completion arteriograms are obtained of the treated carotid artery and of the cerebral territory that it supplies with injection of contrast through the long sheath. The long sheath is then removed over its dilator and a pushewire to avoid vessel trauma during exit. Systemic anticoagulation therapy is discontinued. After sheath removal, the femoral artery puncture site is sealed with either manual compression or use of a closure device.

TRANSCAROTID APPROACH FOR CAROTID ANGIOPLASTY

For patients with challenges of the aortic arch mentioned previously, femoral access may not provide a reliable or safe way to deliver the therapy. In such cases, transcarotid artery stenting (TCAR) approach offers an acceptable alternative. We perform this intervention using a superficial cervical plexus nerve block on the side of the procedure. Alternatively, general anesthesia with motor and sensory evoked potentials can be employed.

A transverse incision is made at the base of the neck, preferably in right territory. The sternocleidomastoid muscle is exposed and retracted laterally. The vagus nerve and internal jugular vein are identified and preserved. A 3- to 4-cm segment of the common carotid (CCA) artery is exposed, and the patient is systemically heparinized (Fig. 4). The CCA is accessed in the same manner as in the percutaneous sequence, including micropuncture, exchange for a 45-cm 6Fr sheath, systemic heparinization, crossing the lesion and deployment of the filter, delivery of the stent, and posttreatment dilation as needed.

Transcarotid artery stenting is still dependent on the presence of favorable neck anatomy. A short, thick neck can make access and control of the CCA challenging, and scarring from prior CEA can limit the space available for manipulation of endovascular devices. The exchange and manipulation of wires, sheaths, and stent devices are severely restricted when the distance from the plaque to the arterial puncture is short. Even with routine exchanges, the risk of embolization and dissection is increased. To overcome these challenges, we have modified the TCAR procedure by using a prosthetic arterial conduit. This technique has been used successfully in other endovascular procedures, such as iliac artery prosthetic conduits for aortic endograft delivery, and it requires no special training or devices. We believe this provides a stable access route for CAS with sufficient room to maneuver even in the setting of constrained neck anatomy.

When employing a conduit, the common carotid is exposed as mentioned above. After systemic heparinization, the CCA is controlled, and a longitudinal arteriotomy is performed. A 6-mm PTFE conduit is anastomosed to the CCA in end-to-side fashion (Fig. 5). In cases with a steep angle at the clavicle, the proximal end of the graft is tunneled and brought out through a counter incision on the anterior chest wall. The free end of the conduit is secured with Rumel's tourniquet and, with the patient in Trendelenburg position, the conduit is de-aired and flushed with heparin saline. A 45-cm sheath is advanced into the conduit to provide a stable platform for delivery of an embolic protection device and deployment of the stent as described previously (Fig. 6). At completion of the intervention, the conduit is transected close to the surface of the CCA and closed to prevent narrowing, effectively creating a patch angioplasty. The neck incision is closed routinely.

EMBOLIC PROTECTION DEVICES

Currently, the techniques to provide protection from embolic events during CAS are based on one of the following three principles: (1) distal balloon occlusion of the ICA, (2) filters in the distal ICA, and (3) flow reversal from the ICA by proximal and ECA balloon occlusion (Fig. 7).

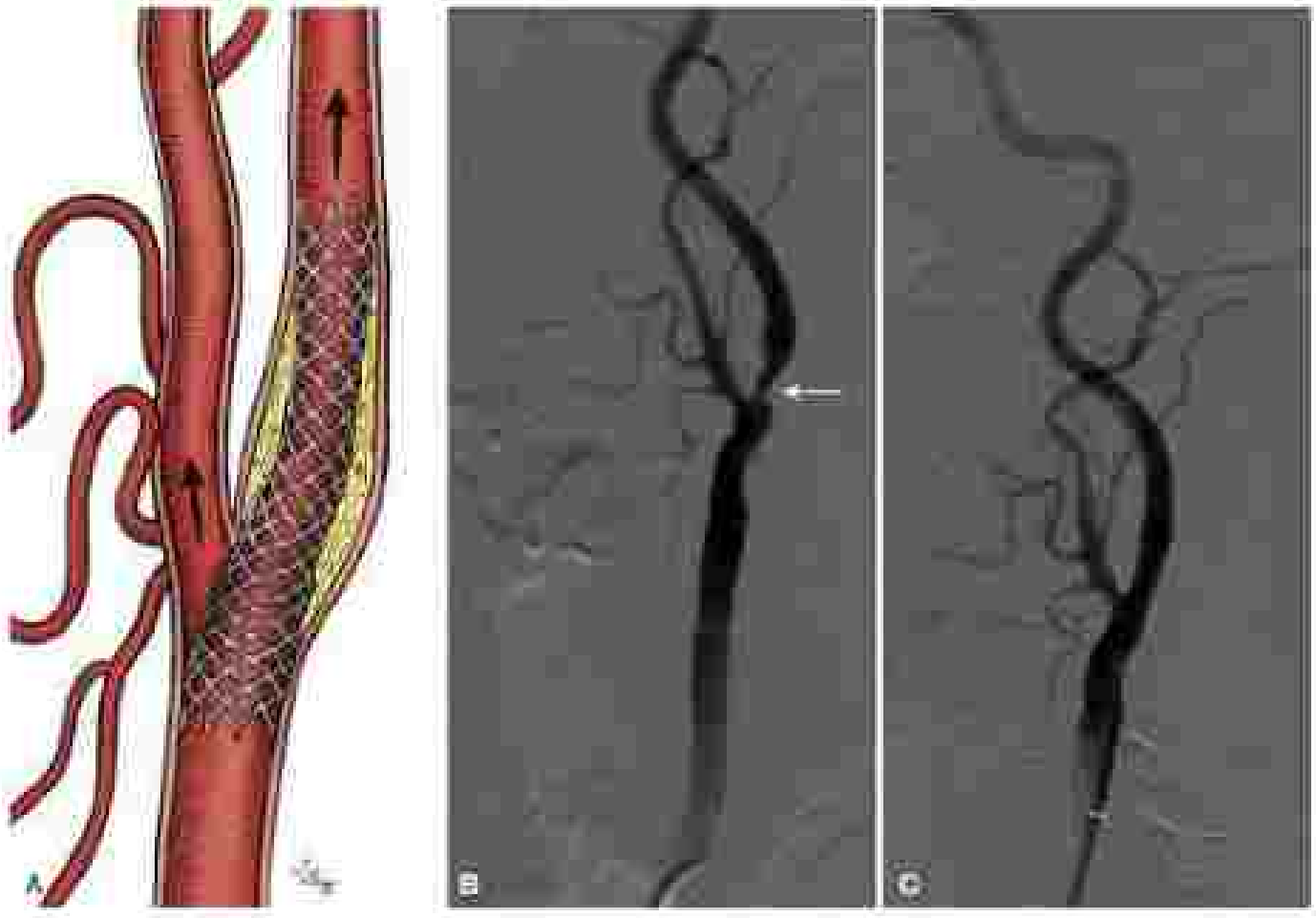

FIG. 2 (A) Schematic representation of a stent deployed across the carotid bifurcation to treat a proximal internal carotid artery lesion. Blood flow continues into the external carotid artery through the interstices of the stent. (B) Digital subtraction arteriogram (DSA) of a left common carotid injection, lateral oblique projection showing a severe stenosis in the proximal internal carotid artery (arrow). (C) Completion DSA after placement of a stent across the carotid bifurcation. Note correction of the internal carotid artery stenosis with continued perfusion of the external carotid artery and its branches. (A, courtesy Lynn Gregg, copyright 2018 Society of Interventional Radiology.)

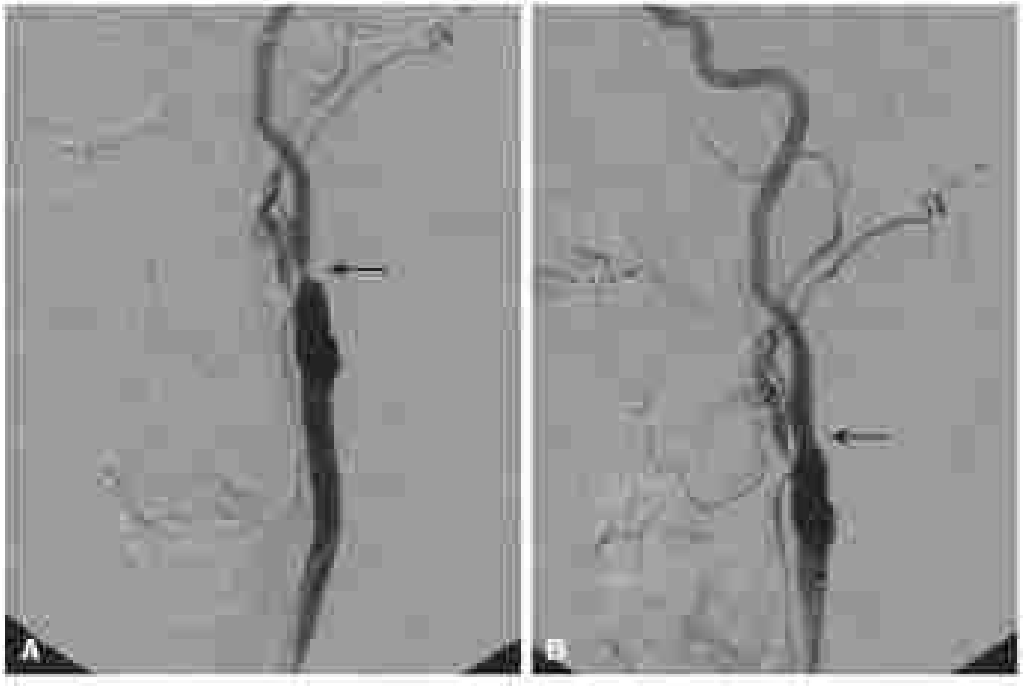

FIG. 3 (A) Digital subtraction arteriogram (DSA) of a left common carotid injection, lateral oblique projection showing severe stenosis in proximal internal carotid artery (arrow). (B) Completion DSA after carotid artery stenting. Note the residual mild stenosis (arrow) at the site of the lesion, which was judged acceptable even though not angioplastied further.

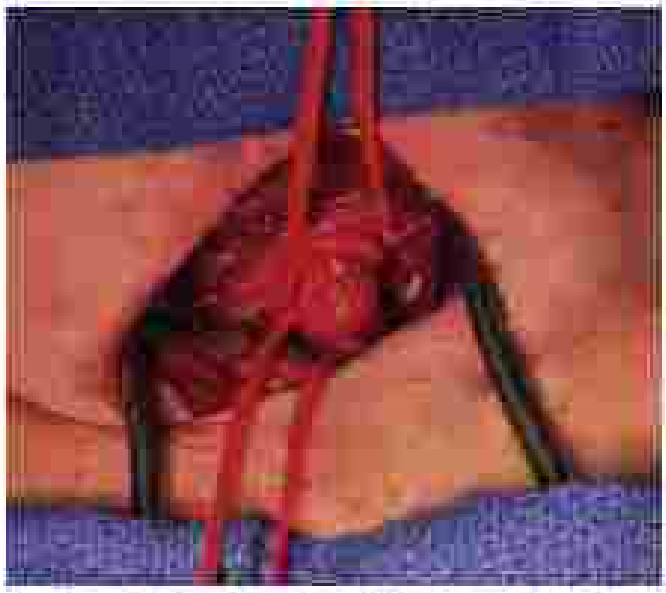

FIG. 4 Exposure of the common carotid through an oblique incision at the base of the neck in the right territory of the appropriate side. Dissection is then carried deep between the two heads of the sternocleidomastoid to expose a 3- to 4-cm segment of the common carotid artery (From Mesas IV, Khalifeh A, Jiménez CR, et al. Transcervical carotid artery stenting using a proximal carotid cardiac outflow occlusion balloon as a novel surgical technique. Ann Vasc Surg. 2018;51:1–7.)

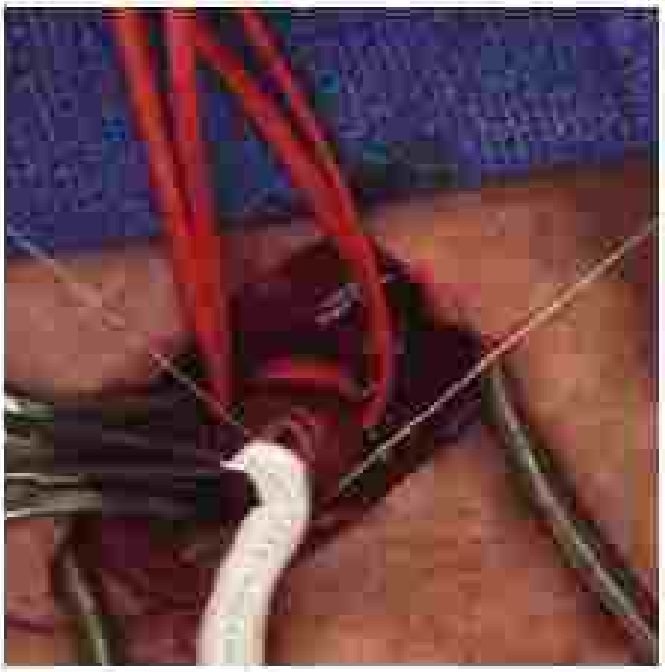

FIG. 5 Following systemic heparinization, the common carotid artery is controlled with vessel loops and clamped, and a longitudinal arteriotomy is performed. The 6-mm PTFE conduit is anastomosed to the vessel in end-to-side fashion and the proximal vessel is then unclamped, flushing the conduit with blood. (From Mesas IV, Khalifeh A, Jiménez CR, et al. Transcervical carotid artery stenting using a proximal carotid cardiac outflow occlusion balloon as a novel surgical technique. Ann Vasc Surg. 2018;51:1–7.)

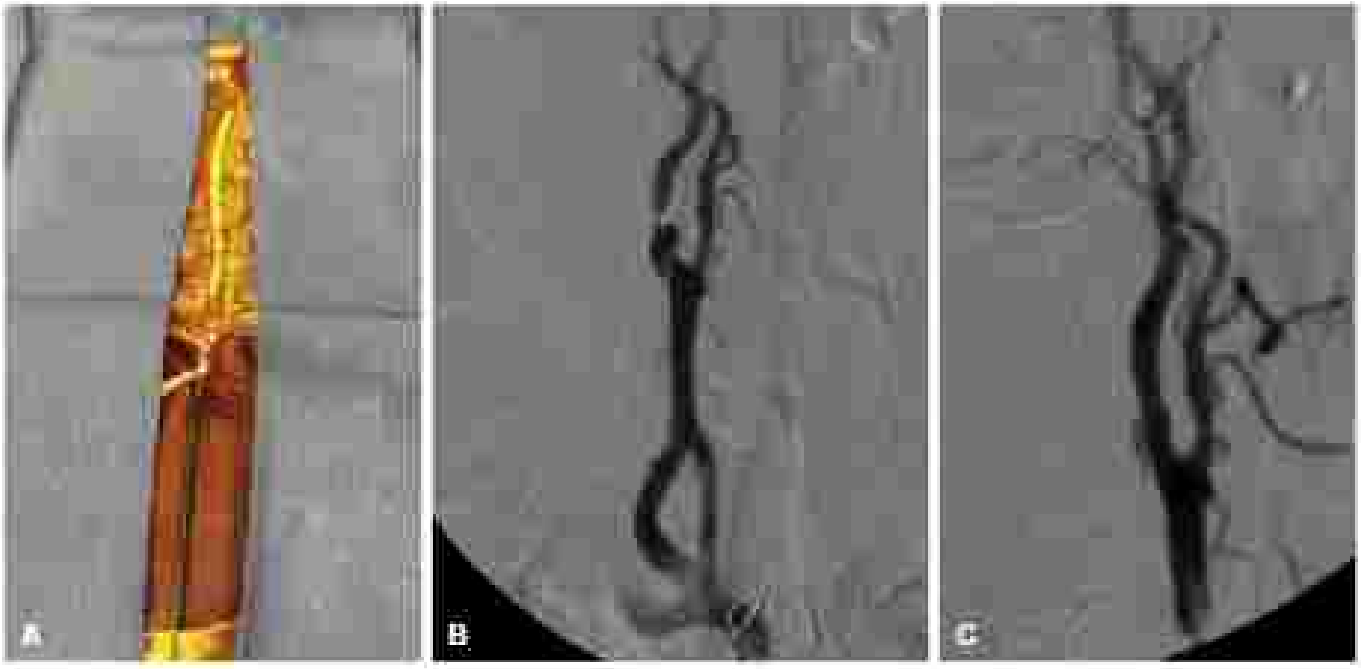

FIG. 6 (A) Kassiotis Investigator is used to access the end of the conduit and the conduit is flushed with heparin saline solution. A 90° sheath is then advanced through the conduit to provide a stable platform for embolic protection device and stent deployment. (B) Digestic angiography is performed to visualize the lesion and establish a roadmap. The embolic protection device is deployed and a second guidewire is placed to guide placement of the self-expanding carotid stent. (C) Once the stent is deployed, flow is confirmed by completion angiogram. The embolic protection device is removed and the conduit is assessed and oversewn as a patch. (From Mesas IV, Khalifeh A, Jiménez CR, et al. Transcervical carotid artery stenting using a proximal carotid cardiac outflow occlusion balloon as a novel surgical technique. Ann Vasc Surg. 2018;51:1–7.)

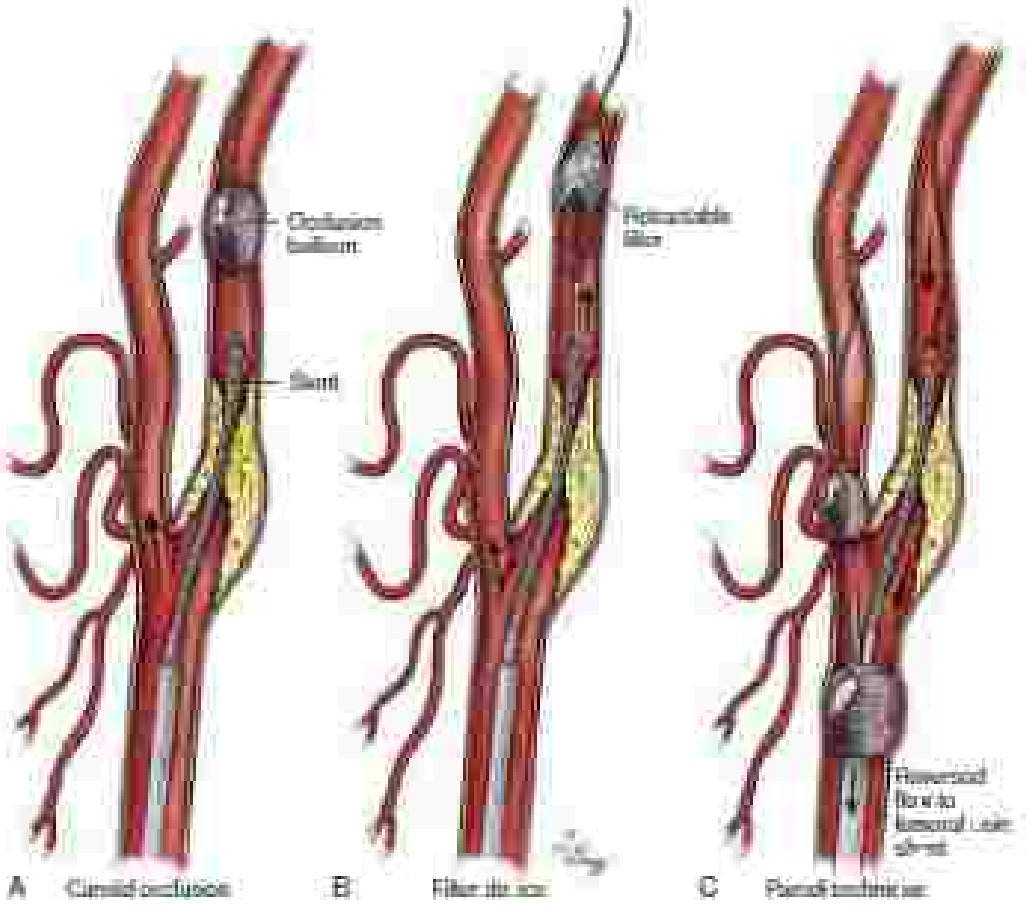

FIG. 7 Schematic representation of the different methods of embolic protection device. Arrows indicate the direction of blood flow. (A) Distal occlusion. Stenting is performed with internal carotid artery flow temporarily interrupted by inflating a balloon within the distal internal carotid artery. After stent deployment and after dilation, stagnant blood proximal to the balloon, which may contain plaque debris, is aspirated through the delivery catheter. After aspiration, the distal space below the balloon is flushed with saline solution to clean any remaining material from the internal carotid artery. The balloon is then deflated and removed. (B) Distal filtration. A filter is advanced through the stenosis and deployed in the distal internal carotid artery by withdrawing its constraining sheath. After stenting, a recovery catheter is used to retrieve the filter and its contents. (C) Proximal protection. During stenting, two occluding balloons are inflated, one in the common carotid artery and the other in the external carotid artery. Flow reversal is created either with active aspiration from the delivery catheter in the common carotid artery distal to the common carotid artery balloon or with directing flow from the catheter to a sheath in the femoral vein. With use of a system that returns blood to the femoral vein, a filter is used within the construction to trap debris from the carotid plaque. (Courtesy Cook Group, copyright 2005 John F. Eidem, commercial relationship.)

Distal protection with either balloon or filter has the disadvantage that the carotid lesion must be crossed before initiation of cerebral protection. Nevertheless, because of simplicity and ease of use, combined with avoidance of carotid flow interruption, distal protection with a filter has become the most commonly used method for embolic protection. However, transcranial Doppler scan studies have shown that particles smaller than the pore size of the filters (60–140 μm) can flow through the filter and evade capture. Such microemboli may be associated with new white lesions on the diffusion weighted MRI of the brain, but the clinical consequences of this "controlled embolization" are uncertain.

Embolization can also occur while crossing the lesion prior to deploying the device intended to prevent them in the first place. Incomplete apposition of the filter rim to the vessel wall may allow emboli of various sizes to pass around the filter. Furthermore, filters occasionally can be difficult to retrieve, and they may become occluded from obstructing debris captured during CAS.

The MoMa Ultra device (Medtronic) is the only available Food and Drug Administration approved flow reversal embolic protection device. It is a catheter with two balloons, one of which is placed in the ECA and other in the CCA, both mounted on a single sheath. A working channel allows delivery of the stent. After stenting, blood in the ICA is aspirated until clear of debris through the same working channel. The retrieved blood is then filtered and delivered back to the patient via a venous cannula placed percutaneously in the femoral vein. The concept of proximal protection is appealing because crossing the lesion with the protection device is not required.

Recent reports suggest that proximal protection, in experienced hands, is associated with low risk of microembolic events during CAS, acceptable 30 day stroke and death rates, low incidence of femoral access complications, and low (<1%) rate of patient intolerance to temporary proximal occlusion. In addition, proximal embolic protection provides an option when marked arterial tortuosity or a limited landing zone precludes use of distal protection. Nevertheless, clinicians have been slow to adopt proximal protection devices because they require larger sheath access (9Fr or 8.5Fr), are more complicated to use than distal filter devices, and may be poorly tolerated by patients with inadequate intracranial collateral circulation. Also, this method of embolic protection has the disadvantage of limiting the ability of the operator to visualize angiographically the precise location of the lesion during stent deployment.

PERIPROCEDURAL MANAGEMENT

Distal embolization is a principal concern with CAS, but the consequences of cerebral embolic events vary widely. Microemboli may produce white lesions on diffusion-weighted MRI scan without apparent neurologic sequelae. Larger emboli may produce a small stroke by MRI criteria yet remain clinically silent, or they may cause devastating neurologic deficit, depending on the function of the cerebral tissue that has been damaged. Therefore, operators who perform CAS must be familiar with the anatomy of the brain and its vasculature so that intracranial cerebral branch vessel occlusion can be readily identified. It is equally important that operators be thoroughly familiar with normal neurologic function and the clinical manifestations of stroke. In addition, dedicated expert neurologic support is essential for a successful carotid stenting program.

Inflation of an angioplasty balloon in the proximal internal carotid artery sometimes provokes bradycardia and hypotension. This must be addressed with intravenous atropine 0.6 mg either preemptively before balloon postdilation or effectively when it occurs. Patients with severe aortic stenosis may be intolerant of even mild bradycardia and hypotension with balloon inflation, and consideration should be given in such patients to using monitored anesthesia and placing a temporary pacemaker prior to the procedure. Bradycardia and hypotension with carotid balloon angioplasty are rarely seen in patients who have previously undergone CEA, probably because of the denervating effect of surgical dissection near the carotid bulb.

Distal cervical ICA vasospasm is sometimes induced by catheter or wire manipulation or by distal filter or balloon placement. Avoidance of movement of the distal filter once deployed helps to minimize vasospasm at this site. Resolution of the vasospasm often occurs spontaneously but can be hastened with transcatheter administration of nitroglycerin (200 μg bolus) into the involved artery.

As mentioned previously, antiplatelet therapy is essential for success of CAS. Dual antiplatelet therapy with clopidogrel (75 mg daily) and aspirin (81 or 325 mg daily) is the current standard. The considerable individual variation in the degree of platelet inhibition provided by antiplatelet therapy is now well known. Also, the impact of clopidogrel or aspirin resistance on long-term stent patency and restenosis rates is being increasingly recognized. Testing for such resistance is commercially available and should be considered preoperatively in all patients when timing allows.

If a patient has less than 20% inhibition on the platelet assay, a higher dosage of antiplatelet medication is warranted. This increase in target level of inhibition does not translate to higher risk for bleeding, durning this increase safe. Ticlopidine (250 mg twice daily) can be used in patients who cannot tolerate clopidogrel. If a patient cannot take antiplatelet therapy, carotid stenting should be reconsidered, as the periprocedural stroke risk may thus be unacceptably high.

Dual antiplatelet therapy should be continued for at least 3 months after the stent procedure, and daily aspirin should be continued indefinitely thereafter. Glycoprotein IIb/IIIa inhibitors are associated with increased risk of intracranial hemorrhage after carotid stenting, and their use should be confined to the treatment of acute thrombus formation during or immediately after the procedure.

For management of acute in-stent thrombosis, alteplase is administered by giving half of the 0.25 mg/kg bolus dose intra-arterially near the clot and administering the second half of the bolus dose intravenously over 5 minutes, followed by an intravenous infusion of 0.125 μg/kg per minute for 12 to 24 hours.

Postprocedural hypotension may accompany periprocedural bradycardia and is usually managed with volume expansion. Moderate bradycardia and mild hypotension, similar to that seen occasionally after CEA related to carotid baroreceptor stimulation, are best treated with fluid supplementation, close observation for any neurologic dysfunction, and occasional use of low-dose vasopressor support.

Control of postprocedural hypertension is important to minimize risk of cerebral hyperperfusion syndrome (CHS). Severe headache associated with hypertension after CAS should heighten suspicion of CHS, which can also present with seizures and focal neurologic deficits. Proper management of CHS entails early diagnosis, rapid control of hypertension, anticonvulsant therapy, smooth diuresis, and neurologic consultation.

FOLLOW-UP

Patients are usually discharged from the hospital on the day after undergoing CAS. Follow-up office visit occurs 4 to 6 weeks after surgery, again 6 months later, and annually thereafter. Follow-up includes a complete neurologic assessment and carotid ultrasound scan examination. Each visit also includes a global cardiovascular evaluation with emphasis on possible coronary, renal, and peripheral arterial occlusive problems. Hypertension and hypercholesterolemia are managed aggressively. Because of antiinflammatory and plaque stabilization effects, statin therapy is advised for almost all patients, even in the absence of laboratory evidence of cholesterol abnormalities. Healthy lifestyle habits are encouraged, with emphasis on regular aerobic exercise, dietary discretion, and complete abstinence from tobacco use.

Hemodynamically significant restenosis of carotid stents is not frequent and has been quoted as less than 5%. By carotid ultrasonography, velocity criteria of native vessels may overestimate the degree of in-stent stenosis if used for CAS surveillance. We follow the criteria of Bruennle and colleagues, who use a peak systolic velocity of 350 cm/s or greater in the stent as a reliable indication of 70% or greater restenosis in a stented carotid artery. Although this approach requires prospective validation, consensus is building that routine native carotid duplex velocity criteria are likely to overestimate the incidence and severity of in-stent restenosis in the CAS patient.

SUMMARY AND PERSPECTIVE

Results of clinical trials have shown that both CAS and CEA are effective procedures for stroke prevention; each has an important place in carotid disease management. Currently, concerns about higher stroke risk with CAS, coupled with reimbursement restrictions and cost effectiveness issues for asymptomatic CAS, make CEA the standard, and much more commonly performed method of treating carotid occlusive disease when intervention is warranted. In our practice, CAS is reserved for patients with recurrent stenosis after CEA, a history of neck irradiation or radical neck dissection, lesions located high in the neck (above the level of the C2 cervical vertebra), contralateral vocal cord paralysis, and traumatic dissections with neurologic symptoms in the absence of significant atherosclerotic disease.

Most of our patients undergoing CEA are at high risk with traditional risk criteria, and only rarely are we compelled to use CAS because of extreme cardiopulmonary risk factors that make surgical treatment prohibitive. Carotid endarterectomy should be used with reservation in situations where the risk of periprocedural stroke is higher than usual.

These circumstances involve both clinical and anatomic factors. Clinical factors include age older than 80 years and recent (within 2 weeks) neurologic ischemic symptoms. Anatomic factors include vessel angulation greater than 60 degrees, and a severely diseased aortic arch, especially when combined with branch vessel configuration that is hostile for sheath access. More frequent use of proximal embolic protection, replacement of bare metal stents with covered stents, and selective use of transcervical access may lower the stroke risk of CAS.

In the meantime, skilled vascular surgeons who are trained and experienced in performing both CAS and CEA bring a unique perspective and ability to judge the multiple variables that must be weighed carefully in deciding which of these two good procedures is the better choice for an individual patient.

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Management of Aneurysms of the Extracranial Carotid and Vertebral Arteries

Vikram S. Kashyap, MD, and Gabriel L. Rose, MD

Arterial aneurysms of the extracranial circulation of the carotid and vertebral arteries are a truly rare entity. Only 0.1% to 2% of all carotid interventions are performed for aneurysmal disease, and these lesions account for less than 1% of peripheral aneurysms overall. The available literature is notable for the predominance of small, single-center retrospective series, the single largest published experience with true extracranial carotid artery aneurysms (ECAA) was reported recently by Ni and colleagues who intervened on 34 such lesions over a 20-year period. This slight platform of evidence represents the bulk of guidance available to practitioners who see and treat these aneurysms.

Extracranial vertebral artery aneurysm (EVAA) is yet less common than ECAA, and the available published experience is confined largely to case reports, many of which come from the neurosurgical literature. These aneurysms too can be treated successfully, and the evidence base, however slim, does provide guidance for clinical decision-making and treatment.

EXTRACRANIAL CAROTID ARTERY ANEURYSMS

Etiology

True ECAA is most often attributable to arterial wall degeneration, with histologic features such as thinning of the media and weakening of the elastic lamina, which are typical to peripheral aneurysms in general. Although atherosclerosis is believed to be a co-existing, rather than inciting, factor, as many as 83% of patients with ECAA have a reported history of hypertension. Most of these aneurysms are fusiform. The most common site for aneurysmal degeneration is the common carotid artery at the carotid bifurcation, or at the proximal internal carotid artery (ICA). ECAA found outside these locations tend to be saccular. External carotid artery aneurysms are exceedingly rare.

Other causes of aneurysms include blunt and penetrating trauma. Blunt penetrating trauma resulting in ECAA involves the common carotid, although any artery is vulnerable depending on the pattern of injury. Aneurysmal degeneration occurs as the result of either direct arterial damage resulting in early pseudoaneurysm formation, or as a late consequence of a weakened or dissected arterial wall. The ICA near the skull base (zone III) is particularly prone to dissection in blunt trauma, with subsequent aneurysm formation. Fibromuscular dysplasia, collagen vascular disorders, cystic medial necrosis, granulomatous disease, and congenital defects have also been identified as causes of ECAA.

Aneurysms as a result of infection are now relatively unusual in the antibiotic era. When these are seen, they are most often the consequence of angioplasty patch infection following carotid endarterectomy (CEA). Pseudoaneurysm has also been reported as a late complication of CEA. No difference has ever been conclusively demonstrated between polyester (Dacron), expanded polytetrafluoroethylene) or autogenous patch material in the rates of post-CEA infection, possibly because the incidence of infection following this procedure is so low that any difference that actually exists would be statistically very difficult to demonstrate.

Natural History, Presentation, and Diagnosis

Neurologic symptoms are the hallmark of extracranial carotid aneurysmal disease. Perhaps half of patients present with amaurosis fugax, transient ischemic attack, or stroke, and these patients also represent the majority of interventions. These events are thought to be due to distal embolization from the lesion, but can also develop from slow arterial flow through the aneurysmal sac. Other symptoms that can lead to the diagnosis of ECAA are the results of mass effect from the enlarged artery. Nerve compression can lead to facial pain or cranial nerve palsies, hoarseness, or even Horner's syndrome (ipsilateral ptosis, miosis, pseudoenophthalmos, and anhidrosis) from compression of the sympathetic chain. Dysphagia can also occur. Rupture with associated hemorrhage or erosion either into the pharynx or via a sinus tract through the skin of the neck is uncommon, but has been reported. This is most often seen with mycotic aneurysms and pseudoaneurysms and is frequently fatal. Likewise, ipsilateral embolic changes in association with a palpable neck mass can suggest an infected aneurysm. Degenerative aneurysms are found in older patients with the usual risk factors for peripheral arterial disease. Aneurysms due to trauma, infection, or systemic conditions can be seen in patients of all ages.

On physical examination, the most common finding is the presence of a palpable lateral neck mass. A submandibular mass suggests common carotid artery disease, whereas a mass at the mandible ramus can be associated with an ICA lesion. Some aneurysms can resemble a deep peritonsillar abscess as they expand into the oropharyngeal space. The differential diagnosis also includes redundant carotid artery, tumors, lymphadenopathy, and congenital disorders such as cystic hygroma or branchial cleft cyst. One proposed algorithm for diagnosis and treatment is depicted in Fig. 1. Any suspicion for ECAA should be interrogated promptly with advanced imaging techniques such as duplex ultrasonography, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA). These modalities are typically diagnostic and will assist with preoperative planning. Duplex ultrasound in particular is favored as the initial screening test of choice because of its ready availability, low cost, and noninvasive nature, although it is most useful when employed by a skilled operator for most ECA lesions. The sensitivity of ultrasound can

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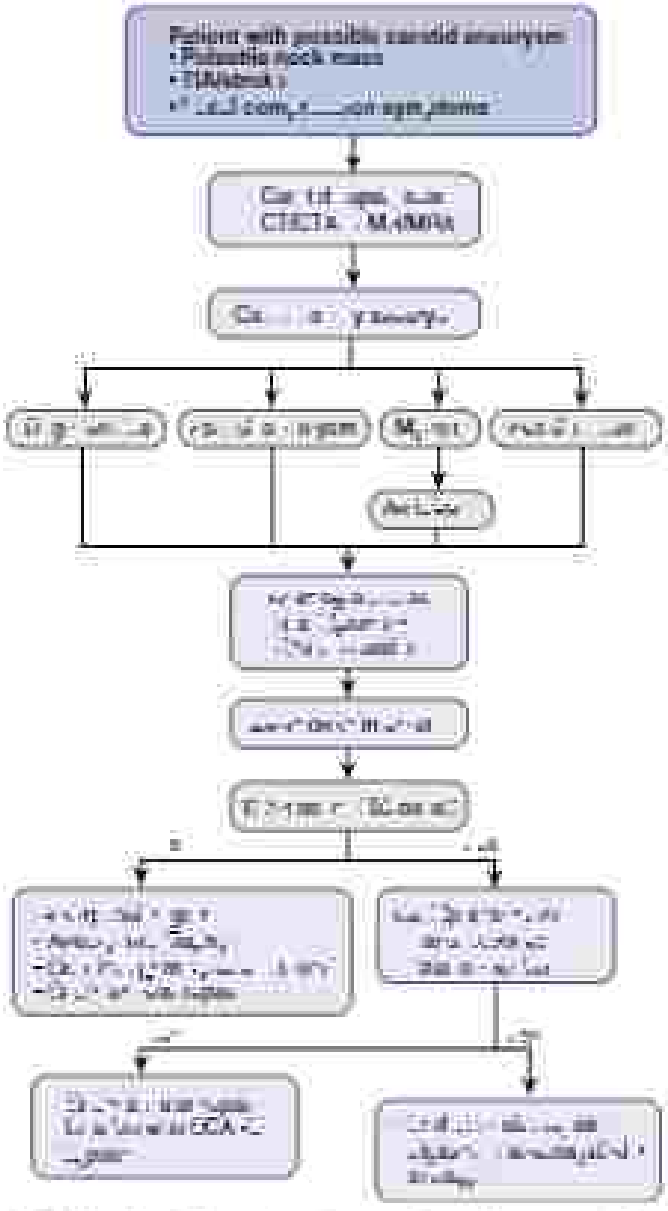

FIG. 1 Algorithm for diagnosis and treatment of carotid aneurysms. *CT* computed tomography, *CA* computed tomographic angiography, *ICA* internal carotid artery, *ECA* external carotid artery, *MR* magnetic resonance, *MRA* magnetic resonance angiography, *TIA* transient ischemic attack. (Modified from Schmidt J, Jacobs A. Carotid artery aneurysms. In: Rutherford R, ed. Vascular Surgery. 6th ed. Philadelphia: Saunders; 2005:1.)

also be compromised by tortuous or heavily kinked arteries. The use of catheter based carotid angiography is now mainly limited to the operating room itself at the time of intervention, although unmatched in its resolution and utility as an arterial imaging technique, the fact that it essentially represents a "luminogram" makes it a poor initial screening test for aneurysmal disease.

Indications for Intervention

Whether symptomatic or asymptomatic, the presence of ECAA represents in and of itself an indication for intervention in suitable patients. Indeed, the natural history of these aneurysms is for most patients to present with symptoms, and those patients asymptomatic at presentation are likely to become symptomatic with time. Given that most symptomatic ECAA present with acute neurologic events, a strategy of aggressive invasive treatment is warranted. ECAA that are ruptured or appear near rupture (skin drainage, bronchial blood, pain, suspicious imaging findings) should be considered for urgent repair.

The generally accepted definition of aneurysmal disease in the carotid bed is similar to that identified for arteries in other distributions, in other words, 1.5 times larger than the adjacent normal artery or what would be expected from anatomic series. However, because the normal carotid bulb can be 100% larger than its associated ICA, some authors have proposed that a lower bound of 2 times the adjacent normal ICA diameter be used to avoid confusion with what might otherwise be simply a generously sized but normal carotid bulb.

Treatment

The options for treatment of ECAA are no different from those available for treatment of aneurysms generally. Medical management has been proposed in patients who represent prohibitive risk for invasive intervention, or for those asymptomatic patients who for unrelated reasons are not expected to survive long enough to benefit from a prophylactic repair. For these patients, various combinations of therapies consisting of antiplatelet and/or anticoagulation medications are available, some of which are well validated for this indication by anything other than expert opinion. The two options for intervention are open surgical repair and endovascular therapy, with the latter becoming increasingly common in medium series.

Preoperative Evaluation

The preoperative evaluation should for the most part be familiar to any interventionalist who performs carotid procedures for occlusive disease. A thorough history and physical examination is taken, paying particular attention to the pattern of symptoms if present, any prior neurologic events, and the baseline neurologic examination. An appropriate cardiovascular risk assessment should be performed in older patients and those patients presenting with atherosclerotic lesions. Capacity for neck extension and rotation, as well as neck size and distance from the clavicle to the angle of the mandible, are useful for preoperative planning. One consideration specific to open aneurysm resection is the potential need for conduit in the event of interposition bypass. Bilateral lower extremity vein mapping should be obtained. However, carotid reconstruction can be performed using prosthetic conduit with good results.

The use of advanced imaging modalities such as CTA or MRA is mandatory for preoperative planning. These techniques provide invaluable information about the location and morphology of the aneurysm. Imaging should be obtained of the entire neck, as well as the aorta, arch, head vessels, and the intracranial circulation.

If an infectious etiology is believed likely, soft tissue coverage of the carotid repair may be a concern, and assistance from a colleague experienced with oncologic reconstructions of head and neck cancers may be indicated. Decisions regarding anesthetic technique and intraoperative neurologic monitoring are best done when considering the strengths and preferences of the team in the operating room, although a general anesthetic may be preferred for open surgical repair because of the possibility of extended procedure time with difficult dissection and prolonged carotid clamp time as compared with standard CEA.

The decision for open versus endovascular treatment demands deliberation over multiple aspects of the patient presentation and must be tailored to each individual case. Although reported results limit endovascular intervention have the advantages of lower in-hospital mortality and morbidity rates, reduced risk of cranial nerve injury, potentially lighter anesthetic requirements, and greater utility for distal ICA lesions, it is important to remember that these results were achieved in carefully selected patients. An endovascular approach is believed to be particularly well suited to aneurysms

secondary to traumatic injuries, carotid dissection, or for pseudoaneurysm after CEA, provided infection can be ruled out. Endovascular intervention is also believed to be advantageous in patients with very distal or near III lesions, and in those patients with hostile necks (prior surgery, history of radiation) or who represent a prohibitive risk with a general anesthetic. However, endovascular treatment via transluminal access carries an increased risk of stroke as compared with open carotid interventions, especially in patients with heavy calcific disease or unfavorable aortic arch anatomy. In addition, the thrombus burden typically associated with these aneurysms is thought to represent a higher embolic risk during endovascular repair than does an occlusive lesion. Patients with tortuous carotid anatomy may not be suitable for endovascular treatment based on the limitations of current stent grafting technology. In particular, endovascular treatment of aneurysmal lesions in this bed, especially degenerative, carries with it the same concerns about durability and need for reintervention as it does for arterial aneurysms of the abdomen and the lower extremities.

Patients presenting with compressive symptoms have traditionally been believed to be best served with open surgery, however, good results have been reported with endovascular therapy. ECAA with infectious etiology is considered a strong relative, although not prohibitive, contraindication to endovascular repair.

Open Surgical Repair

Traditionally, the operation of choice and that with the longest history in the literature is aneurysm resection with either primary end-to-end anastomosis or interposition grafting. Frequently, ECAA is associated with a degree of redundancy in the artery, especially in the case of ICA aneurysm. This is often the scenario for which resection with primary anastomosis is the preferred approach. The external carotid artery can be ligated with impunity, however, any variation to that technique in the potential for distal external carotid artery dilation with end to end anastomosis of the proximal external carotid to the distal ICA to restore inflow. Common carotid aneurysms and those involving the carotid bulb are usually best treated with interposition grafting. Reversed great saphenous vein graft is an excellent option with a proven track record, and usually provides a good size match to the nondiseased native carotid arteries. The choice of graft material is between prosthetic and autologous vein, either can be used with good results in the absence of infection. Open reconstruction in the presence of infection mandates the use of autologous conduit; if no vein is available in any extremity, then the use of superficial femoral artery has been described, or external carotid transposition as described earlier.

Dissection of the aneurysm and the associated arteries can be difficult because of the dense inflammatory reaction these lesions commonly provoke (Fig. 2). Nevertheless, meticulous technique is necessary to ensure safe identification of all important structures, most notably the cranial nerves. The nerves most at risk will depend on the location of the aneurysm; in a recently published large series, the most commonly injured nerves were the recurrent laryngeal, hypoglossal, glossopharyngeal, and the motor branch of the facial nerve. An endoaneurysmorrhaphy technique can also be used, in which the aneurysm is identified and opened, and the interposition graft then placed in anatomic position and covered with the residual aneurysmal sac. This may minimize the chance of nerve injury as compared with radical sac resection.

As in CEA, the aneurysm should be manipulated as little as possible during dissection to minimize the chance for downstream athero-embolization. Systemic heparin is given once proximal and distal control of all arteries to achieved, in dose sufficient to double the baseline activated clotting time as measured serially in the operating room.

Exposure of distal ICA aneurysms can prove challenging. Some alternatives well known from the CEA literature can be used in this situation, albeit at the cost of increased morbidity and added potential for cranial nerve injury. Division of the styloid process or mandibulectomy is now rarely done. Conversely, division of the posterior belly of the digastric muscle or mandibular advancement can be employed with relatively little risk. Very high ICA aneurysms can be treated using balloon occlusion for distal control, usually in conjunction with intraarterial shunt placement. ICA ligation is an alternative, although this maneuver has been historically associated with unacceptably high rates of stroke exceeding 25%. However, the safety of ligation can be assessed in the operating room using carotid stump pressure measurement. A 20-gauge Angiocath is inserted into the ICA just distal to the intended endpoint of resection, following heparinization and control of the common and external carotid arteries but prior to opening the aneurysm. This is connected to a standard arterial line setup provided by the anesthesia team and the arterial pressure waveform is assessed. A mean ICA pressure of >50 mm Hg suggests adequate collateralization of the Circle of Willis without need for a shunt. We use this method routinely to determine the need for placement of a shunt in CEA with excellent results. If used, the shunt is placed into the open ends of the normal arteries distally and proximally immediately after opening the aneurysm. If stump pressure suggests that ICA ligation is not safe, and the lesion is too high for grafting to be technically feasible, extracranial to intracranial bypass has been proposed. Alternately, many would consider this type of lesion to be a strong relative indication for consideration of endovascular treatment. In any event, ligation is best reserved as a fallback technique for situations in which carotid reconstruction is believed to be difficult or impossible. In addition to stump pressure measurement, these patients undergoing ligation should be anticoagulated postoperatively for a minimum of 3 months to prevent embolization (carotid stump syndrome).

The principles for treatment of infected carotid aneurysm are concurrent with those of arterial infections in general. All these patients require expeditious evaluation and operative repair. Parenteral broad-spectrum antibiotics are administered perioperatively beginning prior to any operation, and subsequently narrowed on the basis of intraoperative culture results. The entire infected field and any prosthetic material must be aggressively debrided back to healthy tissue. Adequate soft tissue coverage is mandatory. The sternocleidomastoid muscle is often sufficient, although a myocutaneous flap may be the best option in the case of prior neck irradiation or radical neck dissection.

The approach to exposure is dependent on location of the aneurysm. The choice incision for all these exposures is along the anterior border of the sternocleidomastoid muscle, although some I common carotid aneurysms below the level of the clavicle may require mobility to achieve proximal control.

Endovascular Repair

Modern series of ECAA have demonstrated a definite trend toward endovascular techniques for treatment, representing as many as 70% of interventions in the later periods of hospital reported experiences. This technique generally mirrors the development of successful approaches to the treatment of disease in the treatment of abdominal aortic aneurysm, utilizing available stent graft technology (albeit off-label) in combination with coil embolization of the external carotid artery. Advantages of endovascular treatment are likewise similar to those found with this technique in other aneurysms, lower in-hospital mortality and morbidity rates, reduced risk of bleeding and damage to nearby structures, and greater flexibility in the treatment of lesions for which surgical exposure may come with increased risks. An endoluminal approach to ECAA is particularly appealing when considering treatment of high cervical lesions.

The consideration unique to endovascular repair of ECAA lies in maintaining cerebral blood flow while minimizing the risk of downstream athero-embolization to the brain without use of an ICA clamp. Indeed, although the risk of cranial nerve injury is lower

than with open repair, the operative stroke risk is believed by many authors to be higher with endovascular intervention. Here too, the risk of subsequent arterial degeneration and possible need for reintervention remain significant limitations common to all endovascular therapies.

The standard access for endovascular treatment is via the common femoral artery, but the common carotid artery can also be accessed by direct surgical cutdown. A general anesthetic is not necessary unless in cases of hemodynamic instability. Aortic arch aortography is performed using a pigtail flush catheter and a power contrast injector to delineate the anatomy of the head vessels. Systemic heparin is administered. A long sheath is advanced into the arch, and the common carotid artery is selected using a Glidewire and the operator's choice of appropriate catheter. Cerebral angiogram is then obtained, and a low profile system is positioned across the lesion for intervention. Identification of the proximal and distal extent of the aneurysm will not always be obvious based on angiogram alone, and knowledge of anatomic landmarks from preoperative imaging or the use of on table cone beam computed tomography (CT) may be helpful. Distal cerebral protection is mandatory in our view if technically feasible, positioned in the ICA distal to the aneurysm at the earliest possible time prior to stent deployment.

A broad variety of endovascular devices have been used for ECAA repair; an exhaustive list of every possibility and product is beyond the scope of this text. Use of both bare metal stents and covered stents have been described. A proximal and distal landing zone of healthy noncarotid arterial (a healthy to healthy bridge) is required for durable aneurysm exclusion, although little guidance exists for exactly how long these zones must be to achieve an adequate repair. Use of devices outside the indications for use is routine. Postdeployment balloon dilation should be undertaken for most cases but must be done judiciously given the attendant risk of dissection. Completion cerebral angiogram is then obtained to assess for any complication. Placement of a covered stent across the origin of the external carotid artery is often necessary and well tolerated by patients, representing the endovascular equivalent of a vessel ligation. When this is undertaken, coil embolization of the external carotid artery prior to stent deployment is advocated as protection against endoleak, the phenomenon whereby an aneurysmal sac continues to grow as a result of arterial flow from an open collateral vessel.

Covered stents are perhaps the strongest choice and most frequently used devices as they provide the most straightforward means of aneurysm exclusion, thus preventing aneurysm growth or rupture while isolating the embolic source posed by thrombus in the aneurysm wall. Some reports have emerged, however, associating covered

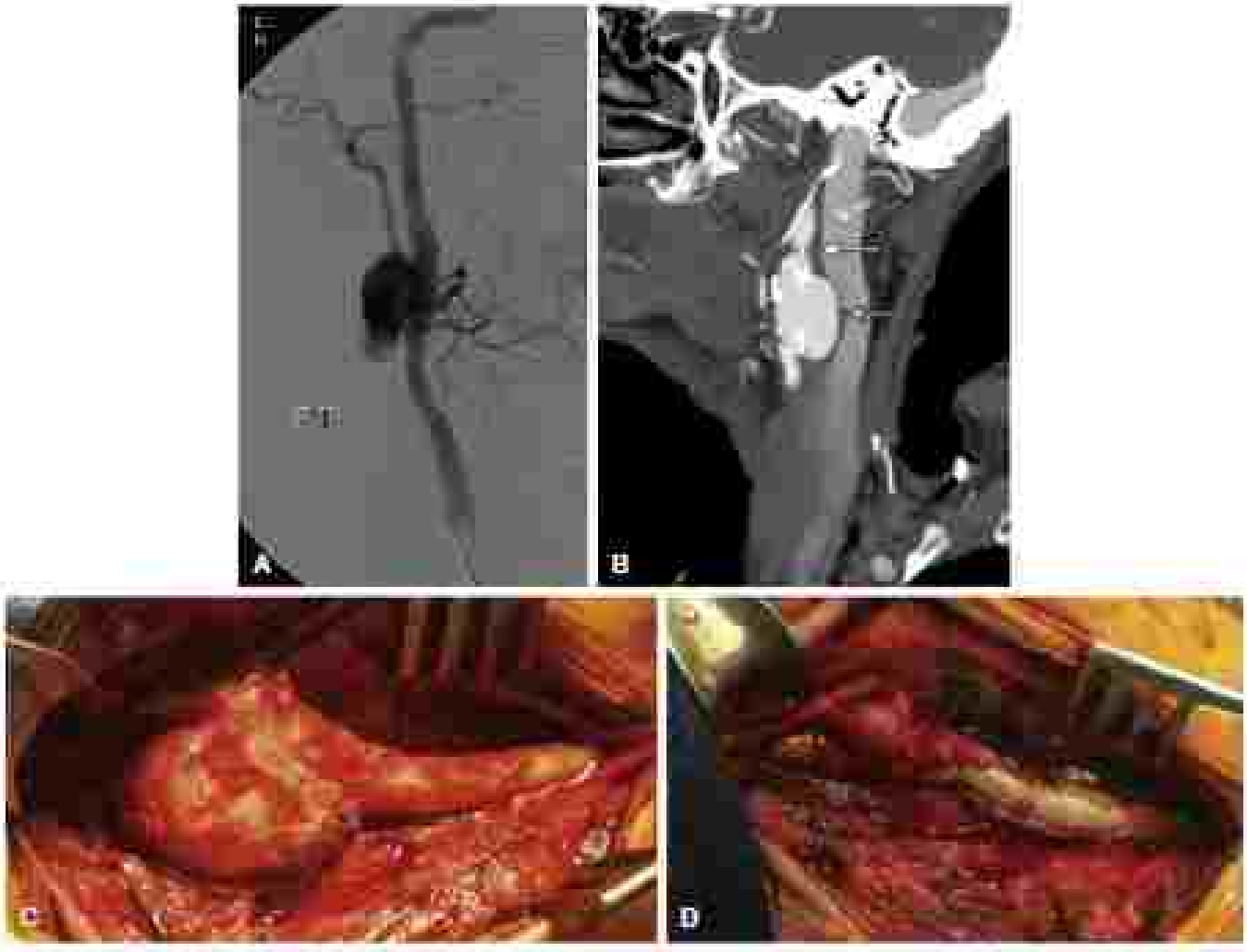

FIG. 2. (A) Digital subtraction angiography of a right carotid artery aneurysm at the site of carotid endarterectomy performed 36 years previously. (B) Computed tomographic angiography performed 4 years later showing further enlargement of the aneurysm (gray arrow) and development of severe stenosis (white arrow) in the internal carotid artery distal to the aneurysm. Operative photographs showing (C) exposure of the aneurysm and (D) bovine pericardial patch angioplasty repair. (Courtesy Dr Daniel Bandyk.)

stents with an increased risk of early thrombosis, despite chronic oral anticoagulation. Bare metal stents are less commonly used but are sometimes needed in situations in which the additional radial force they exert against the arterial wall is required; they are the treatment of choice for dissections. In addition, some lesions are treated with bare metal stents in arteries with diameters too small to accommodate a covered stent or its associated larger introducer sheath. In vessels of this size, the placement of the stent alone may be sufficient to induce thrombosis of the sac.

Saccular aneurysms or large pseudoaneurysms can be excluded by inducing thrombosis of the aneurysm with coils, followed by reapposition of the flow lumen by stenting. Another technique places a closed-cell stent initially, followed by introduction of coils through the interstices of the stent using a microcatheter. Alternatively, complications of coil migration or embolization can be avoided entirely if coil embolization is delivered and performed as an interval procedure only if the sac fails to thrombose (Fig. 3).

Hybrid techniques represent an exciting new frontier in the treatment of ICAA, with variations that allow for near infinite variability in customization of the repair to the patient. Their presence in the literature is limited to case reports and extremely small subsets of reported series. In some cases, as with hybrid aneurysm repair in other arterial beds, an open procedure is used as a bridge for successful endovascular intervention, creating an acceptable landing zone for a stent where none was available. The applicability of this technique to challenging cases of ICA lesions is obvious. Another described use of a hybrid strategy involves the use of endovascular therapy to temporize an unstable patient, even in the case of rupture or infection, in anticipation of a definitive open repair at another time shortly thereafter.

Results of Treatment

The small number of overall reported patients over a decades of treatment in the modern era complicates any rigorous comparisons of therapy. No randomized controlled trials are available, nor are there ever likely to be any. The strongest published evidence consists of single-center retrospective consecutive series and literature reviews. Within these limitations, the modern literature supports that treatments for ICAA can be carried out safely. Moreover, there is little doubt that the results of surgery are superior to what is known about the natural history of the disease.

For true ICAA, surgical repair represents the standard of care in the present day. Contemporary results for open surgical resection with arterial reconstruction remain excellent. Recent data demonstrate 30-day stroke rates between 0.7% and 10%, and 30-day mortality less than 2%. Cranial nerve injury remains the feared complication, with rates approaching 30%. It should be noted, however, that most of these injuries are not permanent in the series so stratifying them. Long-term follow-up after open surgical repair again demonstrates good results with 85% to 95% survival, with similarly acceptable stroke-free survival rates greater than 85%. Freedom from reintervention is also excellent, with reported rates of more than 90%, and thrombotic graft occlusion was for the most part well tolerated.

Results of endovascular treatment continue to reinforce the efficacy of this strategy as an alternative to open reconstruction. Technical success is consistently greater than 90%. Perioperative stroke rates are comparable with open repair, ranging from zero to 6% in contemporary series. The rates of cranial nerve injury are frequently reported to be zero. Reintervention rates are reported to be as high as 30%, the most frequent indications for return to the angiographic suite were incomplete sac thrombosis and in-stent restenosis.

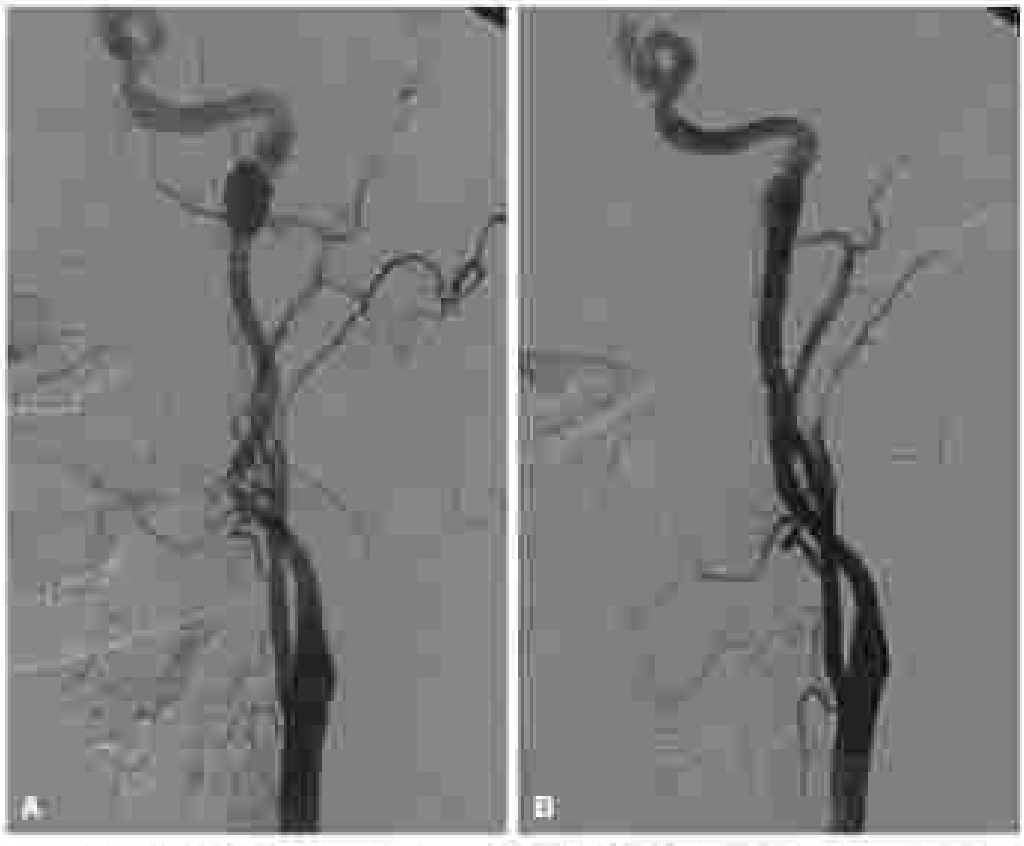

FIG. 3 Digital subtraction angiography of a left internal carotid aneurysm at the skull base with associated mild flow stenosis. (A) Before treatment by bare metal stent placement. (B) After treatment. Note the absence of residual aneurysm and presence of a small residual aneurysmal sac, which subsequently clotted completely.

Medical therapy alone without invasive intervention has not been embraced as an acceptable strategy, given that most ECAA present with symptoms and of those that do not, most are thought to be a significant threat to become so. Antiplatelet and/or anticoagulation medication can be given, in a manner informed by the existing carotid disease literature, without surgery in selected patients. The best support for a nonoperative strategy is suggested by a recent retrospective review by Lumsden and colleagues at the Mayo Clinic, who reported a series of 141 patients with ECAA, most of whom were managed medically. The lesions managed without surgery tended to be small, asymptomatic pseudoaneurysms, but it should be noted that none of these patients developed symptoms requiring intervention during a mean follow-up of 77 months. These results suggest that nonoperative management with medical therapy and close follow-up may be appropriate for highly selected patients, but confirmation of these outcomes by additional authors is required.

VERTEBRAL ARTERY ANEURYSMS

EVAA are very uncommon and are usually the late result of dissection or pseudoaneurysm. Trauma is often the incipient cause. True degenerative EVAA are quite rare, fewer than 1% of all vertebral artery lesions, and are most frequently associated with connective tissue disorders that predispose to aneurysm formation in other arterial beds. The scarcity of this entity has to date precluded any large cohort based studies on which to base natural history or treatment, the majority of the guidance must be derived from the larger literature on vertebral artery disease due to occlusion or embolism.

As with ECAA, trauma to the head and neck can result in damage to the vertebral arteries, resulting in dissection or pseudoaneurysm. Although pseudoaneurysm is often associated with penetrating trauma and dissection with blunt force injuries, it is important to remember that either type of injury is possible with any type of trauma. Either type of lesion can eventually lead to progressive aneurysmal dilatation. Even seemingly trivial mechanisms can result in injury, including a mere head rotation of the neck or other minor accidents, symptoms for which may not appear until the arterial source becomes apparent. These perhaps surprising presentations are especially common in the elderly although arterial injury has increasingly been recognized in younger patients with active lifestyles. Iatrogenic (manipulation) or rapid deceleration (whiplash) injuries are often implicated.

The vast majority of vertebral artery aneurysms are intracranial. Among EVAAs, the V2 segment of the artery is most susceptible to aneurysmal degeneration. Most patients are asymptomatic, and the aneurysm is detected as an incidental finding on CT or magnetic resonance (MR) imaging performed for some other purpose. Duplex ultrasound is an unreliable screening test, especially in the V3 segment approaching the skull base. Patients may present with persistent ipsilateral head and neck pain following trauma. Uncommonly, an EVAA may present as a cause of vertebrobasilar insufficiency or posterior stroke. The pathophysiology is either embolism from the aneurysm or slow arterial flow through the lesion. Pulsatile neck mass can be seen, but is probably less sensitive a finding than with ECAA. Reports of rupture are rare.

Traditionally, an aggressive treatment strategy has been favored by most published authors for EVAA. As noted previously the natural history is poorly defined, and there may well be a difference in the danger posed by EVAA that arise as a result of arterial trauma as opposed to those rarely seen aneurysms that are truly degenerative. It is now known that most vertebral artery dissections do heal spontaneously without sequelae, and no definitive treatment exists that has been shown to prevent onset of neurologic complications or progression to EVAA. Specific consensus indications for intervention are lacking. In our view, most EVAAs can be observed with antiplatelet therapy for 3 to 6 months and follow up imaging with CT or MR to assess for resolution. Surgical treatment is indicated for symptoms that can be reasonably attributed to the EVAA, or for aneurysms that are enlarging on serial imaging. A careful assessment of the suitability of the patient for elective aneurysm repair is however essential; higher-risk patients and those with limited potential to benefit from elective repair should prompt a higher threshold for recommendation of intervention.

Open surgical repair of EVAA is probably best attempted only by experts experienced in the field. Vertebral reconstruction surgery is marked by the many variations in anatomic exposure that may be necessary, via approaches that are rarely familiar to most surgeons. For this reason, preoperative imaging with MRA or CTA is essential for planning.

In general, the operative strategy is similar to that for ECAA, with resection of the offending lesion and interposition grafting with harvested vein or artery. Arterial transposition is another option for vertebral disease, and extraanatomic bypass with aneurysm ligation has also been described. The most straightforward exposure is probably to the V1 segment, which encompasses the portion of the artery from the usual origin at the subclavian to the vertebral foramen at C6. Proximal vertebral occlusive disease is frequently amenable to repair via a vertebral-common carotid artery transposition. This is accessible from a supraclavicular incision similar to that used for carotid subclavian bypass and involves ligation of the aneurysmal portion of the vertebral artery with reimplantation of the distal portion to the adjacent common carotid artery. The subclavian artery or the thyrocervical trunk is alternate source of inflow.

The V2 segment is found within the transverse foramina of the cervical vertebrae and represents much greater challenges to exposure because of the need for bone resection and the meticulous dissection required of the associated venous plexus. Exposure of the distal V3 segment is more appealing, especially from a posterior approach, but should probably only be attempted by those experienced in the field. Possibilities for distal reconstruction are transpositions of the vertebral to the external or internal carotid, or interposition grafting using saphenous vein to the vertebral from the common carotid, the external carotid, or the subclavian artery. These operations can be performed safely and demonstrate the same durability profile as with their counterparts in other areas of the peripheral circulation.

The last decade has seen increasing use of endovascular treatment for vertebral artery lesions. Despite questions about durability, starting with or without use of coil embolization is appealing considering the challenges of open vertebral reconstruction. In our view, endovascular treatment of EVAA should only be considered in the presence of a robust contralateral vertebral artery because of the relatively high incidence of in-stent restenosis reported for treatment of occlusive disease. The promise of endovascular therapy of EVAA has yet to meet the reference standard set by open repair.

Suggested Readings

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Brachiocephalic Reconstruction

Rebecca Sorber, MD, and Caitlin W. Hicks, MD, MS

The brachiocephalic vessels, also known as the great vessels, supply the circulation of the upper extremities and head, including the entirety of intracranial blood flow. Given the intimate association of these vessels with the aortic arch and their proximity to the aortic root, it is rare that the general surgeon must intervene on pathology in this region. However, a basic understanding of the potential manifestations of brachiocephalic disease and options for repair or reconstruction will facilitate the care of these patients with respect to all procedures.

The embryologic origin of these vessels is complex, like the aortic root and transverse arch themselves, they arise as an intricate admixture of the embryonic aortic arches and often have considerable variability in their anatomic configuration. The most common configuration is to the form of three separate vessels arising from zones 0 to 2 of the transverse aortic arch (Fig. 1). The innominate artery arises from zone 0 and subsequently branches into the right common carotid and right subclavian arteries; the left common carotid arises from zone 1; and the left subclavian artery arises from zone 2 and gives off the left vertebral artery just distal to its origin (Fig. 2A). The most common variant to this configuration is a bovine arch, which has the innominate and the left common carotid arteries arising from a common trunk (8%, Fig. 2B) or variant (16%). Less common variants include a left vertebral artery, which arises from the arch at a separate origin proximal to the left subclavian (6%, Fig. 2C), or a right subclavian artery, which arises from the arch distal and posterior to the left subclavian artery and runs retroesophageal to supply the right upper extremity (0.5%, termed *aberrant right subclavian artery*).

While the brachiocephalic system possesses a unique origin, its pathophysiology is governed by the same set of universal principles applying to the arterial system as a whole. Thus, the potential pathologies affecting the brachiocephalic vessels can largely be categorized into two main groups: occlusive disease and aneurysmal disease. The location of these vessels, as well as their intimate relationship to central neurologic and upper extremity function, result in unique manifestations of arteriopathy in this region; it is these symptoms that drive the decision to intervene.

Historically, reconstruction of brachiocephalic pathologies has required open surgery. However, the nature of these vessels as tributaries of the aortic arch makes such open procedures challenging and maximally invasive. For this reason, endovascular therapy for lesions within the brachiocephalic system has recently expanded as an adjunct or replacement for many open surgical procedures in this region. Additionally, a growing indication for brachiocephalic reconstruction includes debranching procedures to facilitate endovascular repair of thoracic aortic aneurysms and dissections by increasing the proximal landing zone for stent graft placement.

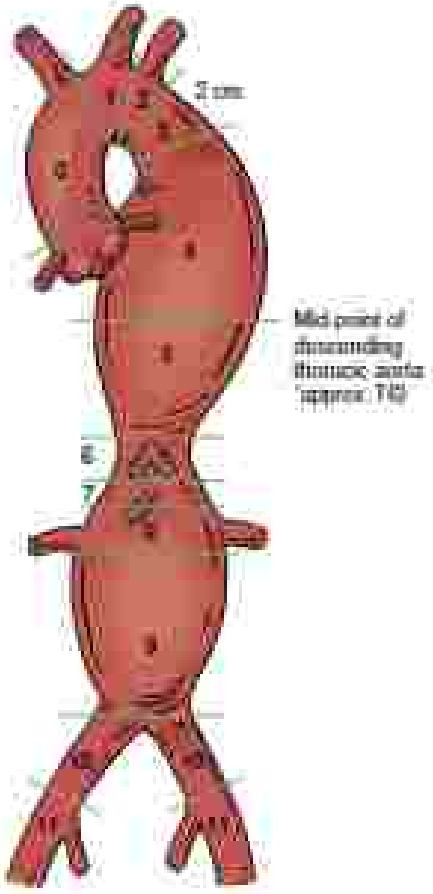


FIG. 1 Zones of the thoracic and abdominal aorta. [Modified from Singh M, Mukherjee MS. Hybrid thoracic surgery and endovascular therapy. Perioperative Medicine. 2019;8:1000. 1074.]

BRACHIOCEPHALIC PATHOLOGIES

The vast majority of lesions affecting the brachiocephalic vessels are occlusive or stenotic in nature (Figs. 3 and 4). Most frequently these are related to atherosclerotic disease, although large vessel vasculitis such as Takayasu's arteritis or complications of prior radiation to the head, neck, and mediastinum can also play a role. The progressive narrowing of vessels supplying the upper extremity and/or intracranial circulation may result in a number of distinct symptoms. Upper extremity ischemia may manifest as fatigue with routine activity and a changed or asymmetric pulse exam with exercise. However, limb ischemia symptoms related to proximal brachiocephalic lesions are relatively uncommon. This is due largely to the extensive collateral network that supplies the upper extremities.

Vertebrobasilar insufficiency results from a reduction of blood flow to the vertebral arteries, creating relative ischemia of the posterior circulation and resulting in vertigo, ataxia, visual symptoms and syncope. A subset of vertebrobasilar insufficiency is subclavian steal syndrome, which occurs when a high-grade stenosis or occlusion of the proximal subclavian artery causes reversal of flow in the ipsilateral vertebral artery. Classically, subclavian steal syndrome is exacerbated with exercise of the ipsilateral upper extremity. Likewise, some patients with proximal subclavian lesions and an ipsilateral internal mammary artery bypass graft may experience significant angina with upper extremity exertion (termed *coronary steal*).

Because the vast majority of occlusive disease in the brachiocephalic vessels is secondary to atherosclerosis, atheroembolic events of the supraaortic circulation can occur. Atheroembolism to the upper extremity circulation may manifest as discoloration or, in extreme and chronic cases, autoamputation of the digits. Atheroembolism to the intracranial circulation may manifest as a transient ischemic attack (TIA) or stroke symptoms. It is important to note that while cerebrovascular embolic phenomena frequently implicate carotid artery stenosis occurring at the carotid bifurcation, disease affecting

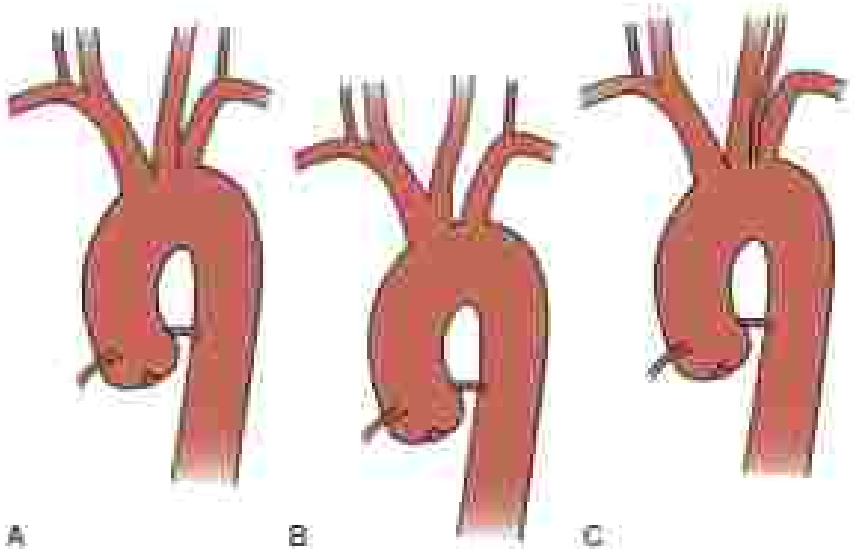


FIG. 2. Normal aortic arch (A), bovine aortic arch (B), isolated left vertebral origin (C). (From Lawrence P, Gloviczki P, Rutherford's Vascular Surgery. 8th ed. Philadelphia: Elsevier; 2014.)

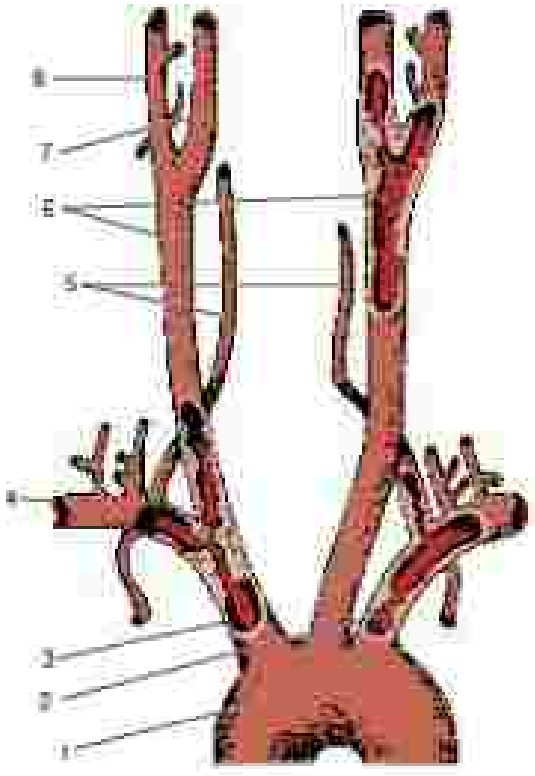


FIG. 3. Sites of atherosclerosis in the brachiocephalic vessels. (1) Aortic arch, (2) left subclavian artery, (3) innominate artery, (4) right subclavian artery, (5) right and left vertebral arteries, (6) right and left common carotid arteries, (7) right internal carotid artery, (8) right external carotid artery. (From Rockman W, Sonpal N, Kandarpa K. Noninvasive Vascular Diagnosis: A Practical Guide to Therapy. 3rd ed. London: Springer-Verlag; 2013.)

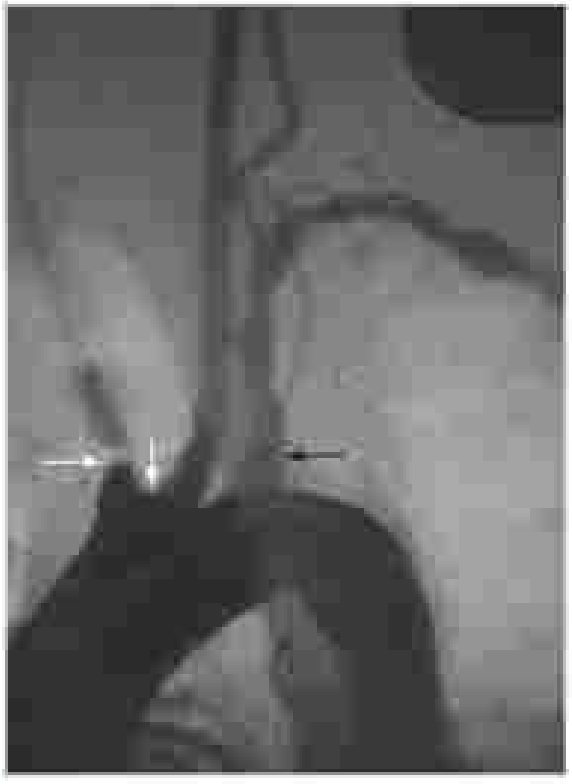


FIG. 4. Digital subtraction angiogram showing multivessel atherosclerosis involving brachiocephalic (white horizontal arrow), left common carotid (white vertical arrow), and left subclavian (black arrow) arteries.

the ostia of the innominate or left common carotid arteries can result in hemispheric symptoms.

Aneurysms of the brachiocephalic vessels can also occur, most frequently affecting the left subclavian artery (Fig. 5). These are generally degenerative or traumatic in nature but can also be associated with connective tissue disorders (e.g., Marfan's syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome). When symptoms arise, these lesions are often identified incidentally on imaging studies performed for unrelated reasons. These patients frequently have concomitant carotid or additional peripheral aneurysms and should be evaluated for additional aneurysms when a brachiocephalic aneurysm is identified. When symptomatic, often the manifestation is one of a pulsatile mass or compression of surrounding structures. Particularly fusiform aneurysms can develop associated thrombus and may present due to subsequent thromboembolic sequelae.

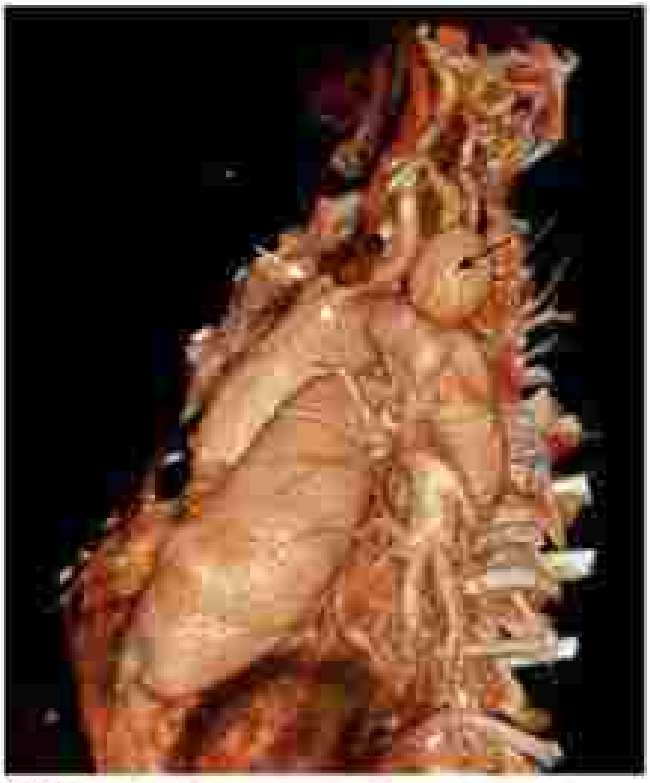


FIG. 5 Three-dimensional reconstruction of computed tomography angiography imaging showing 3.6-cm left subclavian artery aneurysm in a patient with Loeys-Dietz syndrome. White arrow: innominate artery; white arrowhead: left carotid artery; black arrow: left subclavian artery aneurysm.

DIAGNOSTIC EVALUATION

Evaluation of suspected brachiocephalic pathology is founded on a comprehensive history and physical exam with keen focus on the neurologic and vascular systems. History taking should include symptoms of vertebrobasilar insufficiency or steal phenomena, as well as prior TIA symptoms. The neurologic exam should focus on evaluation for deficits from prior stroke, and the upper extremities should be evaluated for asymmetry in strength and pulses. Brachial artery blood pressures should be taken bilaterally, with a difference of more than 15 mm Hg between extremities considered significant. All patients should be asked about standard atherosclerotic risk factors, including smoking history, diabetes, and radiation history. In the setting of patients suspected to have a connective tissue disorder or vasculitis, serologic testing including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) labs and collection of a detailed family history may also be useful.

Duplex ultrasonography is generally the first line of imaging employed in the setting of brachiocephalic disease, as it is noninvasive, low risk, and provides dynamic flow information. Low flow velocities within the common carotid arteries with a dampened waveform are indicative of distal lesions or proximal stenosis. In the setting of high-grade subclavian or innominate disease, reversal of flow may be noted within the vertebral arteries. Classically, ipsilateral reversal of vertebral flow is noted in the context of subclavian steal syndrome; however, this finding is not uncommon in brachiocephalic disease and is often not associated with symptoms on history or physical exam. Transcranial Doppler ultrasound can provide additional data on intracranial flow patterns to help determine whether flow abnormalities are physiologically significant. In addition, axial imaging in the form of computed tomography angiography and magnetic resonance arteriography can provide high-quality images of the arterial anatomy that will aid in both the diagnosis and treatment planning for affected patients (Fig. 6). These imaging studies have largely replaced conventional catheter-based arteriography in most cases.

INDICATIONS FOR INTERVENTION

The decision to intervene on common carotid or subclavian artery disease is largely driven by cerebrovascular or upper extremity symptoms localizing to a specific lesion. As a general rule, asymptomatic subclavian artery stenoses do not need intervention, whereas aneurysmal pathology may require repair even in asymptomatic cases due to risk of progression and rupture. Lesions arising from an inflammatory process such as Takayasu arteritis should only be considered for intervention once the acute inflammatory phase has passed. This is usually monitored based on ESR and CRP levels, and in some instances positron emission tomography–computed tomography can be helpful to rule out the presence of active vasculitis.

For patients with asymptomatic common carotid artery lesions, it is generally accepted that stenosis of more than 75% is considered to be an indication for intervention even in the absence of attributable symptoms. If common carotid and bifurcation disease of more than 75% luminal stenosis are present concomitantly, common carotid repair via an endovascular or open approach may be considered at the time of carotid endarterectomy, although the data supporting this practice is controversial. In the setting of ipsilateralizing cerebrovascular symptoms or global cerebral hypoperfusion, any brachiocephalic lesions of more than 75% luminal stenosis can be considered for repair.

Subclavian artery stenosis or occlusion should not be intervened upon without clinically evident subclavian steal symptoms, reversal of vertebral flow on duplex alone is not criteria for intervention. Asymptomatic high-grade stenosis or occlusion of the subclavian arteries may require intervention in the setting of coronary revascularization with an internal mammary artery conduit. In order to maximize perfusion to the proximal coronary graft and to maintain accurate intraoperative continuous invasive blood pressure monitoring, a carotid-subclavian artery bypass or a subclavian-carotid artery transposition procedure may be considered.

The preferred threshold for brachiocephalic artery aneurysm repair is somewhat controversial. The rationale for intervention is to prevent aneurysm growth, which can lead to dissection, compression of nearby structures, or rupture. Rawanduzi et al. recently examined 147 brachiocephalic aneurysms and observed an average growth rate of 0.06 cm/y, with 19% demonstrating no growth over 4 years of follow-up. There were no instances of aneurysm rupture during the follow-up period. Based on these data, the authors recommended a repair threshold of 3.0 cm for asymptomatic brachiocephalic aneurysms. It should be noted that brachiocephalic aneurysms associated with dissection have been associated with faster rates of growth and may warrant repair at a lower size threshold.

OPEN SURGICAL APPROACHES

Open surgical revascularization of the brachiocephalic vessels may be accomplished via direct or extraanatomic means. Direct revascularization is usually performed in a transthoracic fashion, requiring a median sternotomy for lesions of the innominate and left common carotid arteries and a left posterolateral thoracotomy for left subclavian lesions. The transthoracic approach is associated with significant surgical insult and tends to be reserved for young, robust patients who are able to tolerate aortic cross-clamping. Most commonly, this approach is applied in patients with complex aneurysmal pathology, traumatic transection of the brachiocephalic vessels, or when brachiocephalic reconstruction is combined with coronary revascularization.

The open surgery alternative to a transthoracic approach for brachiocephalic reconstruction is an extraanatomic revascularization. This is usually performed via transverse supraclavicular and/or cervical incisions and is a viable approach for the majority of isolated

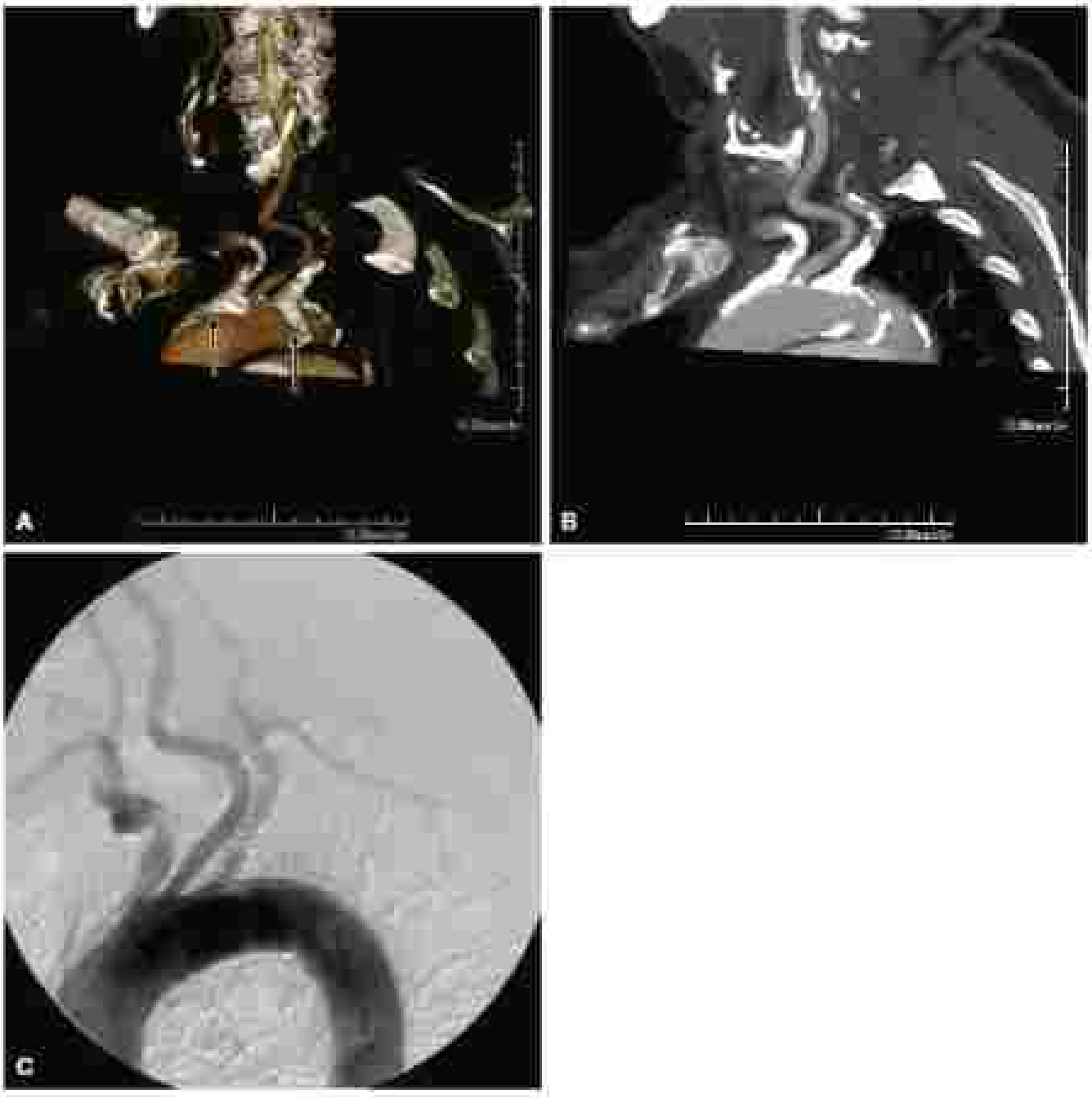


FIG 4 (A) Computed tomographic (CT) three-dimensional surface rendering of the aortic arch showing severe calcific disease of the origins of the innominate and left subclavian arteries (arrow). (B) Maximum intensity projection images of the same patient reconstructed from the CT scan. (C) Arteriogram of the same patient. Note the extensive calcification at the origins of the innominate and proximal left subclavian arteries. (From Cheshire JW Jr, Stallworth JM, Reul GJ: Subclavian-Vascular Surgery. Rich RH, Fleisher LA, Shanley CJ, Wilson SE, Humphries TJ, Hobson RW II, Calligaro KD, Troutman WB, Warriner RA III, Anderson CA, eds. Philadelphia: Saunders Elsevier, 2010.)

brachiocephalic lesions, with the exception of those affecting the innominate artery. Extraanatomic revascularization is the preferred approach for older patients unable to tolerate thoracotomy, those with prior sternotomy, minimal radiation, or severe calcific disease of the ascending aorta. This indirect approach is generally well tolerated and has low morbidity and mortality rates.

Innominate Artery Revascularization

Lesions of the innominate artery are uncommon, even among lesions of the brachiocephalic vessels. The optimal open surgical approach to lesions of the innominate artery is generally via a median sternotomy, although a mini-sternotomy that divides only the upper sternum from the sternal notch to a T incision at the third intercostal space can also be employed to expose the vessels (Fig. 5). For focal atherosclerotic disease of the mid-innominate artery, endarterectomy with patch angioplasty may be carefully considered. However, for more proximal lesions involving the innominate ostium with extension into the aortic arch, an attempt at endarterectomy is likely to be incomplete, resulting in potential atherothrombosis or aortic dissection.

More frequently, bypass grafting of the innominate is performed, from the lateral ascending aorta to one or more distal targets (Fig. 6). This approach utilizes a 10- to 12-mm Dacron tube graft anastomosed in an end-to-side fashion to the lateral ascending aorta, then

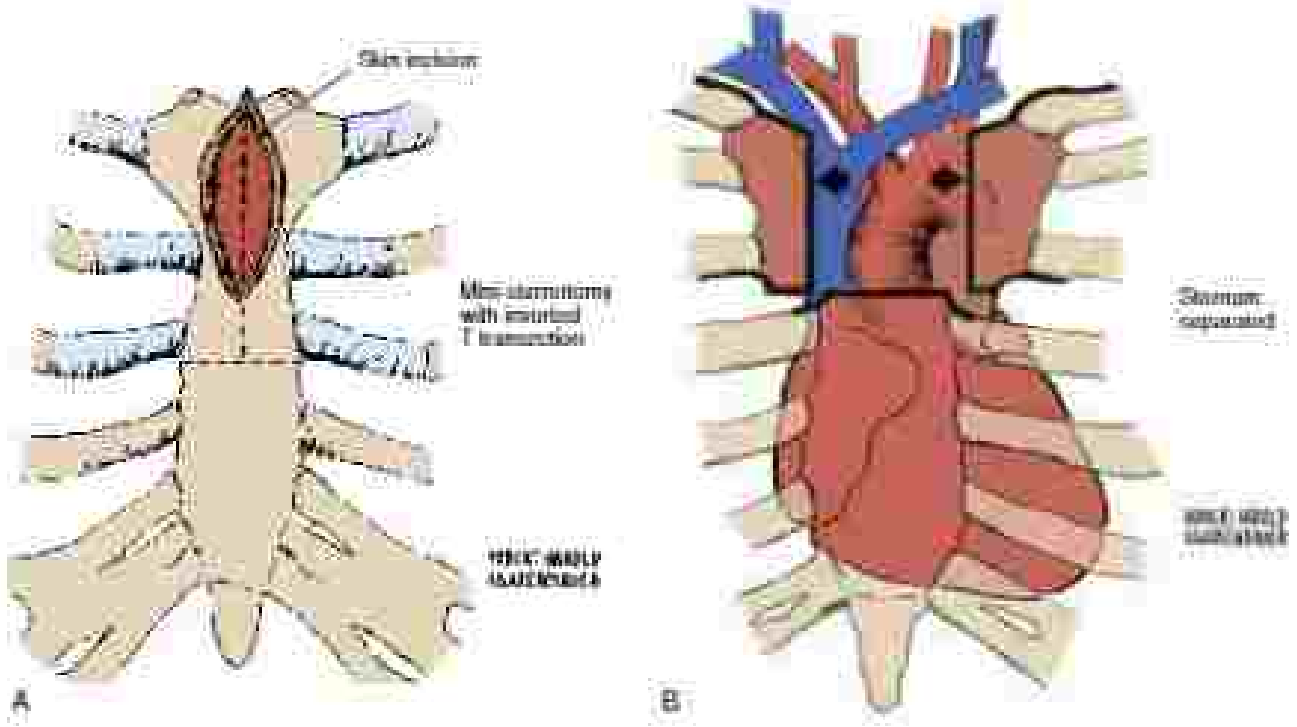


FIG. 7 (A) Skin incision and mini-sternotomy sternal division. (B) The upper sternum is divided and separated (arrows), exposing the ascending aorta and arch vessels. (From Ueyama K, Jindani F, Gandy SP. Minimally invasive approach for aortic arch branch vessel reconstruction. Ann Surg. 2008;71:200-202.)

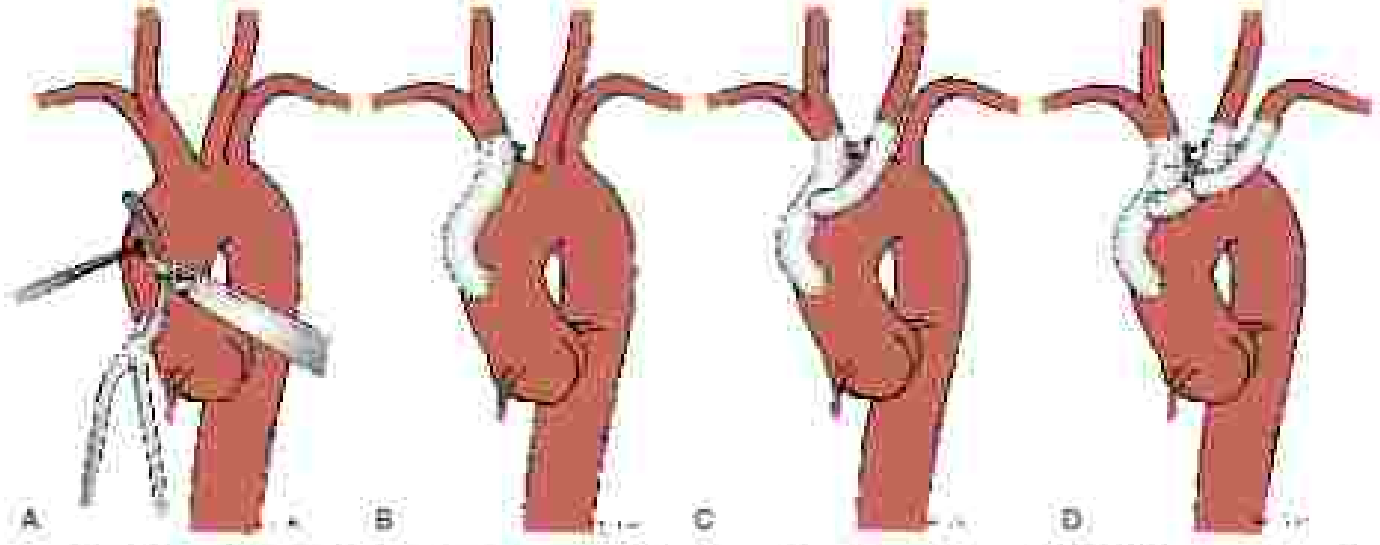


FIG. 8 Various proximal configurations for aortic arch debranching with reconstruction of the brachiocephalic vessels. (A) Partial occlusive clamp placed on the ascending aorta with creation of a punch arteriotomy. (B) Creation of an aortic/innominate bypass. (C) Tabuns graft to the left carotid artery. (D) Tabuns graft to the left subclavian artery. (From Greenwald S, Moxon KW, eds. Rutherford's Vascular Surgery. 8th ed. Philadelphia: Elsevier; 2014.)

ramified posterior to the innominate vein to avoid compression in the retrosternal space. The distal anastomoses are performed in an end to end fashion; if more than one distal revascularization target is required, an 8 mm Dacron tube graft is anastomosed end to side to the larger tube graft proximally, and then end to end to the second distal target (generally the common carotid or subclavian artery). This configuration prevents redundancy and kinking of the grafts in the retrosternal space once the sternum is closed.

Shunting during open repair is not routinely required but should be considered in patients with a contralateral carotid stenosis and those who are otherwise at risk for cerebral malperfusion. When repairing the innominate artery via an open surgical approach, consideration must also be given to those patients with bovine arch anatomy, as clamping of the innominate artery in such a setting will result in complete cerebral ischemia.

Common Carotid Artery Revascularization

Stenosis of the left common carotid artery is the second most common brachiocephalic lesion after stenosis of the left subclavian artery.

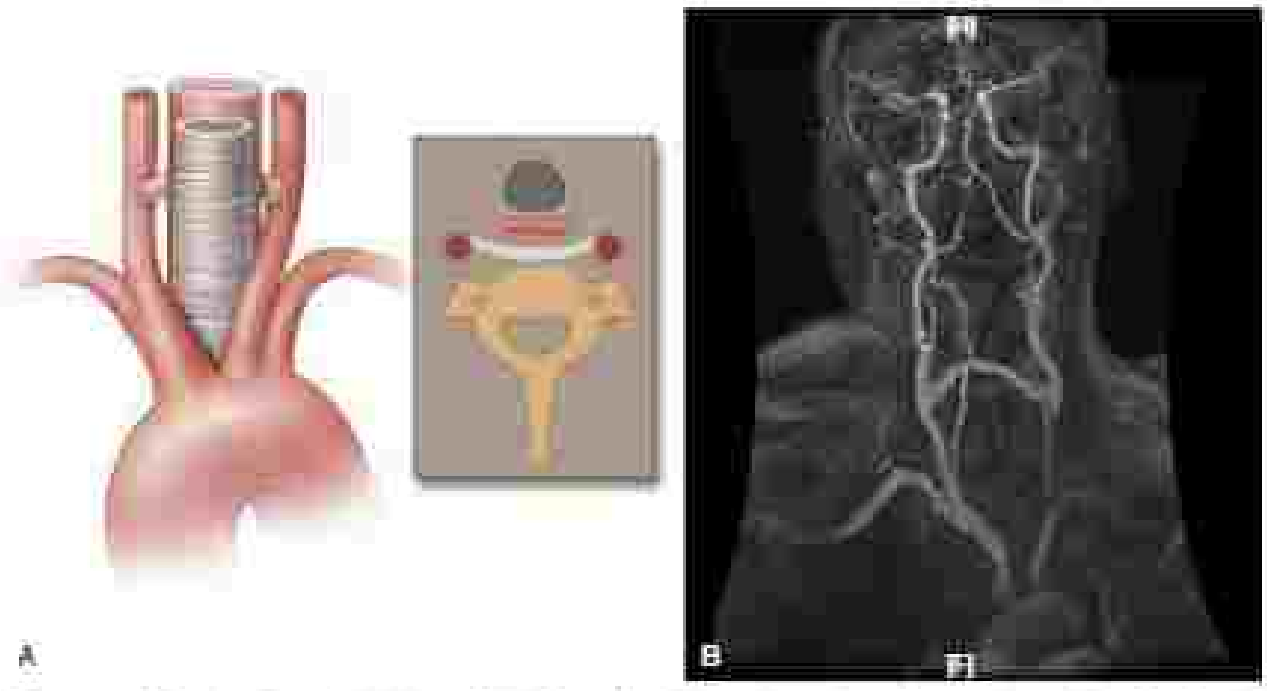


FIG. 9 Carotid-carotid bypass. (A) Illustration depicting a right-to-left carotid-carotid artery bypass using an 8-mm ringed prosthetic graft configured with end-to-side anastomoses at both common carotid arteries. (B) Completion angiogram after carotid-carotid bypass. (Modified from Chaikof, Lee KH, Hill AB, Veith FJ, Hallett Jr JW, Gloviczki P, Rutherford's Vascular Surgery and Endovascular Therapy, Philadelphia, [date]; 2019. p. 1[illegible].)

Due to the potential risk for cerebral atheroembolic events, left carotid artery lesions are the most common lesions to be repaired in asymptomatic patients. While a median sternotomy gives excellent access to the proximal left common carotid artery, the majority of common carotid lesions can be addressed via a cervical approach utilizing a carotid subclavian or carotid-carotid artery revascularization. Unique to carotid revascularization is the carotid-carotid artery bypass (Fig. 9). This procedure is performed by exposing the common carotid arteries bilaterally via anterior vertical neck incisions and tunneling an 8-mm prosthetic bypass graft via a direct path in the retropharyngeal space by passing a finger medial to the carotid artery and behind the esophagus. The graft can alternatively be passed anteriorly, but this tends to erode tissues with contents due to the superficial nature of the graft and presents an issue in the event that the patient needs a tracheostomy or intubation in the future.

Left Subclavian Artery Revascularization

Left subclavian artery stenosis is the most common brachiocephalic lesion requiring intervention. Carotid subclavian revascularization can be performed either as a bypass or as a transposition procedure, and both approaches can be utilized as a means to address pathology to either the subclavian or the common carotid artery. It is worth noting that in patients with subclavian disease, ligation of the diseased vessel proximal to the bypass must be performed in order to prevent continued subclavian steal following revascularization.

A carotid subclavian artery bypass (Fig. 10) is performed via a transverse supraclavicular incision lateral to the clavicular head of the sternocleidomastoid. The skin, subcutaneous fat, and platysma are divided, and the sternal head is retracted medially to expose the common carotid artery. Care must be taken to identify the phrenic nerve prior to division of the anterior scalene muscle, and to retract the vagus nerve and internal jugular vein laterally. During exposure of the subclavian artery on the left, attention must be also be given to the thoracic duct, which enters the posterior confluence of the internal jugular and subclavian veins. If the thoracic duct can be identified, it should be ligated to prevent a postoperative chyle leak. Once the

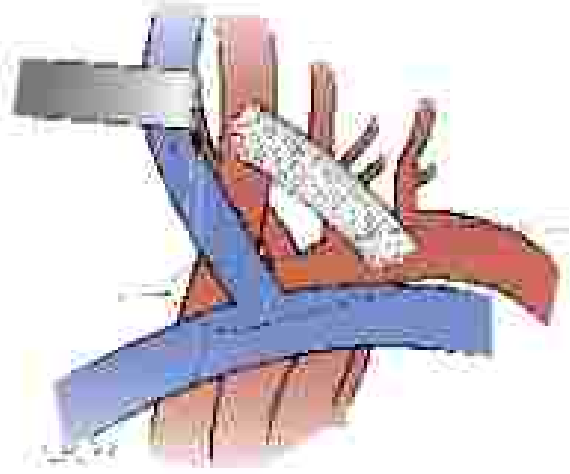


FIG. 10 Left carotid subclavian bypass using an 8-mm ringed prosthetic graft configured with end-to-side anastomoses to both targets.

common carotid and subclavian arteries are exposed and mobilized, a prosthetic graft is sutured to the common carotid artery proximally in an end-to-side fashion. It is then tunneled behind the internal jugular vein and sutured to the subclavian artery in an end-to-side or end-to-end fashion depending on the pathology being treated. Prosthetic grafts have been shown to have significantly better 5-year patency than autogenous veins in this setting (74% vs 54%, respectively); this difference is thought to be due to a lower rate of kinking and compression with prosthetic materials compared to vein.

An alternative to the carotid subclavian artery bypass is a subclavian-carotid artery transposition procedure (Fig. 11), which allows revascularization of the subclavian or carotid arteries without implantation of prosthetic material. To accomplish this procedure, a more extensive dissection of the subclavian artery must be performed to allow a tension free anastomosis with the common carotid. The

extent of the dissection and the mobility required of the subclavian artery to facilitate transposition precludes subclavian-carotid artery transposition in those patients with an existing or future need for an internal mammary graft to a coronary artery.

To perform a subclavian-carotid artery transposition, a transverse supraclavicular incision is made from the medial aspect of the sternal notch extending laterally. Dissection is performed between the heads of the sternocleidomastoid muscle, the omohyoid is divided, and the internal jugular vein is retracted laterally to expose the carotid artery. The thoracic duct should be identified and ligated at this point for all left-sided procedures. The vertebral vein is also identified and ligated,

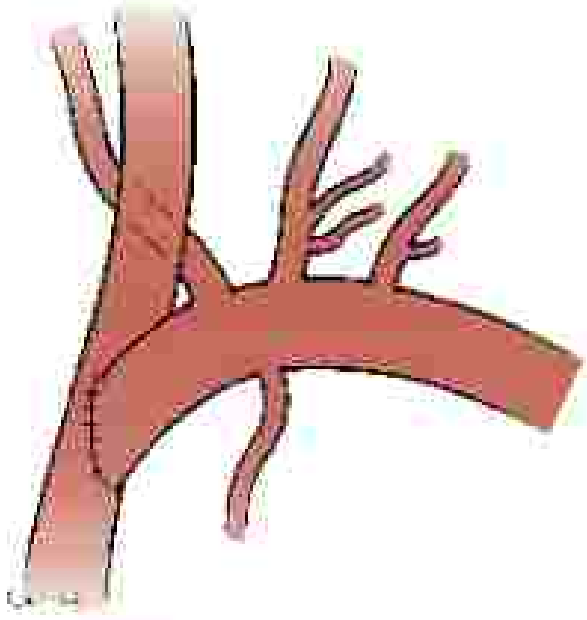


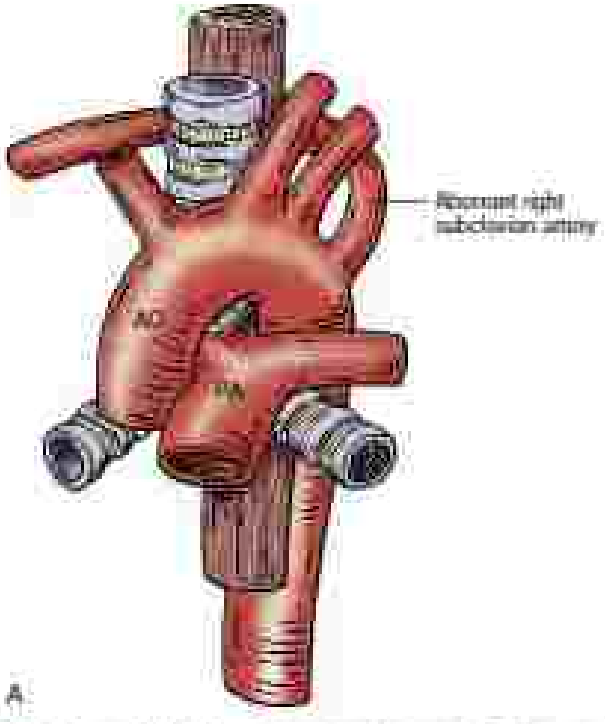
FIG. 11 Left subclavian-carotid transposition.

and the subclavian artery is dissected free proximal to the takeoff of the vertebral and internal mammary arteries. Once the carotid and subclavian arteries are exposed, the proximal subclavian artery is clamped, divided and suture ligated at least 1 to 2 cm proximal to the vertebral artery. It is critical that suture ligation of the proximal subclavian stump is performed immediately, as the artery is generally under tension to facilitate exposure and has the tendency to retract back into the thoracic cavity once divided. The distal end of the divided subclavian artery is then anastomosed to the carotid artery in an end-to-side fashion, with special attention paid to the orientation of the vertebral artery to prevent kinking.

Alternatives to carotid-subclavian revascularization include axillofemoral and subclavian-subclavian bypass procedures. These techniques are rarely utilized but can be used to address left subclavian or innominate disease that is not amenable to more standard open reconstruction approaches. Subclavian grafts are tunneled posterior to the sternocleidomastoid muscles, while axillary grafts run posterior to the pectoralis major muscles in the prosternal space. These grafts are relatively long and tunneled low in the prosternal space, making them at higher risk for compromised patency; however, they remain acceptable choices for revascularization in high-risk patients without other feasible options.

Right Subclavian Artery Revascularization

Right subclavian artery lesions are largely managed in the same manner as left subclavian artery lesions, but the pathologies tend to be slightly different. Although atherosclerotic disease can affect any of the brachiocephalic arteries and require subsequent revascularization, variant anatomy in the form of an aberrant right subclavian artery is much more common than an aberrant left subclavian artery. The aberrant right subclavian artery usually presents in patients aged 40 to 50 years of age as difficulty swallowing (i.e., dysphagia lusoria). In these cases, the right subclavian artery arises from the proximal descending thoracic aorta and courses dorsally between the esophagus and the spine to supply the right arm (Fig. 12). While this anatomy may be asymptomatic in some patients, the aberrant



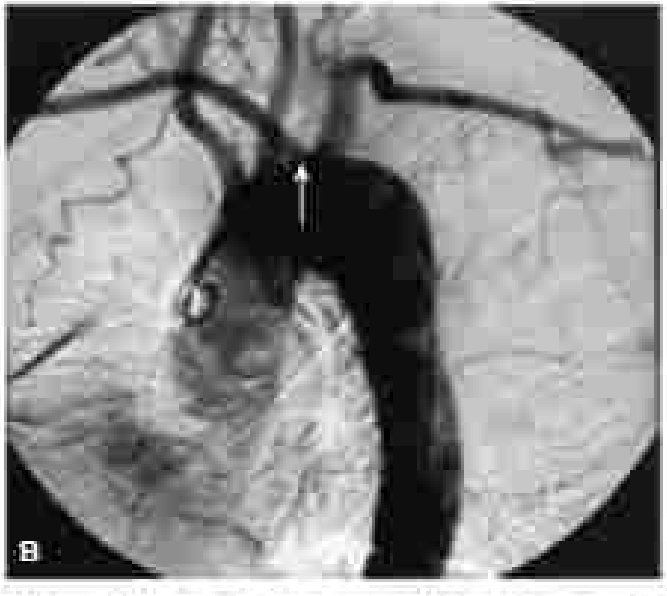


FIG. 12 Schematic (A) and digital subtraction angiogram (B) demonstrating the anatomic configuration of an aberrant right subclavian artery (arrow). Ao, Aorta; PA, pulmonary artery.

subclavian artery can compress the esophagus to the point that patients experience dysphagia. Patients presenting with this complaint should be fully worked up for gastrointestinal sources of their dysphagia via upper endoscopy, esophageal pH monitoring, and esophageal manometry prior to considering brachiocephalic reconstruction. Once other diagnoses have been exhausted, they can be considered for subclavian artery reconstruction. We prefer a carotid-subclavian artery bypass or subclavian artery transposition with proximal ligation of the subclavian artery via a supraclavicular incision. In most cases this procedure alone results in symptomatic relief. In patients with persistent symptoms after subclavian artery ligation and reconstruction, the subclavian artery stump can be completely resected via a left lateral thoracotomy or decompressed via a thoracic aorta stent graft placement (thoracic endovascular aortic repair [TEVAR]).

Brachiocephalic Artery Debranching

Even in the setting of normal brachiocephalic vessels, aneurysmal degradation or dissection of the adjacent descending thoracic aorta may require intervention on the brachiocephalic arteries. In the setting of aneurysm, dissection, or traumatic transection of the thoracic aorta, TEVAR is now employed as the treatment modality of choice. As the stent graft utilized in TEVAR requires a proximal landing zone of at least 2 cm, obtaining adequate exclusion or coverage of the aortic pathology in question would otherwise lead to coverage of one or more of the brachiocephalic vessels. Hybrid procedures, which combine open debranching of the brachiocephalic vessels with endovascular aortic stenting, increase the availability of complex thoracic aortic repair to patients who would otherwise be deemed nonoperative candidates due to their inability to tolerate open surgery.

The most common debranching procedure performed in anticipation of TEVAR is for planned left subclavian artery coverage. Historically, the left subclavian was not routinely revascularized prior to TEVAR; only patients with symptoms of arm claudication or ischemia postoperatively were offered revascularization. However, it is now appreciated that coverage of the left subclavian artery can iatrogenically result in vertebrobasilar and spinal cord ischemia as well. Controlla et al. examined outcomes of left subclavian coverage versus revascularization in the setting of TEVAR, and demonstrated 11% versus 3% stroke rates, respectively ($p = .0003$). Currently, it is recommended that left subclavian artery revascularization be performed preoperatively for all elective TEVAR procedures, usually in the form of a carotid-subclavian artery bypass or subclavian-carotid artery transposition. For emergent or urgent TEVAR requiring left subclavian artery coverage, revascularization can be considered on a case by case basis and may be performed postoperatively in asymptomatic patients. Importantly, left subclavian artery revascularization is considered mandatory in all patients with a left internal mammary coronary bypass graft, and strongly recommended in those patients with a left radial artery/venous fistula or antibrachial bypass.

Stent graft placement into the aortic arch with planned coverage of the left common carotid and/or innominate arteries requires a more complex revascularization approach. Given the role that these vessels play in cerebrovascular circulation, preoperative revascularization is not optional. In the setting of left common carotid coverage, a right-to-left crossover bypass in the form of a carotid-carotid, subclavian-subclavian or axillo-axillary bypass can be performed in conjunction with a left carotid-subclavian bypass or transposition to provide the necessary perfusion to the cerebrovascular bed. More proximal stent graft placement involving coverage of the innominate artery requires a total arch debranching procedure as described above (see Fig. 5). Extra-thoracic bypasses are uncommon in this setting, as the cerebrovascular perfusion would be entirely dependent on an antibrachial bypass graft or similar extra-anatomic configurations with concerning durability long term.

OUTCOMES OF OPEN SURGICAL REVASCULARIZATION

Overall, the results for open brachiocephalic revascularization procedures are satisfactory with an acceptable risk profile. It is generally accepted that cervical revascularization is better tolerated than transthoracic repair, with average perioperative mortality and stroke rates of 1.0% and 1.2% versus 6.6% and 5.6%, respectively. However, the long term patency of transthoracic reconstructions may be superior. Takach et al. reported results of their experience with transthoracic reconstruction versus cervical revascularization procedures in 457 consecutive patients and demonstrated no significant differences in perioperative mortality (2.7% vs 2.3%) and stroke (2.7% vs 0.8%) for both approaches, but a significantly improved freedom from graft failure 10 years after surgery in the transthoracic group (94% vs 60%, $P = .002$). This was not a randomized controlled trial and thus the equivalent morbidity and mortality between the operative approaches should be interpreted accordingly. The improved graft patency and repair durability noted among transthoracic reconstruction patients is likely secondary to the preservation of direct aortic inflow to the brachiocephalic vessels and, as such, most experts agree that this approach is the optimal approach for younger patients able to tolerate sternotomy.

For those patients unable to tolerate direct reconstruction of the brachiocephalic vessels, cervical revascularization remains well tolerated with acceptable patency. The reported patency rate for carotid-subclavian bypass procedures is estimated to be 94% to 96% and 89% at 5 and 10 years, respectively, and the 5 year patency rate for subclavian-carotid artery transposition procedures is approximately 90%. The favorable patency associated with prosthetic grafts in this setting, as well as the limited dissection associated with carotid-subclavian bypass over both preserves the internal mammary artery and provides a durable repair for young patients in need of subclavian revascularization.

Debranching of the brachiocephalic vessels for planned stent graft placement has excellent results in the current literature, equivalent or better than those found in the setting of revascularization for occlusive disease. Scali et al. compared the outcomes of left subclavian artery revascularization for occlusive disease versus TEVAR debranching and found 3 year patency rates of 73% and 93%, respectively. The estimated 1 year graft patency for debranching procedures incorporating the innominate, left common carotid, and left subclavian arteries is reported to be between 89% and 96%.

ENDOVASCULAR INTERVENTIONS

While the outcomes of open surgical brachiocephalic revascularization are excellent from a durability standpoint, the rapid progression of endovascular technology has led to a growing interest in less invasive revascularization techniques. In particular, the challenging exposure that is inherent to most open brachiocephalic revascularization procedures has made angioplasty and stenting an increasingly popular approach in this region. However, surgeons must be careful not to remove options for future open surgical repair should endovascular options fail. Optimal lesions to be addressed with catheter based interventions are those that involved isolated, short segment stenoses in the mid vessel. For those lesions that are occlusive, heavily calcified, aberrant, involving the aorta or a major branching vessel, surgical revascularization is preferred.

When cannulating the brachiocephalic vessels, careful thought must be paid to the risk of emboli to the cerebral circulation. Frequently, antegrade access to these vessels is obtained via a transfemoral approach; however, at times the angulation of the vessels with respect to the aortic arch makes antegrade selective cannulation challenging and increases risk of emboli with repeated attempts. This is particularly true in patients with heavily calcified aortic arches (i.e., eggshell aorta). In these cases, retrograde access via the ipsilateral brachial artery may be helpful, particularly for innominate artery lesions. Likewise, when concomitant endarterectomy of the carotid

bifurcation is performed, retrograde access via the ipsilateral common carotid artery is also an option. Embolic protection of the vertebral artery is not routinely employed during left subclavian artery interventions due to the low risk (<1%) of emboli to the vertebrobasilar system. The risk of emboli when cannulating the innominate or common carotid arteries is higher, but remains rare (3%). There are no good data to support routine use of cerebral protection in brachiocephalic angioplasty and stenting procedures, although use of an embolic protection device is now considered standard of care for carotid interventions, and, along with placement of a buddy wire in the external carotid artery, can serve as a stabilizing anchor for more proximal common carotid lesions (Fig. 13).

When treating proximal brachiocephalic lesions close to or involving the vessel ostium, an attempt should be made to extend the stent 1 to 2 mm into the aortic lumen. The effect of angioplasty and stenting on the neighboring vessels must be considered closely before deciding to intervene because the brachiocephalic vessels lie in close proximity to one another; treatment of one lesion can sometimes cause plaque shifts to adjacent vessels (Fig. 14). Similarly, treatment of subclavian or innominate artery lesions adjacent to the takeoff of a branching vessel can result in unintended "pulling" of that vessel. For innominate lesions, this may require use of a kissing stent technique in which the right subclavian and common carotid are stented simultaneously to preserve the origin of both branching vessels (Fig. 15). For protection of the vertebral artery, this may require passage of a single balloon expandable stent over two double wires, one extending into the axillary artery and one into the vertebral artery in order to protect the vertebral artery origin as the stent is expanded.

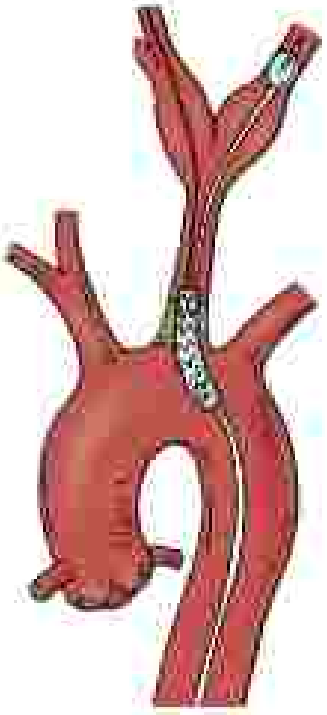


FIG. 13 Use of a balloon anchor in the internal carotid artery and a buddy wire into the external carotid artery to stabilize the plate at the origin of the carotid artery.

OUTCOMES OF ENDOVASCULAR INTERVENTIONS

Initial attempts at endovascular revascularization procedures in the brachiocephalic vasculature were limited to angioplasty and had limited durability. However, with improvements in endovascular technology, the durability of these interventions has become acceptable. Paukovits et al. described 7 year primary and secondary patency rates following percutaneous transluminal angioplasty and/or stenting of proximal innominate carotid artery lesions of 74% and 89%%, respectively. Suga et al. reported outcomes of endovascular interventions for subclavian artery stenosis and found primary and secondary patency rates of 80% and 88%, respectively at 5 years. Factors associated with reduced patency included long segment stenoses, smoking, and clinically evident subclavian steals at the time of intervention, including cerebrovascular disease and hand ischemia.

Perhaps the most important question to be answered is how the durability and safety of endovascular interventions for brachiocephalic lesions compares to that of open surgical reconstruction. Takach et al. examined 391 consecutive patients with aortic arch brachiocephalic arterial disease undergoing either operative bypass or percutaneous transluminal angioplasty and stenting. They reported that, although technical success, perioperative stroke and perioperative mortality rates

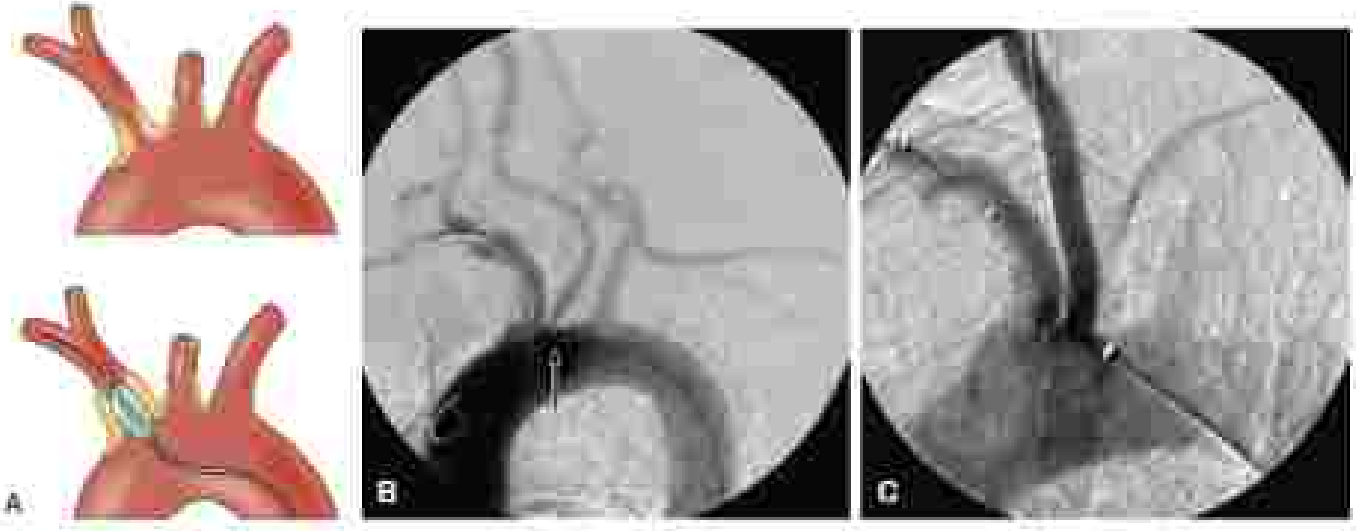


FIG. 14 (A) Treatment of a neighboring arch vessel can force treatment of an adjacent arch branch. After treatment of the innominate artery, the left common carotid can be impinged on by a shift of aortic plaque. (B) Angioplasty and stenting of the innominate artery has shifted aortic plaque, which resulted in narrowing at the origin of the left common carotid artery (arrow). (C) Treatment of the common carotid origin and simultaneous protection of the innominate artery's ostium origin.

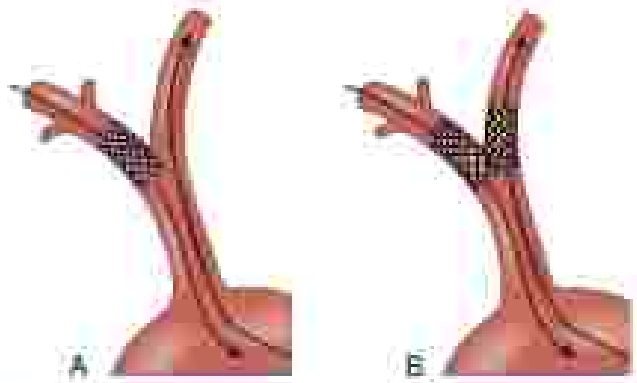


FIG. 13 (A) Treatment of the right subclavian artery origin can result in "piling" the origin of the right common carotid artery by the proximal end of the stent projecting into the common carotid lumen, as shown. (B) Treatment of the innominate artery branch origin with a kissing balloon stent technique to preserve both origins.

were equivalent between the two groups, the operative group had significantly better freedom from intervention failure at 5 years postoperatively even after risk adjustment (93% vs 84%, $P = .03$). Similarly, Abdulhannan et al. compared percutaneous transluminal angioplasty/stenting versus carotid subclavian bypass for isolated subclavian artery disease and reported 5-year primary patency rates of 70% versus 96%, respectively ($P < .0001$). Based on these data, most experts agree that open surgical reconstruction of brachiocephalic disease is associated with improved overall graft patency and fewer additional secondary procedures. However, endovascular interventions have been shown to be associated with potential short-term cost savings, eliminate the need for general anesthesia, and is likely better tolerated than more invasive open approaches, especially in patients with multiple other comorbidities. As a result, endovascular interventions should be considered as an adjunct in the armamentarium against brachiocephalic disease in selected patients.

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Upper Extremity Arterial Occlusive Disease

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Symptomatic arterial occlusive disease of the upper extremity (UE) is seen by the vascular surgeon significantly less frequently than its lower extremity counterpart. Extensive collateral networks around the shoulder, elbow, and wrist, along with the lack of heavy load repetitive use activities of the UE compared with the lower extremity, allow many patients to remain asymptomatic despite significant occlusive lesions. However, when ischemic symptoms of the hands and digits do manifest, the loss of function can lead to significant disability and limitation. Although atherosclerosis is the most common cause of clinically significant arterial ischemia of the UE, many cases of UE ischemia are caused by nonatherosclerotic disease states. These factors make the diagnosis and treatment of UE ischemia more complex than the management of lower extremity ischemia.

Etiology

A wide variety of disease states may lead to UE ischemia. Box 1 offers a broad, conceptual categorization that is far from exhaustive. The most common cause of symptomatic UE ischemia is vasospasm involving the digital vessels, but this is rarely severe and is almost always managed medically (see chapter on Raynaud's phenomenon). Large artery vasospasm is rare but can be caused by ergot poisoning, most often from migraine medications containing ergotamine (Fig. 1).

Intrinsic Arterial Disease

Atherosclerosis of the UE vasculature is usually limited to the more proximal aortic arch vessels. The origin of the left subclavian artery is the most frequently involved segment. Atherosclerosis involving the distal extremity vasculature is seen most often in patients with end-stage renal disease with steal from hemodialysis access, especially with concomitant diabetes, leading to critical limb ischemia and is associated with a poorer prognosis.

A number of inflammatory diseases also can affect the UE arteries. Takayasu's disease and giant cell arteritis (GCA) are large vessel vasculitis. These diseases are associated with an initial inflammatory phase—which may have symptoms of fever, arthritis, and myalgias, along with laboratory findings of elevated erythrocyte sedimentation rate—before ischemic symptoms and signs such as effort fatigue and

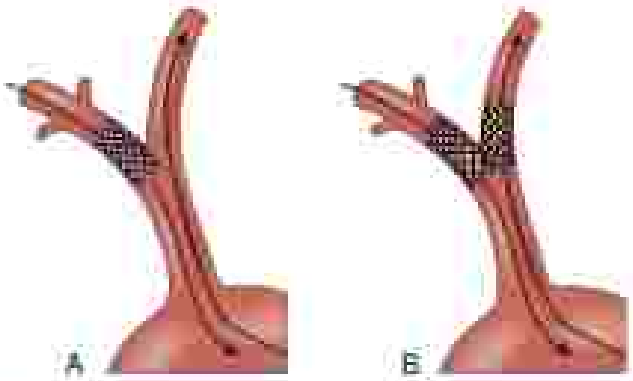

FIG. 13 (A) Treatment of the right subclavian artery origin can result in "piling" the origin of the right common carotid artery by the proximal end of the stent projecting into the common carotid lumen, as shown. (B) Treatment of the innominate artery branch origin with a kissing balloon stent technique to preserve both origins.

were equivalent between the two groups, the operative group had significantly better freedom from intervention/failure at 5 years postoperatively even after risk adjustment (93% vs 84%, $P = .03$). Similarly, Abdullahi et al. compared percutaneous transluminal angioplasty/stenting versus carotid subclavian bypass for isolated subclavian artery disease and reported 5-year primary patency rates of 70% versus 96%, respectively ($P < .0001$). Based on these data, most experts agree that open surgical reconstruction of brachiocephalic disease is associated with improved overall graft patency and fewer additional secondary procedures. However, endovascular interventions have been shown to be associated with potential short-term cost savings, eliminate the need for general anesthesia, and is likely better tolerated than more invasive open approaches, especially in patients with multiple other comorbidities. As a result, endovascular interventions should be considered as an adjunct in the armamentarium against brachiocephalic disease in selected patients.

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Upper Extremity Arterial Occlusive Disease

Satinderjit S. Latcham, MBBSc, MRCS(Ed), BAO, and Mahmood B. Malas, MD, MHS, FACS

Symptomatic arterial occlusive disease of the upper extremity (UE) is seen by the vascular surgeon significantly less frequently than its lower extremity counterpart. Extensive collateral networks around the shoulder, elbow, and wrist, along with the lack of heavy load repetitive use activities of the UE compared with the lower extremity, allow many patients to remain asymptomatic despite significant occlusive lesions. However, when ischemic symptoms of the hands and digits do manifest, the loss of function can lead to significant disability and limitation. Although atherosclerosis is the most common cause of clinically significant arterial ischemia of the UE, many cases of UE ischemia are caused by nonatherosclerotic disease states. These factors make the diagnosis and treatment of UE ischemia more complex than the management of lower extremity ischemia.

Etiology

A wide variety of disease states may lead to UE ischemia. Box 1 offers a broad, conceptual categorization that is far from exhaustive. The most common cause of symptomatic UE ischemia is vasospasm involving the digital vessels, but this is rarely severe and is almost always managed medically (see chapter on Raynaud's phenomenon). Large artery vasospasm is rare but can be caused by ergot poisoning, most often from migraine medications containing ergotamine (Fig. 1).

Intrinsic Arterial Disease

Atherosclerosis of the UE vasculature is usually limited to the more proximal aortic arch vessels. The origin of the left subclavian artery is the most frequently involved segment. Atherosclerosis involving the distal extremity vasculature is seen most often in patients with end-stage renal disease with steal from hemodialysis access, especially with concomitant diabetes, leading to critical limb ischemia and is associated with a poorer prognosis.

A number of inflammatory diseases also can affect the UE arteries. Takayasu's disease and giant cell arteritis (GCA) are large vessel vasculitis. These diseases are associated with an initial inflammatory phase—which may have symptoms of fever, arthritis, and myalgias, along with laboratory findings of elevated erythrocyte sedimentation rate—before ischemic symptoms and signs such as effort fatigue and

BOX 1 Causes of Upper Extremity Ischemia

Vasospasm

Raynaud phenomenon (palmar digital)
Drug induced: ergotamine, β-blockers, vasopressors

Intrinsic Arterial Disease

Atherosclerosis (uncommon: subclavian)
Radiation arteritis (uncommon: axillobrachial)
Anatomic: arteriopathy (radial/ulnar, palmar digital)

Inflammatory Diseases

Connective tissue disorders (palmar digital)
Hypersensitivity angiitis (palmar digital)
Thromboangiitis obliterans (Buerger's disease: radial/ulnar, palmar digital)
Takayasu's arteritis (uncommon: subclavian)
Temporal arteritis (axillobrachial)

Medical Diseases

Immunoglobulin states (palmar and digital arteries)
Myeloproliferative disorders (palmar and digital arteries)
Hepatitis associated vasculitis (palmar and digital arteries)
Cryoglobulinemia (palmar and digital arteries)

Environmental

Cold injury
Vinyl chloride exposure

Embolism

Cardiac (brachial)
Arterial source
- Arterial thoracic outlet syndrome (subclavian artery source)
- Peripheral aneurysm
- Atherothrombosis

Trauma

Blunt or penetrating trauma
Iatrogenic
- Angiography (brachial, radial)

Hypothenar hammer syndrome (ulnar)
Vibration (palmar, digital)
Sports or athletic injury (axillosubclavian)

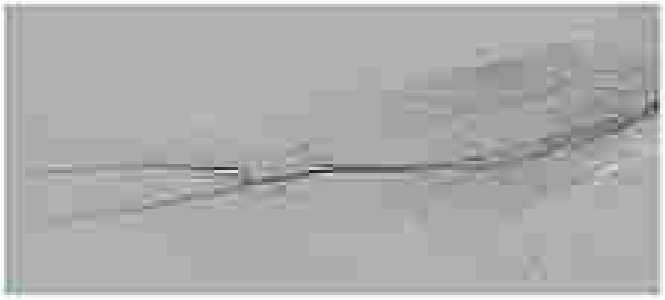

FIG. 1 Right upper extremity angiogram demonstrating severe brachial artery occlusion in a 45-year-old woman taking an ergotamine-containing medication for treatment of migraine headaches.

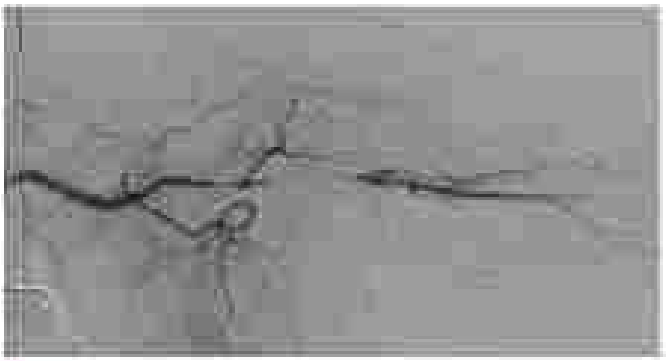

FIG. 2 Left upper extremity angiogram demonstrating an area of smooth tapering stenosis and adjacent occlusion in the brachial artery of a 52-year-old woman with gait and arm/leg claudication who experienced ulcer fatigue of the hand and forearm.

asymmetric brachial blood pressure measurements develop. In the case of GCA, patients can lose their vision if diagnosis is not confirmed and appropriate treatment with steroid not initiated early. Angiographic findings typically reveal a smooth tapering stenosis resulting from inflammation involving all three layers of the vessel wall. Takayasu's disease typically involves the carotid and subclavian arteries in women age 20 to 40 years. GCA usually affects older women (>50 years), most commonly involving the extracranial carotid artery. When GCA involves the UE it affects the distal subclavian artery, axillary artery, and brachial artery (Fig. 2). Thromboangiitis obliterans, or Buerger's disease, is a segmental, inflammatory, obliterative disease of the medium and small arteries of the extremities seen in heavy smokers (see chapter on Buerger's disease). It frequently affects the forearm and palmar digital arteries, sparing the more proximal arteries.

A number of connective tissue disorders can cause small vessel disease affecting the palmar digital vessels. These include scleroderma, CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, lupus, and rheumatoid arthritis. A similar small vessel disease pattern can be seen with a variety of relatively rare medical disorders (e.g., cryoglobulinemia or hepatitis associated vasculitis), which should be looked for only after connective tissue disease have been excluded. In the absence of an identifiable cause, which occurs in approximately one third of cases, such small artery occlusive disease is termed hypothenar hammer syndrome.

Embolism

Most emboli to the UE are of cardiac origin and are macroemboli that typically lodge in the brachial artery just proximal to the take-off of the deep brachial artery or at its bifurcation into the ulnar and radial arteries. These emboli usually result in acute episodes of forearm or hand ischemia in patients with an underlying cardiac condition but may be seen more chronically in older or debilitated patients who do not use their UE enough to induce symptoms. However, up to 30% of UE emboli have an arterial site of origin and tend to be microemboli that lodge in more distal arterial segments (palmar digital). The most common culprit is an aneurysm or ulcerative lesion within the distal subclavian artery associated with thoracic outlet syndrome (see chapter on thoracic outlet syndrome). In this situation, repetitive compression of the subclavian artery by anomalous myofascial bands attached to a cervical rib (or other osseous anomaly) leads to a focal stenosis. Poststenotic dilatation (aneurysm) or intimal ulceration results in mural thrombus formation. Subsequent embolization of luminal debris can produce both large and small artery occlusions distally. Unilateral Raynaud's phenomenon is a common presentation. Degenerative aneurysms of the subclavian artery or posttraumatic aneurysms of other UE arteries (e.g., crutch induced axillary artery aneurysms) are other rare causes of ischemia and produce symptoms either through distal emboli or, less commonly, by in situ thrombosis. Ulcerative atherosclerotic plaques within the aorta or proximal brachiocephalic arteries also can lead, rarely, to emboli.

Trauma

Undiagnosed or neglected arterial injuries are a well recognized cause of UE occlusive disease. Although bleeding and significant ischemia are obvious manifestations of arterial injury requiring treatment in the acute setting, intimal injuries from both penetrating and blunt trauma may lead to delayed arterial thrombosis with less dramatic symptomatology. Iatrogenic injuries are particularly common. Brachial artery injuries are a well recognized complication of cardiac catheterization procedures performed via this approach. Such occlusions may go undetected in the acute setting because of the abundant collaterals around the elbow. The only manifestation may be the development of effort fatigue in the forearm on resumption of normal activities. Cumulative occupational trauma also can lead to significant vascular injury. Hypothenar hammer syndrome results from repetitive blunt trauma to the proximal portion of the ulnar artery in Guyon canal (formed by the pisiform, the hook of the hamate, and the transverse carpal ligament in the proximal palm). This injury is caused by repetitively striking objects with the base of the palm. Segmental occlusion or aneurysm formation of the ulnar artery, with or without distal digital artery embolism, can result (Fig. 1). Vibration-induced injury to the digital arteries occurs after prolonged exposure of the hands to vibratory tools or machinery. The tools most commonly implicated are pneumatic tools and chainsaws. Patients initially report neurologic complaints (i.e., numbness or paresthesia) in the affected hand and digits. As the syndrome progresses, Raynaud's phenomenon develops. Tissue loss is rare. Sports-related trauma is a rare cause of ischemia, but can occur in individuals who use a hand, repetitive UE motion in competitive athletic endeavors. Axillary and subclavian artery injuries in baseball pitchers are the most frequently encountered.

EVALUATION

Performing a thorough history and physical examination is the first step in narrowing down the multiple causes of UE arterial occlusive disease to come to the appropriate diagnosis, and thus be able to formulate a comprehensive treatment plan. Symptoms can range from the incidental finding of a blood pressure differential in the UE by a patient's primary care physician on physical examination, to color changes, coolness, numbness, weakness, effort-induced fatigue, and ischemic rest pain, and all the way to tissue loss. Raynaud's phenomenon, which may result from pure vasospasm, is also a frequent manifestation of distal occlusive lesions. Most patients will note only one or two of the classic vascular digital changes, pallor (white) to cyanosis (blue) to hyperemic rubor (red). Exercise-induced fatigue in the musculature is brought on by repetitive use and, like its lower extremity counterpart claudication, is relieved quickly by a short period of rest. This phenomenon usually results from large vessel occlusive disease. Symptoms manifested in the hand or digits may result from large vessel disease, small vessel disease, or multifocal disease. Digital tissue loss is nearly always associated with small artery occlusive disease, with or without more proximal involvement.

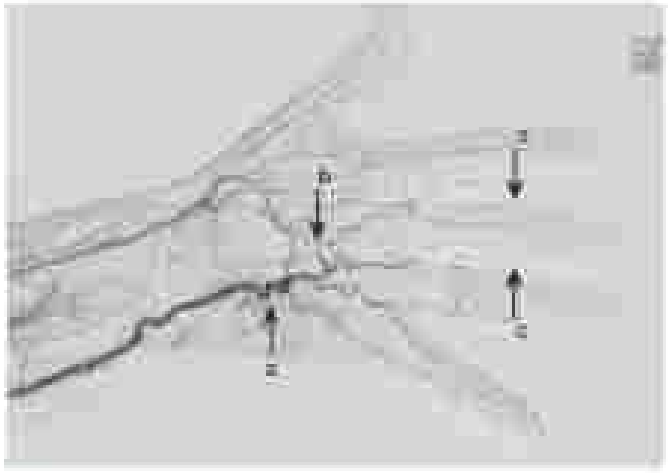

FIG. 1. Angiogram of the left hand of a patient with hypothenar hammer syndrome seen with color changes and pain in the fingers, specifically the middle finger. Note the irregularity of the distal ulnar artery (arrow a), embolic filling defect in the superficial palmar arch (arrow b), and occlusion of digital arteries of the middle finger (arrow c).

Laterality of symptoms should be assessed. Bilateral UE symptoms suggest the presence of a systemic cause, such as a connective tissue or inflammatory disease. Patients also should be questioned about possible underlying connective tissue disorders or associated symptoms—tight skin or dysphagia in scleroderma, facial rash in lupus, or joint complaints in rheumatoid arthritis. The patient also should be interrogated for other systemic symptoms such as weight loss and myalgias. Unilateral complaints suggest localized arterial pathology such as arterial thoracic outlet syndrome, arterial aneurysm, or hypothenar hammer syndrome.

Because atherosclerotic disease is the most common cause of UE arterial occlusive disease, pathology should be evaluated thoroughly in all cases and associated risk factors identified (i.e., tobacco use, dyslipidemia, hypertension, diabetes mellitus, renal insufficiency, and family history). Symptoms or history of arterial occlusive disease in other vascular beds, including the coronary arteries, lower extremities (claudication), and cerebrovascular circulation, should be sought. Specifically, if concomitant posterior cerebral circulation symptoms such as dizziness, ataxia, or diplopia are identified, possible involvement of the subclavian or proximate arteries proximal to the takeoff of the vertebral artery should be investigated.

In the medical history, one should inquire about hypercoagulable states, renal insufficiency, cardiac arrhythmias and disorders, medication and supplement use, and drug abuse. A history of prior trauma to the neck or UE should be sought. The history also should include any catheter-based procedures in the UE as well as catheters placed for invasive hemodynamic monitoring. Patients with renal failure should be evaluated for prior vascular access procedures. Social history includes occupational or environmental exposures, athletic activities, and hobbies that may be important. The family history should focus on connective tissue disorders, hypercoagulable states, and premature atherosclerotic disease.

The physical examination includes measurement of blood pressure in both UEs. A complete pulse examination of the neck, UEs, and lower extremities is essential and remains the primary modality for diagnosing UE occlusive disease. A decreased or absent pulse indicates a proximal high-grade stenosis or occlusion; however, the presence of a pulse does not completely exclude proximal disease, particularly in the setting of a chronic occlusion, given the rich collateral pathways present in the UE. An irregular pulse should prompt a more detailed cardiac examination to identify atrial fibrillation or other arrhythmias that may predispose to cardioembolism. Auscultation for bruits over all major arteries should be performed. The skin envelope of the digits is examined for signs of color or temperature differences, tissue loss, or trophic changes. In patients with unilateral complaints, the symptomatic extremity should be examined carefully for occult disease. Allen's test can be used to assess patency of the palmar arch. In this test the patient's radial and ulnar arteries are occluded with digital pressure while the patient opens and closes the hand. Once the hand is pale, the ulnar artery is released and reperfusion of the hand is assessed; then the maneuver is repeated, except the radial artery is released first.

Noninvasive Vascular Laboratory Assessment

All patients with ischemic symptoms should undergo bilateral UE arterial segmental pressure testing. This testing provides objective and reproducible data that may identify focal obstructions as well as indicate vasospasm and also quantify the degree of arterial

insufficiency. Serial examinations allow for objective assessment of disease status and evaluation of the effectiveness of therapeutic interventions. Bilateral brachial, upper forearm, and wrist systolic pressures are obtained along with associated Doppler waveforms. The normal pressure differential between arms should not exceed 15 mm Hg, and a pressure drop of 20 mm Hg or more between levels indicates an interceding hemodynamically significant lesion. Reduced brachial pressure bilaterally, particularly when associated with bruits or monophasic Doppler waveforms, should prompt high thigh pressure measurements to exclude the possibility of bilateral proximal UE arterial disease. Although digital pressures and waveforms are notoriously temperature dependent, they can be extremely helpful in documenting the presence of small artery occlusive disease or vasospasm. An absolute digital pressure less than 70 mm Hg, a wrist/digital gradient greater than 30 mm Hg, and an interdigital gradient greater than 15 mm Hg are all considered abnormal. The finding of normal or near normal digital pressures with vasospastic waveforms is helpful in establishing a diagnosis of Raynaud's phenomenon. Arterial duplex scanning may provide even more information than segmental pressures but has limited utility proximally because of the bony structures of the thoracic outlet. We have found it most useful when dealing with suspected lesions in the axillary, brachial, and forearm arteries.

Imaging

Advanced imaging usually is reserved for patients with critical limb ischemia or debilitating symptoms with evidence of proximal disease amenable to intervention. Significant improvements in imaging equipment and technique have increased the use of both computed tomographic angiography and magnetic resonance angiography in the evaluation of UE arterial disease. Both are valuable in evaluating the aorta arch and larger, more proximal vessels. The use of postprocessing techniques and three-dimensional reconstruction also is useful in planning invasive intervention. However, these modalities do have limits, specifically in providing adequate detailed imaging of the distal forearm, hand, and fingers. When such imaging is required, conventional catheter angiography remains the gold standard, using digital subtraction technology to minimize the radiocontrast load. Angiography also allows for concomitant administration of vasodilators, such as nitroglycerin or nitroglycerin, which are often necessary to adequately visualize the arteries of the hand and fingers. Selective studies of both UEs should be obtained because many disease processes affect both UEs. With the proliferation of endoluminal treatment modalities, catheter angiography also provides the opportunity for simultaneous therapeutic intervention.

Laboratory Testing

Specific laboratory studies are obtained based on the index of suspicion and are most useful when dealing with distal small artery occlusive disease. Routine chemistries, blood counts, and coagulation profiles should be drawn when the diagnosis is unclear. If a hypercoagulable state is considered, patients should be checked for factor V Leiden, antithrombin III deficiency, protein C and S deficiencies, antiphospholipid antibodies, the prothrombin gene mutation, and hyperhomocysteinemia. Testing for connective tissue disorders should include rheumatoid factor, antinuclear antibodies, complement levels, and a sedimentation rate. Additional tests looking for cryoglobulinemia, heparin, or myeloproliferative disorders may be helpful if the other, more common causes of small artery occlusive disease have been excluded. When a cardioembolic source is suspected, electrocardiography is obtained to evaluate for arrhythmia, and echocardiography may be obtained to evaluate for a cardiac structural abnormality or residual cardiac thrombus. Similarly, plain films of the neck looking for a cervical rib or other osseous abnormalities are useful to exclude most arterial thoracic outlet problems.

MANAGEMENT

Appropriate treatment of UE occlusive disease depends on both its etiology and its degree of symptomatology. Medical therapy is frequently the first-line treatment, as invasive intervention is neither indicated nor helpful for many of the causes of UE ischemia.

Patients with vasospasm are advised to abstain from tobacco and to avoid cold. Vasodilators, primarily calcium channel blockers, have been used with varying degrees of success to treat severely symptomatic Raynaud's phenomenon. Patients with atherosclerotic lesions should undergo aggressive risk factor modification implemented in the same way as occurs when atherosclerosis is identified in other vascular beds.

Patients with a large to medium sized systemic vasculitis (i.e., Takayasu's arteritis or GCA) generally have an initial inflammatory phase for which corticosteroid treatment should be initiated. Alternative immunosuppressive and immunomodulating agents such as cyclophosphamide, methotrexate, and azathioprine also can be used. These patients benefit from well coordinated multidisciplinary care. Invasive intervention should be avoided during the active inflammatory phase because of the high risk for recurrence and failure.

Revascularization for chronic occlusive disease is limited to limb salvage situations for patients with critical ischemia (tissue loss or rest pain) or debilitating symptoms of effort fatigue secondary to large or medium vessel occlusive disease. Acute arterial occlusions resulting from arterial emboli or trauma generally should be addressed when diagnosed, as operative intervention is easiest in the acute setting, and ischemic symptoms frequently develop once the patient recovers from the acute event.

Regardless of the indication, great care is necessary when operating on the UE vasculature. The proximal UE arteries lack the thick muscular layer of the femoral artery and are torn easily if handled roughly. The forearm arteries are also problematic because of their extreme tortuosity. Avoidance of excessive manipulation is critical. Operative intervention is most useful for treating atherosclerotic occlusive disease of the proximal arteries. Intrathoracic procedures to treat innominate and subclavian artery occlusive disease are discussed in the chapter on brachiocephalic reconstruction.

Endovascular Therapy

Endovascular technique is most commonly used to treat short segment occlusive lesions found in the proximal vessels of the UE, specifically in the proximal left subclavian artery. Standard endovascular techniques typically are used with an antegrade approach via femoral access or, if necessary, a retrograde approach via the brachial artery. Typically long sheaths are used to give adequate support. Because of the larger sheaths that are required (6Fr and larger), open exposure of the brachial artery is preferred to limit access site complications when a retrograde approach is used. Prior studies have reported good outcomes following endovascular stenting and angioplasty for proximal lesions. However, the evidence is lacking for the more distal lesions. Common complications included stent fracture, restenosis, and thrombosis. Angioplasty alone is inferior to combined stenting and angioplasty, especially for occlusive subclavian lesions.

Subclavian Angioplasty/Stenting

Common indications of subclavian angioplasty and/or stenting of subclavian artery stenosis or occlusion include subclavian steal syndrome, vertebrobasilar symptoms, upper limb ischemia, and protection of left internal mammary artery coronary axillofemoral, and axillobrachial bypass. Excellent technical success rates have been reported, though success rates are somewhat lower in cases of chronic total occlusions compared with stenotic lesions. This procedure is associated with low morbidity and mortality. Short- and midterm patency rates are comparable with open surgical reconstruction. Longer term, open repairs have superior patency compared with endovascular interventions. However, given the low complication rates,

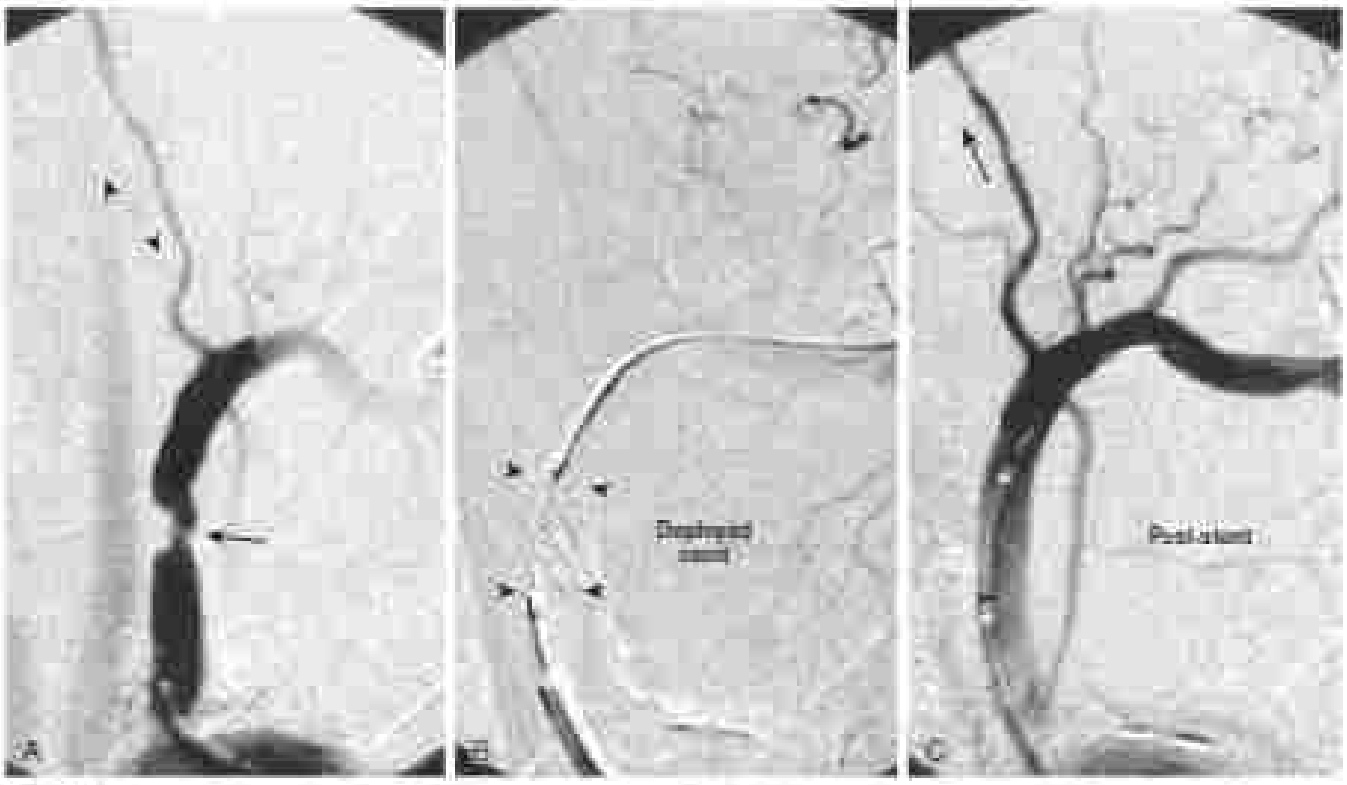

FIG. 4 Endovascular angioplasty and stenting of subclavian artery stenosis. (A) Stenotic lesion in a patient with severe subclavian artery stenosis (arrow). Arrowhead demonstrates perfusion of the arm through reversal of flow in the vertebral artery. (B) Deployment of the stent (arrowheads). (C) Completion angiography poststenting.

the minimally invasive nature, and the often frail patient population that requires such interventions, endovascular therapy is assuming its place as first line therapy for many of these lesions.

Endovascular management of subclavian artery stenosis is performed as follows (Fig. 4). Prior to the procedure, all patients should receive a low to medium dose of aspirin therapy. Clopidogrel can be considered in patients with aspirin sensitivity. Aortic arch aortogram and arteriography of the affected vessels is needed specially to show the location of the lesion with respect to ostium of subclavian artery and origin of its branches. Ultrasound guided micropuncture technique is used for access of the femoral artery. A 6Fr sheath is then placed to allow for easy positioning of the delivery system. Intravenous heparin is used (80 U/kg). After arch angiogram and road mapping of the lesion, 5Fr diagnostic catheter, such as vertebral catheter, is advanced over the wire through the sheath to engage the ostium and select the vessel. Then 0.014-inch, 0.018-inch or 0.035-inch wire is advanced to pass the stenotic lesion through the diagnostic catheter. A long guiding sheath (90-cm Cook select) is then positioned proximal to the lesion. Balloon angioplasty is commonly used prior to stenting. A 5 to 6 mm × 20 to 40 mm balloon is adequate for predilation of most subclavian stenotic lesions. Balloon-expanded stents are recommended to provide adequate radial force in orificial calcified lesions. Stent sizes can vary between 6 and 8 mm in diameter and 20 and 40 mm in length. The stent is delivered through the sheath over the wire and deployed to cover the entire lesion. A completion angiography is performed to rule out any complications (dissection or perforation). A key point to consider is not to oversize the stent in calcified lesions to avoid vessel rupture and bleeding. Also, since the vertebral artery is close to these lesions, care must be taken to avoid dissection and embolization to this vessel.

Endovascular management of subclavian occlusion is better performed through retrograde brachial approach. A 6Fr sheath is placed in the brachial artery distal to the subclavian occlusion. This approach can increase the risk of retrograde dissection into the aortic arch. A 0.035-inch glide wire supported with a curved catheter is used to cross the occlusion. Remaining steps involving angiography to confirm true lumen selection, predilation and stent placement are similar to the antegrade subclavian stenotic lesion as described previously. Angiography of the aortic arch can be performed using femoral access to aid in the proper placement of the stent.

Dual antiplatelet therapy (aspirin and clopidogrel) is required for at least 3 weeks following stenting.

Other Lesions

The use of endovascular techniques for other lesions of the UE is not well defined. Traumatic disruptions of the subclavian axillary artery, which can be difficult to approach surgically, have been treated successfully with cover stent grafts (Fig. 5). Catheter directed thrombolysis has been used for thrombotic occlusions of the UE. Technically successful balloon angioplasty of arterial occlusive lesions in the arm, forearm, and hand has been described. The infrequency of the UE pathology and the lack of long term follow up make it difficult to establish the role of these interventions.

Open Surgical Revascularization

Subclavian

Provided that the ipsilateral common carotid artery is disease free, both carotid subclavian bypass and subclavian transposition can be considered for the treatment of proximal subclavian artery occlusive disease. Although bypass is technically simpler, transposition has superior long term patency. Although endovascular techniques have reduced our reliance on these operations for the treatment of occlusive disease, these operations have in fact become more commonly performed as part of debranching the aortic arch in preparation for endovascular repair of thoracic aortic pathology.

The procedure is performed as follows. The patient is placed on the operating table in a semi Fowler's position, with the head of the table elevated 30 to 50 degrees. A roll is placed under the shoulders to allow for moderate extension of the neck, and the head is rotated

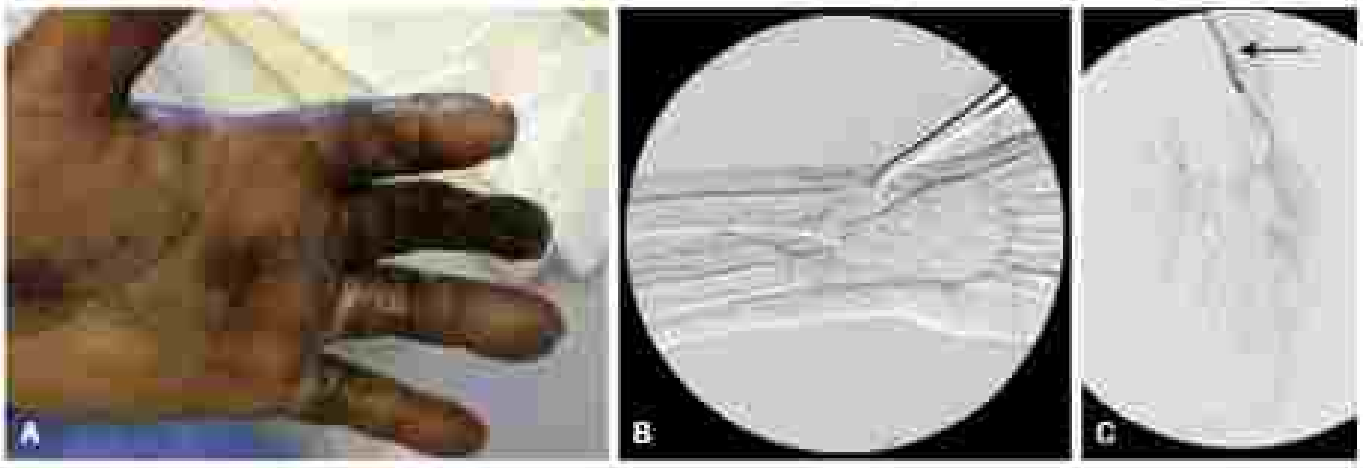

FIG. 3 (A) Ischemic left hand with gangrene of the middle finger in a patient with end-stage renal disease and neglected thromboembolization of the fistula after percutaneous dialysis access graft thrombectomy. (B) Angiography demonstrating occlusion of the ulnar and radial arteries with reconstitution of the radial artery at the wrist. (C) Angiogram demonstrating distal anastomosis and runoff of brachial artery to radial artery bypass with reversed great saphenous vein (arrow).

slightly toward the contralateral side. The ipsilateral arm is placed at the side with the shoulder depressed as much as possible. A transverse incision is made approximately one fingerbreadth (2 cm) above the clavicle, extending from the edge of the sternocleidomastoid muscle to the midportion of the clavicle. Subcutaneous tissues and platysma are divided, and the clavicular head of the sternomastoid muscle is transected. The omohyoid is identified and divided. The underlying scalene fat pad is mobilized along its medial and inferior aspects and retracted superiorly and laterally. During this dissection one must be alert for lymphatic structures, which are carefully ligated before division. However, the thoracic duct or right lymphatic duct is not routinely ligated if encountered unless it is injured. After retraction of the scalene fat pad, the anterior scalene muscle is exposed. The phrenic nerve is identified (coursing lateral to medial along the surface of the anterior scalene) and carefully mobilized and retracted to allow division of the anterior scalene from its tubercle on the first rib. Care is taken not to injure the underlying subclavian artery and adjacent brachial plexus. The subclavian artery is gently dissected free. Exposure of the carotid artery is accomplished through the medial portion of the incision. Injury to the vagus nerve and internal jugular vein is avoided by retracting them laterally. If exposure of the carotid bifurcation is necessary (e.g., for concomitant endarterectomy), a separate incision can be made along the medial border of the sternocleidomastoid. For both bypass and transposition, we create a tunnel posterior to the internal jugular vein, and systemic heparin is administered.

Transposition of the subclavian artery to the carotid artery is suitable only when plaque extends no more than a few centimeters beyond the subclavian artery origin. Transposition requires mobilization of the subclavian artery as proximally as possible. Small branches are divided, but an effort should be made to preserve the vertebral and internal mammary arteries. However, if additional mobilization of the subclavian artery is required to avoid kinking, it may be necessary to divide the internal mammary branch. To minimize the risk of embolization, the distal subclavian, vertebral, and internal mammary arteries are clamped before ligating the proximal subclavian artery. The subclavian is transected proximally with very careful ligation of the proximal stump. A 4- to 5-cm segment of the common carotid artery is clamped proximally and distally, and a short vertical arteriotomy is made along the lateral wall of the carotid, approximately sized to accept the diameter of the subclavian artery. An end-to-side anastomosis is fashioned with running Prolene sutures. Flow is restored after appropriate venting. We do not routinely monitor cerebral perfusion with an electroencephalogram during this procedure.

If a bypass is planned, only a short segment (1–2 cm) of the subclavian artery just distal to the thyrocervical trunk must be exposed. Small branches can and should be ligated to improve exposure. As outlined previously, care should be taken when retracting the subclavian artery to avoid inadvertent injury. A 7- to 8-mm prosthetic graft or a large-caliber saphenous vein graft typically is chosen as the conduit. It is technically easier to perform the subclavian artery anastomosis first. After systemic heparinization, the subclavian artery is clamped proximally and distally, and a short longitudinal arteriotomy is made along the superior surface of the artery at the highest point of its arc above the clavicle. The graft should be beveled to promote a slightly downward course of the graft. An end-to-side anastomosis then is constructed with 5-0 Prolene sutures. Then the graft to the carotid artery anastomosis is performed in an end-to-side fashion with running Prolene sutures as described for the transposition. We routinely leave a small closed suction drain in place; this is removed only after the patient has resumed normal oral intake.

Both carotid subclavian bypass and subclavian transposition have low morbidity and excellent long-term patency (75% to 80% at 5 years for bypass and almost 100% for transposition). Complications include injury to adjacent nerves (brachial plexus, phrenic nerve, and sympathetic chain) and lymphatic structures (thoracic and accessory thoracic ducts). Nerve injuries are usually self-limited. Lymphatic injuries can be problematic, and if drainage is significant or persistent, early reexploration and thoracic duct ligation is advised. Alternatively, therapeutic lymphangiography can be attempted with or without computed tomographic–guided sclerotherapy. This approach has up to 70% success rate in sclerosing the duct.

Axillary Artery

Occlusive lesions of the axillary artery are extremely unusual. Trauma or iatrogenic emboli are the most common causes. Bypass procedures originating from or terminating on the axillary artery also are relatively rare. In the past, axillaxillary bypass was advocated as an alternative procedure for dealing with subclavian disease when the ipsilateral carotid was an unsuitable inflow site. This bypass largely has been abandoned, however, because of its superficial location and reduced patency. Carotid axillary bypass has been used to manage extensive subclavian disease, whereas axillobrachial bypass has been implemented for distal axillary or proximal brachial occlusions. To expose the first and second portions of the axillary artery, the arm should be positioned at the patient's side (a narrow arm board is helpful). Significant abduction must be avoided because this position stretches the axillary artery. A transverse incision is made one

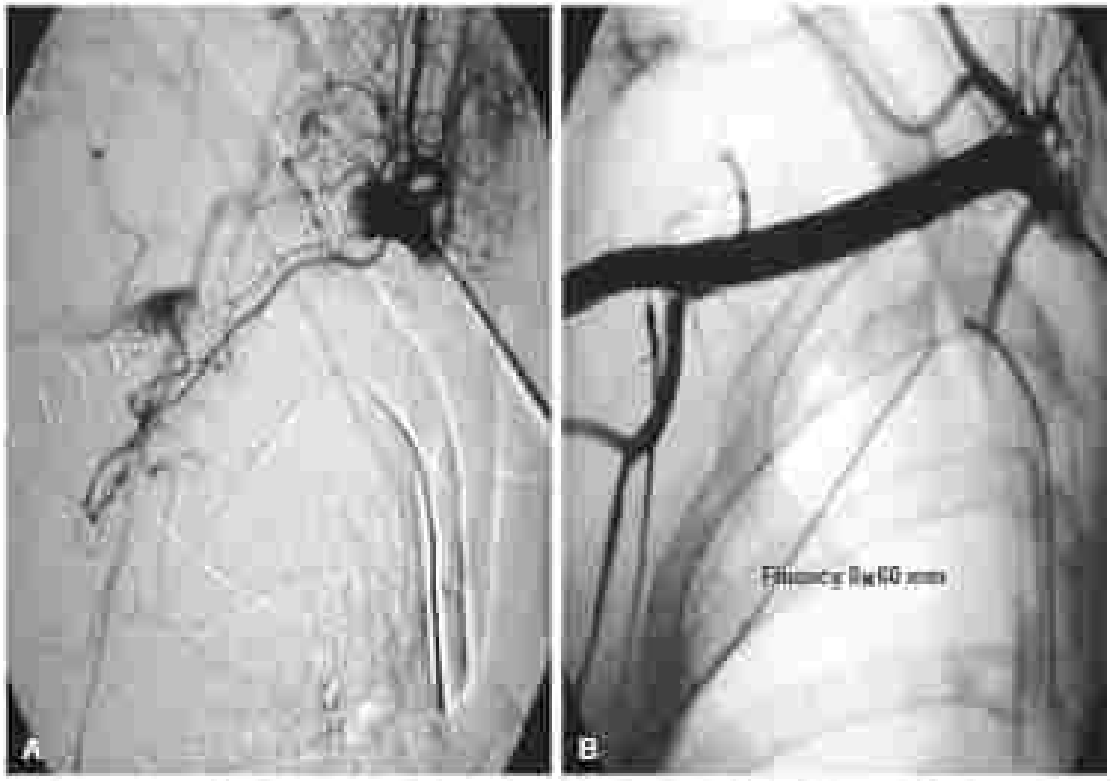

FIG. 8 A 19-year-old woman presented to the emergency with a gunshot wound to the right shoulder with absent radial or ulnar pulses. (A) Preoperative angiography showed absent flow distally. (B) The antegrade endovascular stenting and completion angiography demonstrated normal flow.

longitudinally below the clavicle, extending from the midclavicular line to the deltopectoral groove. The fibers of the pectoralis major muscle are split, and the underlying clavipectoral fascia is incised. Tributaries of the axillary vein are divided and ligated to the axillary vein, which lies inferior and slightly anterior to the artery. If encountered, the crossing medial and lateral pectoral nerves should be preserved to avoid postoperative atrophy of the pectoralis muscles. It is usually necessary to divide a branch or two of the thoracoacromial artery to gain exposure. The artery is located just above the vein, with the cords of the brachial plexus lying superiorly and posteriorly. As with the subclavian artery, care should be taken when mobilizing this thin-walled artery, which frequently has small posterior branches. The head of the pectoralis minor can be divided to facilitate exposure laterally (second portion of the axillary artery). Saphenous vein is the conduit of choice for bypasses originating from or terminating on the axillary artery.

Brachial Artery

Brachial artery lesions are rare and most commonly caused by catheterization and trauma. CEA is a rare cause of proximal brachial occlusive disease. For brachial artery exposure, the arm is abducted and the hand supinated on an arm board. The proximal brachial artery is exposed through a longitudinal incision along the medial aspect of the upper arm to the bicipital groove. Dissection along the posterior aspect of the muscle belly reveals the artery, accompanied by the median and ulnar nerves. The proximal brachial–distal axillary artery can be exposed through a hockey stick–shaped extension of this incision along the lateral border of the pectoralis major. Brachial exposure immediately proximal to the elbow is achieved through an incision along the bicipital groove extended laterally across to the antecubital fossa. The median nerve lies immediately medial to the artery at this level. Alternatively, the distal brachial artery and its bifurcation into the radial and ulnar arteries can be exposed by making a longitudinal incision in the antecubital fossa just distal to the elbow crease and dividing the bicipital aponeurosis. If more distal exposure is required, the incision can be carried inferiorly along the volar aspect of the forearm. If the entire brachial artery at the elbow requires exposure, a lazy S incision is used to avoid scar contracture across the elbow crease. Saphenous vein is the only conduit suitable for bypasses involving the brachial and more distal arteries.

Radial and Ulnar Arteries

Repair to the forearm arteries is rarely necessary and is most often used for trauma and neglected embolic occlusions (Fig. 8). In diabetic patients, these arteries can be affected by a particularly aggressive form of atherosclerosis (isolated arteriopathy) that is rarely amenable to revascularization. Buerger's disease is another cause of forearm occlusive disease that usually is not reconstructable. Exposure of these arteries at the wrist is relatively straightforward, but more proximal exposure requires a thorough understanding of forearm anatomy. Topical papaverine or nitroglycerin is helpful to combat dissection-induced vasospasm. Hypothenar hammer syndrome can be treated by an interposition vein graft of the involved segment of ulnar artery in the proximal hand. A distal limb vein provides the best size match.

Embolism

The management of large artery embolism is discussed in more detail in the chapter on peripheral arterial embolism. Because of increased vascularity and the inevitable resulting vasospasm, multiple passages with balloon embolectomy catheters should be avoided with UE emboli. For this reason, we have a lower threshold for obtaining preoperative imaging when dealing with acute arterial occlusions of the UE, even with a good clinical story for embolism. Imaging can confirm the diagnosis and allows a more directed approach, a particularly important concept when dealing with emboli in the axillary and subclavian arteries.

Although retrograde removal of such proximal clots usually can be performed through a brachial approach, we sometimes prefer to expose the occluded segment directly if there is significant clot burden. This approach minimizes the number of catheter passages necessary to extract the embolus and avoids stripping off clot into patent branches of the segment between the arteriotomy and the occlusion. Although most macroemboli originate from the heart, an arterial source sometimes can be responsible and, if identified, must be addressed. Treatment of arterial thoracic outlet syndrome requires not only excision of the compressive thoracic outlet elements but also some type of arterial reconstruction (discussed in more detail in the chapter on thoracic outlet syndrome).

Trauma

As outlined previously, most traumatic occlusions should be fixed at the time of diagnosis. Isolated radial or ulnar artery occlusions are an exception because they are usually well tolerated. Iatrogenic occlusions usually can be relieved with local exploration, thrombectomy, and repair of associated vessel wall injury. For more significant injuries, formal arterial reconstruction is required. Resection with end-to-end anastomosis can be performed rarely, but in the vast majority of cases interposition grafting with saphenous vein of appropriate caliber is required. A more detailed description of how to manage traumatic occlusions is provided in the chapter on management of vascular injuries.

SMALL ARTERY OCCLUSIVE DISEASE

Treatment of occlusive disease affecting the small arteries of the digits and hands can be challenging. After a proximal embolic source has been ruled out, attention is focused on identification and treatment of any underlying causative diseases. Patients with Buerger's disease frequently experience significant improvement with successful tobacco abstinence. Vibration induced injury will respond to avoidance of the causative vibratory machinery. The rare patient with cryoglobulinemia or hepatitis associated vasculitis will respond to appropriate therapy. Unfortunately, in the majority of cases, no specific therapy is available. In our practice, there are patients with an associated connective tissue disorder, hypersensitivity angiitis, or renal failure. For these individuals, care is focused on supportive measures. Abstinence from tobacco and avoidance of cold are routinely advised. Antiplatelet therapy (aspirin or clopidogrel) and hemorheologic agents (cilostazol) usually are prescribed. Vasodilators, primarily calcium-channel blockers, can be used to treat associated vasospasm with variable success. Areas of tissue loss are treated with local wound care and debridement as indicated. Sympathectomy, both cervicothoracic and digital, can lead to a temporary improvement in skin blood flow but has such limited durability (approximately 6 months) that most authorities have abandoned it except in highly selected patients with residual ischemia after revascularization.

CONCLUSIONS

UE arterial occlusive disease is an uncommon problem with diverse causes. Accurate diagnosis depends on a thorough history and physical examination supported by noninvasive vascular testing. Angiography remains the primary modality of diagnosis. Treatment depends on the nature of the disease process and the severity of the ischemia. Patients with embolic or traumatic occlusions and significantly symptomatic proximal large artery disease usually can undergo vascular intervention with good results. On the other hand, revascularization options for patients with distal small artery occlusive disease are extremely limited. In this setting, after a careful search for treatable causes, management is primarily supportive. Fortunately, progression to limb loss is rare.

Suggested Readings

Abularrage AS, Hirami MC, Shutz PA, et al. Angioplasty and stenting versus carotid endarterectomy for the treatment of isolated subclavian artery disease. *J Cardiovasc Surg* 2007;48:699–704.

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Aortoiliac Occlusive Disease

Joseph-Vincent V. Rizo, MD, and Spencer M. Taylor, MD

Peripheral arterial occlusive disease (PAOD) is highly prevalent and affects an estimated 3% of the population of the United States. The incidence and prevalence of PAOD is directly related to risk factors associated with the development of atherosclerosis, by far the most common cause of aortoiliac occlusive. These include age, tobacco use, gender, ethnicity, diabetes, hypertension, dyslipidemia, a family history of PAOD, renal disease, and hyperhomocysteinemia. Of these, cigarette smoking is the single most powerful risk factor associated with the development of PAOD. In fact, there is a dose related association with development and severity of PAOD in tobacco users. The prevalence of PAOD increases with age over 40 years, with increasing prevalence in 15% of patients older than 70 and almost 25% of patients older than 80. PAOD generally affects men more than women, although some studies have shown higher disease prevalence in women. Other, nonatherosclerotic, causes of aortoiliac occlusive disease include trauma or radiation-induced arteritis, occlusive disease, cystic adventitial disease, fibromuscular dysplasia, and a congenital persistent sciatic artery. While these pathologies usually present with similar symptoms, their detailed management is beyond the scope of this chapter and will not be discussed.

The presenting symptoms of PAOD depend on the location(s) and anatomic severity of the distribution. Most commonly, PAOD is asymptomatic and discovered incidentally. Ankle brachial indices are a reliable screening modality for the presence of PAOD (normal >0.9). Symptoms may range from claudication (i.e., activity-induced pain) to critical limb ischemia (CLI) defined as ischemic rest pain, and/or ulceration or gangrene. The limb-specific natural history of PAOD depends on the severity of disease at presentation. Furthermore, PAOD is a strong predictor of future adverse

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cardiovascular outcomes (e.g., stroke and myocardial infarction) and death. All-cause mortality and cardiovascular mortality in patients with PAOD is higher in symptomatic patients (5-year risk of 24% and 7.3%, respectively) than asymptomatic patients (5-year risk of 10% and 2.3%, respectively). In general, only a minority of patients with symptomatic PAOD or intermittent claudication worsens over time (~20%) and only 1% to 3% of all claudicants can be expected to develop critical limb ischemia. In the absence of progression, the estimated risk of major amputation in patients with claudication is 12% over a 10-year period (~1% per year). In patients with critical limb ischemia, 25% die of a cardiovascular event or require limb amputation within 1 year of diagnosis. Although aortoiliac occlusive lesions usually begin at the aortic bifurcation and progress proximally and distally, the disease may progress to cause iliac occlusion and aortic occlusion to the renal arteries. In this chapter, we will focus attention on PAOD affecting the aortoiliac distribution.

DIAGNOSTIC EVALUATION

A thorough history with identification of atherosclerotic risk factors is paramount as risk factor modification is a cornerstone of treatment for PAOD. Symptoms of aortoiliac disease are typified by hip, thigh, and/or buttock claudication, leg muscle atrophy, erectile dysfunction, and absent or diminished femoral pulses. When the constellation of proximal claudication, leg muscle atrophy, erectile dysfunction, and absent femoral pulses is present, the patient has Leriche syndrome, described in 1948 by René Leriche. *Pseudoclaudication* is how to pain that is position dependent, not stereotypically associated with activity, and can occur in the absence of activity. It is important to differentiate pseudoclaudication from true occlusive disease symptoms. Causes of pseudoclaudication include musculoskeletal issues (e.g., spinal stenosis, radiculopathy) or neurogenic issues (e.g., sciatic nerve impingement or diabetic neuropathy).

In many cases, a clinical history and thorough physical examination is sufficient for diagnosis of aortoiliac occlusive disease. The ankle-brachial index (ABI) serves as the best initial test for evaluation of PAOD. With a compatible history, ABIs less than 0.9 are diagnostic of PAOD and can correlate with the severity of disease. In general, with progressively more levels of occlusive disease (e.g., aortoiliac plus femoropopliteal plus tibial occlusive disease), the severity is increased and, consequently, the ABI will be lower. Duplex ultrasonography or segmental limb pressures combined with ABIs give a more complete assessment of the extent and severity of PAOD. In our experience, the presence/absence and quality of the ipsilateral femoral pulse is pivotal to the diagnosis of aortoiliac occlusive disease. An absent or weak femoral pulse associated with a segmental pressure difference of 20 mm Hg or higher between the brachial pressure and the thigh suggests an aortoiliac occlusive lesion. In addition, an asymmetric thigh segmental pressure of 15 to 20 mm Hg or higher suggests a unilateral occlusive lesion. Aortoiliac disease alone, per se, is rarely the cause of ischemic rest pain or tissue loss, except in the setting of acute or subacute ischemia such as embolization. This is due to a rich collateral network robust enough to supply the lower extremities with sufficient resting tissue perfusion. In these cases, an exercise arterial duplex with ABI could elicit symptoms of occlusive disease and corroborate it with a decreased ABI.

Computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or conventional arteriography can be used to delineate the extent and severity of the aortoiliac segment disease. Although conventional contrast angiography is considered the gold standard for PAOD, CTA is rapidly becoming the diagnostic modality of choice. Compared to conventional angiography, CTA gives better contrast resolution and provides three-dimensional views of the aortoiliac segment, albeit at the expense of being able to assess flow through the segment, which conventional angiography is able to provide. Our approach is to obtain an arterial duplex/ABI and cross-sectional imaging with CTA.

MEDICAL TREATMENT

Medical management is the cornerstone of treatment of PAOD, including aortoiliac occlusive disease, to reduce cardiovascular morbidity and mortality. Risk factor modification includes cessation of tobacco use, initiation of antiplatelet therapy (e.g., aspirin and/or clopidogrel), initiation of HMG-CoA reductase inhibitors (i.e., statins), as well as management of other cardiovascular equivalent diseases (diabetes, hypertension, renal disease, etc.) in accordance with guidelines from the American Heart Association. Further medical therapy can include cilostazol, a phosphodiesterase inhibitor, to provide symptomatic improvement in claudicants' exercise tolerance and walking distance. The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial, a randomized controlled trial comparing supervised exercise therapy with endovascular treatment of aortoiliac disease, showed that supervised exercise therapy group had improved short-term walking performance than the group undergoing endovascular intervention. In general, walking exercise is performed at least three times a week for duration of 30 to 45 minutes. That said, in our experience, as few as 30% of patients are either physically able or motivated to engage in meaningful exercise therapy as a sole means of the therapy. However, medical management is imperative for all patients with PAOD, if for no other reason than to improve overall cardiovascular health. Intervention with medical management is best assessed on a case by case basis, taking into account the severity of occlusive disease, the overall condition of the patient and the severity of symptoms.

As will be discussed, the addition of endovascular intervention is safe and effective and, in our practice, offered more liberally for claudication than patients with other patterns of PAOD. In most cases, patients with critical limb ischemia present with multisegmental disease and undergo aortoiliac intervention first to prevent limb loss. Intervention can be divided into an endovascular approach, an open surgical strategy, or a combined (endovascular and open) or hybrid approach.

ENDOVASCULAR TREATMENT

The 2007 Inter-Society Consensus for the Management of Peripheral Artery Disease guidelines (TASC II) provided a framework to aid in choosing an endovascular or open surgical approach for specific anatomic aortoiliac occlusive lesions (Fig. 1). The guidelines recommend endovascular therapy preferably for short, simple type A and type B lesions. Surgery is preferred for more extensive and complex type C and type D lesions, though an endovascular first strategy may be considered. Modern endovascular techniques allow all TASC lesions to be approached percutaneously and, in fact, the number of endovascular interventions for aortoiliac occlusive disease has risen markedly for all aortoiliac lesions. In our practice, open repair is only rarely offered to patients with claudication who have anatomy amenable to a percutaneous approach.

Our method of endovascular intervention involves the following steps:

- Establishing arterial access
- Diagnostic arteriogram and identification of the culprit lesion(s)
- Traversal of the lesion(s)
- Balloon angioplasty with or without the adjunctive use of stents
- Completion arteriogram to assess result
- Successful closure of the arterial access site

Establishing Arterial Access

Anatomic site for access is dictated by the anticipated site(s) of intervention and can be assessed with noninvasive imaging for the most favorable site(s). Aortoiliac lesions can be approached via a percutaneous or open exposure of the ipsilateral and/or contralateral common femoral artery (e.g., subclavian or brachial access) or the brachial artery. Again, the distribution and extent of disease will dictate the access site(s). Our preferred access is with a "micropuncture" small caliber access needle. Once arterial access is secured with an

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (<3 cm) stenosis of EIA

Type B lesions

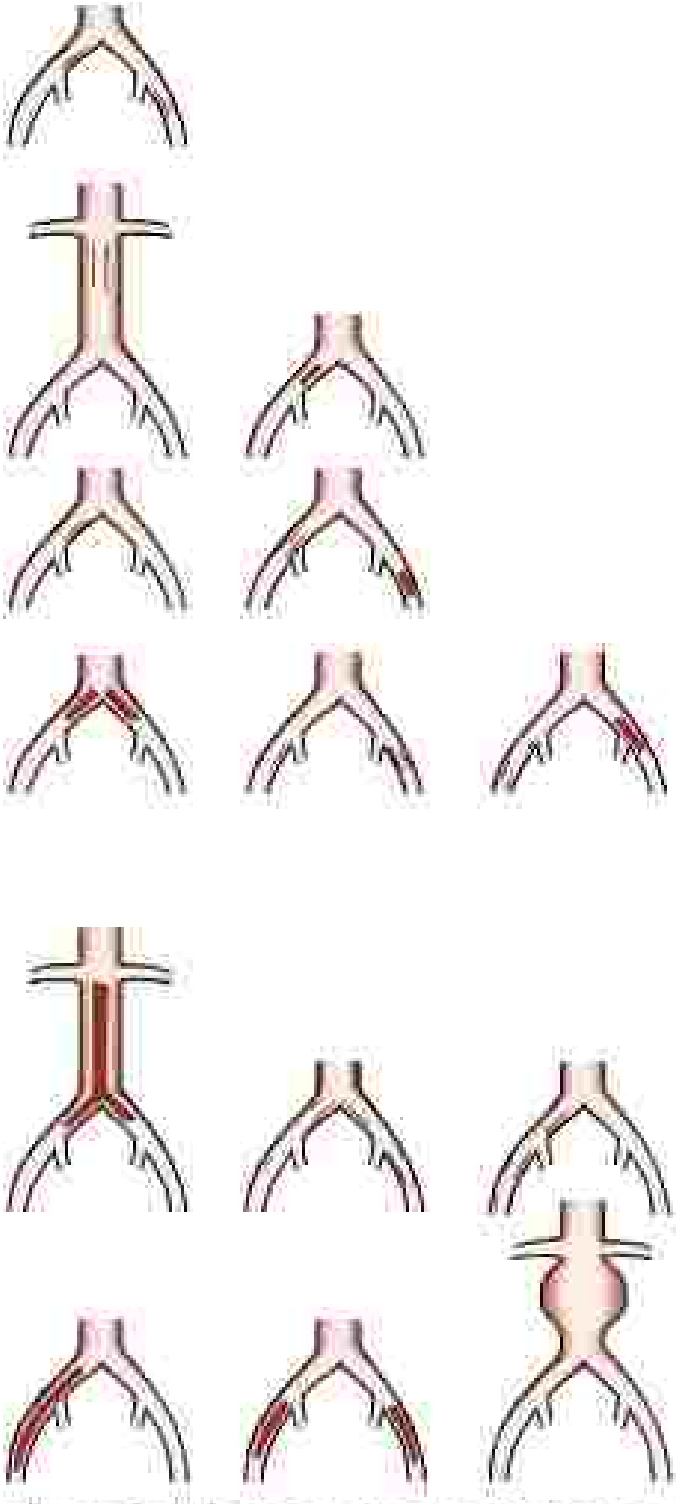
- Short (<3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infrarenal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusion of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery



0.035-inch guidewire, a 5 French sheath and a flush catheter is used for diagnostic arteriography (Fig. 2).

Diagnostic Arteriogram and Identification of the Culprit Lesion(s)

Anteroposterior and oblique images are obtained of the aortoiliac and common femoral bifurcations. Arteriographs of the lower extremities is obtained using a "bolus chase" technique. In cases of trunk occlusions, the flush catheter should be positioned to fill the collateral network to exactly the distal extent of occlusion. Careful review of the diagnostic arteriogram identifies the culprit lesion(s). An occlusion or 50% or more diameter reduction or a pressure drop of 15 to 20 mm Hg across the stenosis defines a hemodynamically significant lesion. The patient should then receive 50 to 80 U/kg of systemic heparin.

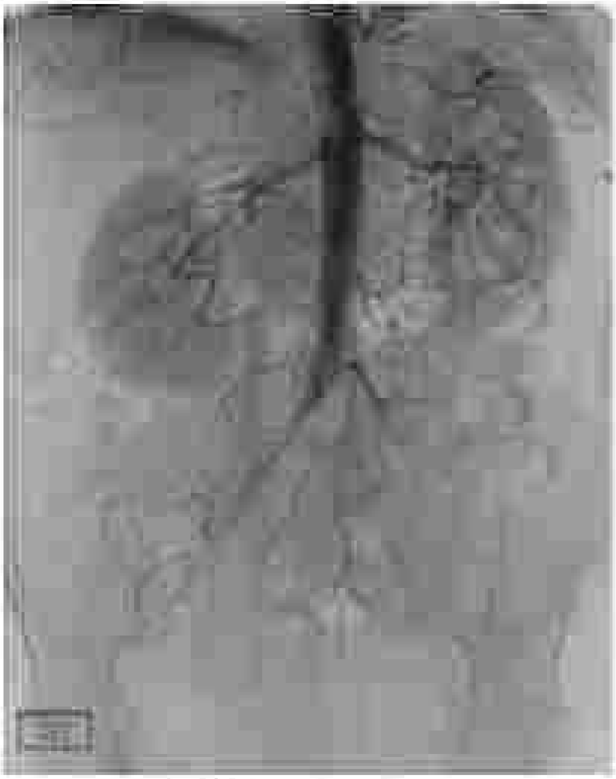


FIG. 2 Diagnostic aortogram.

FIG. 3 "Kissing" stent technique [illegible]

Traversing the Lesion

Stenoses and occlusions are approached [illegible] [illegible]

[illegible]

[illegible]

[illegible] With or Without [illegible] Stent [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

disease devices is that it allows the patient to ambulate sooner after a procedure, reducing the length of stay in the hospital or outpatient interventional suite.

Results of Endovascular Interventions for Aortoiliac Disease

Balloon angioplasty remains an option for isolated, short segment iliac disease. The initial technical success rate of iliac angioplasty is greater than 9.%, with 5-year primary patency rates of .5%, and assisted primary and secondary patency rates over ~%. Primary stenting, however, has become the most common approach for most lesions due to the improved long-term primary patency. The prospective, randomized Control versus Balloon Expandable Stent Trial (CREST) concluded that covered balloon expandable stents have less incidence of restenosis, less incidence of stent occlusion, and therefore better long-term patency rates than bare metal balloon-expandable stents in aortoiliac occlusive disease, particularly in TASC C and TASC D lesions (Fig. 4). Perioperative mortality is less than 1% and morbidity ranges from 5% to 20%.

URGICAL TREATMENT

Open surgical revascularization is broadly categorized into a ... [illegible] ... revascularization procedures, or the aortoiliac segment, anatomic revascularization refers to aortobifemoral, axillofemoral bypass or aortoiliac endarterectomy. Extraanatomic revascularization procedures include femorofemoral bypass, cross-iliofemoral or iliofemoral bypass, axillofemoral bypass, or thoracofemoral bypass. Extraanatomic bypasses are generally reserved for patients considered high risk for a major open abdominal surgery. A comprehensive review of all the listed procedures is beyond the scope of this chapter; however, the most common procedures will be discussed.

Aortofemoral Bypass

Aortofemoral (or aortobifemoral) bypass is still considered the gold standard for aortoiliac revascularization. Several important anatomic factors dictate the operative approach and procedure. These factors should be coherently assessed with high-quality cross-sectional imaging (e.g., CTA). Assessment of concomitant renal or visceral artery disease is critically important. The proposed proximal aortic clamp site should be free of large atheromatous burden or calcium. The left renal vein typically will serve as the anatomic landmark for the renal arteries and the proximal aorta clamp site. A retroaortic left renal vein is present in approximately .% of patients, and a circumaortic left renal vein is present in approximately .% of patients. These left renal vein variants are vulnerable to injury and occur in about 40% of patients.

The status of a patient's pelvic circulation may influence the proximal anastomotic configuration (end-to-end vs end-to-side). ...ost favor an end-to-end configuration, which allows for direct aortic thrombectomy/endarterectomy, more favorable blood flow dynamics, and theoretically less risk of development of an aortoduodenal fistula. However, the end-to-side configuration should be strongly considered in patients whose pelvic perfusion or inferior mesenteric artery perfusion would be unlikely sacrificed with an end-to-end configuration. One example is a patient with severe external iliac artery disease or bilateral external iliac occlusives. An end-to-side proximal anastomosis would confer continued antegrade pelvic flow through the existing patent common iliac and hypogastric arteries (Fig. 5). Another example is a patient with a large, patent inferior mesenteric artery with concomitant proximal visceral disease (e.g., celiac or superior mesenteric artery stenosis). Based perfusion would be maintained with an end-to-side proximal anastomotic configuration in this scenario (Fig. ...). A final example is a patient with a sizeable accessory renal artery arising from the infrarenal aorta that would lose substantial kidney function with sacrifice of antegrade renal artery flow in an end-to-end configuration.

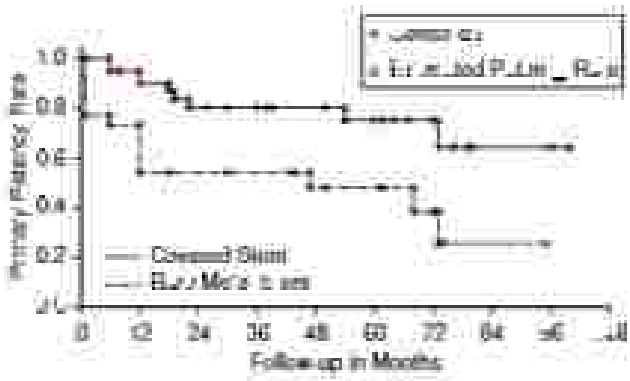


FIG. 4 Primary patency in Iliac Stenting: Comparison of the Management of Peripheral Arterial Disease (C.D) trials after balloon-expandable covered versus bare metal stents.

The patient is widely prepped and draped from the level of the nipples to the feet bilaterally. The procedure begins with bilateral groin incisions to expose the common femoral, profunda femoral, and superficial femoral vessels. Groin incisions prior to the abdominal incision limit the fluid loss through an open abdomen. In unique situations where the external iliac arteries and femoral arteries are spared of disease, an axillofemoral bypass may be performed to the distal external iliac arteries via a retroabdominal approach. Assessment of the femoral vessels is important to determine the need for a common femoral or profunda femoris endarterectomy and or angioplasty. In general, a distal anastomosis incorporating the origin of the profunda femoris artery is critical for achieving durable long-term patency of the graft. ...ith chronic occlusive disease, the inferior epigastric and circumflex iliac arteries can develop into large collateral vessels and should be meticulously protected and maintained. The aorta is exposed through either a midline laparotomy incision or retroperitoneal incision. ...some surgeons primarily favor a retroperitoneal approach. The retroperitoneal approach may be attractive to patients with multiple previous abdominal operations. After entering the peritoneum through a midline laparotomy, the abdominal cavity is inspected for unanticipated concomitant pathology (e.g., malignancy). A nasogastric tube is placed to decompress the stomach and to aid in identifying the esophagus in cases where suprarenal aortic control is anticipated. The transverse colon is retracted cephalad and the small bowel retracted to the right upper quadrant. A final retractor system (i.e., Omni Tract) is placed. The retroperitoneal tissue overlying the aorta and the ligament of Treitz is incised to expose the underlying aorta from the renal arteries to the aortic bifurcation. If necessary, the inferior mesenteric vein is ligated to provide better exposure. Care is taken to protect the left renal vein, the inferior mesenteric artery, and the autonomic nerve plexus located near the bifurcation and left common iliac origin.

Construction of the tunnels for the bypass graft limbs is done by gentle, blunt dissection simultaneously from the groin posterior to the inguinal ligament and from the abdomen. The tunnel must be constructed to run posterior to the ureters to prevent the development of hydronephrosis. Umbilical tape or red rubber catheters are inserted through the tunnel to facilitate passage of the graft limbs.

The patient is systemically treated with 50 to 100 U/kg of intravenous heparin to achieve an activated clotting time greater than 250 seconds. The aorta is clamped distally and then proximally just inferior to the renal arteries to minimize the chance for embolization. ...cases with posterior calcific plaque, clamping the aorta in an anterior to posterior fashion may limit the potential for aortic clamp injury and embolization. Other proximal aortic clamp sites include the suprarenal or supraceliac aorta. Percutaneous insertion of an occlusion balloon is another option for proximal control. If suprarenal or supraceliac control is performed, the clamp should be moved caudal to the renal arteries as soon as the proximal anastomosis is performed successfully to limit visceral and renal ischemia time.

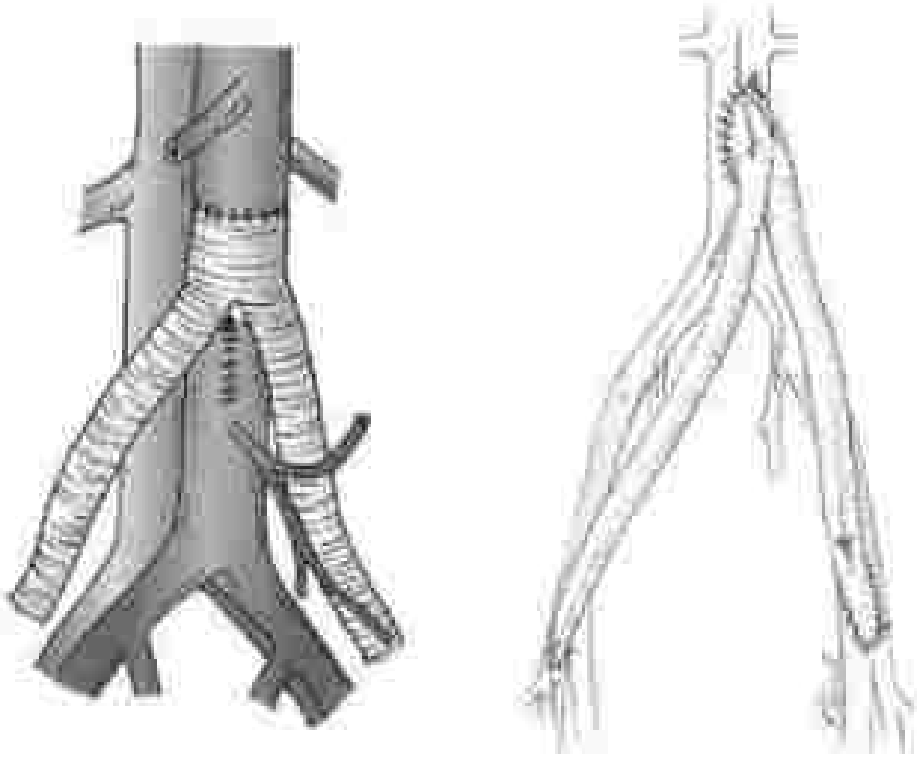


FIG. 5 Proximal anastomosis [illegible] not be aligned so [illegible] [illegible] Surgery in Vascular Disease. 2005.]

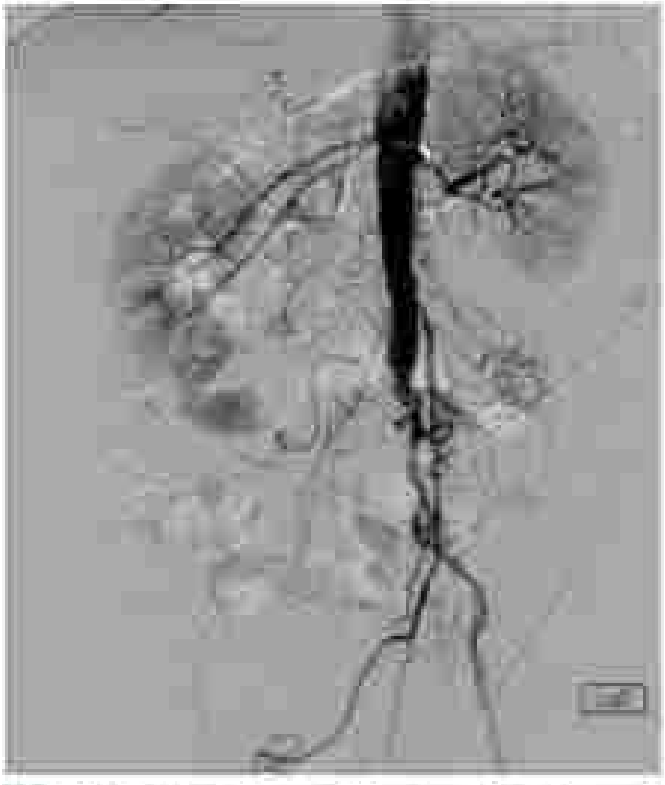


FIG. 6 Aortofemoral occlusive disease with a large patent inferior mesenteric artery.

If an end-to-end configuration is chosen, the aorta at the proximal anastomotic site is transected. The distal stump is oversewn with permanent, monofilament suture (e.g., polypropylene). Pledgeted sutures may be needed for a highly diseased distal aortic stump. An appropriately sized knitted polyester (Dacron) graft is chosen. Typically used bifurcated grafts include 18 mm × 9 mm grafts for 16 mm × 8 mm grafts for men and 14 mm × 7 mm grafts or 12 mm × 6 mm grafts for women. The main body of the graft is trimmed 3 to 4 cm from the bifurcation. The proximal anastomosis is performed using a running 2-0 polypropylene suture. If the aorta wall is thin or fragile, a 3-0 polypropylene interrupted mattress pledgeted suture technique is advisable.

In the end-to-side proximal anastomotic configuration, the aorta is clamped as described above. A longitudinal arteriotomy is done and the edges of the aorta are trimmed to form an ellipse for the anastomosis. The graft is trimmed and beveled to achieve as low a profile as possible. This limits the risk of kinking and limits the amount the graft extends into the abdomen so, theoretically, limits the risk of aortoduodenal fistula formation. The anastomosis should start close to the renal arteries and extend distally to facilitate a low profile anastomosis. In either proximal anastomotic configuration, after the completion of the anastomosis, the proximal clamp is released to examine the anastomosis integrity and hemostasis. Pledgeted sutures may be used to reinforce the anastomosis.

The graft limbs are passed through the prefemoral tunnels with care to avoid twisting. The femoral anastomosis is performed in an end-to-side configuration using running 5-0 polypropylene. As stated previously, outflow through the profunda femoris is crucial for long-term graft patency. In cases requiring a profunda femoris artery endarterectomy or profundaplasty, the distal end of the aortofemoral graft can be used as a profunda femoris artery patch angioplasty. Alternatively, an autogenous vein patch or prosthetic patch can be used for the patch angioplasty with the anastomosis subsequently performed to the patch. In cases of chronic superficial femoral artery

occlusion, the primary outflow vessel is the profunda femoris artery. Adequate outflow through the profunda femoris is assessed on the preoperative cross-sectional imaging and/or angiography. In addition, at the time of operation, the profunda femoris can be assessed with a deflated embolectomy balloon catheter to interrogate the length of the profunda femoris artery. A profunda femoris origin that accepts a 4 mm diameter probe and measures of 20 to 25 cm in length is adequate in nature as autofemoral graft. Concomitant distal revascularization (e.g., femoropopliteal or femoretibial bypass) is necessary in about 15% to 25% of patients and is indicated in cases of compromised outflow. Prior to completion of the anastomosis, the distal vessels are allowed to backbleed and the graft is flushed of debris. In general, with the chronic occlusive nature of disease, reestablishment of leg perfusion results in only small hemodynamic changes. Collaboration with the anesthesia team is paramount, however, prior to reestablishment of distal perfusion to limit the potential for hemodynamic lability. The distal leg is assessed for perfusion prior to beginning closure of the incisions. Lack of distal perfusion with adequate inflow (i.e., systolic flow through the graft) should prompt evaluation of the distal anastomosis for a technical error or raise the concern for a distal embolism. Redo anastomosis is indicated for an anastomotic technical error. Distal embolization is treated with balloon catheter embolectomy.

After satisfactory perfusion is assessed and hemostasis is achieved, we reverse the effects of heparin with protamine. Abdominal closure begins with reapproximation of the retroperitoneal tissue to cover the graft, if possible. An alternative coverage option is to mobilize an omental pedicle placed via a transverse colon mesenteric window. The abdomen is closed in standard fashion. Meticulous groin incision closure is important to limit the risk of infection and wound breakdown.

Results of Aortofemoral Bypass

Perioperative mortality is less than 5%. Primary graft patency approximates 100% initially, with 5 year and 10 year primary patency ranging from 90% to 100% and 75% to 80%, respectively. Cumulative secondary graft patency for 2-, 5-, and 10 years was 97.7%, 95.9%, and 94.4%, respectively. Inferior patency results are documented for patients with ulceration or tissue loss compared to patients with claudication or ischemic rest pain. In addition, age and native aortic diameter have been shown to influence patency after aortofemoral bypass. In fact, patients younger than 50 and those with aortic diameters 18 mm or less have much lower primary patency rates after aortofemoral bypass (50%–65% 5 year primary patency). Infection occurs in 0.3% to 0.7% of cases and anastomotic pseudoaneurysm formation occurs in 1.4% of cases.

Aortoiliac Endarterectomy

Aortoiliac endarterectomy is an option for patients with well localized aortoiliac disease limited to the distal aorta and proximal common iliac arteries. With the increased use of endovascular interventions and the long-term durability and success of aortofemoral bypass, aortoiliac endarterectomy is uncommonly chosen as a primary procedure. The limited disease amenable to aortoiliac endarterectomy is commonly found in young or middle aged women with a history of tobacco use. Operative exposure is done through a standard midline laparotomy, similar to the abdominal portion of an aortofemoral bypass procedure. Complete mobilization of the distal aorta, inferior mesenteric artery, aortic bifurcation and proximal bilateral common iliac arteries is achieved with care to protect the autonomic nerve plexus (nerve sparing). A longitudinal aortic incision is made and may be carried into one of the common iliac arteries. A contralateral common iliac artery can be made to the case of bilateral common iliac disease. Endarterectomy is performed in the subintimal plane with care to taper or feather the distal end of the endarterectomy. Tacking sutures at the distal edge of the endarterectomy can be used to prevent distal dissection. The proximal plaque is transected to a smooth edge. The aorta and iliac arteries are flushed of debris and assessment of the proximal and distal ends of the endarterectomy are performed prior to closure. The arteriotomies are closed with 4-0 or 5-0 polypropylene suture.

Results of Aortoiliac Endarterectomy

Perioperative mortality rates are similar to aortofemoral bypass grafting (2.7% perioperative mortality). Patency rates also appear similar to aortofemoral bypass, 89% 5 year patency and 89% 10 year patency.

Unilateral Iliofemoral Bypass

Unilateral iliofemoral bypass is indicated in cases with limited distal aortic disease and limited ipsilateral proximal common iliac disease. Otherwise, aortofemoral bypass would be preferred. Poor risk patients for open abdominal surgery (e.g., severe cardiopulmonary dysfunction) may also be candidates for this procedure as this is typically performed through a limited retroperitoneal exposure. The patient is positioned supine. Added retroperitoneal exposure is facilitated by a "hump" placed under the ipsilateral flank and/or flexing the table to expand the space between the ribs and the anterior superior iliac spine. A retroperitoneal curvilinear incision is extended from the anterior axillary line to the midline inferior to the umbilicus along the line of the 10th rib. The anterior rectus sheath is incised and the rectus abdominus muscle is grasped and retracted medially. The posterior rectus sheath is incised. The internal and external oblique muscles are incised with electrocautery to expose the transversus abdominis muscle. Beginning laterally, the transversus abdominis muscle and the underlying transversalis fascia are opened to enter the retroperitoneal space. The peritoneum is stripped from the lateral pelvic wall and retracted medially with the intraabdominal contents to expose the underlying psoas muscle. The ureter is identified, protected, and retracted medially. The external iliac artery is readily identified in the distal aspect of the wound and can be followed proximally to the common iliac artery and aortic bifurcation. Proximal clamp site can be done at the proximal ipsilateral common iliac artery or, alternatively, with clamping of the distal aorta and contralateral proximal common iliac artery. A standard exposure of the common femoral artery, similar to that for an aortofemoral bypass, is performed. A tunnel is created anterior to the external iliac artery and posterior to the inguinal ligament. The patient is systemically heparinized. An 8 mm polyester graft is the typical conduit of choice. Proximal anastomosis is performed to the ipsilateral common iliac artery using 4-0 or 5-0 polypropylene suture. The graft is tunneled distally and a distal anastomosis is performed similar to an aortofemoral bypass described above. After satisfactory reperfusion and hemostasis, the retroperitoneal incision and groin incision is closed in the standard fashion.

Results of Iliofemoral Bypass

Perioperative mortality mirrors aortoiliac endarterectomy at 2.7%. Our group published a contemporary review of iliofemoral bypass showing primary patency rates of 87.5%, 76.8%, and 53.9% at 1-, 2-, and 5 years, respectively. Secondary patency rates were 92.5% and 93.3% at 1 and 5 years, respectively. Limb salvage was achieved in 88% to 95% of patients with critical limb ischemia and no amputations were necessary in claudication patients undergoing iliofemoral bypass.

Axillofemoral Bypass

In severely high risk or elderly patients with critical limb ischemia, an axillofemoral (or axillobifemoral) bypass is an alternative to direct aortoiliac revascularization. In addition, it is a reasonable alternative for patients with a "hostile" abdomen, previous radiation therapy, intestinal stomas, infected prosthetic arterial grafts, or aortoenteric fistulae. The axillary artery serves as the inflow for both lower extremities. Blood pressures are obtained in both arms

to determine the optimal side for inflow. Although previous studies have shown improved patency of axillobifemoral bypasses over axillounifemoral bypasses, more recent studies show no significant difference. The patient is positioned supine with the arm(s) abducted to 90 degrees. The patient is propped from the neck and chest down to the knees or bilateral legs. A transverse infraclavicular incision is made along the midportion of the clavicle. The underlying pectoralis major is split along its fibers to expose its underlying clavipectoral fascia. The clavipectoral fascia is incised to expose the underlying neurovascular bundle and axillary sheath with its contents. The axillary anastomosis is generally performed in the first part of the axillary artery due to its relationship with the brachial plexus. At this site, the brachial plexus runs posterior to the axillary artery conferring less risk for injury. In the lateral wound, the pectoralis minor is identified and retracted laterally or transected. The lateral pectoral nerve runs just posterior to the medial border of the pectoralis minor and should be protected. The axillary sheath is incised. The axillary vein is anterior to the sheath and is encircled and retracted inferiorly to expose the axillary artery. Proximal and distal control and control of branches are obtained with elastic vessel loops. The bilateral femoral arteries are exposed, as previously described. An externally supported 8-mm diameter prosthetic graft is chosen. Tunneling is performed with a blunt hemostat created parallel and anterior to the axillary artery, posterior (under) the pectoralis minor muscle and down the anterior axillary line to the subcutaneous space anterior to the iliac crest down to the ipsilateral groin. A subcutaneous tunnel is created between each groin in an inverted U configuration. The graft(s) are passed through the tunnels. The patient is systemically heparinized. The proximal anastomosis is created with running 5-0 or 6-0 polypropylene suture and is oriented parallel to the axillary artery. Placement of the axillary anastomosis in the first portion of the axillary artery and tunneling parallel to the artery and posterior to the pectoralis minor allows some redundancy in the graft to prevent anastomotic disruption with arm abduction. The ipsilateral femoral anastomosis is created with 5-0 polypropylene suture. The femorofemoral component is created onto the hood of the axillofemoral bypass graft using 5-0 polypropylene suture. The contralateral luminal anastomosis is created in standard fashion, as described above. Prefabricated externally supported expanded polytetrafluoroethylene (ePTFE) axillobifemoral grafts are also available.

Results of Axillofemoral Bypass

Historically, the patency rates for axillofemoral bypasses varied widely (20%–80%). Perioperative mortality remains less than 5%; however, published long-term survival rates are reported to be approximately 50%, confirming the high-risk status of these patients. More contemporary studies have shown improved primary 1-year and 5-year patency rates of 75% to 90% and 50% to 80%, respectively. No significant difference in patency is evident between unilateral or bilateral distal configurations.

Femorofemoral Bypass

Femorofemoral bypass is used as an alternative revascularization strategy to axillofemoral or iliofemoral bypass in high-risk patients with unilateral iliac artery occlusive disease or in patients with a hostile abdomen. The bypass is dependent on one iliac artery to provide blood supply to both legs. Thus, the status of the donor artery must be assessed. The presence of a pressure gradient greater than 5 to 10 mm Hg down the proposed donor iliac artery necessitates intervention to prevent arterial steal phenomenon. The patient is positioned supine. This procedure can be done with locoregional or spinal anesthesia in high-risk patients for general anesthesia. The bilateral femoral arteries are exposed, as previously described. A subcutaneous tunnel between incisions is made to achieve an inverted U configuration. This configuration reduces the acute angle of the anastomosis and reduces the risk of kinking. Tunneling in the subcutaneous space, as opposed to the preperitoneal, iliofemoral plane, prevents bowel or bladder injury. We prefer prosthetic grafts as our primary conduit (6 mm or 8 mm externally supported ePTFE); however, there is no current evidence to suggest superiority of one prosthetic conduit choice over another. Standard end-to-side anastomoses to the femoral arteries and groin closure complete the operation.

Results of Femorofemoral Bypass

Perioperative mortality is less than 5%. The primary patency rate at 5 and 10 years are 71.8% and 55.6%, respectively, in a contemporary study. Primary assisted patency rates at 5 and 10 years are 84.3% and 74.8%, respectively. Secondary patency rates at 5 and 10 years are 89.8% and 82.9%, respectively. Overall, these rates remain lower compared to "anatomic" methods of revascularization.

Thoracofemoral Bypass

The descending thoracic aorta is an excellent inflow source for revascularization in patients with a hostile abdomen, multiple failed anatomic abdominal aortic operations (e.g., failed axillofemoral bypasses), multiple failed extraanatomic revascularization attempts due to compromised inflow, or in the case of aortic graft infection. The patient is positioned in a modified right lateral decubitus position with a double-lumen endotracheal tube to allow deflation of the left lung. The thorax is elevated 30 to 45 degrees and the pelvis is maintained as flat as possible to allow access to the right groin. A left thoracotomy incision is made, typically as high as the sixth intercostal space or as low as the ninth intercostal space. The exact location of the thoracotomy is dictated by the proposed site for proximal anastomosis that is free of disease. Bilateral groin incisions are made, as previously described. A 10-mm externally supported prosthetic graft is the usual conduit. A retroperitoneal counter incision is made in the left flank to facilitate tunneling from the posterior diaphragmatic recess to the left groin. A standard femorofemoral tunnel is created. After systemic anticoagulation, an end-to-side proximal anastomosis is created using 3-0 polypropylene suture. Proximal control for the anastomosis is obtained using partial occlusion clamps or standard proximal and distal clamps. Distal anastomoses are fashioned to penetrating grafts or to the femoral arteries, as previously outlined. Chest tube drainage and closure of the incisions completes the procedure.

Results of Thoracofemoral Bypass

Perioperative mortality remains around 5% to 8%. Primary patency rates range from 63% to 100% at 4 to 5 years, with secondary patency rates of about 83% with longer follow-up.

Hybrid Revascularization Procedures

In unilateral or bilateral aortoiliac disease extending into the common femoral arteries, a hybrid open surgical technique to treat the common femoral arteries combined with endovascular angioplasty and stenting to treat the iliac or inflow vessels is an alternative to axillofemoral or iliofemoral bypass grafting. Perioperative mortality is around 2% to 15%, reflecting the overall patient health undergoing these procedures. Initial technical success with this approach is reported to be 99% to 100% with 2-year to 5-year primary patency rates between 90% and 100% and secondary patency rates of 98% to 100%.

SUMMARY

Aortoiliac occlusive disease can be a debilitating disease. A structured approach to diagnosis and treatment is crucial for successful results. Management is dictated by the severity of disease and the health of the patient. Many options for revascularization exist and the prudent interventionalist or surgeon should tailor their approach on a case-by-case basis.

Suggested Readings

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Femoropopliteal Occlusive Disease

Ali F. AbuRahma, MD, and Zachary T. AbuRahma, DO

Peripheral artery disease (PAD) is a global epidemic that affected over 200 million patients worldwide in 2010. Most of these patients are asymptomatic; however, patients with intermittent claudication usually experience a limb loss rate of less than 5% over 5 years, while patients with critical limb ischemia (CLI) have a 1-year major amputation rate of 25% and death rates of 25%.

Femoropopliteal disease has been treated traditionally with open surgery (femoropopliteal bypass [FPBP]) with favorable 5-year patency rate when saphenous vein (ASV) grafts are used. Several meta-analyses have shown that CLI did not occur for up to 5 years in 50% to 70% of patients who underwent ASV grafting to tibial or pedal targets, with perioperative mortality and limb salvage rates of 3% and 80%, respectively.

A recent study of 667 bypass grafts compared outcomes for ASV and polytetrafluoroethylene (PTFE) grafts and showed the patency rate with ASV was better than PTFE grafts at 5 years (62% vs 36%, $P < .05$); however, good quality vein may not be available (20%–30%). Bypass with PTFE should therefore be limited to select patients.

Open surgical bypass has certain limitations, for example perioperative morbidity/wound complication rate of 10% to 20%, prolonged hospital stay/outpatient care, and patient discomfort. De novo stenosis in vein grafts may also occur in 30% to 40% of patients in the first 2 years, which may necessitate graft surveillance or reintervention. Other systemic complications may occur (e.g., cardiac, pulmonary and renal).

Recently, endovascular therapy has been advocated as an alternative to open bypass. Several studies analyzing outcomes of patients with CLI treated with endovascular therapy have largely been retrospective single center with significant heterogeneity. The OLIVE registry, a multicenter prospective study, analyzed the outcomes of endovascular therapy for infrainguinal disease in 314 patients with CLI and showed a 12-month amputation-free survival of 74%, whereas 34% of patients required reinterventions (endovascular, 31.7% and bypass surgery, 2.6%). These results were satisfactory in

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Femoropopliteal Occlusive Disease

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Peripheral artery disease (PAD) is a global epidemic that affected over 200 million patients worldwide in 2010. Most of these patients are asymptomatic; however, patients with intermittent claudication usually experience a limb loss rate of less than 5% over 5 years, while patients with critical limb ischemia (CLI) have a 1-year major amputation rate of 25% and death rates of 25%.

Femoropopliteal disease has been treated traditionally with open surgery (femoropopliteal bypass [FPBP]) with favorable 5-year patency rate when saphenous vein (ASV) grafts are used. Several meta-analyses have shown that CLI did not occur for up to 5 years in 50% to 70% of patients who underwent ASV grafting to tibial or pedal targets, with perioperative mortality and limb salvage rates of 3% and 80%, respectively.

A recent study of 647 bypass grafts compared outcomes for ASV and polytetrafluoroethylene (PTFE) grafts and showed the patency rate with ASV was better than PTFE grafts at 5 years (62% vs 26%, $P < .05$); however, good quality vein may not be available (20%–30%). Bypass with PTFE should therefore be limited to select patients.

Open surgical bypass has certain limitations, for example postoperative morbidity/wound complication rate of 10% to 20%, prolonged hospital stay/outpatient care, and patient discomfort. De novo stenosis in vein grafts may also occur in 30% to 40% of patients in the first 2 years, which may necessitate graft surveillance or reintervention. Other systemic complications may occur (e.g., cardiac, pulmonary and renal).

Recently, endovascular therapy has been advocated as an alternative to open bypass. Several studies analyzing outcomes of patients with CLI treated with endovascular therapy have largely been retrospective single-center with significant heterogeneity. The GLOVE registry, a multicenter prospective study, analyzed the outcomes of endovascular therapy for infrapatellar disease in 314 patients with CLI and showed a 12-month amputation-free survival of 71%, whereas 34% of patients required reintervention (endovascular, 31.7% and bypass surgery, 2.6%). These results were satisfactory in

those high risk patients (71% diabetics and 22% on hemodialysis) and with severe anatomic disease (42% below knee lesions and ~50% Trans Atlantic Inter Society Consensus [TASC] type C and D).

CLINICAL EVALUATION/IMAGING

A thorough history and physical examination is important. Cardiovascular risk factor identification is critical and includes history of cigarette smoking, hypertension, diabetes, and dyslipidemia. In general, a patient's clinical symptoms and a thorough pulse examination should facilitate in diagnosing PAD. Hemodynamically significant disease can be asymptomatic or present with intermittent claudication or limb-threatening ischemia (rest pain and/or trophic changes, e.g., ulceration or gangrene). Claudication (from the Latin word *claudicare*, means limping) generally manifests as cramping pain in the calf, which is precipitated by walking that occurs at a reproducible distance. It is relieved with rest, and the location of pain is almost always one joint distal to the occlusion. Once the clinical diagnosis is made, noninvasive vascular laboratory can be helpful in confirming the diagnosis and localizing the disease. The most common testing is the ankle brachial index (ABI), which can be combined with color duplex scanning of the lower extremity. The ABI is generally calculated as the ratio of the higher systolic pressures in the arm divided by the highest systolic pressure at the ankle whether the dorsalis pedis or the posterior tibial artery. A normal ABI is generally around 1 ± 10%; an ABI of less than 0.9 is diagnostic of PAD. It is generally believed that an ABI between 0.4 and 0.9 is present in patients with claudications, while an ABI below 0.4 is compatible with rest pain or tissue loss. An ABI greater than 1.2 may be indicative of arterial calcification, which is seen in diabetics and mid stage renal disease (chronic kidney disease (CKD)). Some believe that in these patients an ABI can be greater than 1.3 to 1.4. Patients with vasculogenic claudications will also show an ABI drop when the patients walk to the point of calf claudications using treadmill testing. If an ABI is greater than 1.3 to 1.5, particularly in diabetics or in patients with CKD, obtaining Doppler toe pressures and/or pulse volume recordings might be helpful. A toe brachial index (TBI) of less than 0.7 is indicative of significant disease. Color duplex ultrasound is also available in many of the vascular laboratories where B Mode imaging and color flow Doppler sampling will determine the location and severity of the disease, including occlusion, which will facilitate proper treatment of open or endovascular therapy. For patients who need invasive therapy, further imaging is obtained to show both inflow and outflow arteries, for example contrast computed tomographic angiography (CTA), or magnetic resonance angiography (CCTA to contraindicated). However, if endovascular therapy is anticipated, contrast arteriography may be all that is needed to minimize cost.

TREATMENT

Conservative Medical Therapy

Conservative medical therapy is offered to patients with claudicating claudication, or even as initial step for patients with disabling symptoms. This therapy includes risk factor modifications, such as smoking cessation, dietary and pharmacologic therapy to include statin to lower dentite lipoprotein cholesterol and triglyceride, treatment of hypertension, and diabetes. Patients should also be given aspirin to reduce the risk of cardiovascular morbidity and mortality. Cilostazol (a phosphodiesterase inhibitor) may provide symptomatic improvement in certain patients with claudication. Exercise programs have been advised to improve walking distance. Supervised exercise programs being more effective than unsupervised. However, if an unsupervised program is initiated it should be performed at least 3 times a week for 30 to 45 minutes, and patients should be encouraged to do it to a point where the claudication symptoms appear. Medical treatment is not the first line of therapy for patients with critical limb ischemia.

Open Surgical Versus Endovascular Therapy

The decision to perform open surgical therapy versus endovascular therapy should be based on several factors including patient's age, severity of ischemia, long term prognosis, and anatomic complexity. To many, open surgical therapy is still considered the gold standard for patients with ischemic rest pain or tissue loss. However, for many others endovascular therapy has been advocated as initial therapy. The classification of arterial lesions, which was established by the Trans Atlantic Inter Society Consensus for the Management of PAD (TASC II) may be helpful in choosing the appropriate therapy (Fig. 1). It is agreed upon that endovascular therapy is preferable for type A, B, and C lesions; however, type D lesions are treated mainly by an open surgical bypass. However, some authorities recommend endovascular therapy even for type D lesions as initial therapy, with open bypass if it fails.

Open Surgical Therapy

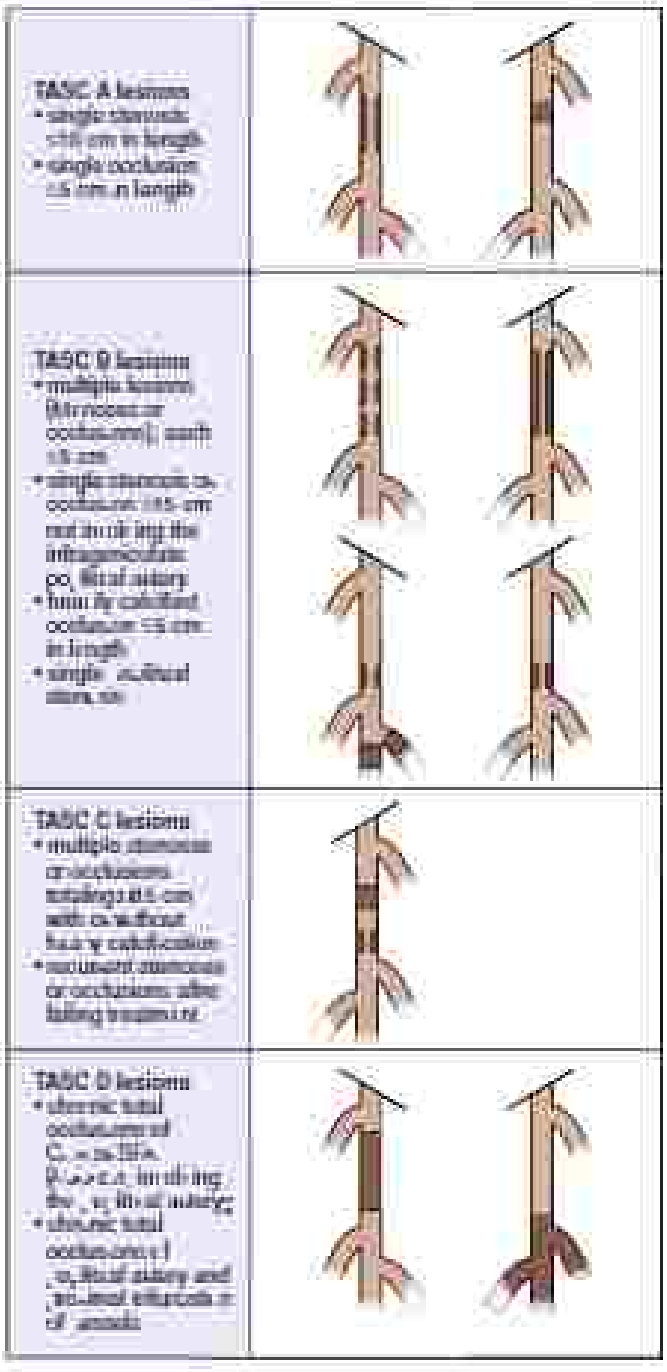
FPBP is the procedure of choice, which involves a bypass of the occlusive disease with or without endarterectomy of the common femoral artery (CFA), if needed. For successful bypass, adequate inflow vessel (arterial), outflow vessels, and conduit are needed. The proximal target should be the CFA; however, the superficial femoral artery (SFA) or the proximal profunda can be used with caution. The distal target site can be above- or below-knee popliteal segment or the tibial vessels. The groin incision can be done either as vertical or oblique just above the crease (Fig. 2). Vertical incision is preferable if common femoral endarterectomy or profundoplasty is needed. A good outflow vessel should be the least diseased with continuous flow to the foot. Every effort should be made to revascularize the target artery that supplies the area of ulceration is present (Fig. 3) based on the angiosome concept.

Exposure of Above- and Below-Knee Popliteal Artery

The above knee popliteal artery is exposed with a longitudinal incision placed along the anterior border of the sartorius muscle in the distal thigh (Fig. 4). Incision is deepened through subcutaneous tissue to the muscular fascia between the vastus medialis anteriorly and sartorius posteriorly. The adductor hiatus is identified to expose the popliteal artery emerging from the distal SFA. The artery lies medial to its accompanying vein upon entering the vascular sheath. Small branches of the popliteal artery should be handled carefully and not divided to minimize compromising leg circulation if the graft failed. To expose below-knee popliteal artery, the incision is positioned below the knee along the medial aspect (Fig. 4). If this was anticipated before vein harvest, the same below knee incision for vein harvest can be used. This incision is generally placed one fingerbreadth posterior to the tibia and carried through the fascia. The gastrocnemius muscle is identified and retracted posteriorly to expose the popliteal space. Further proximal exposure of the popliteal artery/space may be obtained by dividing the tendinous attachment of the sartorius, gracilis, and semitendinosus muscles. For distal grafting to individual tibial vessels, the dissection should continue by detaching some of the soleus muscle fibers, which will expose the tibioperoneal trunk, posterior tibial and peroneal arteries. The anterior tibial artery is generally identified once this process is done.

Conduit of Choice

Autogenous vein has been the first choice for all infrainguinal bypasses. The greater saphenous vein is the preferred choice and should be evaluated with preoperative duplex vein mapping. If this vein is inadequate, a mapping of alternative veins including a lesser saphenous, contralateral greater saphenous vein, and upper arm veins (basilic and cephalic vein) is done. The vein should be sonographed and at least 3 mm in diameter. Vein bypasses can be placed in a reversed, nonreversed, or in-situ configuration. Both reversed and nonreversed vein bypasses have similar patency, particularly for above knee positions. The in-situ configuration is reserved for distal popliteal artery or tibial vessels because of better matching between



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the arteries and the vein. Other conduits have been used (e.g., PTFE or Dacron), with or without heparin bonding, with no clear superiority of one over the other. Cryopreserved and human umbilical vein might be used with a similar patency as prosthetic graft; however, they are expensive and used only in exceptional cases.

Vein Harvest/Bypass Technique

Vein harvest is generally done with several long anterior incisions with skip incisions, which I prefer. (A.F.A.) versus continuous long incision. Endoscopic vein harvest can also be done; however, comparative results with open vein harvest have been unsatisfactory. The incision is extended distally along the path that is marked at the time of preoperative vein mapping or using a bedside ultrasound machine. Vein harvest must be meticulous to minimize damage to the vein. A vessel loop can be used to retract the vein from side to side and help identify all side branches, which should be tied 1 to 2 mm away from the vein to minimize kinking or narrowing of the vein. Once the vein is removed, gentle dilation with heparinized saline solution is done. Every effort should be made to minimize the amount of time the harvested vein is not being perfused with the patient's blood. We generally prepare the vein just after exposing both proximal and distal inflow and outflow arteries, so once the vein is harvested it is ready to be used. Due to size mismatch, the vein is spatulated, and if anastomosis to the most proximal valve is excised with direct vision. The end-to-side anastomosis is created with 5-0 or 6-0 polypropylene suture. Flow in the vein is then reversed into the bypass. Valvulotome (Leonhartt) is then used and inserted from the distal end where the remaining valves are gently cut. If the bypass is done to reverse failure, a tunneler is used, which is inserted just deep to the sartorius muscle and superficial to the SFA, and for below-knee popliteal artery bypass, the graft is inserted from above to below knee, with the index finger creating a tunnel between the heads of the gastrocnemius muscle to prevent compression.

Once the tunnels and the conduit are prepared, the patient should receive 80 to 100 U/kg heparin intravenously. A few minutes later, the procedure starts by occluding the CFA, profunda femoris and SFA, and any other branches. A longitudinal incision is made in the CFA with a No. 11 blade and extended using angled Potts scissors. Using double-armed 5-0 or 6-0 polypropylene sutures, the proximal anastomosis is done ballistically. The vein is allowed to distend with blood after loosening the vascular loops. It is then marked along one side to maintain orientation and prevent vein twisting. Once the vein is tunneled distally, the distal anastomosis is performed in a similar fashion using 5-0 or 6-0 polypropylene sutures (Fig. 5).

It is generally recommended to have completion duplex imaging to assess both proximal and distal suture line including the conduit. However, completion contrast angiography can be used if there is any question concerning the technical results. It is critical to evaluate the distal pulses by palpation and the use of continuous wave Doppler. The groin is then closed with multiple layers of absorbable sutures. The skin is closed as usual.

FIG. 3 Groin incision can be done either as vertical (A) or oblique (B) just above the inguinal [illegible]

FIG. 3 Angiosome concept. Six angiosomes of the lower extremity are supplied by the three main arteries (anterior tibial artery, posterior tibial artery, and peroneal artery). Each angiosome is supplied by a distinct source artery and is the tissue territory supplied by that artery. The angiosomes are separated by watershed zones. Direct cutaneous perforators are present in the skin overlying the angiosomes. Indirect perforators supply the skin through the underlying muscle.

Perioperative Management

Medications are started including statins and β-blockers. All patients are given one aspirin daily, which continues indefinitely. Sequential compression devices (SCDs) are applied on postoperative day 1 and continued until the patient is ambulating. Intravenous heparin is generally started in select patients at admission and discharged on warfarin, aiming for an INR of 2–3 for 3 months.

Postoperative Graft Surveillance

Duplex surveillance of the graft is performed at 1, 3, 6, 12, 18, and 24 months postoperatively. Patients are generally instructed to check their pulses daily and to call the vascular clinic immediately if they notice any decrease in pulses. Duplex surveillance is performed every 3 months for the first 2 years and then every 6 months thereafter. Approximately one third of vein grafts will develop lesions within the first 36 days after bypass surgery. Most lesions in graft patency within the first 30 days implies

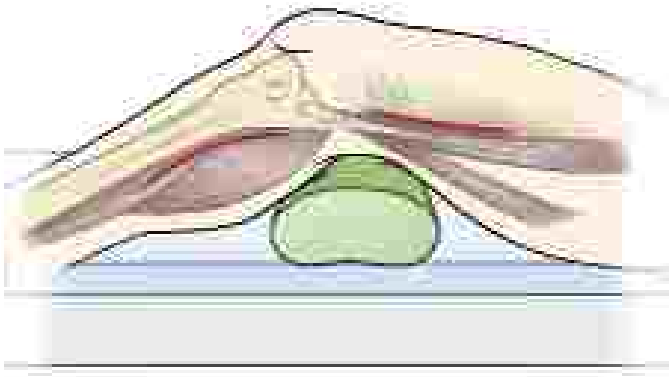

FIG. 4 Exposure of above- and below-knee popliteal artery

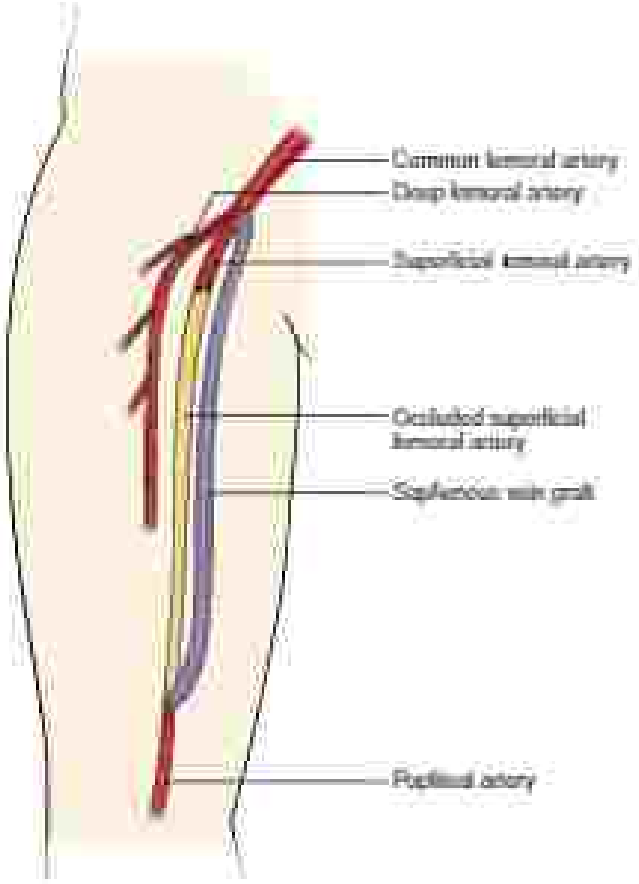

FIG. 5 Bypass done in reverse fashion.

a technical factor. Graft failure is impending [illegible] [illegible] of hyperplasia [illegible] [illegible] [illegible] of 3 to [illegible] [illegible] [illegible] [illegible] [illegible] endovascular [illegible].

Femoropopliteal Bypass Using Prosthetic Conduit

Both PT[illegible] [illegible] have been utilized to [illegible] particularly for above knee [illegible] similar [illegible] described earlier [illegible] diameter [illegible] generally [illegible] for above knee locations [illegible] below knee using prosthetic grafts [illegible] because [illegible] reserved as a last option.

We [illegible] conducted a prospective [illegible] of [illegible] saphenous veins [illegible] patients with bilateral above knee (AK) [illegible] patients [illegible] [illegible] with [illegible] [illegible] with PTFE [illegible] with saphenous vein graft [illegible] SVG [illegible] PTFE. All patients were followed [illegible] [illegible] The perioperative complication rates were [illegible]% for PTFE and 12% for SVG. There were no operative deaths or perioperative amputations [illegible]. The Kaplan-Meier estimate of primary, secondary [illegible] patency rates at 72 months were [illegible]% and 77% [illegible] 76%, 83% [illegible] for SVG. There were no statistically significant differences between primary and secondary patency rates, but [illegible] grafts, however, the assisted primary patency rates were higher for SVG ($P < .05$). The crude limb salvage rate at 72 months was 98% for PTFE and 98% for SVG. We concluded that PTFE and SVG for above knee bypasses have comparable patency and limb salvage rates in claudicant patients with bilateral SF[illegible] occlusion and 2 to 3 vessel runoff. This may justify the use of PTFE for above knee locations in these selected patients.

Results of Vein Surgical Bypass

Several studies compared the results of autogenous with various prosthetic FPBP in both above- and below-knee locations. A recent meta-analysis showed that SVGs were superior to prosthetic bypasses in both above- and below-knee locations. However, as indicated earlier by our experience, some authorities believe patients who are claudicant and needed only AK FPBP who had good runoff (2 to 3 vessels) might be better off served by the use of PTFE or a prosthesis, with the understanding the vein can be saved for future use for below-knee or distal vessels. If autogenous veins were not available for below-knee locations, a PTFE graft with distal anastomotic vein cuff has been suggested to be superior to prosthetic distal anastomosis alone (Table 1).

ENDOVASCULAR THERAPY FOR FEMOROPOPLITEAL DISEASE

Current endovascular therapy includes percutaneous transluminal angioplasty (PTA)/stenting, cutting PTA, atherectomy, covered stents, drug-coated balloons/stents, and cryoplasty. Commonly used modalities are discussed below.

Angioplasty/Stenting

The principle of angioplasty is balloon dilation of the reference lesion by inflating the balloon (several atmospheric pressures) and cracking

TABLE 1 Graft Patency, Aggregate of Multiple Studies

	Suprageniculate Femoropopliteal Bypass			Infrageniculate Femoropopliteal Bypass			Femorotibial Bypass		
Type of bypass	1 y	3 y	5 y	1 y	3 y	5 y	1 y	3 y	5 y
SAPHENOUS VEIN									
Primary patency	84%	79%	73%	84%	83%	71%	82%	72%	69%
Secondary patency	[illegible]	83%	80%	82%	87%	83%	88%	[illegible]	79%
Limb salvage	82%	80%	81%				90%	[illegible]	89%
Survival	84%	81%	70%		68%	78%	85%	[illegible]	60%
PTFE									
Primary patency	80%	58%	53%	74%	52%	38%	60%	50%	28%
Secondary patency	87%	65%	70%	69%	60%	56%	65%	47%	28%
Limb salvage	84%	79%	72%	79%	71%	63%	75%	69%	57%
Survival	86%	81%	70%			42%	78%	53%	40%
DACRON									
Primary patency	79%	67%	62%	74%	64%	51%			
Secondary patency	88%	75%	25%						
Limb salvage		94%							
Survival	87%	77%	77%	86%		60%			

PTFE, Polytetrafluoroethylene.
[illegible]

the plaque. PTA is considered by many to be a controlled dissection. PTA has a favorable outcome in larger caliber arteries, in stenosis rather than occlusion, short and focal rather than multiple with good runoff. PTA has a better result when the indication is claudication rather than CLI.

Technical Consideration

Technical consideration starts by obtaining arterial access then identifying the lesion with diagnostic arteriography, followed by crossing the lesion with a guidewire, balloon angioplasty with or without stenting, and completion angiography to evaluate the result. The contralateral CFA is preferable arterial access, however, in certain thin patients the ipsilateral CFA may be used for antegrade access. The brachial artery may be used occasionally, particularly in patients with prior iliac artery/femoral artery bypass graft. The access is either obtained by conventional standard 18 gauge puncture needle or a micropuncture small catheter access needle. Once an access is obtained, 0.035 inch guidewire can be advanced into the iliac system then the aorta using contralateral catheter, access is obtained of the ipsilateral iliac, CFA, then SFA/popliteal artery through the lesion. To facilitate the intervention exchanging the access (6Fr 10 cm sheath) for a longer 45 to 55 cm (8Fr or 6Fr) sheath, which is positioned at the level of the external iliac or CFA on the side of the intervention, which facilitate for wire and catheter support. Spot angiography is used to delineate the lesion. The size and the length of the balloon are tailored to the size and length of the artery. Every effort should be made to avoid ballooning a healthy native artery. After completion angiography if more than 30% residual stenosis exists or if angioplasty has created a dissection (with significant impairment of the flow) then a self expanded stent should be placed across the lesion. We prefer giving 3000 to 5000 U heparin, which is administered intravenously at the start of the procedure once access is achieved. All patients should already be on aspirin regimen for intervention, which is continued afterward in addition to clopidogrel (Plavix), which is prescribed for 4 weeks after PTA. PTA after stent placement is usually necessary for complete expansion of the stent.

Crossing an occlusion can be accomplished with several techniques. An angle support catheter in combination with a straight, stiff hydrophilic wire is generally used initially to traverse a total occlusion. A combination of the support catheter and hydrophilic guidewire allow crossing many of these total occlusions. However, if that was not successful, other maneuvers might be utilized, including subintimal (external), if necessary. This can be achieved by pushing a hydrophilic angle guidewire into the subintimal plane with a loop orientation. ...sing catheter support, the loop is shortened to provide a smaller profile to reenter the luminal space. If that was not successful, reentry into the lumen may be done using reentry catheters (e.g., Pioneer (Volcano) or Outback (Cordis,).

It is generally not recommended to stent the popliteal artery since it is highly mobile and because of its location across the joint, which may lead to stent fracture and higher restenosis rate. Therefore, stenting to this location should be done only in select patients. ... se of the Supera stent (Abbott) has been associated with favorable results in this location.

...hese the procedure is done, the arterial access site can be closed using a variety of closure devices based on the size of the access sheath and the state of the access vessel (particularly calcification). Manual pressure may be appropriate for smaller access sheath and certain calcific lesions.

PTA for CLI can achieve a 5 year limb salvage rate of 89%, similar to earlier reported values with surgical revascularization, which ranged from 70% to 80%. Although the primary patency after PTA for CLI may be low, the limb salvage rate is quite high. The Society of Cardiovascular & Interventional Radiology Transluminal Angioplasty and Revascularization (STAR) registry analyzed 205 patients (79% with stenosis and 21% with occlusions were treated) with mean lesion length of 3.8 cm for stenotic lesions and 8.7 cm for occlusions. The technical success rate was 95%. The primary patency rates were 87%, 80%, and 69% at 1, 2, and 3 years, respectively. Diabetes and poor runoff scores were associated with decreased patency rates.

The use of stents was initially advanced to improve long term patency rates from PTA, especially to longer segment disease. Stenting may reduce elastic recoil and provide a scaffold in the setting of dissection. Initial study results were disappointing, with several randomized trials failing to show any benefit of stent placement over PTA alone. These findings led to the recommendation for stenting only in the setting of a suboptimal technical result following PTA. However, these studies were done using balloon expandable stainless steel stents, and more recent studies using self expanding nitinol stents have shown significantly better results. Three major randomized trials comparing primary nitinol stent placement with stent assisted angioplasty have been reported and show differing results.

The Femoral Artery Stenting Trial (FAST) analyzed outcomes with stent alone PTA versus primary stenting with a single self-expanding nitinol stent. Only single short segment lesions of less than 10 cm were included, with a mean lesion of 45 mm for both groups. A total of 123 patients were assigned to primary stenting and 121 were randomized to PTA alone. Technical success was achieved in 79% of the PTA group versus 93% of the stenting group. Restenosis rates at 1 year, as determined by ultrasound, were not significant (39% in PTA, 32% in stent). Maximal walking distance was slightly improved in the stenting group, but there was no difference in resting ABI or change in rutherford class. Stent fractures were found in 12% of patients, with no significant increase in restenosis with the presence of fractures.

The SUPERA JENT trial is a prospective multicenter trial of 234 patients that compared bare nitinol stents (Lifestent, C.R. Bard) to patients with a mean lesion length of 7.1 cm to PTA patients with a mean lesion length of 6.4 cm. Forty percent of patients with PTA had balloon stent for greater than 30% residual stenosis or dissection. This study suggested a statistical advantage of improved patency with stent over PTA alone. The technical success rate was better with stenting (96% vs 84%). Freedom from target lesion revascularization was better in the stent group than the PTA group at 6 and 12 months: 94% and 81% versus 67% and 57%, respectively. The stent fracture rate was 3% at 12 months and was not associated with any adverse clinical sequelae. The study showed continued advantages of bare metal stents versus PTA at 3 year follow up. The study authors concluded that for moderate length lesions, primary stent placement is superior to PTA alone.

The A SCAFFOLD trial (Balloon Angioplasty versus Stenting with Nitinol Stents in the SFA) included 104 patients with severe intermittent claudication and/or tissue loss (Rutherford classes 3–5) with lesions longer than 30 mm. Patients were randomized to PTA plus optional stenting or primary stenting. Mean target lesion length was 112 mm for the stent group and 93 mm for the PTA group. Restenosis rates were significantly lower in the primary stenting group at 2 years (46% vs 69%). There was no difference between the two groups with respect to Rutherford class at follow up, but there was a trend toward improved walking capacity and resting ABI in the stent group. Overall, reintervention rates were lower in the primary stent group.

Challenges in Stenting Superficial Femoral Artery/Popliteal Lesions

The SFA and popliteal arteries, unlike other arteries, are subject to triplanar intermittent mechanical stresses, including contraction, extension, torsion, flexion, and compression. The efficacy of stents in this location is limited by the fact that they can only deform to a limited extent to stresses exerted on the artery. The lack of flexibility and resistance to stent may reduce stent fractures and promote poorer patency.

Cutting Balloon Angioplasty

Cutting balloon angioplasty uses low pressure balloon catheters mounted with microsurgical blades or microtomes that cut into

luminal vessel during inflation. The mechanism of action is controlled disruption of the vessel wall, resulting in more controlled dilatation at lower balloon inflation pressures.

A prospective randomized controlled trial of de novo SFA lesions of 43 patients (19% had CLI) compared cutting balloon PTA versus conventional PTA and showed a restenosis rate of 32% in PTA and 42% in the cutting balloon PTA group at 6 months ($P = .048$). Therefore, cutting balloon PTA is not routinely used, due to higher costs and inferior results, but can be used for in-stent restenosis and diseased arteries in diversion points (CIA or popliteal artery stent fracture risk).

Atherectomy

Atherectomy involves debulking or atherosclerotic plaque removal. Current devices for this modality include rotational, directional, orbital, and laser atherectomy. Atherectomy for PAD patients is currently used as adjunctive/alternative therapy to traditional PTA or stenting. Plaque debulking leads to an immediate increase in lumen size, which should result in reduced stretch injury of the arterial walls. One potential complication is embolization, although the TALON registry reports a very low embolization rate (0.1%).

The DEFINITIVE LE[illegible] study included 133 patients with calcified femoropopliteal lesions treated with the Silverhawk or Turbohawk (Covidien) and distal embolic protection. They reported a 93% freedom from major adverse events, which included clinically significant embolization. However, the definitive clinical benefit of atherectomy over PTA was not clear. Larger prospective multicenter trials are needed to highlight the role of atherectomy in femoropopliteal arterial disease.

Covered Stents

Stent grafts using endovascular techniques attempt to duplicate open prosthetic femoropopliteal bypass. The Viabahn stent graft (W. L. Gore) consists of a self-expanding nitinol stent bonded to a graft made of expanded PTFE. They perform well in long segment occlusions and SFA restenosis; however, appropriate sizing and adequate runoff are required for optimal outcome and also dual antiplatelet therapy for at least 1 month.

The VIASTAR trial (Viabahn Endoprosthesis with Propaten Bioactive Surface versus Bare Nitinol Stent in the Treatment of Long Lesions in SFA Occlusion) studied 181 patients randomized to Viabahn or bare metal stents. The 1-year patency rate was higher with long lesions (>20 cm) with covered stents versus bare metal stents (71% vs 37%, $P = .01$). The Viabahn stent was then modified and heparin was bonded to the stent. This was examined in the VIPER trial for the treatment of SFA occlusion where the primary and secondary patency rates were improved to 79% and 92%, respectively. Laurinec et al. reported that PAD patients with long femoropopliteal lesions had significantly improved primary patency rates with covered versus bare metal stents at 24 months; however, there was no significant impact on clinical outcomes and target lesion revascularizations.

Drug Eluting Balloons and Stents

Drug-coated angioplasty balloons (DCBs) and drug-eluting stents (DES) are designed to limit the proliferative, reactionary process of neointimal hyperplasia. DCBs were developed to improve the durability of PTA, without the potential drawbacks of stents. It has been hypothesized that stents may actually increase neointimal hyperplasia by causing repetitive trauma and an increased inflammatory reaction. DCBs are designed to curb neointimal hyperplasia by delivering large doses of antiproliferation agents directly to the site of vessel injury.

Paclitaxel is a potent antiproliferative drug that stops cell division and induces apoptosis. The IN.PACT Admiral DCB coating consists of paclitaxel and urea, a carrier molecule. When exposed to blood during inflation, the urea hydrates and releases paclitaxel. Subsequently, the drug transfers into the wall of the artery and migrates through the vessel wall into the media. The IN.PACT Admiral DCB delivers paclitaxel in solid phase, thus establishing reservoirs of drug within the vessel wall. These reservoirs permit sustained drug availability (up to 6 months) and release with subsequent long-term antiproliferative effect.

There are several ongoing studies of paclitaxel DCBs in de novo and restenotic femoropopliteal lesions. Using DCBs to treat in-stent restenosis is preferred over placing additional stents because additional overlapping stents are associated with a higher rate of stent fracture and restenosis. Currently, there are two DCBs approved for use in the United States, Lutonix 035 (Bard) and IN.PACT Admiral (Medtronic). The majority of clinical trial data on DCBs has predominantly included patients with claudication and lower Rutherford classifications, as opposed to CLI patients. Late lumen loss, target lesion revascularization, and angiographic restenosis significantly favored DCBs in these trials.

The LEVANT trial randomized 101 patients to Lutonix DCBs or uncoated balloons. There was a significant increase in primary patency at 12 months with the Lutonix 035 DCB versus plain balloon angioplasty (74% vs 57%, $P = .03$). At 24 months, the major adverse events (death, amputation, target lesion thrombosis/hemorrhage) were 39% for DCB and 46% for uncoated balloon patients ($P = .45$). It should be noted that the results of DCBs have not been encouraging for below-knee vessels. The IN.PACT DEEP study identified a potential safety signal with a trend towards an increased rate of major amputations in the DCB study arm.

Medtronic's IN.PACT SFA trial is a prospective, multicenter, randomized trial in which 331 patients with intermittent claudication and CLI, secondary to femoropopliteal PAD, were randomly assigned in a 2:1 ratio to treat with DCB (Paclitaxel) or PTA. Over 90% of lesions were de novo, with a mean lesion length of 8 cm or greater in both groups. A higher primary patency at 12 months in the IN.PACT Admiral DCB group was noted, compared with the PTA group (83% vs 52%, $P < .001$). The rate of clinically driven target lesion revascularization was 2.8% in the DCB group versus 20.6% in the PTA group ($P < .001$). There was no device/procedure related death or major amputation.

The THUNDER trial followed 154 patients who were treated with DCBs, angioplasty with paclitaxel in contrast medium, or no paclitaxel (control group) for 5 years. The target lesion revascularization was significantly lower in the DCB versus the control group (23% vs 56%, $P = .0005$). DCBs also had lower binary restenosis (17% vs 54%, $P = .04$). DCBs had reduced target lesion revascularization over 5 years.

Limitations of DCBs

The use of cytostatic agents, such as paclitaxel, may have an adverse impact on wound healing. Furthermore, patients with PAD, especially those with CLI, often present with calcified plaque, which is difficult to treat and is often associated with poor procedural and long-term success. Preparing the vessel with atherectomy prior to using DCBs is a strategy that may hold some promise in improving the therapeutic effect of DCBs in calcified lesions.

Drug-Coated Stents

ZEPHYR I and II trials (zotarolimus-eluting stents (Cordis Smart nitinol self-expanding stent) were compared to bare metal stents. There was no difference in in-stent restenosis at 6 months and 2 years. However, the Absolute PTX (paclitaxel) stents (Cook Medical) proved safety and efficacy, and it was superior to PTA with provisional stent placement. In a study by Duke et al. with the Absolute PTX stent, 474 patients were randomized to primary DES or PTA with provisional stents, with subsequent secondary randomization to bare metal stents or DES for patients requiring provisional stents. The event-free survival at 1 year was 90% for primary DES versus 83% for the control arm ($P = .004$). The primary patency rate at 1 year was 83% for DES versus 73% for PTA alone.

Later studies with Zilver PTX stents reported a primary patency rate of 83% for DES and 65% for PTA, excluding acute PTA failure ($P < .001$). The data still supported safety and efficacy of DCS at 5 years. In a larger prospective registry of 787 patients, the 2-year freedom from target lesion revascularization with primary DES placement was 80.5% in the single-arm study. The Zilver PTX stent was also examined for the treatment of in-stent restenosis. In patients with a mean lesion length of 13 cm (91% total occlusions), procedural success was 98%, primary patency rate at 1 year was 79%, and freedom from target lesion revascularization at 2 years was 81%. Dual antiplatelet therapy is recommended for 6 months with the use of the Zilver PTX. Later 5-year data showed that DCS (paclitaxel) had better patency rates than standard PTA (66.4% for lesion 65 ± 40 mm in length) and better freedom from target lesion revascularization (85%).

Drug-Coated Angioplasty Balloon Versus Drug-Eluting Stents for Superficial Femoral Artery Interventions

Lesion length, type of revascularization (subintimal vs intraluminal), degree of calcification, and lesion site (distal, popliteal) should all be considered when choosing the primary strategy. As a general rule, one must avoid stenting when unnecessary due to the possibility of a worse behavior of stent restenosis. It is generally recommended to use a DCB for a TASC II, C, or D lesion upon first presentation and also for restenotic lesions, as well as for in-stent restenosis in the femoropopliteal area. If significant flow-limiting dissection remains, use of a DES as a kind of bailout stent is appropriate.

Primary Amputation

Some authorities feel primary amputation may be appropriate in select patients; for example, a patient with significant tissue loss, who is not likely to return to ambulation and who has a long-standing functional impairment, is best served with primary amputation. Patients who are also paralyzed with contractures, short life expectancy, severe sepsis, end-stage renal disease, or other systemic illness would be better served with primary amputation.

CONCLUSION

Based on a nearly universal procedure success rate, low morbidity and mortality, and improving patency rates with new devices, endovascular therapy is the recommended treatment of choice for TASC A to C lesions, although open surgical bypass with ASV grafts is a durable choice in low-risk patients. Two new studies, BASIL 2 and 3 and BEST CLI, are enrolling patients to further compare open versus endovascular therapy for selected patients with CLI. Until more well-designed randomized trials are completed, physicians should rely on their best clinical judgment.

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MANAGEMENT OF TIBIOPERONEAL ARTERIAL OCCLUSIVE DISEASE

Robert J. Rosenfield, [illegible] and [illegible] Mark Hamilton, MD

A generation ago, vascular disease isolated to the tibioperoneal arteries was uncommonly encountered. At that time, the typical vascular patient was a long-term smoker with ischemic and/or [illegible] disease, and distal involvement represented the distal extension of the disease. Since endovascular therapies were nonexistent or in their infancy, distal disease came into play when a leg bypass had to be extended into the tibial vessels and was not commonly the primary indication for operation. Currently, with the high prevalence of diabetes mellitus, peripheral artery disease (PAD) isolated to the tibioperoneal arteries has become a common pattern. Additionally, PAD has increased in prevalence in every type of country regardless of socioeconomic status. This is due in large part to the explosive growth in the number of diabetics. This rise in prevalence has had a significant economic impact, which will undoubtedly worsen with time. Annual healthcare expenditures in patients with PAD are over three times that of age-matched, comorbid-matched cohorts due to

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MANAGEMENT OF TIBIOPERONEAL ARTERIAL OCCLUSIVE DISEASE

Robert J. Beaulieu, MD, and Thomas Reifsnyder, MD

A generation ago, vascular disease isolated to the tibioperoneal arteries was uncommonly encountered. At that time, the typical vascular patient was a long-term smoker with occlusive and/or stenotic disease of the aortoiliac segments, and limb involvement represented the distal extension of the disease. Since endovascular therapies were nonexistent or in their infancy, tibial disease came into play when a leg bypass had to be extended into the tibial vessels and was not commonly the primary indication for operation. Currently, with the high prevalence of diabetes mellitus, peripheral artery disease (PAD) isolated to the tibioperoneal arteries has become a common pattern. Additionally, PAD has increased in prevalence in every type of country regardless of socioeconomic status. This is due in large part to the explosive growth in the number of diabetics. This rise in prevalence has had a significant economic impact, which will undoubtedly worsen with time. Annual healthcare expenditures in patients with PAD are over three times that of age-matched, comorbid-matched cohorts due to

increased costs of interventions and hospitalizations. Therefore, knowledge of the risks, diagnosis, and management of this patient population is of paramount importance, especially to mitigate the morbidity associated with this condition and drive improved high-value care.

ASSESSMENT AND DIAGNOSIS

Assessment of patients with suspected or confirmed chronic limb-threatening PAD should begin with a complete history and physical, aiming to not only define the symptomatology and severity of the disease but also the functionality of the patient. A majority of patients with chronic limb-threatening PAD will be asymptomatic and warrant no vascular intervention. Most patients who need invasive treatment will present with rest pain and/or tissue loss on the foot or a diabetic foot infection. Comorbid conditions that may impact the treatment strategy in particular, a history of major adverse cardiovascular events, such as stroke or MI, as well as the presence of diabetes, hypertension, chronic kidney disease and tobacco abuse should be elicited. However, in ambulatory patients with a limb-threatening problem the work up of the patient revolves around maximizing their current physiologic state since limb salvage is always preferable and less stressful than limb loss.

Noninvasive evaluation of the limb is the next step. An ankle-brachial index (ABI) should be obtained in all patients with suspected PAD. Patients with chronic limb-threatening PAD who are typically diabetic or have chronic renal failure often have incompressible arteries, so the ABI will be falsely elevated or cannot be calculated. However, the addition of digital pressures and pulse volume recordings should allow an accurate assessment of the degree of ischemia. A first toe pressure less than 50 mm Hg is concerning and pressures less than 30 mm Hg in a patient with a foot wound indicate that healing without intervention is unlikely.

In patients with critical limb ischemia (CLI), additional diagnostic imaging will be required to delineate the affected anatomy. Catheter-based angiography is the gold standard to evaluate the extent and location of disease (Figs. 1 and 2). Additionally, it allows for the possibility of simultaneous intervention, the role of which will be discussed in detail later in this chapter. However, the near ubiquity and ease of obtaining magnetic resonance angiography and multidetector computed tomography have increased the use of these modalities. In particular, both of these methods obviate the risks of vascular injury associated with traditional angiography while maintaining greater than 90% sensitivity for diagnosing a stenosis greater than 50%. Since all methods involve the administration of contrast, they are not risk free.

MANAGEMENT

Medical Therapy

Cardiovascular optimization is the cornerstone of medical therapy for limb-threatening PAD. In particular, a healthy diet, smoking cessation, and good glucose control in diabetics are a must. Smoking cessation has been shown to significantly reduce the risk of both amputation and mortality in patients with PAD. Pharmacologic smoking cessation aids, including bupropion and varenicline, should be explored in all patients with a willingness to quit. Additionally, patients who are not in a limb-threatening situation should be encouraged to start an aerobic exercise regimen such as a walking program and enroll in a supervised walking program when possible.

FIG. 1 Digital subtraction angiogram of a patient with dysplastic left common, external, and internal iliac arteries. Atherosclerotic plaque is also noted throughout the abdominal aorta, bilateral common iliac arteries, and left external iliac artery. Collateral vessels are noted in the pelvis, providing retrograde flow to the left common femoral artery (arrow).

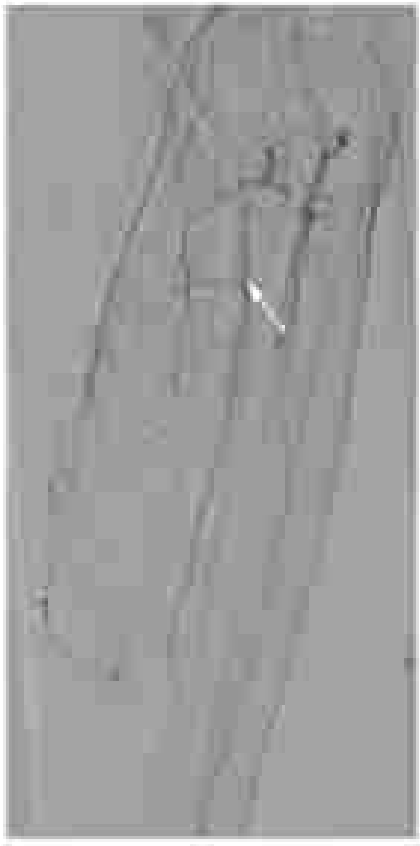


FIG. 2 Digital subtraction angiogram of a patient with dry gangrene of the left fifth toe. Occlusion and stenosis of tibioperoneal arteries with reconstitution of the peroneal artery (arrow) are noted.

Patients with infrapopliteal PAD should also be placed on aspirin or an alternative antiplatelet agent if aspirin intolerant. In addition, statin therapy is a must. Statin therapy has been shown to multiple trials to improve amputation free survival and lower mortality rates in patients with PAD and particularly in those with CLI.

Surgical Intervention

Deciding between the endovascular versus open surgical management of infrapopliteal PAD depends on multiple factors including symptoms, patient anatomy, severity of disease, patient comorbidities, and, importantly, the specialty and skill set of the treating physician. Clearly, both bypass surgery and infrapopliteal angioplasty should be part of the treating physician's armamentarium. No randomized control trials regarding the treatment of infrapopliteal disease have been conducted, but retrospective reviews have yielded consensus guidelines that can be used to direct management (Fig. 3).

Retrospective data include a large meta-analysis of infrapopliteal surgical bypass, which demonstrated an impressive 5 year primary patency rate of 73% and a nearly 80% rate of limb salvage at 5 years. Although it is generally accepted that the patency rates of tibial vessel angioplasty are not as good as surgical bypass (50% 1 year primary patency and 30% limb salvage at 5 years), the physiologic impact of the intervention is clearly less. There are a couple of considerations in choosing between surgical bypass versus tibial angioplasty. First off, tibial angioplasty works best on focal lesions less than 10 cm in length. Long lengths of occluded tibial vessels can be opened with angioplasty resulting in impressive final angiographic results; however, the patency of an endovascular intervention is generally measured in terms of months not years. Next, if the intervention is being undertaken for wound healing then long term patency may not be necessary and tibial angioplasty would be an appropriate choice. An example would be a previously asymptomatic diabetic patient with undiagnosed tibial artery occlusive disease who presents with a diabetic foot infection. After debridement of the infection, the patient has a large defect in their forefoot that will require a modified transmetatarsal amputation to close. Tibial vessel angioplasty can restore normal circulation to the foot, and even if the angioplasty fails after several months, the foot should remain healed since it was asymptomatic prior to the infection. Less often, the patient with infrapopliteal disease presents with ischemic rest pain and tissue loss of the foot. In this patient population, the vascular reconstruction must be durable because if it fails the rest pain will return and the patient's limb will once again be threatened. In these patients, the superior patency of autogenous surgical bypass outweighs the increased risk of the procedure. The bottom line is that the intervention should be customized to the patient, and if the treating physician can skillfully perform tibial angioplasty or a popliteal to distal pedal bypass then the optimal procedure will be chosen for that particular patient.

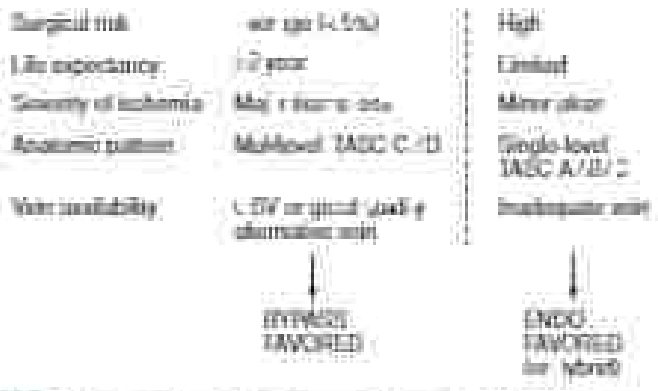


FIG. 3 Schema for bypass or endovascular treatment. ENDO, GSV great saphenous vein; TASC, transatlantic Inter-Society Consensus.

TECHNIQUES

Overview

The concept of a leg bypass for infrapopliteal PAD is simple and is predicated on dissection of adequate inflow and outflow arteries and harvesting an appropriate conduit. The word *harvesting* was purposely used since removing a prosthetic graft from a box is not harvesting. Autogenous vein should always be used. Since the distance that needs to be traversed is relatively short, there is no reason that enough autogenous vein cannot be found. If the surgeon is uncomfortable harvesting small saphenous, cephalic, or basilic veins then the patient should be referred to a surgeon adept at these techniques. While recent evidence suggests no difference in primary or secondary patency rates and limb salvage rates between arm and leg vein, data are clear regarding the superiority of either vein conduit, even upper arm vein, compared to infrapopliteal prosthetic graft use. While the great saphenous vein is typically used, it is not uncommon to preferentially harvest arm vein in the obese diabetic patient who needs a popliteal to pedal bypass thereby avoiding the thigh incision. The vein harvest is the most important part of the operation. This phase should be done by the most experienced person, as there is no room for error.

Procedure

Generally, the patient is placed supine on the operating room (OR) table, although in an occasional redo bypass utilizing small saphenous vein, a prone technique is used, particularly for the vein harvest and ankle below knee popliteal artery dissection. If ipsilateral great saphenous vein is being used and the operation will be continued to the leg distal to the mid thigh, in high risk patients we use a femoral sciatic nerve block for anesthesia. If the patient is not particularly high risk or if the vein is not coming for the ipsilateral limb then a general anesthetic is used. A Foley catheter is only placed if the expected OR time is going to exceed 3 hours and the patient does not have end stage renal disease. With practice, most of the bypass operations involving the infrapopliteal arteries can be accomplished in the 2- to 2.5-hour range. Next the extremities are prepped in the usual fashion. If arm vein is being used then the attending harvests that while the resident/fellow assistant surgeon circumferentially dissects out the popliteal or distal superficial femoral artery and then dissects out the distal target on its anterior surface only. The vein harvest is best accomplished through a continuous incision uncovering the entire length of necessary vein. An elastic vessel loop is placed around the vein at one end and the dissection proceeds toward the opposite end. All side branches, no matter how small, are ligated with a 4-0 braided, absorbable synthetic suture (polyglactin) on the conduit side, with the other side occluded with a small or medium vessel clip.

If ipsilateral calf great saphenous vein is going to be used then the team jointly harvests the vein and, once mobilized, that same incision is used to obtain control of the inflow popliteal artery. The other main variant in conduit occurs when the outflow distal pedal or plantar artery is very small or difficult to identify by preoperative angiography. In these cases, we identify the outflow vessel first, and make a small arteriotomy in the vessel to confirm a lumen before harvesting the vein.

At the last of the dissection is completed the patient is given 5000 units of intravenous heparin, and started on Dextran 40 at 25 ml/hr to continue for 20 hours. Dextran is not used in the end stage renal failure patients since it acts as a volume expander. In an experience of well over 1000 bypasses involving the infrapopliteal arteries this combination has worked well, and we have never found the need to check activated clotting times or other costly and time consuming confirmations of anticoagulation.

The proximal anastomosis is done first. We make the decision on conduit orientation depending on how the vein tapers. If the vein is uniform in size throughout its length, then we place it reversed. If it tapers, then the big end goes to the large or inflow artery and the smaller end goes to the distal vessel. We utilize an open arteriotomy technique with a 7-0 stitch in the heel, which is then run up

both sides to the midpoint followed by another U stitch in the vein, which is run down both sides to meet the first suture. Either 5-0 or 6-0 polypropylene is used for the proximal anastomosis, generally 7-0 is used for a distal tibial or pedal vessel. The valves are then cut if necessary and the vein tunnelled. There are many options for tunnelling, but in general we try to tunnel as much of the graft subfascially as possible, although it is not uncommon for the majority of the graft to be tunnelled subcutaneously. Once tunnelled, the distal end of the vein is marked, and a tourniquet is placed around the leg. Any kinks or twists in the conduit during tunnelling will result in limited flow, so confirm good continuous flow from the distal end of the bypass prior to inflating the tourniquet. The leg is exsanguinated, and the tourniquet inflated, and the distal anastomosis completed in the same manner as the proximal. This technique avoids crush injury or intimal damage due to externally clamping small calcified distal target vessels.

Once the bypass is in place, the incisions are closed with 2-0 absorbable suture in the fascia and 3-0 nylon interrupted vertical mattress sutures. We have tried every type of skin closure and have found that the number and severity of incisional problems is minimized with this closure. However, if there is an arm incision it may be closed in the most expeditious fashion, as it will eventually heal regardless of technique.

The patient is then taken to the recovery room, and then to a regular surgical floor bed. Unless the patient cannot be extubated or there is an unstable cardiac rhythm, there is no indication for the expense of the surgical intensive care unit for routine recovery. If the operation is appropriately conducted and autogenous vein used as the conduit then the bypass will be working the next day and there will rarely be a need to have a pulse check every 1 or 2 hours that first night.

On the first postoperative day a compressive dressing is placed from the ball of the foot to just below the knee. Our preference is a soft cast consisting of soft cotton padding (such as Covidien Webril Undercast Padding or BSN Medical Artiflex padding) over the surgical dressing (surgical dressing is sterilely changed if soiled) covered with Coban self adhesive wrap at medium stretch. Once that is in place the patient may be out of bed and may be full weight bearing regardless of where the incisions are located. If the patient is able to ambulate and is stable they can be discharged as early as that first postoperative day. Particularly in patients with strong family support, discharge on postoperative day 1 is not uncommon so long as this expectation is stated preoperatively.

Follow up is weekly to change the soft cast and check the incisions. On the third postoperative week, the sutures are removed, and duplex imaging of the bypass and physiologic testing is performed to confirm what has been obvious clinically and to make sure there is no stenosis in the bypass.

Surgical Approaches

Anterior Tibial Artery

Throughout its length the anterior tibial artery is fairly easy to find. A longitudinal incision slightly anterior to the midpoint between the shin and the fibula is made and carried down through the fascia. Since the vessel bundle sits on or near the interosseous membrane the muscle is preferably split between bundles, although if some of the muscle has to be cut it will not affect the patient's functionality. Once the vessel bundle is identified the anterior 50% of the vessel is freed from the surrounding veins and soft tissue. Circumferential dissection is somewhat difficult and unnecessary, as any sidebranches to a tibial vessel should be done under tourniquet control, and ligation/clamping of the vessel and control of any side branches is unnecessary.

Posterior Tibial and Proximal Two-Thirds of the Peroneal Artery

The approach is nearly identical. A medial calf incision is made approximately 2 cm posterior to the posterior edge of the tibia (if saphenous vein has been harvested use the vein harvest incision) (Fig. 4A). Once the superficial fascia has been opened the gastrocnemius muscle is retracted posteriorly and the soleus muscle is seen. The soleus muscle is attached to the deep posterior compartment fascia. This muscle is taken off the deep fascia by gently applying traction to the muscle and cauterizing the muscle attachments off the fascia. This should be done for the entire length of the incision or about 10 cm of length. For the posterior tibial artery the dissection should be about 2 cm in depth, while for the peroneal artery, more like 3 cm of muscle must be cleared off of the fascia. The deep fascia is then opened longitudinally. The posterior tibial vessel bundle runs with the large and easily identifiable tibial nerve (Fig. 4B). Generally, this bundle is just deep to the deep fascia. Once the posterior tibial artery is identified then 2 to 3 cm of the artery are dissected out on its anterior surface. The peroneal artery is usually in the same plane as the posterior tibial artery but deeper. The only landmarks for the peroneal artery are the accompanying paired veins. If the peroneal artery does not seem like it is in a deep hole through this approach then you are probably dissecting out the posterior tibial artery.

Distal Third of the Peroneal Artery

It is difficult to find and dissect out the distal peroneal artery through a medial approach. The distal artery should be approached from the lateral side of the distal calf. A longitudinal incision is made along the distal fibula with the distal end of the incision ending just proximal to the lateral malleolus. The incision is carried down to the fibula using the cautery and all of the soft tissue is cauterized off of the fibula being careful to stay right on the bone. Bending the tip of the cautery can help dissect the tissue off the deep side of the fibula. An alternative technique is to use a key periosteal elevator although it tends to create a bloodier operative field. Once about 8 to 10 cm of fibular are dissected out the bone is divided at the both ends. Although this can be done with a large bone cutter or Gigli saw I have found that it is much easier to accomplish using a micro sagittal or a micro oscillating saw. Once the bone is out the peroneal artery is usually just deep to the bone. Again, dissection is limited to the anterior 50% of the vessel for several centimeters.

Dorsal Pedal Artery

A 2- to 3-cm-long incision is made on the dorsum of the foot just lateral to the easily palpable extensor hallucis longus tendon. The cautery is used to open the fascia. Frequently the vessel will be more medial or lateral than expected and it is acceptable to lengthen the incision if you are having difficulties finding it. Two things help find the vessel: the first is it is generally a thickened and/or calcified vessel so it is frequently easy to palpate once the dissection is deep to the fascia. The second is that there are usually one or two dorsal venae comitantes veins that are easy to see. Again, dissect out the anterior 50% of the vessel for a couple of centimeters.

Plantar Arteries

Although the mid to distal plantar artery can be found through an incision on the plantar aspect of the instep, in the great majority of cases the more proximal medial or lateral plantar arteries are patent and clearly easier to find. The easiest approach is with a longitudinal incision about a finger-width posterior to the medial malleolus. There is a thick fascia deep to the skin that is opened, and usually the distal posterior tibial veins are obvious once that fascia is opened. Between the veins lurks the included and thickened posterior tibial artery. Follow that distally until the vessel bifurcates and that is your medial and lateral plantar arteries. Choose whichever one was patent on preoperative angiography and dissect out a couple of centimeters on its anterior surface. Of note, there is nothing you can harm that lies between the artery and the skin, so cautery dissection is easy and quick. However, all crossing venous branches should be ligated with 4-0 or smaller suture and divided. Despite the ischemia, these veins can cause annoying bleeding, and even small clips used on the veins end up getting in your way later on when sewing the anastomosis.

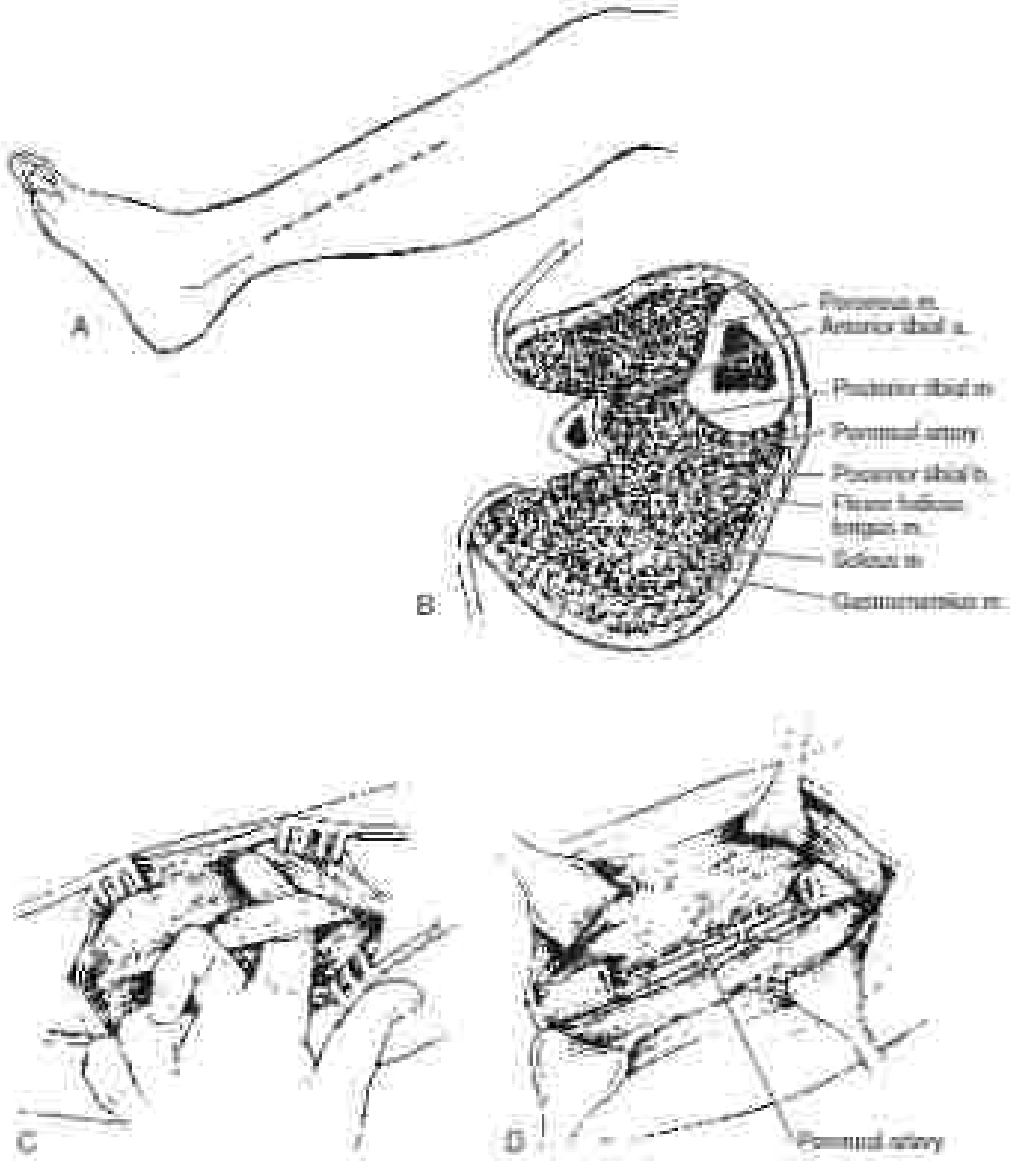


FIG. 4 Lateral exposure of the peroneal artery. (A) The incision is made longitudinally over the fibula. (B) Cross-section view of the lower leg, illustrating the lateral approach with fibula resection. (C) The muscle and fascia are stripped from the fibula, and an 8-cm section is removed. (D) The peroneal artery is exposed and rests to lie on the surface of the tibialis longus muscle. (C-D, pages 1406-1407.)

Tourniquet

A below knee or above knee tourniquet should be used when accessing tibial or pedal vessels. It makes the dissections easier, and damage to the vessels from clamps is avoided. Place a moist lap pad over any incision that the tourniquet is going to cover then place the sterile tourniquet around the leg. I choose the level by using my best guess as to where the calcification is least. Exsanguinate the leg with an Esmarch bandage and inflate the tourniquet to 250 or 300 mm Hg. Proceed with the arteriotomy and the anastomosis.

ENDOVASCULAR TECHNIQUE

All patients should be on aspirin and clopidogrel preprocedure and given full heparin anticoagulation prior to the angiography. Standard multivascular techniques are used; however, bear in mind that working distances tend to be long. Arterial access points include retrograde contralateral common femoral, antegrade ipsilateral common femoral, and retrograde access from the dorsal pedal or tibial anterior or posterior tibial arteries. Standard micropuncture access is obtained from the common femoral artery followed by placement of a 5Fr or 6Fr sheath, preferably with the tip positioned in the proximal superficial femoral artery. For selection of the tibial artery, use an angled glide wire and catheter. Once the catheter is positioned in the appropriate tibial then the glide wire is exchanged for a 300 cm long 0.018 or 0.014 wire. A Quick Cross Support Catheter (Spectranetics, Colorado Springs, CO) helps to pass the wire through occluded vessels, but frequently the wire will pass on its own. Once the wire is beyond the obstruction then a suitably sized balloon (2.5 to 3 mm larger than the measured luminal diameter) is placed over the wire and inflated for 2 to 4 minutes. The results on completion angiography tend to be quite rewarding (Fig. 5). If unable to cross the lesion in an antegrade fashion then the options are surgical bypass or retrograde pedal access. There are several commercially available pedal access kits that may be used or if unavailable a standard micropuncture kit. Under ultrasound guidance, the micropuncture needle is placed into the dorsal pedal artery followed by a 0.018 wire. Only the inner dilator of the micropuncture sheath is placed over the wire and the starter wire exchanged for the 300 cm long 0.018 wire. If the wire

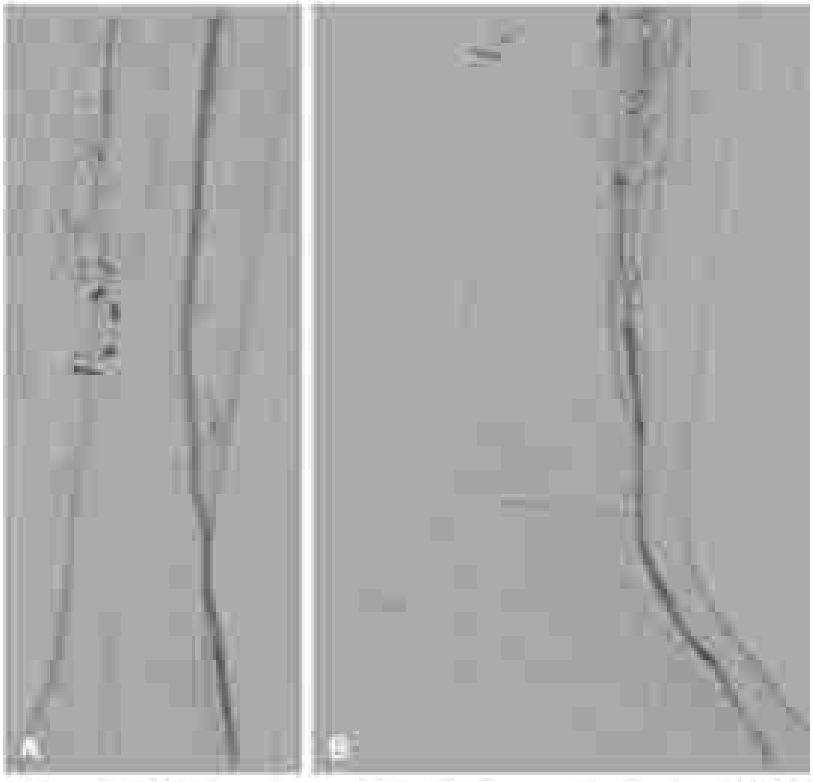


FIG. 5 Digital subtraction imaging of anterior tibial endovascular recanalization. (A) Anteroposterior view of occluded tibial anterior tibial artery before successful angioplasty with surgical clips identifying the level of occlusion. (B) Lateral projection of successful recanalization following angioplasty.

patient easily on further pedal access is necessary. If a microcatheter or Quick Cross Support Catheter will be needed, then a low profile 6Fr sheath is placed. Once the wire is maneuvered into the popliteal artery, s/e femoral access is obtained and the floppy end of the wire in the popliteal artery is snared and pulled out of the femoral sheath. The wire is pulled out far enough until the opposite end nearly disappears. Next, a microcatheter is placed over the wire from the groin to beyond the site of future angioplasty. With the catheter in place the wire is removed and replaced such that the floppy end is in the distal tibial or pedal artery. Now proceed with angioplasty as described above. Once the angioplasty is completed then all catheters and wires are removed. Standard femoral closure is performed, but if there was pedal access we prefer to hold pressure on that site. As a principle, interventions are limited to balloon angioplasty as the available stents are quite short and have an unproven patency rate when used in the tibial vessels. The use of drug coated balloons is becoming an area of increased interest, but experience is limited, and they significantly increase the cost of the procedure.

CONCLUSION

Tibial artery disease with severe ischemia is readily treatable, and every effort should be made to prevent a major amputation. Whether to repair endovascularly or with a surgical bypass depends on the patient's presenting symptoms, location and extent of the disease, and the skill set of the treating physician.

SUGGESTED READING[1]

Conte MS, Pomposelli FB, Society for vascular surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61(3 suppl):2S.

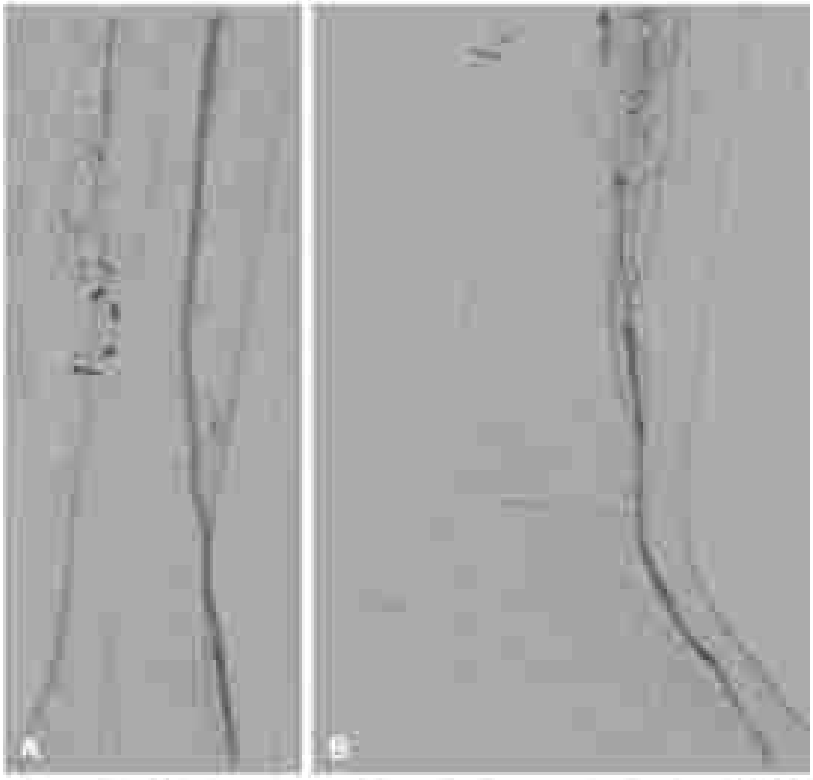
Mills JL. Infrapopliteal disease surgical treatment. In: Sidawy Anton N, Perler Bruce A, eds. *Rutherford's Vascular Surgery, and Endovascular Therapy*. Philadelphia: Elsevier; 2019:1939–1962.

Lepantalo AM, Gillespie JI. Current concepts. Vascular and microvascular disease of the foot in diabetes. implications for foot care. *N Engl J Med*. 2008;359(15):1649.

PROFUNDA FEMORIS RECONSTRUCTION

Luke J. [illegible], MD, PhD, and Addi Z. Rizk, M

The profunda femoris artery (PFA)—also called the deep femoral artery or deep artery of the thigh—serves critical functions in the perfusion of the lower extremity. It provides the majority of blood flow to the thigh muscles, supplemented by the obturator artery and descending branches of the superior and inferior gluteal arteries. In addition, it provides rich collateral flow to the tibial arteries in the setting of significant arterial occlusive disease of the superficial femoral artery (SFA) or popliteal artery and collateral flow to the pelvis in the setting of iliac arterial occlusive disease (Fig. 1). The PFA plays an important role in lower extremity revascularization procedures. It frequently is relatively spared of significant atherosclerosis disease compared with the common femoral and superficial femoral arteries. Thus, it can serve as a bypass target for outflow or as a source vessel for inflow in infrainguinal arterial bypass procedures.



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Luke X. Zhao, MD, PhD, and Addi Z. Rizvi, MD

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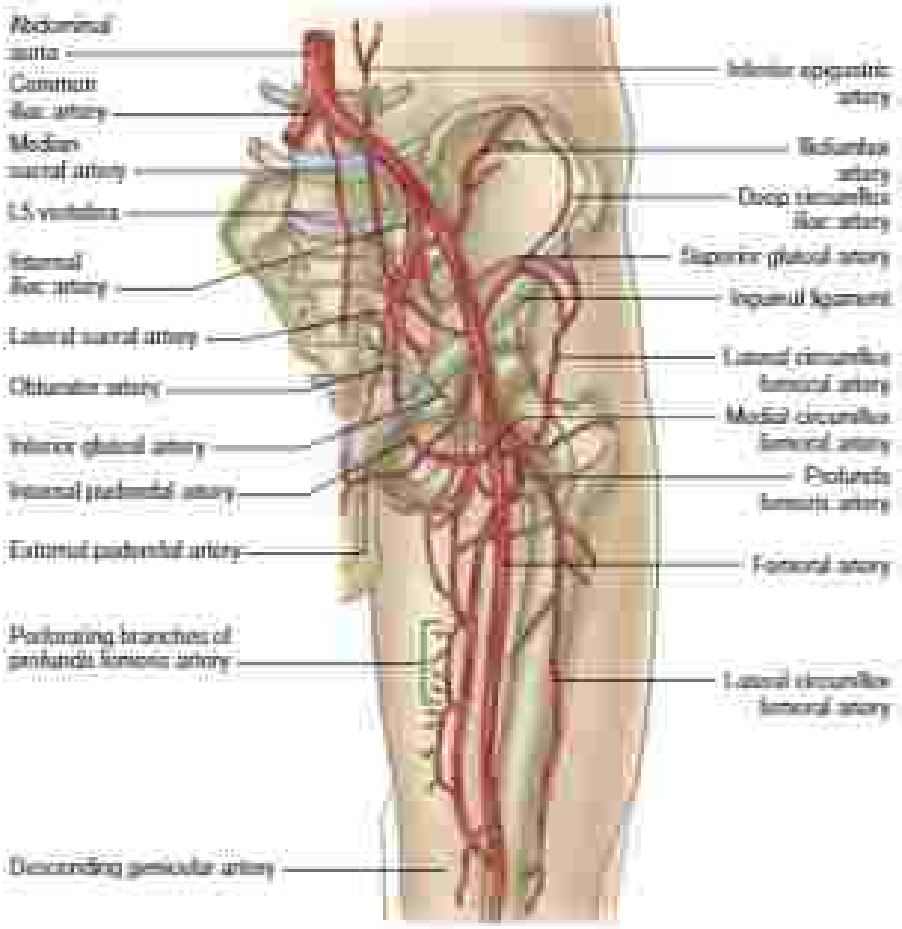

FIG. 1 Vascular anatomy of the thigh depicting the rich collateral network between the internal iliac artery profunda femoris artery and popliteal artery.

A stand-alone profunda artery with open endarterectomy or endovascular angioplasty can also be a main source of leg perfusion in selected patients (Fig. 2).

SURGICAL ANATOMY

Basic Anatomy

The common femoral artery (CFA) bifurcates into the PFA and the SFA 3 to 5 cm inferior to the inguinal ligament. The PFA usually arises from the posterolateral aspect of the CFA and travels in a posterior direction deep to the SFA. A visible change in caliber in the CFA usually marks the femoral bifurcation. An important anatomic relationship in surgical exposure is that the lateral circumflex femoral vein travels between the SFA and PFA. The PFA travels down the thigh close to the femur, running between the pectineus and the adductor longus muscles and on the posterior surface of adductor longus muscle. The PFA typically gives off three branches. The lateral circumflex femoral artery arises from the lateral side of the PFA, passing horizontally between the division of the femoral nerve and posteriorly to the sartorius and rectus femoris muscles. It divides into ascending, transverse, and descending branches. The medial circumflex femoral artery arises from the medial and posterior aspect and winds around the medial side of the femur. The lateral and medial circumflex femoral arteries can originate directly from the CFA 14% to 20% of the time. They can provide collateral branches to pelvic and gluteal vessels. The PFA continues as the perforating arteries, so named because they perforate the tendon of the adductor magnus muscle to reach the posterior and medial compartments of the thigh. The perforating arteries usually have three branches. The first perforating artery passes posteriorly between the pectineus and adductor brevis muscles. The second branch, usually the largest branch, perforates the tendon of the adductor brevis and magnus muscles. The third branch arises below the adductor brevis and pierces the adductor magnus to supply the posterior compartment. These three branches have rich anastomoses with each other.

The PFA is divided into three zones. *Zone 1* (proximal) begins at the origin of the artery and extends to the lateral circumflex femoral artery. *Zone 2* (middle) begins at the lateral circumflex artery and extends to the second perforating branch. *Zone 3* (distal) continues beyond the secondary perforating branch to the inguinal posterior to the adductor longus muscles. The sartorius muscle serves as an important landmark to aid the surgical exposure of zones 1 to 3 of the PFA (Figs. 1, 3, and 4).

Surgical Exposure of the Profunda Femoris Artery

Proximal Zone Exposure

The most common surgical exposure of the PFA is via an upper anterior thigh incision. It allows access to the CFA and the proximal PFA and SFA. The patient is placed in the supine position. Arms may be tucked to facilitate intraoperative angiography. A longitudinal incision that starts approximately two fingerbreadths lateral to the pubic tubercle, directly over the course of the CFA, is created. Palpation of the inguinal ligament and the femoral pulse or direct visualization with duplex ultrasound can demonstrate the course of the CFA and its bifurcation and can be used as an additional guide for incision placement. Even when the CFA is pulseless because of extensive calcification or occlusive disease, it can be localized by anatomic landmarks and is usually palpable as a firm tubular structure when rolled beneath the examiner's fingers. Incision usually begins just proximal

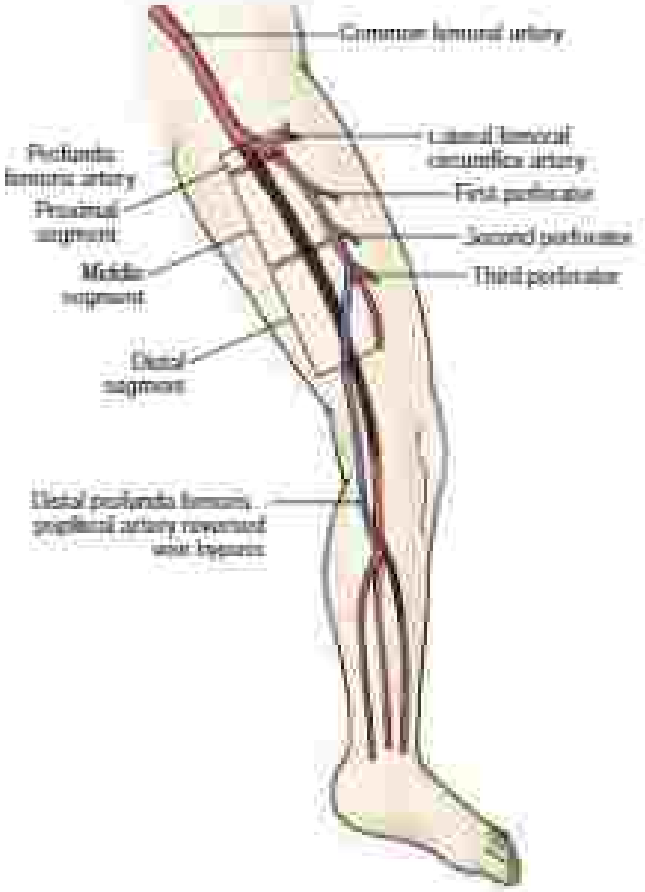

FIG. 2 Schematic of the profunda femoris artery used as an inflow source for an infrainguinal bypass.

to the inguinal crease and is carried distally, inclining slightly toward the medial aspect of the knee. The incision can be extended superiorly or inferiorly to expose the distal external iliac, proximal superficial femoral, or PFA. Alternatively, especially in the obese, a curvilinear incision can be made 1 cm below and parallel to the inguinal ligament, distal to the abdominal pannicular, so as to avoid potential skin maceration and wound complications associated with vertical incisions. Although the proximal superficial femoral and profunda femoris arteries can be exposed via this incision, such a curvilinear or oblique incision limits further distal arterial exposure. It therefore would not be selected if an extensive common and PFA endarterectomy was planned. The dissection is extended more deeply in vertical fashion (even when the initial incision is oblique). It is important to remain directly over the arteries as dissection is carried down deep to the femoral sheath. Encountering muscle structures indicates that one is too medial, whereas encountering underlying iliopsoas muscle, femoral nerve fibers, or lymphatics suggests that dissection is too lateral. Dissection is carried directly along the CIA both superiorly and distally. Proximal dissection along the artery allows exposure of the entire CIA, with the cephalad extent being the inguinal ligament. Caution is necessary when dissecting the CFA segment at or beneath the inguinal ligament. There is usually a vein beneath the inguinal ligament that crosses directly anteriorly over the CFA, making the site of entry or exit of sheaths at the inadvertent transection produces troublesome bleeding. The medial and lateral femoral circumflex arteries are often near the level of the inguinal ligament and should be identified, spared, and controlled with small Silastic vessel loops. As the dissection proceeds distally, an abrupt change in caliber marks the femoral bifurcation and indicates the origin of the

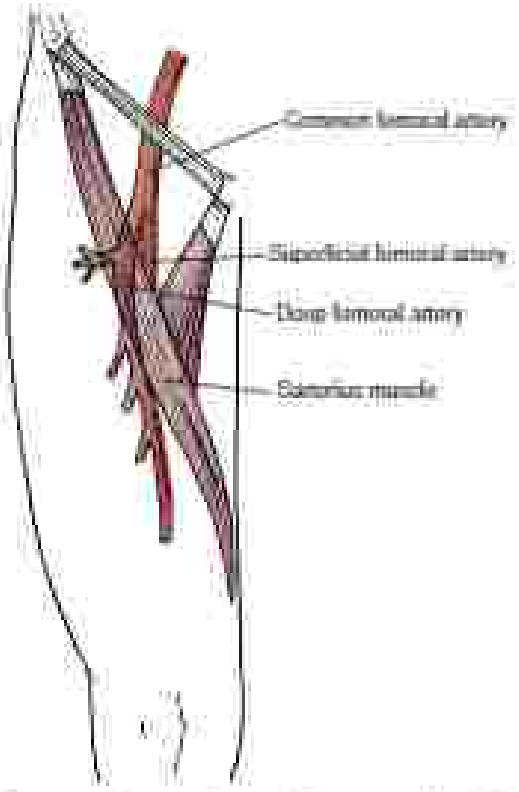

FIG. 3 The course of the circumflex vessels is represented in relation to the profunda femoris artery.

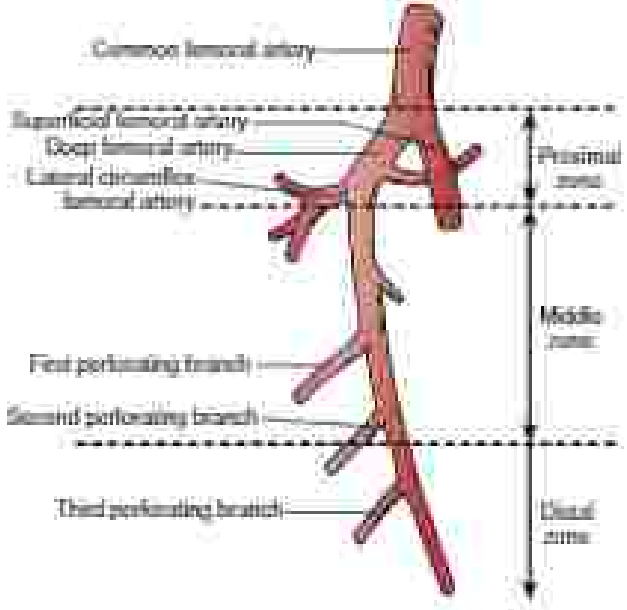

FIG. 4 The branches and zones of the profunda femoris artery.

PFA, usually oriented more deeply and posteriorly. After encircling the common and superficial femoral arteries with Silastic vessel loops, gentle upward traction on either of these loops can help to bring the PFA into view. The lateral circumflex femoral vein may cross under the SFA and course over the PFA near its origin. Division of this vein allows one to mobilize and further expose the first segment of the PFA, which is typically necessary when performing a profunda endarterectomy (see 4, Fig. 5).

Middle and Distal Segments of Profunda Femoris Artery Exposure

The middle (zone 2) and distal (zone 3) segments of the PFA can be exposed with either anterolateral or anteromedial incisions. This exposure for the PFA is useful regardless of whether the PFA is an inflow vessel or outflow target vessel, and the sole goal is to expose the PFA in virgin territory. These two exposures are common in the setting of multiple prior proximal groin exposures, infection in the groin region, or prior irradiation to the groin region. The skin incision is placed along either the medial border (anteromedial approach) or the lateral border (anterolateral approach) of the sartorius muscle. Carry the dissection deeply through the subcutaneous tissue and fascia, passing alongside the lateral or medial edge of the sartorius muscle to the deep layer, respectively. Once you are deep behind the sartorius muscle, mobilize and retract the sartorius muscle laterally or medially, depending on approach. Continue the dissection deeply, passing lateral to the superficial femoral vessels and accompanying nerve, in the valley formed between the adductor longus muscle (medially) and vastus medialis (laterally). The PFA and the profunda femoris vein reside directly underneath. Next, one dissects between the adductor longus and vastus medialis muscles to expose the PFA. It may be necessary to ligate and divide the coming venous tributaries to isolate and control the middle and distal segments of the artery. Alternatively, an incision can be made between the adductor longus (anteriorly) and gracilis muscle (posteromedially). Dissect between the adductor longus and adductor magnus muscles to approach the PFA medially from the distal thigh (Figs. 6, 7, and 8).

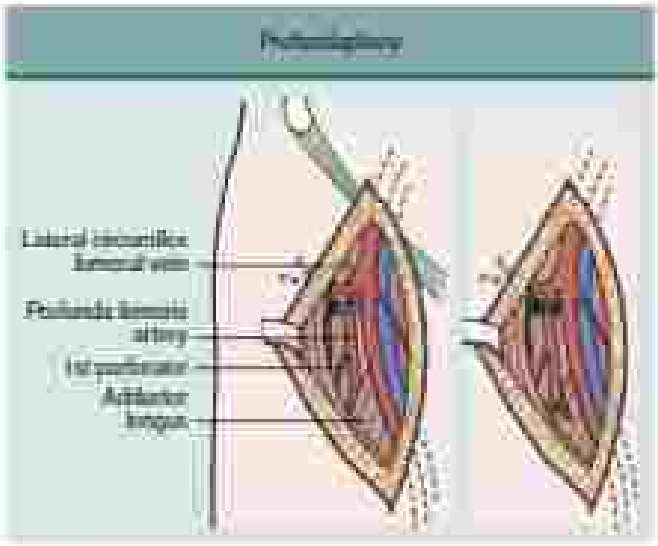

FIG. 5 Standard anterior approach to the profunda femoris artery.

Posterior Medial Approach

The posterior medial approach is also used in the setting of prior groin surgery, groin infection, or a previously irradiated groin. The middle and distal zones of the PFA can be exposed via this incision, and it is a useful exposure in the setting of an ilio-femoral-distal bypass if the PFA is the outflow target vessel. With the knee flexed and the hip rotated externally, a medial thigh incision is placed. The fascia is incised, and the dissection is continued along the posterior surface of the adductor longus muscle and anterior to the adductor brevis muscle. At the deep aspect of this exposure before encountering the femur, the PFA should be identified and isolated (Figs. 6 and 8).

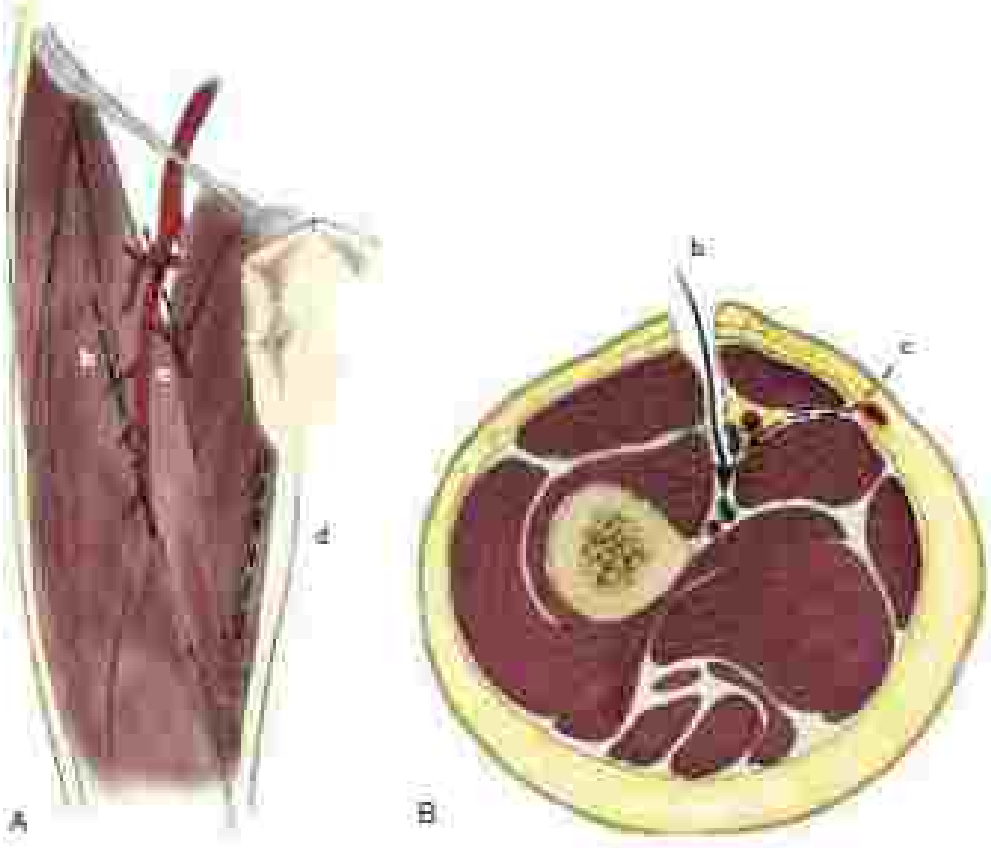

FIG. 6 (A) Incisions to expose the middle and distal profunda femoris artery. b, Anterolateral approach; c, anteromedial approach; d, posteromedial approach. (B) Cross section of the right thigh. b, Anterolateral approach; c, anteromedial approach.

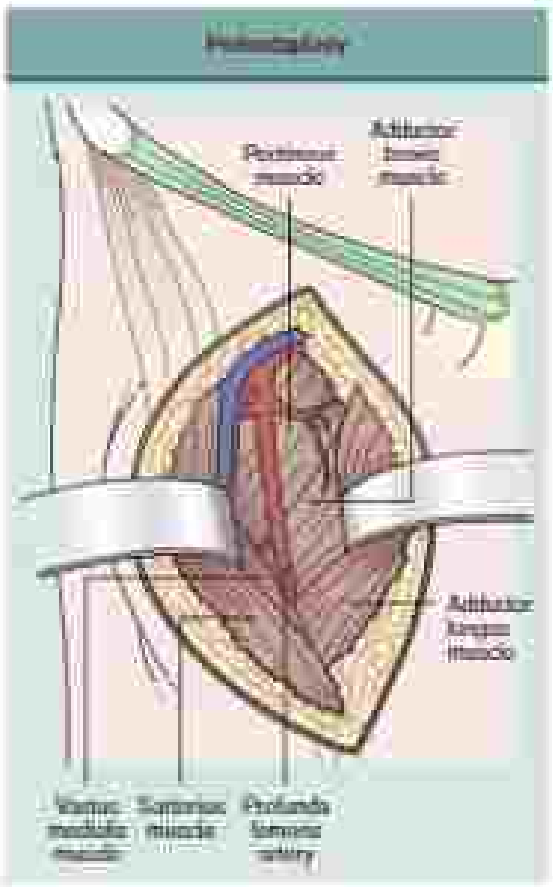

FIG. 7 Schematic depicting a view of the profunda femoris artery through the anteromedial approach.

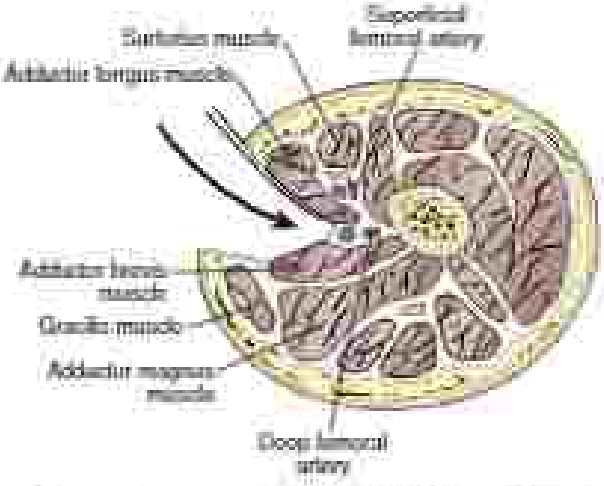

FIG. 8 Schematic depicting posteromedial approach to the left profunda femoris artery.

PROFUNDA FEMORIS ARTERY RECONSTRUCTION

Bypass

Often the PFA is used as a source of inflow, particularly in the setting of a distal bypass if there is inadequate vein length or if exposure of the CFA is challenging (i.e., multiple prior groin dissections, infection, or prior irradiation; Fig. 7). The PFA is an excellent inflow target vessel and is often used in the setting of an aortofemoral, axillofemoral, or femorofemoral bypass. Often, when utilizing the PFA as an inflow target, the CFA and PFA will require an endarterectomy, and the hood of the bypass is sewn to both the CFA and the proximal PFA. Once the PFA is exposed, proximal and distal vessels and branches are occluded with small vascular clamps or Silastic vessel loops, the patient is systemically heparinized, and a longitudinal arteriotomy is created extending into the PFA. Regardless of whether the PFA is the inflow or outflow vessel, the hood of the graft can be anastomosed to the profunda in a standard end-to-side fashion using fine polypropylene sutures. If there is significant atherosclerotic disease involving the PFA, it may be necessary to perform a concomitant extended profunda endarterectomy. After an extended endarterectomy, particularly if the PFA is the inflow vessel, it may be necessary to close the arteriotomy with a patch, and the graft then can be sewn onto the patch.

Isolated Profundaplasty

The PFA is essential for maintaining limb viability when severe occlusive arterial disease affects the extremity. It provides the primary blood supply to the tissues of the thigh and is also the most important collateral vessel for bypassing an obstructed or occluded SFA. Historically, significant occlusive disease of the CFA bifurcation and PFA has been treated surgically with low risk and sustained patency and clinical benefit. However, atherosclerosis of the PFA is usually focal, preferentially involving the origin and the very proximal portion of the artery in the majority of limbs; this is essential to consider during strategic planning of an initial or proximal SFA intervention. An isolated profundaplasty is indicated when the PFA is the only vessel perfusing the thigh directly and the distal leg via genicular collaterals. The PFA also can prove useful in removal of an infected prosthetic graft from the groin, in salvage of a nonhealing above-knee or below-knee amputation, and as primary treatment for critical limb ischemia when other surgical or endovascular options are limited.

The success of an isolated profundaplasty in improvement of distal flow can be estimated with the profunda popliteal collateral index (PPCI).

$$PPCI = \frac{(AKSP - BKSP)}{BKSP}$$

where AKSP is above-knee segment pressure and BKSP is below-knee segment pressure. A PPCI greater than 0.5 indicates poor collateral development and likely failure of a stand-alone profundaplasty. A PPCI less than 0.19 indicates significant collateral formation and likely a good response to stand-alone profundaplasty. However, it is generally accepted that profundaplasty alone without concomitant distal bypass is not sufficient to provide palpable in-line flow to the limb with significant tissue loss.

A profundaplasty typically is performed with a CFA endarterectomy. After systemic anticoagulation, the femoral vessels are occluded. A longitudinal arteriotomy is initiated in the mid-CFA and extends proximally toward the external iliac artery and distally moving toward the profunda. A deep medial plane is entered with a plaque elevator proximally in the CFA. The plaque is divided, and the endarterectomy is continued into the PFA to the distal extent of the case. Sometimes, eversion is necessary to terminate the PFA plaque with a thin, feathered endpoint in the PFA. Any loose flap is trimmed sharply or tacked down with 7-0 tacking sutures. The arteriotomy is closed with a patch fashioned from bovine pericardium, Dacron, autogenous vein, or a piece of endarterectomized occluded SFA segment. The latter two are the preferred patch materials in the setting of an infected field (Fig. 9).

ENDOVASCULAR INTERVENTION

The PFA disease also can be treated with endovascular interventions. This serves as a viable option for patients who are poor surgical candidates because of severe systemic comorbidities or prohibitive

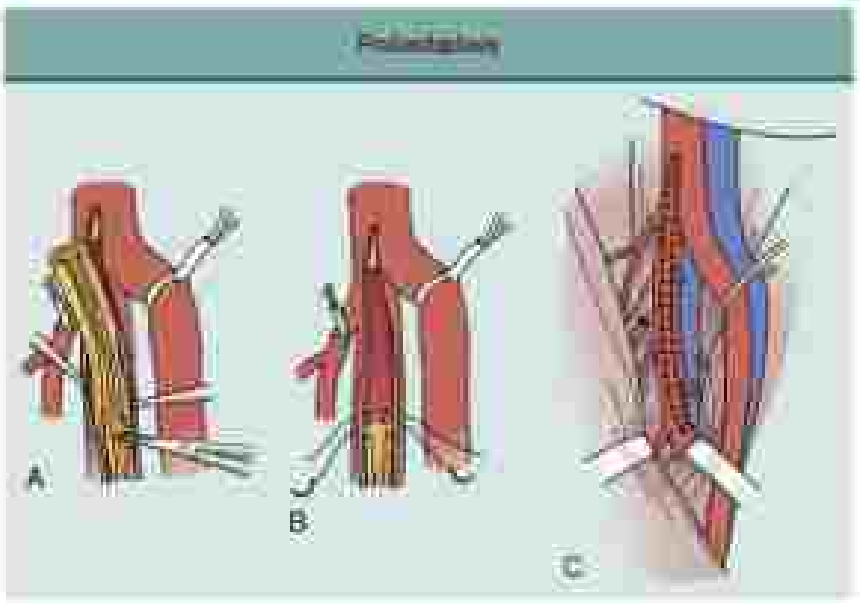

FIG. 9 (A) Endarterectomy of the profunda femoris artery. (B) Patch sutured in place. (C) With patch angioplasty.

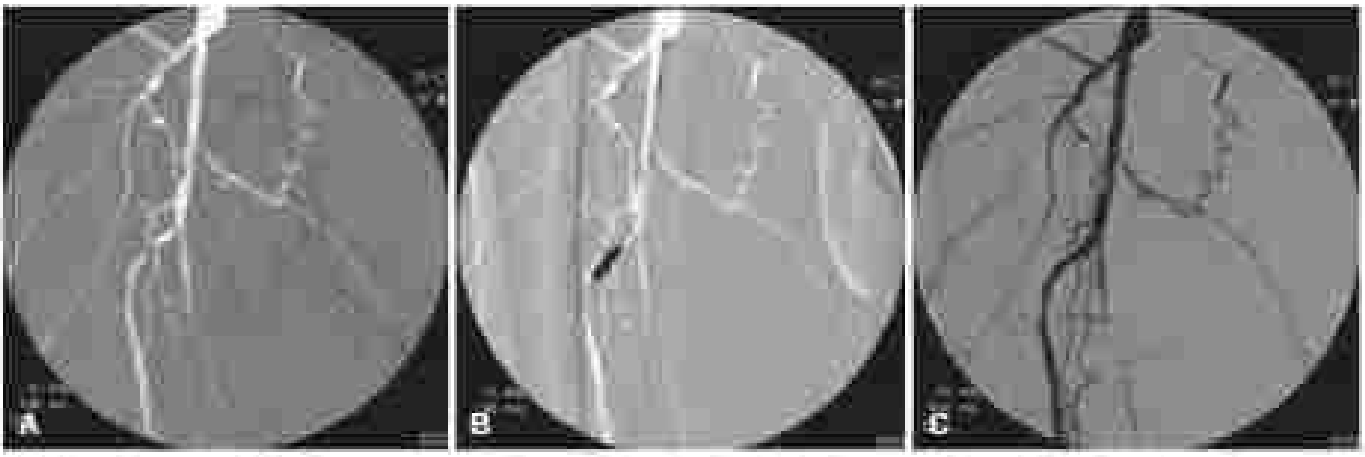

FIG. 10 Arteriograms. (A) Profunda femoris artery stenosis. (B) Angioplasty of profunda femoris artery stenosis. (C) Profunda femoris artery after angioplasty.

challenges to open surgical reconstruction resulting from a hostile groin. It is also indicated as a secondary intervention to maintain the assisted patency of a bypass graft when the PFA was used either as a bypass target or as an inflow source. The access of the PFA for endovascular intervention can be approached from a contralateral retrograde common femoral access in an "up and over" the aortic bifurcation fashion. Alternatively, it can be approached via a retrograde brachial access. The indication for brachial access includes contralateral iliofemoral occlusion, history of aortobifemoral bypass, or presence of a modular bifurcated endograft, as crossing in an up and over technique may be challenging in the latter two settings. The left brachial artery access generally is preferred because it allows access to either lower extremity without crossing the aortic arch. The PFA is best visualized with the imaging intensifier set at an angle of 30 degrees to the ipsilateral oblique view. This offers the best splaying of PFA from the CFA and SFA on angiography. Once the PFA is accessed with a guidewire, balloon angioplasty with or without stenting can be performed. Caution should be used when performing balloon angioplasty at the PFA ostium if the proximal SFA is still open. There is risk of embolization or occlusion of the SFA from the balloon angioplasty. Sometimes, it is worthwhile to place a "buddy wire" into the SFA to maintain access to the SFA for rescue interventions if any of these events occur. The value of PFA angioplasty was demonstrated in a small case series in which PFA angioplasty was the primary treatment in patients with critical limb ischemia and technically demanding open profunda reconstructions, and in patients with expectation strong ischemia at risk of limb disarticulation (Fig. 10).

CONCLUSIONS

The PFA plays a crucial role in maintaining the viability of the lower extremity. It is a versatile vessel that can serve as an outflow target for supragenicular bypass and as an inflow source for infrainguinal bypass. Dedicated profunda angioplasty by either an open surgical or an endovascular approach also may be useful in improving lower extremity perfusion. For vascular specialists involved in lower extremity revascularization, it is a critical skill to possess to preserving the patency of the PFA and to utilize in lower extremity vascular reconstruction procedures.

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Popliteal and Femoral Artery Aneurysm

Dawn [illegible] Sang, MD, MHS, and Elliot L. Chaikof, MD, PhD

Although less common than aneurysm of the aorta, femoral and popliteal aneurysms are a diverse and challenging clinical entity with the potential for substantial morbidity and mortality resulting from limb-threatening complications. To deliver optimal care to the patient, the surgeon must consider the etiology, anatomy, distal perfusion, and array of therapeutic options available for treatment of these aneurysms. This chapter discusses both open and endovascular approaches to femoral and popliteal aneurysms, as well as important considerations for the selection of the most appropriate option for an individual patient.

FEMORAL ANEURYSM

True aneurysms and pseudoaneurysms of the femoral artery are the most common type of peripheral aneurysm encountered. Femoral artery aneurysms can be further classified into true degenerative aneurysms, pseudoaneurysms, including iatrogenic, traumatic, or paranastomotic, and infected or mycotic aneurysms. Treatment options vary significantly depending on etiology, presence of infection, and location of the aneurysm and thus the diagnosis, management, and procedural concerns for each subtype will be discussed separately.

Degenerative Femoral Artery Aneurysm

True degenerative aneurysms of the femoral artery are rare. The common femoral artery is the most likely location while isolated aneurysms in the distal superficial femoral artery or profunda femoris artery are less frequent. Population based studies in 1990s estimated a prevalence of femoral aneurysm of 5 per 100,000 in the United States with a heavy male predominance. An important consideration in the patient with a femoral aneurysm is the synchronous presence of a contralateral femoral aneurysm (24%–30%), abdominal aortic aneurysm (50%–90%), or popliteal aneurysm (27%–40%). A large aortic aneurysm should be addressed before, or in conjunction with, an asymptomatic peripheral aneurysm. Approximately one half of patients are asymptomatic at time of the diagnosis of a peripheral aneurysm with symptomatic patients presenting with a palpable mass, pain, or distal ischemia. Ultrasonography cross sectional imaging such as computed tomography (CT) or magnetic resonance imaging can be used to define the size of the aneurysm and to screen for the presence of other aneurysms.

Indication for Repair

Patients presenting with symptoms from local compression or distal ischemia should undergo repair. In the presence of an asymptomatic aneurysm, the goal is to prevent distal ischemia resulting from thrombosis or embolization or, rarely, rupture. Historical series suggested that a femoral aneurysm larger than 2.5 cm should be repaired but more recent retrospective series suggest that a femoral aneurysm smaller than 3.5 cm without intraluminal thrombus is unlikely to present with rupture or embolism. Current consensus guidelines recommend that 3.0 cm be adopted as a threshold for repair. While perioperative mortality for open femoral aneurysm repair is 1%, morbidity may be observed in 10% to 20% of patients.

Approach

Most graft repair of femoral aneurysm is not a preferred approach because of the risk of graft fracture resulting from hip flexion and the preference to avoid occluding the orifice of the profunda femoris artery. In the setting of distal embolization, thromboembolectomy or pharmacomechanical thrombolysis may be used initially to restore distal perfusion.

Open surgical repair of a femoral artery aneurysm requires reconstruction with an interpositional vascular graft (Fig 1). A longitudinal incision is made over the femoral artery with dissection to the retroperitoneal proximal common femoral or distal external iliac artery. Exposure of the distal external iliac artery will require division of the inguinal ligament or a retroperitoneal approach via an oblique incision two to three fingers breadths above the inguinal ligament. Exposure of the superficial femoral and profunda femoris arteries should also be obtained. If dissection of the profunda femoris artery proves difficult because of the size or location of the aneurysm, control of the profunda femoris can be obtained by balloon occlusion using a 3Fr Fogarty catheter positioned 1 cm distal to the orifice after the aneurysm is opened (Fig 2).

Once proximal and distal control has been obtained, the patient is heparinized, vessels are occluded, the sac is opened, and thrombus removed. If the aneurysm is confined to the common femoral artery without involvement of the superficial femoral or profunda femoris artery, the vessel can be reconstructed using an 8- or 10-mm interposition polytetrafluoroethylene (PTFE) or Dacron graft. If the aneurysm is more extensive and involves the superficial femoral or profunda femoris artery, interposition grafting should be performed with either reimplantation or use of a bump graft to the profunda femoris artery. If the profunda femoris artery cannot be revascularized, distal perfusion should be ensured. In the setting of concomitant occlusive disease, femoral-popliteal or femoral-tibial bypass may be required.

Traumatic Femoral Artery Pseudoaneurysm

The incidence of femoral artery pseudoaneurysm following catheterization varies from 0.2% to 1.8%. Risk factors include large sheath size, anticoagulation, obesity, and a high arterial puncture site. Prevention of a pseudoaneurysm is best achieved by routine use of ultrasound-guided vascular access. A femoral pseudoaneurysm may present as a palpable mass, although physical exam can be limited by body habitus

Suggested Readings

Sonesta J.A., Tawes R., Reinhard S.M., et al. Profunda femoris-to-femoral bypass: a guide to successful limb salvage. *Arch Surg*. 1990;125:1330–1332.

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Daniel J. Wittig, MD, MHS, and Elliot L. Chaikof, MD, PhD

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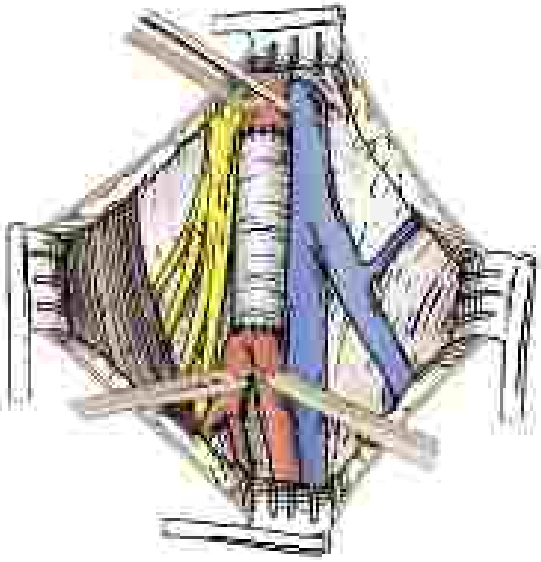

FIG. 9 Interposition graft repair of a femoral artery anastomotic pseudoaneurysm. (From Cronenwett JL, Johnston KW, eds. Rutherford's Vascular Surgery. 7th ed. Philadelphia, PA: Saunders; 2007.)

or hematoma. Duplex ultrasound is the primary means of diagnosis, which allows evaluation of pseudoaneurysm size, neck dimension, and evaluation for the presence of a concomitant arteriovenous fistula.

Indication for Intervention

In the absence of compressive symptoms, including pain, skin blisters, or symptoms of femoral nerve entrapment, small pseudoaneurysms (<1 cm) will often thrombose spontaneously or with ultrasound guided compression, if the patient is not systemically anticoagulated. Follow up ultrasound should be conducted within 2 weeks to confirm thrombosis. A pseudoaneurysm that is larger than 2 cm, symptomatic, or persistent should be treated.

Approach

Ultrasound guided thrombin injection into the pseudoaneurysm sac has become the preferred method of treatment, provided there is a narrow, long neck between the pseudoaneurysm and the femoral artery to minimize the risk of thrombin injection reflux into the artery. Ultrasound guided compression alone, in the absence of thrombin injection, results in option, but is often less well tolerated because of patient discomfort. Therapy typically consists of three successive 20 minute compressions and has a lower success rate than thrombin injection. For thrombin injections, a two-syringe method can be used with one syringe containing 3 mL of saline and the other containing a thrombin solution (1000 U/mL saline) connected using a three-way stop-cock (Fig. 7). Visualization of the tip of the needle can be improved with the use of an echogenic needle. The pseudoaneurysm is punctured and a test injection with saline is visualized on ultrasound. This serves a dual purpose to both confirm needle placement within the pseudoaneurysm, as well as to minimize the risk of accidental injection of thrombin into the native artery, which can result in thrombosis or distal emboli. Small amounts of thrombin are then injected until cessation of flow within the sac is confirmed. If there is a wide neck and the patient is a prohibitive risk for open repair, an intraarterial balloon may be inserted from the contralateral femoral artery and inflated to occlude the pseudoaneurysm during thrombin injection. A follow up ultrasound is performed 24 hours after injection to confirm thrombosis.

Open surgical repair is indicated for a pseudoaneurysm that is expanding, fails nonoperative treatment, displays unsuitable anatomy for thrombin injection, or associated with a painful hematoma, skin breakdown, or symptoms suggestive of femoral nerve entrapment.

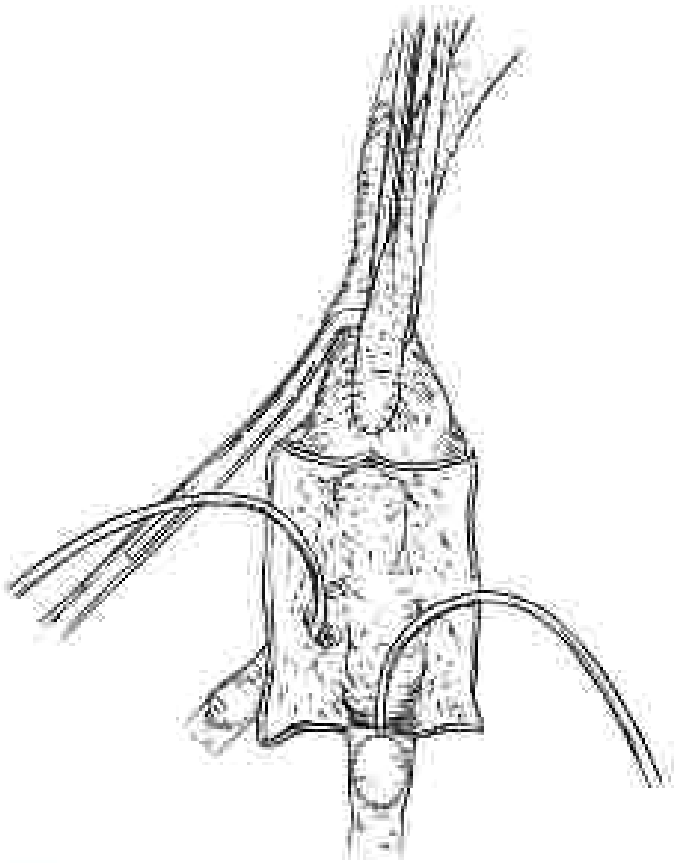

FIG. 8 Distal control of the profunda and superficial femoral arteries can be achieved from within the aneurysm using occluding balloon catheters after the aneurysm is opened. (From Cronenwett JL, Johnston KW, eds. Rutherford's Vascular Surgery and Endovascular Therapy. 8th ed. Philadelphia, PA: Saunders; 2014.)

A longitudinal groin incision over the aneurysm is performed and proximal and distal control achieved. If the sac is inadvertently entered, bleeding is controlled by digital pressure until proximal control is gained, and the puncture site repaired with a 5-0 Prolene suture. The hematoma is evacuated and a 7 mm Jackson Pratt drain placed in the wound.

Anastomotic Femoral Artery Aneurysm

The femoral artery is the most common location of an anastomotic aneurysm associated with an autogenous bypass graft, commonly presenting years after the initial operation as a pulsatile groin mass. An anastomotic pseudoaneurysm may occur from the suture line disruption, infection, or arterial wall degeneration.

Indication for Repair

Operative repair of an anastomotic femoral pseudoaneurysm is recommended if greater than 2.0 cm in diameter or if infection is suspected by the presence of a draining sinus, erythema, or perigraft fluid. CT imaging can assess for the presence of an additional anastomotic pseudoaneurysm at the aortic anastomosis or in contralateral groin. Graft infection should be suspected if exploration reveals a poorly incorporated graft or perigraft fluid. Bacterial cultures should be sent and consideration given to extraanatomic reconstruction or use of an autologous femoral vein or a cryopreserved allograft.

Approach

No Infected Anastomotic Pseudoaneurysm

In the absence of infection, exposure of the nonfemoral graft limb, common femoral, superficial femoral, and profunda femoris arteries

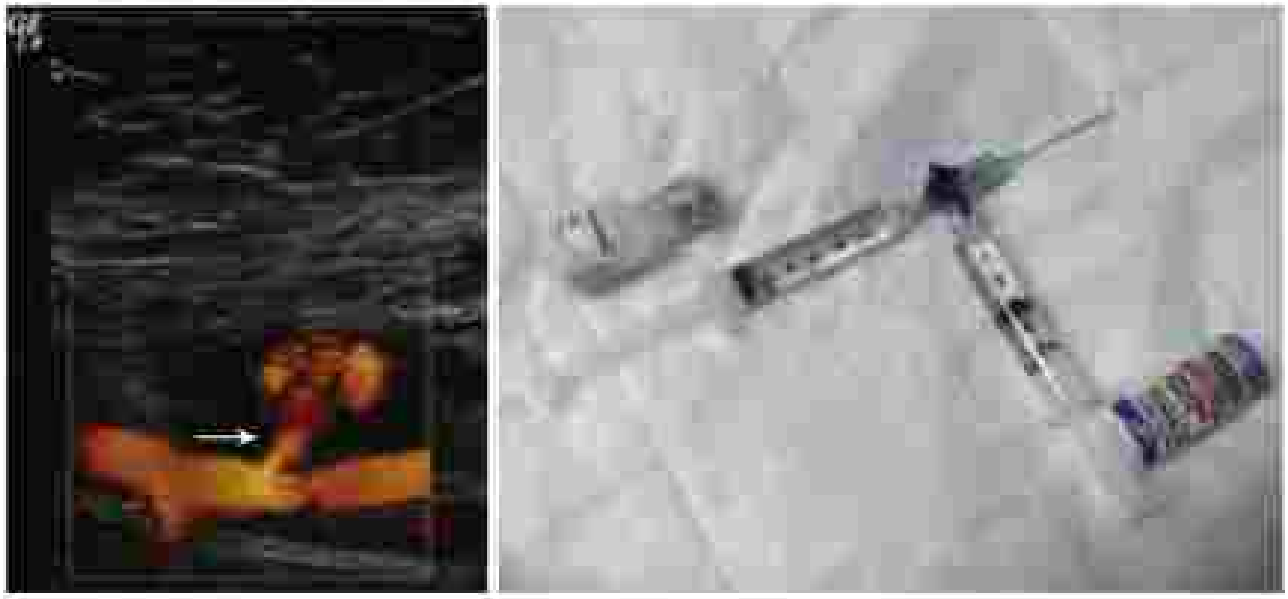

FIG. 3 Duplex ultrasound demonstrating femoral pseudoaneurysm with neck indicated by the arrow. Two syringes with saline and thrombin connected with three-way stopcock used for injection of pseudoaneurysm. [illegible]

should be performed. An ancillary proximal control of the graft limb can be achieved by dividing the inguinal ligament or retroperitoneally via an oblique suprainguinal incision. In a heavily scarred operative field, control of the superficial femoral and profunda femoris arteries can be achieved using Fogarty balloon catheters from within the aneurysm (Fig. 2). Following heparinization, the aneurysm sac is opened, thrombus removed, distal graft resected, and reconstruction performed using an 8-mm interposition PTFE graft, with revascularization of the superficial femoral and profunda femoris arteries.

Infected Femoral Anastomotic Pseudoaneurysm

Graft infection requires removal of the infected graft with restoration of distal perfusion. If infection is suspected, blood cultures should be obtained and empiric antibiotics initiated. CT imaging can help to determine whether infection is limited to the groin or involves the proximal graft or contralateral limb. If infection is confined to the distal limb, the clean portion of the procedure is conducted initially. Proximal control of the uninfected portion of the limb is achieved through a retroperitoneal approach via an oblique incision, extending lateral to the rectus 2 cm above the inguinal ligament, in a point halfway between the distal margin and iliac crest to the midaxillary line. The proximal uninfected graft limb is exposed, avoiding injury to the ureter, and divided with a small margin sent for culture. The distal end of the graft is oversewn, mobilized from surrounding tissues, and displaced distally. Extraanatomic options for revascularization include an iliorenal bypass, an axillofemoral bypass to the superficial femoral artery, or an axillopopliteal bypass. An iliorenal bypass requires creating a tunnel through the medial aspect of the obturator foramen avoiding injury to the obturator artery and nerve, to the superficial femoral artery in the mid-thigh. An end-to-end anastomosis is created using an externally supported PTFE interposition graft between the end of the uninfected graft limb and an end-to-side anastomosis to the superficial femoral artery. Incisions are closed in occlusive sheets using plastic, and the contaminated portion of the procedure performed. A groin incision is made, vascular control obtained, the infected graft removed, and intraoperative cultures sent. Infected tissues should be debrided and the femoral artery defect closed with a vein patch to preserve flow in the profunda femoris artery. A sartorius muscle flap should be mobilized to cover the femoral vessel.

Primary Infected Femoral Artery Aneurysm

A primary infection of the femoral artery must often occur because of a contaminated percutaneous closure system or intravenous drug use. Patients may present with an enlarging pulsatile mass, sepsis, distal emboli, or hemorrhage. Blood cultures are obtained and empiric antibiotics initiated. Goals of the operation include removal of infected tissue, repair of the femoral artery, and restoration of distal perfusion. Options for repair depend upon the extent of local arterial destruction. If limited, a vein patch angioplasty may be feasible, but more extensive arterial destruction may require reconstruction with autologous femoral vein, cryopreserved vein, or an extraanatomic bypass. An obturator bypass may be preferable when the aneurysm is secondary to intravenous drug injection to minimize the likelihood of future needle sticks. Cultures should be obtained and antibiotics continued at least 6 weeks postoperatively. A sartorius muscle flap should be used to provide direct coverage of the arterial repair.

POPLITEAL ANEURYSM

The majority of popliteal aneurysms are true degenerative aneurysms, occur predominantly in men with an estimated incidence of 7 per 100,000 men and only 1 per 100,000 among women. Approximately one-half of patients have bilateral popliteal aneurysms and 30% to 40% have synchronous abdominal aortic aneurysms, which occur in a higher proportion of patients if bilateral popliteal aneurysms are present. Rupture is rare, whereas distal ischemia from thrombosis or embolization is the most common cause of morbidity. Duplex ultrasound, CT, and magnetic resonance imaging are effective methods for diagnosis and establishing size. In contrast to a femoral aneurysm, endovascular treatment of a popliteal aneurysm with a self-expanding covered stent graft may be feasible in many patients. Important considerations to determine whether an endovascular or surgical approach is most appropriate include size of the aneurysm, presence of intraluminal thrombus, compressive symptoms, patency of runoff vessels, and presence of distal ischemia.

Indication for Repair

Asymptomatic aneurysms that are 2 cm or larger in size should be repaired in the healthy adult. All symptomatic popliteal aneurysms should be repaired.

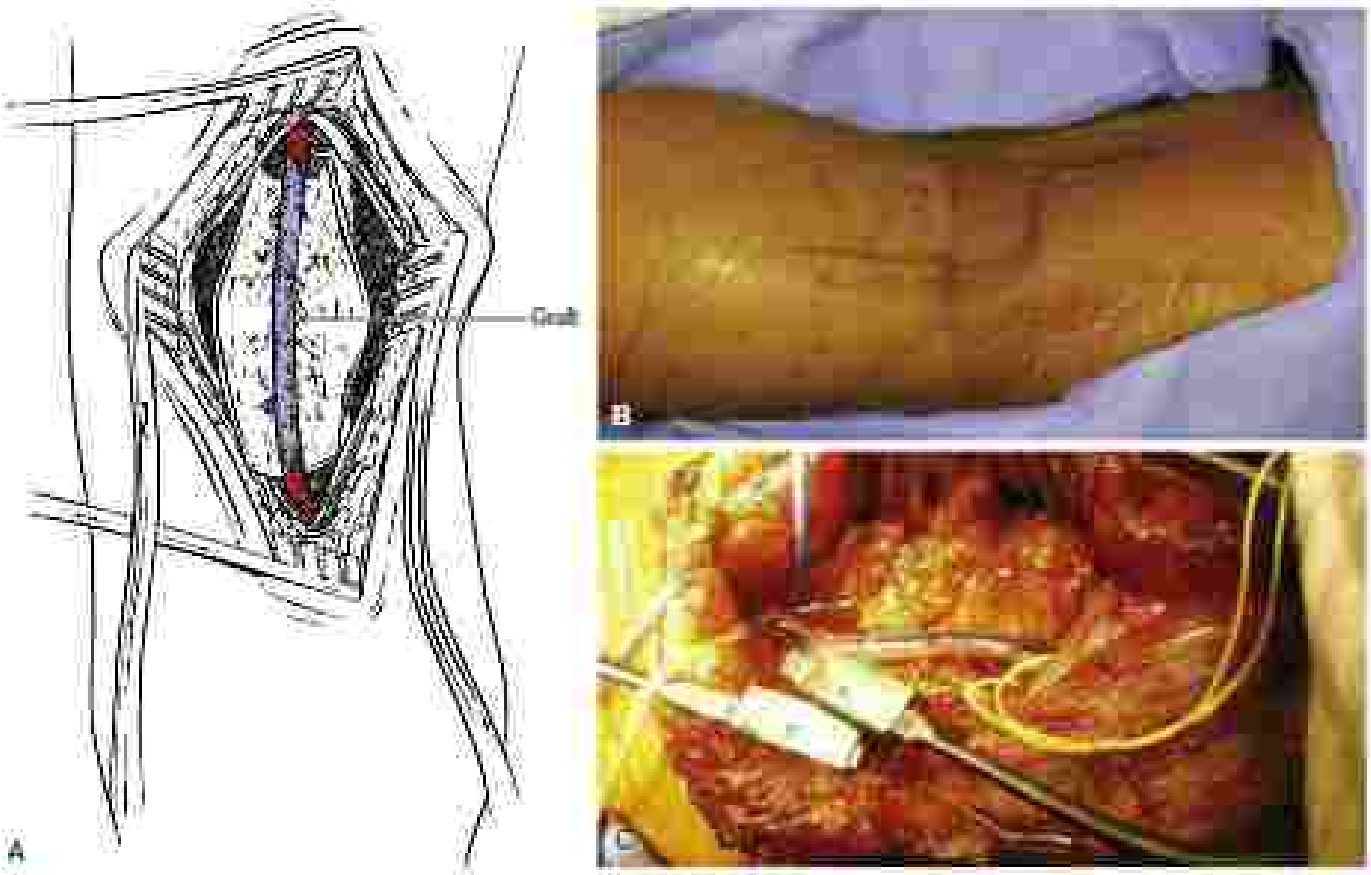

FIG. 4 Posterior approach to popliteal aneurysm repair. (A) Saphenous vein interposition graft. (B) Lazy S incision is used with superior portion beginning medially and extending laterally over fibular crease. (C) Completed saphenous bypass interposition graft. (From Chaikof EL, Lumsden A, Veith FJ. Vascular Surgery and Endovascular Therapy. Anatomy and Technique. Philadelphia: Elsevier; 2014.)

Open Surgical or Endovascular Repair

Open repair consists of revascularization from the distal superficial femoral or proximal popliteal artery to the below knee popliteal or tibioperoneal trunk using a reversed saphenous vein or synthetic bypass graft. A medial surgical approach is common, but a posterior approach is suitable for a localized aneurysm without significant proximal extent. The extent of dissection of a popliteal aneurysm should be minimized to avoid injury of adjacent popliteal veins. Ideally a popliteal aneurysm should be opened and particulate collateral vessels oversewn from within the aneurysm sac. Exclusion of an aneurysm sac alone may be appropriate to select patients without compressive symptoms, but subsequent aneurysm expansion may occur due to collateral vessels. Perioperative mortality associated with open surgical repair is 1% and primary graft patency approximately 90% and 80% at 1 and 5 years, respectively. Endovascular treatment is most suitable for more proximal popliteal or distal superficial femoral artery aneurysms that do not cross the knee or in the patient at high risk for surgical repair because of medical comorbidities. Anatomic criteria dictate proximal and distal landing zones of at least 15 mm in length to achieve an adequate seal for the stent graft. Utilizing antiplatelet treatment is recommended with primary stent graft patency of 80% and 70% at 1 and 5 years, respectively. A recent meta-analysis of surgical and endovascular repair noted that an endovascular approach was associated with a shorter hospital length of stay, fewer wound complications, but led to a greater need for subsequent reintervention.

Approach: Repair in the Absence of Acute Thrombosis

Preoperative vein mapping and a lower extremity CT angiogram or conventional arteriogram are conducted in preparation for repair. Two anatomic approaches are commonly used for surgical repair. The medial approach is preferred for those aneurysms extending beyond the popliteal fossa. The knee is bent and the leg externally rotated. The saphenous vein is harvested and proximal and distal control obtained. A tunnel is created from the above to below the knee popliteal fossa. After heparinization, the aneurysm is opened, arterial branches ligated from within the aneurysm sac, and bypass performed with saphenous vein or a prosthetic graft. If the aneurysm is occluded to avoid extensive dissection and division of the medial musculotendinous attachments of the knee, the artery is suture ligated or divided above and below the aneurysm, prior to revascularization. Following operation, graft surveillance includes quarterly Duplex ultrasound during the first 2 years with annual Duplex imaging thereafter.

The posterior approach is advantageous for an aneurysm confined to the popliteal space. The patient is positioned prone and a lazy S incision is performed with the lateral portion across the posterior fossa crease (Fig. 4). Access to the artery is direct and the popliteal vein can be retracted laterally. Proximal and distal control is established with care to preserve the tibial and peroneal nerves, which usually course lateral to the aneurysm. Following heparinization the sac is opened, collateral vessels suture ligated, and an interposition graft performed. Patients should be maintained on 81 mg of aspirin.

Endovascular repair of a popliteal aneurysm is performed with a flexible nitinol self-expanding covered stent, such as the Viabahn (gore prosthetic (WL Gore, Inc). Characteristically, ipsilateral antegrade femoral artery access is obtained. Angiographic views with the knee in a flexed position is helpful to avoid overlapping stents in the region of maximum flexure. Stent grafts should be oversized by 10% to 20% and if multiple stents are required, 2 cm of overlap is recommended (Fig. 5). Stent graft surveillance includes quarterly Duplex ultrasound during the first 2 years with annual Duplex imaging thereafter.

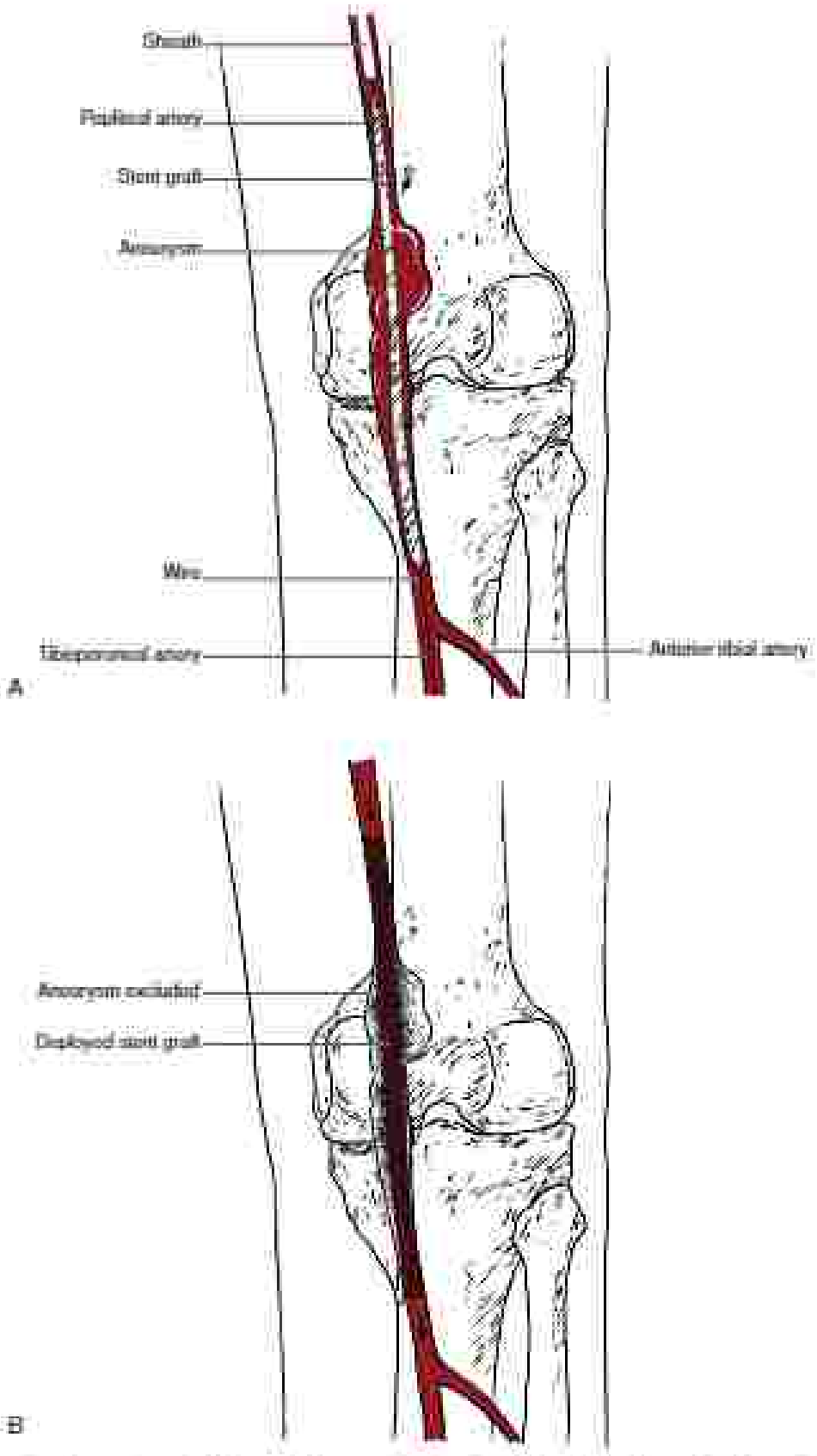

FIG. 5 Covered stent placement excluding popliteal aneurysm. Adequate proximal and distal seal zones are achieved without compromising runoff. (From Chaikof EL, Lumsden E. Atlas of Vascular Surgery and Endovascular Therapy. Anatomy and Technique. Philadelphia: No. Elsevier 2014.)

Approach: Repair in the Presence of Acute Thrombosis

Patients presenting with a popliteal aneurysm and acute limb ischemia, as evident by diminished or absent pedal signals along with pain or motor or sensory findings, have a significantly increased risk for amputation. Anticoagulation is initiated and a CT angiogram or conventional angiography performed to determine if the aneurysm is occluded, the presence and extent of distal embolization, and patency of the infrapopliteal arterial system. If motor and sensory function is intact or symptoms are mild, pharmacomechanical thrombectomy and thrombolysis can be performed followed by definitive endovascular or surgical repair. Should there be evidence of profound motor and sensory dysfunction, the patient should proceed directly to an operating room with imaging capability. Thromboctomy of the popliteal artery and distal tibial vessels can be conducted, the aneurysm excluded, and a bypass performed. A concern for compartment syndrome would necessitate four compartment fasciotomy.

Suggested Readings

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Huang Y, Gloviczki P, Noel AA, et al. Early complications and long-term outcome after open surgical treatment of popliteal artery aneurysms: is exclusion with saphenous vein bypass still the gold standard? *J Vasc Surg* 2007;45(4):706–714.

Lawrence PF, Hallett-Lucke MP, Oderich GS, et al. The current management of isolated degenerative femoral artery aneurysms is too aggressive for their natural history. *J Vasc Surg* 2004;39(2):345–349.

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Stone PA, Campbell JE, Abu-Rahma AF. Femoral pseudoaneurysms after percutaneous access. *J Vasc Surg* 2014;60(5):1359–1366.

Treatment of Claudication

Courtenay M. Holscher, MD, and Maggie Arnold, MD, FACS

The prevalence of peripheral arterial disease (PAD) increases with age and affects nearly 1 in 6 people age 70 years and older in the United States. Intermittent claudication is often the first symptom of PAD. It is defined as reproducible pain in a specific muscle group that is induced by exercise and relieved by rest. The National Health and Nutrition Examination Survey, a population screening study, found that up to one-half of participants with claudication had never consulted a physician for their symptoms. Most patients (70%–80%) with intermittent claudication will have stable claudication at 5 years after diagnosis without further progression. An additional 20% to 30% will have worsening claudication, and only 1% to 3% will develop critical limb ischemia; however, intermittent claudication must be considered a marker of severe atherosclerotic disease as 10% to 15% of patients will die within 5 years of diagnosis of claudication and another 20% will have a myocardial infarction or stroke. Several risk factors for PAD cannot be modified: older age, African American race, and male gender. Some of the biggest risk factors such as smoking, comorbid diabetes, hypertension, and hyperlipidemia can and should be addressed to decrease the morbidity and mortality associated with intermittent claudication.

CLINICAL PRESENTATION

In normal exercise physiology, there is an increase in blood flow to the active muscle groups to meet the metabolic demands of the activity. Claudication occurs because an arterial obstruction proximal to the affected muscle group limits the exercise-induced increase in blood flow, thereby causing muscle ischemia. This ischemia resolves quickly with rest, when the metabolic demands of the muscle decrease. Although the calf is the most commonly affected muscle group, the buttock or thigh muscles can also be involved. It is important to note that the difference between asymptomatic PAD and intermittent claudication is the activity level of the patient. If patients are sedentary or claudicate, they can develop critical limb ischemia without ever having symptoms of claudication as their PAD progresses.

INITIAL EVALUATION

A thorough history is the key to diagnosing intermittent claudication and should include the distance walked before symptoms develop and how quickly the pain resolves. Claudication tends to be highly reproducible: the symptoms occur every time the patient walks a certain distance, the pain occurs in the same muscle group each time, and the pain is relieved quickly with rest. Although nerve compression, venous congestion, and arthritis are other causes of lower extremity pain, a careful history is typically sufficient to diagnose intermittent claudication. Any history of rest pain, nonhealing wounds, or tissue loss suggests more advanced PAD.

Comorbid coronary artery disease, cerebrovascular disease, and other atherosclerotic risk factors including smoking history, diabetes, hypertension, hyperlipidemia, and chronic kidney disease should be noted. About one half of patients with PAD have coexisting coronary artery disease or cerebrovascular disease. Not only can management of these comorbid diseases slow progression of PAD, the presence of these diseases might also limit the treatment options available to a given patient. For example, a patient with cerebrovascular dementia might require direct supervision for a walking program, making it a caregiver-intensive treatment plan.

A physical examination should assess signs of PAD including weakened or absent distal pulses, absent distal hair growth, and dry skin resulting from sparse gland dysfunction. Wounds and areas of skin breakdown are signs of critical limb ischemia and indicate more advanced PAD. Fontaine's stages and Rutherford's categories provide classification systems for PAD and help to differentiate claudication from critical limb ischemia using the history and physical examination (Table 1).

A critical component of the physical examination and the primary assessment for PAD is the ankle brachial index (ABI), determined for each side as the ratio of the higher of the posterior tibial or dorsalis pedis systolic pressures to the higher of the right or left arm systolic pressures. An ABI of 0.90 or less has high sensitivity and specificity for PAD. A resting ABI of 0.5 to 0.7 predicts claudication. ABIs can be falsely elevated from arterial calcifications, particularly in diabetic patients or those with end-stage renal disease on hemodialysis. In the

Approach: Repair in the Presence of Acute Thrombosis

Patients presenting with a popliteal aneurysm and acute limb ischemia, as evident by diminished or absent pedal signals along with pain or motor or sensory findings, have a significantly increased risk for amputation. Anticoagulation is initiated and a CT angiogram or conventional angiography performed to determine if the aneurysm is occluded, the presence and extent of distal embolization, and patency of the infrapopliteal arterial system. If motor and sensory function is intact or symptoms are mild, pharmacomechanical thrombectomy and thrombolysis can be performed followed by definitive endovascular or surgical repair. Should there be evidence of profound motor and sensory dysfunction, the patient should proceed directly to an operating room with imaging capability. Thromboctomy of the popliteal artery and distal bed vessels can be conducted, the aneurysm excluded, and a bypass performed. A concern for compartment syndrome would necessitate four compartment fasciotomy.

Suggested Readings

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TABLE 1 Fontaine's Stages and Rutherford's Categories of Peripheral Arterial Disease

Fontaine Stage	Clinical	Rutherford Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication, symptoms at distances >200 m	I	1	Mild claudication
IIb	Moderate to severe claudication, symptoms at distances <200 m	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

setting of a convincing history and a normal resting ABI, an exercise ABI can demonstrate PAD. This is an ABI measured after walking on a treadmill until symptoms force stopping or for a maximum of 5 minutes.

Vascular laboratory studies including duplex ultrasound, volume plethysmography, and segmental limb pressures including the toes can be useful tools in initial evaluation as well as to identify progression of PAD. Doppler waveforms can identify the level of stenosis and provide a visualization of progressive arterial waveform deterioration (Fig. 1). Volume plethysmography measures changes in limb volume across the cardiac cycle, thereby describing the limb perfusion. Additional imaging such as computed tomographic angiography or digital subtraction angiography is not indicated unless revascularization is being considered.

TREATMENT

The treatment of PAD should include management of comorbid diseases that contribute to PAD progression, pharmacologic management of PAD to include an antiplatelet agent, and a walking program for all patients who can participate. For those who cannot participate or who fail to improve despite a walking program, revascularization can be considered after localization of the causative lesion(s) (Fig. 2).

Management of Comorbid Disease

Smoking Cessation

The association between smoking and PAD has been recognized for more than 100 years. In 1911, Erb reported that claudication was 3 times more likely in smokers compared to nonsmokers. The severity of PAD correlates with the number of cigarettes smoked. Continued smoking with PAD increases risk of amputation, myocardial infarction, and death. For patients with PAD who have undergone bypass grafting, graft failure is 2 to 3 times more likely in those who continue to smoke.

Smoking cessation is a challenging task best addressed through a multidisciplinary approach including behavioral modification, nicotine replacement, and often other pharmacologic management. Behavioral modifications can be taught and supported through group programs. Nicotine replacement through patches, gum, lozenges, inhalers, and nasal sprays can be helpful in addressing nicotine cravings. Little is known about the risks of PAD specifically associated with electronic cigarettes, or vaping, but these should not be considered a method of smoking cessation. Bupropion and varenicline are pharmacologic treatments shown to improve rates of persistent abstinence.

Diabetes

Nearly 1 in 3 patients with diabetes has PAD, and amputation rates in patients with diabetes are as much as 10 times higher than in those without diabetes. Although aggressive glucose control can help decrease risk of cardiovascular events, patients with diabetes and PAD warrant close limb follow-up as well because they have a higher risk for peripheral neuropathy and infectious complications.

Hypertension

All antihypertensive drugs are reasonable approaches to decrease risk of cardiovascular events in patients with hypertension and PAD. Previously β-adrenergic blocking drugs were thought to worsen claudication symptoms, but this was not seen in randomized trials, and often patients with PAD have concomitant coronary artery disease with an indication for β-blockade.

Hyperlipidemia

Dietary modification and statins are important interventions to decrease risk of cardiovascular events in patients with claudication. Although most patients should have a low-density lipoprotein level below 100 mg/dL, those with concomitant coronary artery disease should have more aggressive treatment to decrease low-density lipoprotein to below 70 mg/dL.

Hyperhomocysteinemia

Nearly 1 in 3 patients with PAD have elevated serum homocysteine levels. Although folic acid and vitamin B12 can reduce serum homocysteine levels, there is no evidence that lowering homocysteine levels decreases risk of cardiovascular events. In fact, in a randomized trial of 5522 patients with vascular disease or diabetes randomized to take folate, vitamin B12, and vitamin B6 or placebo, there was a higher rate of hospitalization for unstable angina in the treatment group.

Pharmacologic Treatment for Claudication

Antiplatelet Therapy

Antiplatelet therapy with aspirin at 81 to 325 mg daily has the dual purpose of decreasing risk of limb events and cardiovascular events in patients with claudication. There is no evidence to argue for a particular dose of aspirin. Clopidogrel is an effective alternative in patients with an aspirin allergy or intolerance. Dual antiplatelet therapy with aspirin and clopidogrel has a higher risk of major or life-threatening bleeding without evidence for better limb outcomes.

Symptom Management

Cilostazol is a phosphodiesterase III inhibitor which improves symptoms of claudication through several mechanisms: vasodilator, metabolic, and antiplatelet activity. Cilostazol, compared with placebo treatment, was associated with a longer treadmill walking distance and improved quality of life in several randomized trials. Congestive heart failure is a contraindication for cilostazol use.

Walking Programs for Claudication

The cornerstone of management of intermittent claudication is a walking program (Box 1). Walking should be of sufficient intensity

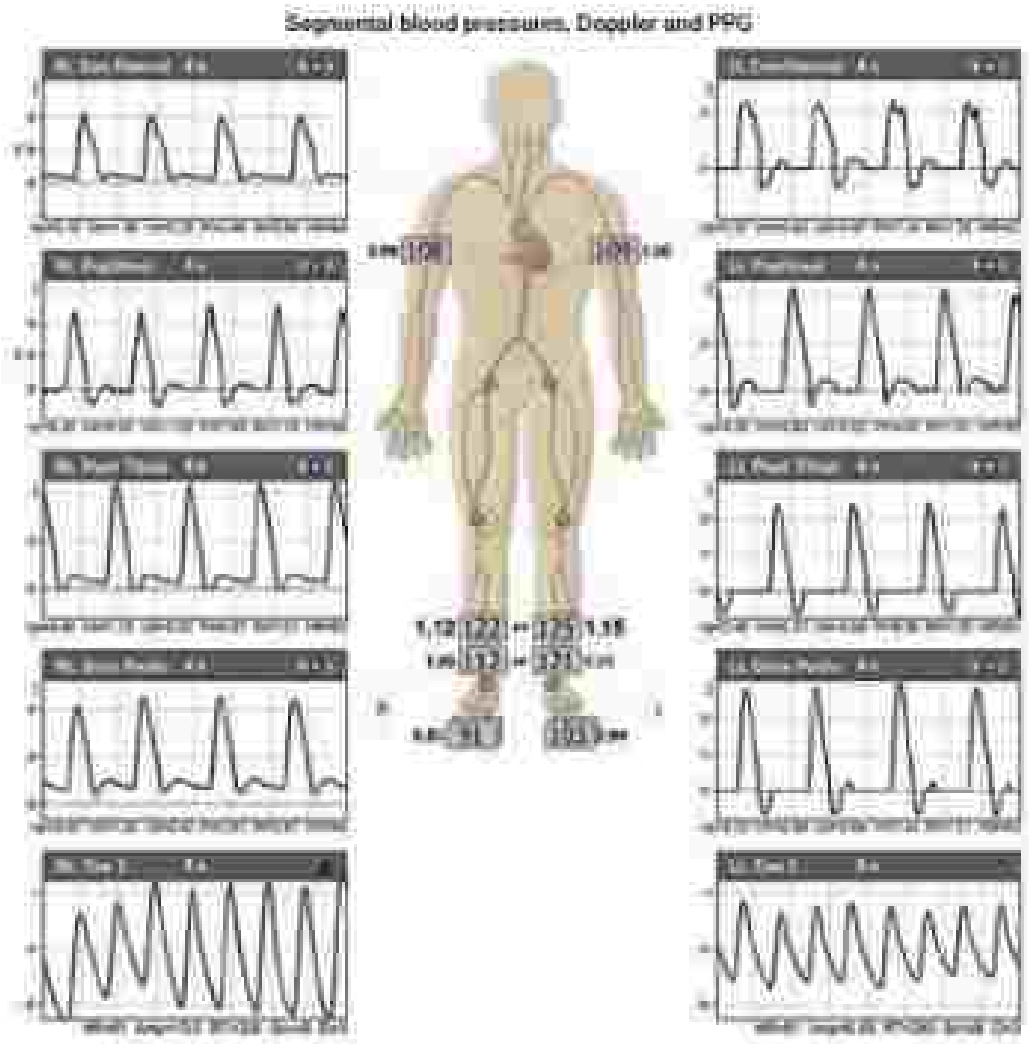

FIG. 1 Lower extremity Doppler waveforms demonstrating right iliac artery obstruction distal with flowing of the proximal waveforms mostly PPG. Photoplethysmography

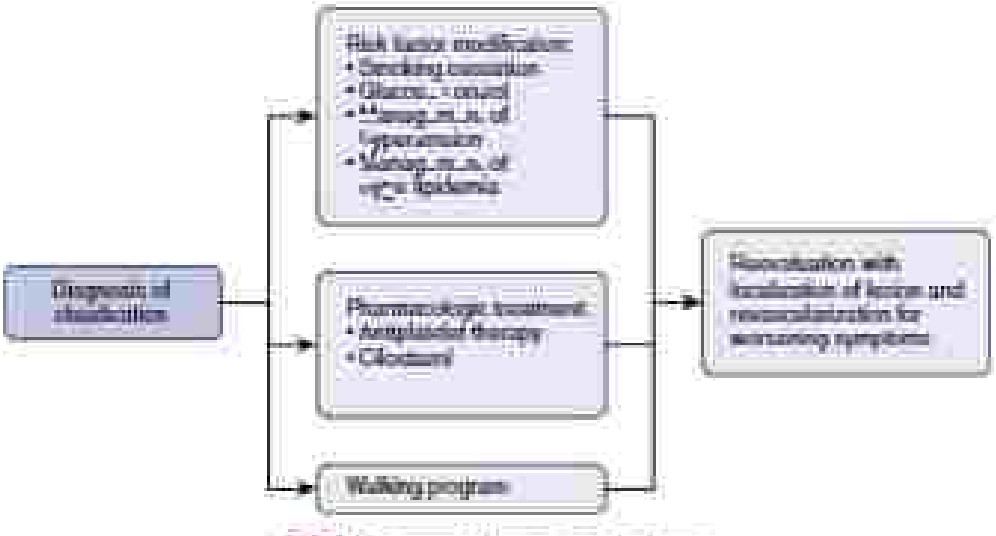

FIG. 2 Management of intermittent claudication.

BOX 1 Sample Walking Program Handout for Patient Use

Benefits of a Walking Program

Using a walking program to treat claudication has many benefits. It not only enables you to walk farther and faster but it also helps with weight reduction and improves your outlook on life (as any exercise program will). The reason that walking is the appropriate exercise for people with claudication (pain in calves or thighs with walking) is that walking is the activity that is limiting you.

Rules of a Walking Program

1. Walk 6 days a week. Take the same day off each week. For example, if you take Sunday off the first week, it is the day you take off each week.
2. Walk at about the same time each day. This enables your walking program to become part of your daily routine. After a week or two, your spouse, family, and friends will know that you will not be available at that time of the day unless they want to walk with you.
3. Start by walking a half hour a day. The time you take to rest (before the pain subsides) counts as part of your one half hour of exercise. Eventually you will be walking intervals for the entire half an hour. After 2 months, increase your time to three-quarters of an hour and only increase it further if you want.
4. A slow, steady walk is the best if you want to walk a maximum distance. Shorter, faster walks with more frequent rests will increase your endurance quicker; our recommendation is to start out with slow, steady walks for the first month or two. After that, try fast, shorter walks several times each week with slow walks on the other days.
5. Remember, the pain that you feel in your legs is not an indication of any damage. It may be annoying and it may make you stop but you are not damaging your muscles. If you can walk with the pain a while, it will help to increase your endurance. Good luck. You will enjoy your walks. Caution: smoking is not permitted while walking.

to induce claudication, followed by a brief period of rest, then continued walking, for a 30- to 60-minute session. Walking programs increase both the total distance walked on treadmill testing as well as the distance walked prior to claudication. The Claudication: Exercise Versus Endoluminal Revascularization trial randomized 111 patients to optimal medical therapy, which included antiplatelet therapy and cholesterol, or to optimal medical therapy plus supervised exercise or optimal medical therapy plus stent revascularization. At 6 months, they found that those managed with optimal medical therapy plus supervised exercise had the best improvement in treadmill walking performance. Although stent revascularization was also associated with an improvement in treadmill walking performance, it carried an additional cost of about $5000 per patient.

Revascularization

A minority of patients who are managed with antiplatelet therapy, cholesterol, a walking program, and comorbid disease management will have progression of symptoms or worsening PAD that requires revascularization. As such, patients with claudication should be evaluated at least yearly by a vascular surgeon or specialist. Discussion of revascularization for claudication should give particular consideration to complications, long term patency, and the patient's individual operative risk. A detailed discussion of revascularization techniques is included elsewhere in this text.

Suggested Readings

Gerhard MA, Hamparsumian FB, Clair DC, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2005;41(Suppl 1): 2S–49S.

Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation. 2012;125(1):130–139.

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Pseudoaneurysms and Arteriovenous Fistulas

Amani D. Politano, MD, MS, and Erica L. Mitchell, MD, MEd

A pseudoaneurysm (PSA), or false aneurysm, is a focal outpouching of an artery that does not include all layers of the arterial wall. This outpouching may be contained by the adventitia or may consist only of a rim of fibrous tissue containing thrombus and arterial flow to communicate with a defect in an artery. In other words, it is a contained bleed from a focal site of the arterial wall. PSAs most commonly result from iatrogenic injury to the arterial wall but can be attributed to other etiologies as well (Box 1). Injury to the arterial wall results in pulsatile flow into the perivascular space, dissection into surrounding tissues, and hematoma formation. A persistent passage from the injury site results in a flow channel, or neck, leading into a false lumen, or sac, with to-and-fro arterial flow between the artery and the sac (Fig. 1). PSAs, unlike true aneurysms, lack all three normal elements of the arterial wall and are therefore at increased risk of rupture with potentially catastrophic bleeding. Postcatheterization femoral artery PSAs are the focus of this chapter.

RISK FACTORS

PSAs are most frequently seen as a complication related to percutaneous arterial access. The common femoral artery (CFA) is the most common access site for catheter based interventions for cardiologists, interventional radiologists, and vascular surgeons alike. Technique for accessing the common femoral artery vary and include direct palpation of the pulse, fluoroscopic guidance, and ultrasound guided access. The latter has become more prevalent because it results in fewer access related complications and is considered the standard of care. Nonetheless, the incidence of femoral artery PSAs is increased when the puncture site is not in the CFA, but rather in the external iliac artery, superficial femoral artery (SFA), or profunda femoral artery (PFA).

Risk factors for the development of iatrogenic PSAs associated with arterial access procedures are listed in Box 2. These can be divided into procedure related and patient related factors. Increased complexity of intraarterial intervention has been shown to increase the risk of vascular complications. Therapeutic interventions such as arterial angioplasty and stenting, atherectomy, and thrombolytic therapy have a higher rate of PSA formation (2%–8%) than diagnostic procedures (0.05%–2%). Related to both the therapeutic nature and complexity of interventions, larger diameter catheter or sheath use is also correlated with higher rates of PSA

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BOX 1 Etiologies of Pseudoaneurysm Formation

Acquired

Trauma
Penetrating
Gunshot wound
Stab wound
Blunt or stretch
Proximity injury

Infection
Drug abuse
Contamination
Bacterial seeding

Iatrogenic

Anastomotic
- Patch
- [illegible]

Vascular access

Spontaneous

Vasculitis
Behçet's disease
Polyarteritis nodosa

BOX 2 Risk Factors for Pseudoaneurysm Formation

Procedural Factors

Therapeutic vs Diagnostic Procedure
Complex procedures
Larger sheath size (>8Fr)
Prolonged procedure
Simultaneous artery and vein cannulation
Use of closure device

Puncture site
Low (CFA or PFA) or high (EIA) puncture sites
Inadequate compression of puncture site

Patient Factors

Advanced age
Female gender
Obesity
Hypertension
Hemodialysis dependent end stage renal disease
Concurrent anticoagulation
Calcified vessels
Steroid use

EIA, external iliac artery; PFA, profunda femoral artery; SFA, superficial femoral artery.

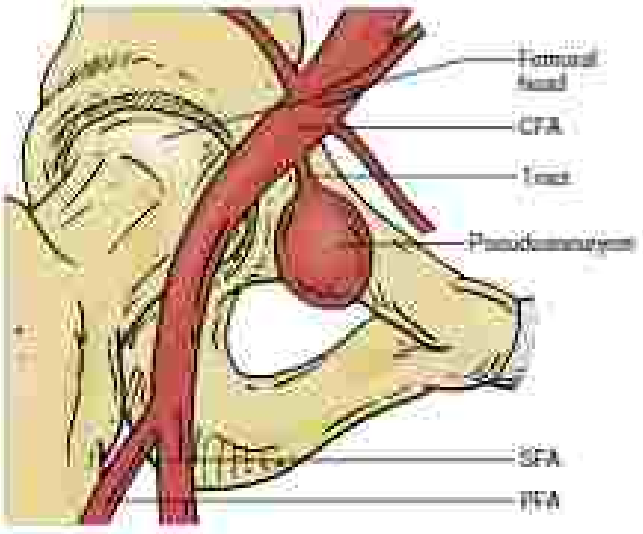

FIG. 1 Common femoral artery (CFA) pseudoaneurysm and neck (necks). PFA, Profunda femoral artery; SFA, superficial femoral artery.

FIG. 2 Mass effect of a pseudoaneurysm causing pressure necrosis of the overlying skin.

formation. Other procedural related factors include simultaneous arterial and venous puncture, urgent versus elective procedures, the use of arterial closure devices, and insufficient duration of puncture site compression after the sheath is removed. PSA formation is less common when ultrasound guidance or fluoroscopic localization of the medial one third of the femoral head is used for femoral artery puncture. Patient related risk factors contributing to PSA formation include advanced age, female gender, obesity, preprocedural thrombocytopenia, and postprocedural antiplatelet or anticoagulation use.

Diagnosis

PSAs may be asymptomatic or may present with mild tenderness to palpation or swelling in the groin after catheterization. Although this is the most common presentation of a PSA, more severe symptoms can be more related to the mass effect of a PSA and associated hematoma. Large PSAs with associated hematoma may result in skin necrosis (Fig. 2) and/or compression of nerves and vessels in the groin. Lower extremity swelling, deep venous thrombosis, and/or ischemia secondary to vessel compression are rare but serious findings. Ruptured PSAs may present with hemodynamic collapse and significant groin or thigh swelling.

Any patient who experiences pain disproportionate to that expected after a percutaneous procedure should undergo evaluation to exclude PSA. Examination should include a thorough peripheral pulse examination, documentation of the ankle brachial index, and limited ultrasonography of the vasculature in the affected groin. Laboratory assessments such as decreased platelet count (<150,000/L) or elevated D dimer values have been shown to correlate with diagnosis of a PSA or duplex.

The diagnostic examination of choice is duplex ultrasound (DUS, 5- to 7-MHz linear transducer). Because B-mode imaging alone is unable to differentiate a PSA from a hematoma, color Doppler should be used to enhance the diagnostic accuracy of ultrasound (sensitivity, 94%; specificity, 97%) as it allows for identification of pulsatile flow within the sac. The typical appearance of a PSA on DUS is demonstrated in Figs. and 4. Active flow within the PSA sac is often referred to as to and fro flow or a yin yang pattern. The PSA sac size (maximal diameter) and the length and width of the neck should be measured with DUS because they are important for guiding treatment options. If an arterial duplex examination cannot be performed or if the results are equivocal, computed tomography imaging (with intravenous contrast) can be used to make the diagnosis of PSA (Fig. 5) or to obtain more detailed anatomic information to plan a surgical repair. In addition to assessing the PSA, DUS or computed tomography angiography should assess for secondary injuries, including posterior arterial injury and presence of an arteriovenous fistula.

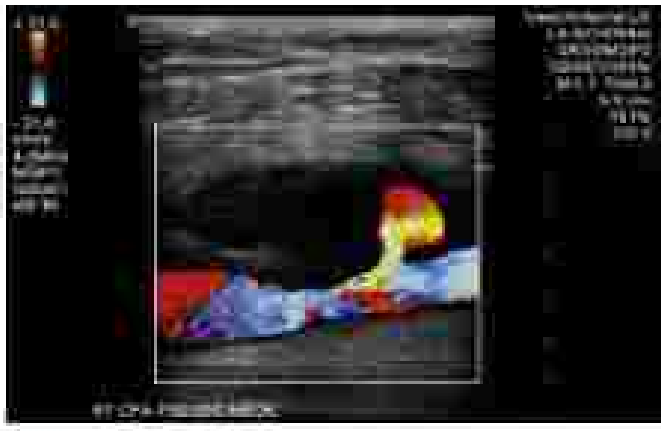

FIG. 3 Duplex ultrasound findings of a pseudoaneurysm include a fluid collection adjacent to the femoral artery a high-velocity jet through the arterial wall and a neck or communication with the artery.

Treatment

A number of treatment options for iatrogenic femoral PSAs exist. The therapeutic choice depends on the PSA size, neck characteristics, and the patient's symptoms. Treatment options include observation, ultrasound guided compression (USGC), percutaneous ultrasound-guided thrombin injection (USTI), and open surgical repair. More recently, creative therapeutic approaches have been described, including more advanced endovascular options and endoluminal interventional techniques.

Observation

Studies have shown that the majority of small PSAs (<2–3 cm) thrombose spontaneously within 4 weeks for patients not on anticoagulants. Conservative management, or a watch and wait policy, has been advocated for small and asymptomatic PSAs. Spontaneous

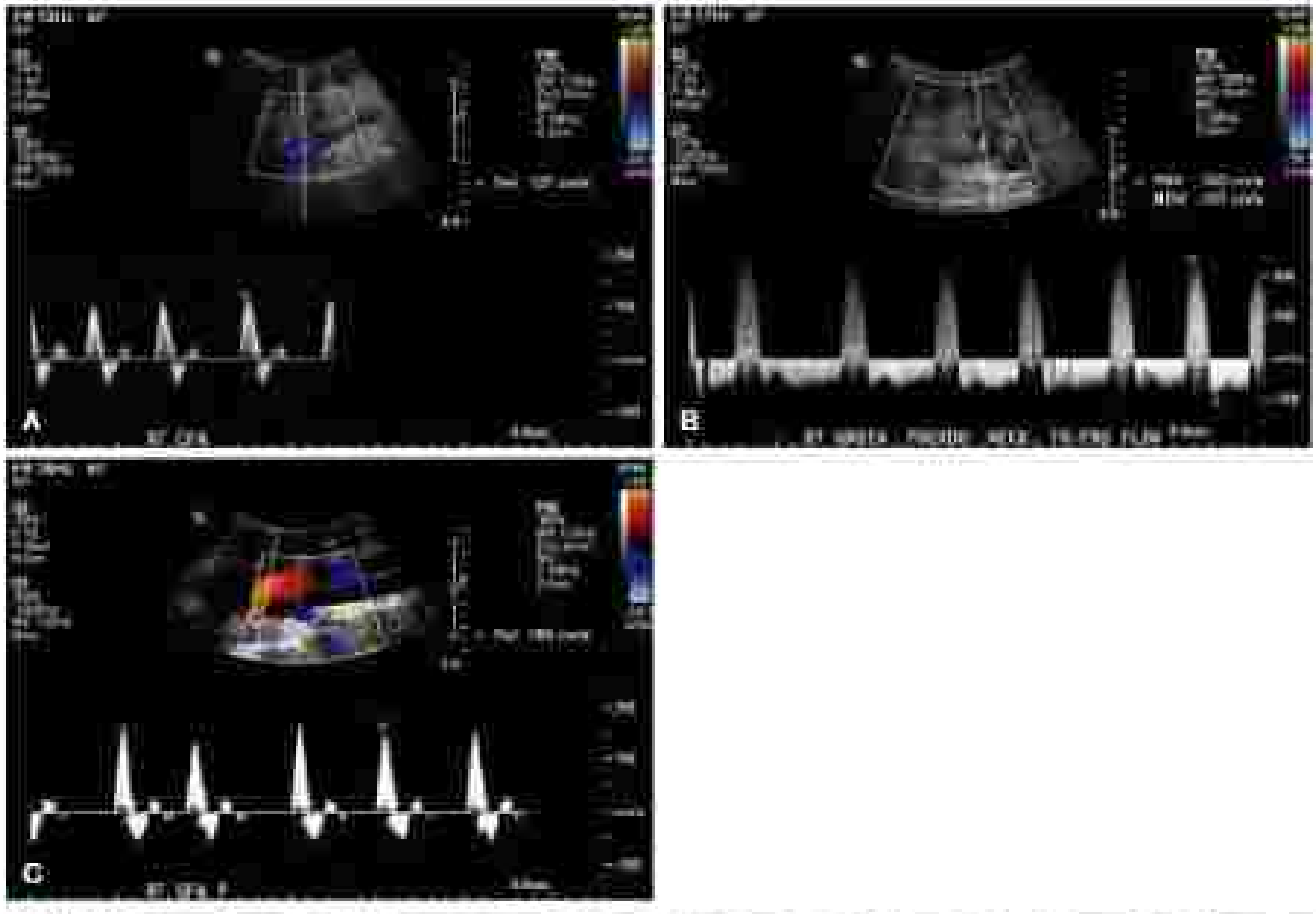

FIG. 4 Duplex ultrasound examination of a (B) pseudoaneurysm as well as the (A) proximal and (C) distal vessels. Duplex ultrasound shows a patent common femoral artery and superficial femoral artery. The pseudoaneurysm arises from the common femoral artery with classical peak systolic velocities and to-and-fro flow representing systolic flow entering the common femoral artery and retrograde diastolic flow exiting the pseudoaneurysm.

resolution can be unpredictable; therefore patients with small PSAs require periodic surveillance with DUS. The disadvantage of this watch and wait policy is that patients undergoing surveillance may have activity restrictions, discomfort with serial DUS, and prolonged hospital stays. PSAs that do not thrombose risk enlargement and additional complications, thus adhering to a scheduled follow up is critical. Patients considered at risk for being lost to follow up should undergo definitive treatment initially.

USGC

USGC therapy has been shown to be a safe and noninvasive method for treatment of PSAs with success rates ranging between 73% and 93%. Ultrasound is used to identify the PSA sac and neck. The ultrasound transducer is positioned over the PSA neck, and pressure is applied until there is obstruction of flow within the neck and sac. During compression of the PSA, cessation of flow within the PSA is verified with continual duplex imaging, whereas flow in the native artery is preserved. Blind manual compression has also been described but lacks continual monitoring to ensure complete occlusion of flow into the PSA, and therefore risks inadequate treatment, especially when even small position changes by the patient can require the operator to make similar adjustments to maintain complete occlusion. Compression is usually held for increments of 10 to 15 minutes. This is repeated until successful PSA sac thrombosis is achieved, or until a discretionary failure time is met. Compression times average 35 minutes for acute PSAs and 51 minutes for more chronic PSAs (>10 days).

Limitations of USGC include both patient specific and operator dependent factors. Patient specific concerns include the location of the PSA, body habitus, and ability to be compliant with or tolerate compression. Supratarsal PSA compression is generally not recommended because it may result in PSA rupture and inability to quickly control bleeding. Brachial artery PSAs usually require open decompression because of symptomatic nerve compression. It is more technically challenging to both achieve and maintain compression in an obese patient without operator fatigue. Compression is also time consuming and may not be well tolerated by patients. Conscious sedation can be administered with improved tolerance but requires increased resources (such as advanced nursing care and appropriate bed/unit placement during the procedure and recovery) and may increase overall risk to the patient. Operator-dependent factors include variable or inadequate compression, fatigue, and the time-dependent nature of the task.

Predictors of poor outcome with USGC include concomitant anticoagulation, large PSA size (>4 cm), and patient obesity. Patients with these negative predictors generally have lower technical success rates (55%–75%), higher recurrence rates (20%), and greater complication rates (3.6%) than patients without these factors. Complications and contraindications to USGC are listed in Box 3.

UGTI

UGTI has become the treatment of choice for midsize mid-post catheterization PSAs (2–5 cm). Thrombin is injected into the PSA sac for immediate thrombosis of the PSA (Fig. 6 and Box 4). This is an off-label use of thrombin; it is US Food and Drug Administration–approved for topical use only. UGTI is contraindicated in the setting of lower extremity ischemia, infection, arteriovenous fistula, and pregnancy.

UGTI has several advantages compared with USGC for the treatment of PSAs. The procedural time is shorter, the procedure is better tolerated by patients, and the technical success rate is greater (>96%). In addition, UGTI can be used effectively in the setting of concomitant anticoagulation or for supratarsal PSAs. The ability to perform this procedure in the outpatient setting or at the bedside also reduces the relative cost. Complications of UGTI include arterial thrombosis (<2%), PSA rupture, treatment failure, or allergic response to bovine thrombin. Arterial thrombosis has been associated with the treatment of small PSAs (<2.5 cm). Complications related to neck length are more variably reported; arterial thrombosis has been shown not to be related to short neck length (<5 mm) although necks shorter

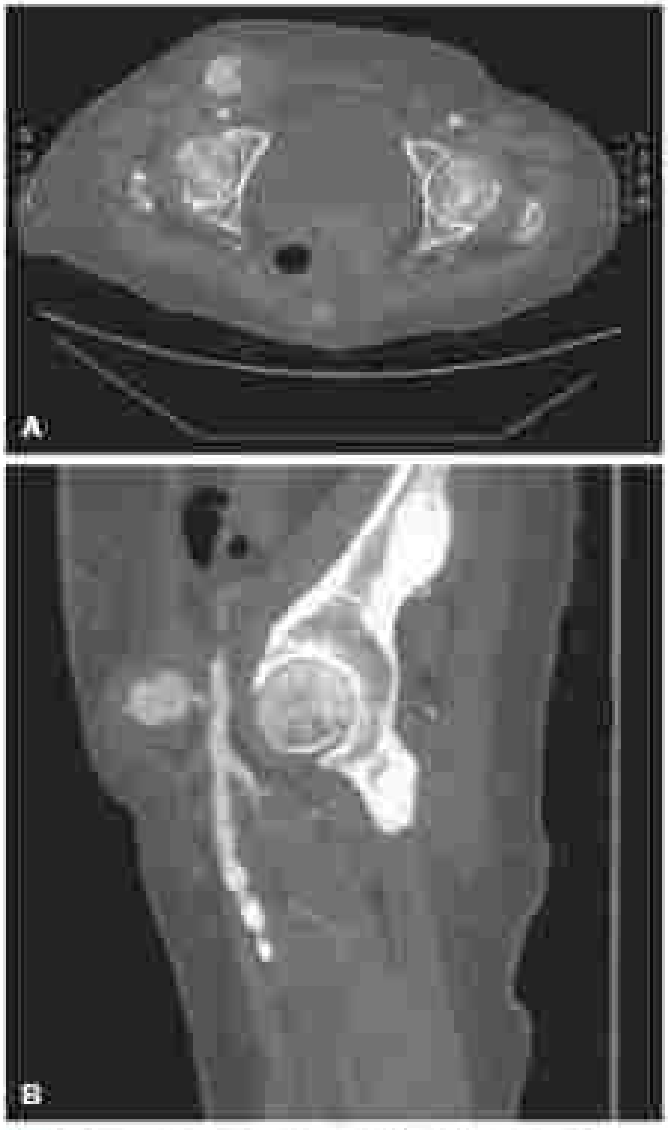

FIG. 5 Computed tomography angiographic axial (A) and sagittal (B) images of a right femoral pseudoaneurysm and neck.

BOX 3 Complications and Contraindications of Ultrasound-Guided Pseudoaneurysm Compression

Complications

Rapid enlargement of the PSA sac
Skin necrosis
Distal embolization
Venous thrombosis
Rupture

Contraindications

Peripheral ischemia
Cutaneous ischemia
Infection
Surgical graft
Supratarsal PSA

PSA, pseudoaneurysm.

FIG. 6 Ultrasound-guided thrombin injection. A 1-mL syringe containing bovine thrombin (1000 units/mL) and a 5-mL syringe with sterile normal saline flush are connected to a three-way stopcock fitted with a 22-gauge needle (40 mm or 1.6 mm). If the pseudoaneurysm (PSA) is deeper than 1.75 cm, then a 22-gauge × 4-cm Echotip needle (Cook Medical) can be used. The PSA sac is visualized in transverse and longitudinal views on duplex ultrasound. The thrombin port is placed in the "off" position and the saline port is placed in the "on" position. The needle and transducer are kept parallel as the needle is advanced under ultrasound guidance. Punctures into the sac at least superficial and far from the PSA tract. Proper needle placement is confirmed by aspiration of blood and a small injection of saline will produce a flash of color on duplex ultrasound. The thrombin port is placed in the "on" position and the saline port is placed in the "off" position. Thrombin is then injected into the PSA sac in 0.2-mL aliquots until there is cessation of blood flow in the PSA sac and tract. This can usually be achieved in seconds. The tract should never be directly injected because of the risk of thrombosis of the native artery. An average of 500 units (0.5 mL) of thrombin (range, 50–1000 units) is required to thrombose the PSA sac. An arterial duplex is repeated 24 hours postprocedure to check for recurrence (0.a., 9.) and to rule out postprocedure complications.

BOX 4 Three-Way Stopcock Technique of Ultrasound-Guided Thrombin Injection

1. The patient's groin is prepped and draped in the usual sterile fashion.
2. The distances from the skin to the most superficial portion of the PSA sac and the distance to the PSA tract are measured.
3. The skin and subcutaneous tissue are infiltrated with 1%–2% lidocaine.
4. A three-way stopcock is prepared as described in Fig. 6.
5. The needle is advanced under DUS guidance to the depth measured in step 2 and the PSA sac is entered superficially. Entry into the PSA sac is confirmed by aspiration of blood and proper placement of the needle tip is confirmed by saline injection on DUS. The needle must be in the PSA sac and not in the tract, artery, or vein.
6. The thrombin port is turned on and the saline port is turned off. Thrombin is injected gently in 0.2-mL aliquots until the PSA sac and tract are thrombosed or until 1.0 mL (1000 units) of thrombin is used.
7. If there are >2 PSA sacs, then the most superficial sac is injected first.
8. If the tract persists, do not inject directly into the tract. Follow the patient as the tract normally thromboses within 24 hours.
9. A DUS is repeated 24 hours postprocedure to check for recurrence (0%–9%) and rule out postprocedure complications such as arterial or venous thrombosis.
10. The procedure may be performed on an outpatient basis with the patient discharged immediately after injection.
11. A PSA that recanalizes after thrombin injection may be reinjected on follow-up visit.

DUS, duplex ultrasound; PSA, pseudoaneurysm.

than 2 mm have demonstrated increased risks of embolic complications. Exposure to bovine factor V may cause some patients to form antibodies that cross react with human factor V and induce coagulopathy. Patients who undergo UGTI should have a follow-up duplex in 24 to 48 hours to ensure continued thrombosis of the PSA.

Endovascular Repair

Covered stents have been widely used in the treatment of aneurysm, but their use in femoral PSAs is limited. Current barriers include high cost, lower patency rates, the need for larger delivery systems, and the lack of long-term data. Endovascular repair is not recommended if treatment of the PSA requires placing a stent across the groin crease or across the origin of the PFA. Covered stent use can be considered for treatment of suprainguinal PSAs where the distal endpoint of the stent does not cross beneath the inguinal ligament. Complications unique to covered stents include infection, migration, and thrombosis. Long-term duplex surveillance is required postprocedure to monitor for in-stent restenosis and stent patency.

The use of covered stents for treatment of infected PSAs is not recommended. In the setting of advanced cancer, definitive treatment of a PSA via covered stent placement with or without coiling and covering of the PFA may have a role. Covered stent use has also been described in intravenous drug abusers who present with ruptured PSAs or acute sepsis associated with an infected PSA. In these settings, the stent provides a bridge to arterial reconstruction by obtaining hemostasis or allowing for surgical debridement of the infected tissue before reconstruction. When definitive arterial reconstruction is anticipated, preservation of the profunda is recommended.

Some authors have described using endovascular balloon occlusion of the origin of the PSA at the time of thrombin injection to reduce the risk of intra-arterial thrombosis, especially if there are concerns for a wide or short neck. This risks across the complications as the contralateral femoral access site but has been performed successfully. Case reports have also described the use of various arterial closure devices (e.g., Angio-Seal and Star-Close, Perclose ProGlide, Amplatzer plug) to treat iatrogenic PSAs.

Open Surgical Repair

Noninfected Pseudoaneurysms

Patients with contraindications to compression therapy or thrombin injection should be considered for open surgical repair. These include peripheral or cutaneous ischemia, infection, surgical graft, large suprainguinal PSAs, or those who present with complicated PSAs (i.e., rapid enlargement, distal embolization, rupture) (Fig. 7). Repair of suprainguinal PSAs requires retroperitoneal access to achieve proximal control of the iliac vessels. Hybrid open and endovascular techniques, in which endovascular balloon occlusion is used to provide proximal and/or distal control through either the PSA itself or via contralateral femoral access, have been described.

Once proximal and distal control are obtained, the pseudoaneurysm can be opened and the defect repaired. Often, the actual arterial injury is small and can be repaired with a simple, interrupted polypropylene suture. The back wall of the artery should be inspected to ensure no posterior arterial injury. Patch angioplasty may be required if the arterial wall is significantly damaged or if there is luminal narrowing of the artery with primary repair. Any hematoma should be evacuated, and in the setting of a large tissue defect or hematoma, drain placement may be necessary. Complications associated with open surgical repair include wound infection, bleeding, lymphocele, radiculopathy, perioperative myocardial infarction, and death.

FIG. 7 Noninfected femoral pseudoaneurysm requiring open surgical repair because of its large size and overlying skin necrosis.

Infected Pseudoaneurysms

Compression or injection of infected PSAs is contraindicated, and they must be treated promptly and aggressively. Management includes appropriate antibiotic coverage, debridement of infected tissue, and arterial repair or replacement with autogenous vein graft. Arterial ligation without revascularization is reserved for aggressive bacterial infection and may be associated with intermittent claudication or limb loss. Muscle flap coverage of the tissue defect may be required to further protect the repair. Except for rare circumstances, such as providing immediate hemostasis of an acute rupture with planned definitive management including dose removal once the patient is stabilized, endovascular occlusion with covered stents should be avoided.

Alternate Percutaneous Methods

Perianeurysmal saline injection has been described as an alternate method to either US-C or US-T for PSAs. This technique uses ultrasound guidance to position a needle outside of the artery along the PSA neck and injects normal saline (30–80 mL) into the extravascular tissue to cause external compression of the PSA neck and obliteration of flow within the PSA. A second injection on the opposite side of the PSA neck is sometimes required, and the injection is followed with five minutes of manual compression.

Cyanoacrylate glue has also been used for percutaneous treatment of PSAs. Various reports describe intrasac injection, much like thrombin, or injection into the collapsed PSA walls. This second method uses ultrasound guided compression of the PSA before injection, with subsequent injection of small aliquots of the glue directly into the opposed walls of the PSA. Compression is continued for 5 minutes, and injection and compression are repeated if signs of separation are seen with gradual release of compression. Administration of cyanoacrylate glue has also been described using contralateral arterial access to provide balloon occlusion across the pseudoaneurysm neck during injection.

Although studies have demonstrated initial success with each of these techniques, further investigation is warranted.

Anastomotic Pseudoaneurysms

Anastomotic PSAs are an infrequent but important late complication of prosthetic arterial reconstruction (Fig. 8). The femoral arterial anastomosis is the most common site for an anastomotic PSA (12.6%). The presence of an anastomotic PSA should raise suspicion of a graft infection, and treatment should be planned with this in mind. An anastomotic PSA is typically composed of a fibrous pseudocapsule surrounding an occult graft infection or arterial degeneration to a previously endarterectomized artery. Because anastomotic PSAs are unpredictable and are associated with a high incidence of rupture, they should be treated early and aggressively.

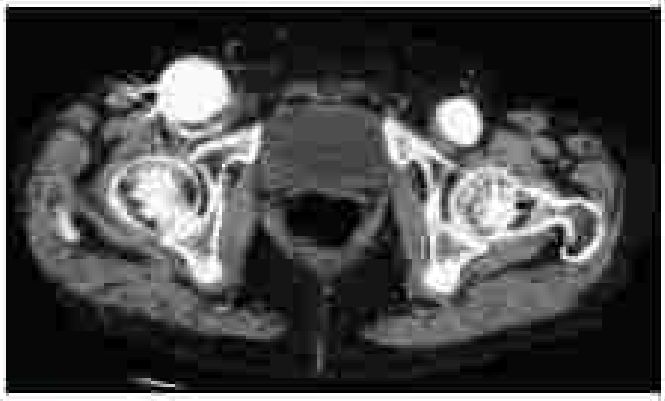

FIG. 8 Ruptured femoral anastomotic pseudoaneurysm. This patient underwent bilateral common femoral endarterectomies and an aortobifemoral bypass for aortoiliac occlusive disease 15 years before presentation. There are no fluid collections or abnormal tissues within the tissue surrounding the pseudoaneurysm, which suggests no evidence of infection. On physical examination and laboratory testing, no clinical evidence of infection was found.

Observation can only be recommended for patients with very small PSAs, prohibitive operative risk, or short life expectancy. Operative repair is generally recommended for all groin anastomotic PSAs greater than 3 to 4 cm in diameter. If there is no evidence of infection and a well-incorporated graft, interposition graft replacement of the degenerative aneurysmal portion of the existing graft can be performed safely. If the graft is infected, removal and replacement of all infected graft and tissue is necessary. Revascularization may require extra-anatomic bypass grafting through a noninfected field or replacement of the infected conduit with autogenous femoral vein. Grossly infected arterial beds may require coverage with sartorius or rectus femoris muscle flaps. Endovascular repair of femoral artery anastomotic PSAs has been reported, however, it is generally not recommended in the setting of infection or when stenting would result in occlusion of the PFA origin.

ARTERIOVENOUS FISTULA

An arteriovenous fistula (AVF) is an abnormal communication between an artery and vein. Although AVFs can be congenital, they are more frequently iatrogenic or traumatic. Femoral AVFs almost always develop secondary to penetrating injuries or percutaneous vascular interventions. The incidence of postcatheterization femoral AVF is 0.2% to 2%. Patient related risk factors include female gender, hypertension, and ongoing anticoagulation. Age and morbid obesity have not been identified as risk factors. Procedural related risk factors include left sided groin punctures and high levels of anticoagulation (>12,500 units of perioperative heparin). Postcatheterization femoral AVFs will be the focus of this section.

Diagnosis

The diagnosis of an AVF in the extremities can be made with history and physical examination. Physical examination may reveal a bruit or thrill on auscultation and a thrill on palpation. A tic and/or holosystolic/diastolic bruit at the puncture site is pathognomonic for an AVF, and the intensity of the sound on auscultation typically correlates with the size of the fistula. Large AVFs may also present with unilateral limb swelling, mild to severe limb ischemia (claudication or tissue loss), or heart failure. If physical examination findings are not diagnostic but an AVF is suspected, DUS can be a useful diagnostic tool. AVFs are characterized by high arterial peak systolic velocities proximal to the fistula resulting from low resistance at the fistula site. Reduced arterial flow distal to the fistula is secondary to shunting, and

bidirectional or turbulent flow is seen at the fistula site. The venous side of the AVF demonstrates pulsatile flow with elevated peak systolic velocities that result from mixing of arterial and venous flows.

Treatment

Iatrogenic AVFs, unlike traumatic AVFs, may close spontaneously. Studies have shown that 20% to 50% of iatrogenic postcatheterization femoral AVFs resolve spontaneously. Iatrogenic AVFs are more likely to persist in patients with chronic renal insufficiency or concomitant steroid use. Patients with small or low flow AVFs may never develop symptoms and can be safely managed conservatively. Repair is indicated for all symptomatic patients.

Open Surgical Repair

Surgical repair is the traditional method for treating femoral AVFs and is associated with morbidity and mortality rates of 27% and 8%, respectively. The principle of surgical repair is obliteration of the connection between the artery and vein with restoration of vessel patency. Proximal and distal control of both the artery and vein is required. Because AVFs can result in significant enlargement of venous structures, operative repair can be associated with significant blood loss. Preoperative placement of arterial or venous balloons for intraoperative occlusion may help decrease blood loss during the repair, and cell saver and rapid infusion devices can be used when large volumes of blood loss are anticipated. Repair can be achieved with primary closure of the fistula tract, vein patch angioplasty, or interposition bypass graft.

Endovascular Repair

Endovascular treatment of iatrogenic or traumatic femoral AVFs is becoming more commonplace. Catheter based interventions are indicated for high risk surgical patients, or those who present with "hostile" anatomy such as morbid obesity, previous femoral interventions, or groin surgery and those with aneurysmal enlargement of venous collaterals. The most common endovascular method of treating AVFs is placement of a covered stent to the arterial system to occlude the connection between artery and vein. Contraindications to endovascular repair include patients in whom endovascular stenting will obliterate the IVA or cross the groin crease. The placement of common femoral artery stents also precludes use of that site for future endovascular access. Venous stents are usually reserved for iliac vein or inferior vena cava AVF occlusion after unsuccessful intraarterial stent placement. Superficial femoral artery stent grafts for iatrogenic femoral AVFs have a reported 1- and 4-year primary patency of 76% and 57%, respectively, and a 4-year secondary patency rate of 80%.

Alternative endovascular methods for treatment of AVFs include embolization with coils, cyanoacrylate glue, collagen or gelatin, and others. During embolization, percutaneous venous access with balloon inflation may be required to occlude the venous outflow if there is a short tract connecting the artery and vein. Using detachable coils and packing smaller coils after larger coils can reduce inadvertent placement. Amplatzer plug occlusion of a femoral PSA with concomitant AVF has also been described.

Suggested Readings

Ahmad F, Turner SA, Torsney P, Ellison M. Iatrogenic femoral artery pseudoaneurysms – a review of current methods of diagnosis and treatment. Clin Radiol. 2006;61:319–330.

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Axillofemoral Bypass Grafting in the Twenty-First Century

John Fatchen, MD, and Evan C. Lipsitz, MD, MTM, FACS

Treatment of atherosclerotic and other occlusive disease of the abdominal aorta and iliac arteries remains a common challenge to vascular surgeons practicing today, despite continued advances in surgical and endovascular technology. Aortoiliac disease affects 8 to 10 million people in the United States annually. Currently, there remains no official consensus on the natural history of aortoiliac occlusive disease. Although some suggest that about one third of patients will progress to occlusive aortic disease involving the renal and mesenteric aorta within 5 to 10 years of diagnosis, others suggest that such estimates is rare. Over time, as the disease progresses to complete occlusion resulting from the accumulation of plaque and vessel wall calcification, patients may experience a wide range of symptoms including thigh and/or buttock claudication as well as impotence in male patients, the constellation of symptoms known as Leriche's syndrome. Anatomic characteristics and disease progression notwithstanding, the symptoms experienced by the patient guides treatment, as in other areas of occlusive vascular disease. Patients presenting with concurrent infrainguinal arterial disease will likely experience more severe claudication and possibly rest pain or tissue loss.

Absent lower extremity pulses, including femoral, are the hallmark of the disease. The diagnosis can be confirmed with a number of additional diagnostic tests. Pulse volume recordings will show decreased waveforms throughout all segments of the lower extremities. Arterial duplex of the aortoiliac segments estimates the degree of stenosis or occlusion and may be combined with infrainguinal duplex to assess the overall circulation to the extremity. Traditional angiography provides detailed anatomic information of the abdominal aorta, pelvis, and lower extremity arterial tree and identifies patterns of collateral flow around obstructions. In the setting of aortoiliac occlusive disease, femoral artery access may be difficult or impossible, and the use of alternative access sites, such as the brachial artery may be required. Computed tomography angiography is a very useful imaging modality for defining aortoiliac anatomy and planning intervention. Computed tomography angiography delineates the degree and extent of vessel calcification and identifies the course of any previous bypass procedures. Magnetic resonance angiography can also be useful although it is not as robust as computed tomography angiography for this application.

Treatment algorithms for aortoiliac disease have gone through several iterations over the past half-century. Initial attempts at surgical reconstruction before the development of synthetic grafting involved femoral and aortoiliac endarterectomy. Although effective, such extensive surgical repair was fraught with high rates of morbidity

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Treatment algorithms for aortoiliac disease have gone through several iterations over the past half-century. Initial attempts at surgical reconstruction before the development of synthetic grafting involved femoral and aortoiliac endarterectomy. Although effective, such extensive surgical repair was fraught with high rates of morbidity

and mortality, especially in high risk populations. By the 1970s, the use of Dacron as aortoiliac and aortobifemoral replacement grafts in open abdominal procedures had completely supplanted aortoiliac endarterectomy. With 5 year patency rates of aortobifemoral grafts reaching and exceeding 90% throughout the contemporary literature, it remains the gold standard for aortoiliac occlusive disease for good risk patients. During this same era of surgical advancement, the first extraanatomic axillofemoral bypass was performed by Blaisdell and Hall for several high risk patients with iliac occlusive disease. This technique was quickly adopted by Sauvage in the 1980s for bilateral occlusive disease, with bifurcated grafts of varying configurations allowing for anastomosis to both femoral arteries. Axillofemoral bypass is an extraanatomic bypass as it does not course along the normal anatomic path of the vessels being bypassed. Grafts are tunneled subcutaneously, avoiding a midline laparotomy and aortic cross clamping, significantly reducing operative stress, making this a favorable choice in high risk patients. Early patency rates were good, plagued by graft compression and unequal flow rates, with reported three year patency as low as 39%; however, the introduction of externally supported prostheses, including polytetrafluoroethylene grafts with external ring reinforcement dramatically improved the durability of the axillofemoral bypass.

INDICATIONS

There are a number of indications for axillofemoral bypass. Axillofemoral bypass is typically performed in patients with chronic arterial insufficiency and symptoms of critical limb ischemia such as disabling claudication, rest pain, ischemic ulceration, or gangrene. The most common etiology of this insufficiency is atherosclerotic, although it may also result from radiation damage to vessels. There are other applications for the procedure including acute occlusion or aortic dissection resulting in acute lower limb ischemia or the presence of an infected aortic graft that is to be removed. Additional indications include those where axillofemoral bypass may be deemed unfavorable because anatomic considerations such as a heavily calcified aorta, a hostile abdomen or the need for peritoneal dialysis, or medical comorbidities such as severe cardiopulmonary, renal or hepatic disease, active sepsis, fistula, or the presence of intraabdominal infection (Box 1). The timing of intervention depends on the indication for the operation as well as the overall health status of the patient.

The recent and rapid advancement of endovascular therapy has had a significant effect on the treatment of aortoiliac disease. Younger, otherwise healthier patients with aortoiliac disease who might otherwise have undergone open revascularization in the past have been treated successfully with endovascular interventions. As a result, many of the patients who ultimately require surgical repair are older and have more significant comorbidities, and are not considered candidates for direct aortic reconstruction, leaving axillofemoral bypass as the best option.

With the ongoing incorporation of advancing endovascular techniques in the standard practice of the vascular surgeon, the rates of direct aortoiliofemoral or extraanatomic revascularization has decreased substantially over the past decade, traded instead for transluminal angioplasty and stenting of diseased aortic iliac segments. Now, such open revascularization techniques appear to be reserved for patients with either extensive aortoiliac occlusive disease or those who have already failed catheter based intervention. The debate between endovascular versus open intervention has been ongoing in the vascular literature for the past two decades. The Trans Atlantic Inter Society Consensus for the Management of Peripheral Arterial Disease (TASC) guidelines and subsequent updated guidelines (TASC II) were published in the early 2000s by an international consortium of vascular, cardiovascular, and radiologic societies to bring together evidence based data to provide recommendations on treatment modalities for lower extremity peripheral arterial disease. Atherosclerotic lesions of the aortoiliac and femoropopliteal systems were classified based on degree and length of occlusion. And although initial guidelines suggested that endovascular techniques were more suited for short segment (TASC type A or B) iliac and femoral lesions, percutaneous technology has now advanced and being successfully applied to long segment (TASC type C or D) lesions.

Another indication for axillofemoral bypass is the use as a temporary bypass or shunt, either to decrease lower extremity ischemia time during placement of a fenestrated aortic endograft or to allow for continued limb, visceral, and renal perfusion during thoracic aortic clamping for thoracoabdominal aortic reconstruction. Axillofemoral bypass has also been described as a temporary extraanatomic shunt in patients with blunt infrarenal aortic injury. And although its use as temporary adjunct may be appropriate in patients with aneurysmal disease, especially in patients with prior kidney transplant, axillofemoral bypass is not definitive repair in this patient population. Rather, these patients require either open or endovascular repair of the diseased aortic segment to prevent risk of future aneurysmal degeneration and rupture.

In patients with combined aortoiliac and infrainguinal occlusive disease, establishment of inflow to the femoral level via axillofemoral bypass may be enough to relieve symptoms, and the infrainguinal disease treated subsequently as needed. For patients with common femoral artery occlusion, patients undergoing axillofemoral bypass may require outflow to either the superficial femoral, profunda femoris, or popliteal artery. In the cases of severe limb threatening ischemia, concomitant axillofemoral and infrainguinal reconstruction may be required.

BOX 1 Indications for Axillofemoral Bypass

Anatomic
- Heavy aortic calcification

Hostile abdomen
- Previous surgery
- Excess fat or scarring
- Pelvic irradiation

Peritoneal dialysis

Comorbid conditions

Severe cardiopulmonary disease

Severe renal or hepatic disease

Otherwise unfit for major surgery

Infection
- Infected intraabdominal graft
- Infected aortoiliac graft

Mycotic aneurysm

Aortoenteric fistula

Temporary
- Bypass for temporary visceral and renal ischemia during endovascular aortic reconstruction

PREOPERATIVE EVALUATION

Patients selected for axillofemoral bypass require the same thorough preoperative evaluation as patients undergoing any major vascular procedure. Because these patients tend to be older and have more advanced comorbid conditions, a complete medical evaluation should be obtained, and the patients medically optimized before surgery.

The choice of inflow axillary artery is based on several physical examination and diagnostic imaging findings. Blood pressure measurements should be performed and compared between both upper extremities. If there is a significant difference (>10 mm Hg) between both sides, the arm with the higher pressure is chosen for inflow. If such a difference exists at baseline, this may prompt further evaluation with upper extremity pulse volume recordings or Doppler waveform analysis to help identify possible proximal occlusive disease and guide further therapy. Patients with abnormal noninvasive testing

may benefit from subsequent imaging with either computed tomographic angiography or magnetic resonance angiography. Digital subtraction angiography of the upper extremity, aortic arch, and great vessels allows for both diagnostic imaging and possible intervention for any lesions identified before bypass. In cases with no notable disease on either side, the right axillary artery is typically selected for inflow because of the higher incidence of atherosclerotic vascular disease to develop in the left subclavian artery. If axillary inflow is adequate and equal in both extremities, some surgeons will advocate the placement of the axillary limb on the side ipsilateral to the more symptomatic leg. Grafts should not be based off limbs where there is evidence of distal arm ischemia or a functioning dialysis access. Additional anatomic considerations include the presence of thoracic outlet syndrome, breast cancer, the presence of an ostomy or abdominal hernia, or other previous surgery. Finally, in patients undergoing intervention in the setting of intraabdominal sepsis, who in the future may be candidates for subsequent aortic reconstruction via a left retroperitoneal approach, the right axillary artery should be used for inflow to avoid interference of a left sided graft with a retroperitoneal approach.

OPERATIVE TECHNIQUES

Axillofemoral bypass is nearly always performed under general anesthesia in the supine position. Although the procedure can be performed under local anesthesia with sedation for patients with prohibitive surgical risks, this requires a large volume of local anesthetic to cover the extensive areas encompassed by the incisions and subcutaneous tunnels. The room should be kept warm to prevent hypothermia, and body warming adjuncts should be considered given the large surface area that is exposed. The donor arm is abducted to 90 degrees. A rolled towel is placed between the scapulae to facilitate exposure of the medial most portion of the axillary artery, and exposure of the lateral body wall that will be the site of the subcutaneous tunnel. The donor artery arm is prepped circumferentially to facilitate passive movement of the arm and direct inspection of the axillary anastomosis during the procedure, ensuring that undue tension is not placed on the anastomosis. The chest, abdomen, pubis, and upper thighs are prepped and covered with iodophor-coated clear plastic drapes, permitting for wide exposure. Perioperative antibiotics are always administered, and care is taken to avoid direct contact of prosthetic graft to skin.

A transverse infraclavicular incision is made approximately one fingerbreadth below the lateral one third of the clavicle and carried through the clavipectoral fascia, exposing the pectoralis major muscle. The pectoralis major muscle fibers are split in the horizontal plane and pushed superiorly and inferiorly, exposing the deep fascia and, beneath it, the investing fascia of the axillary artery, vein, and brachial plexus elements. The pectoralis minor muscle may be retracted slightly laterally to enhance exposure of the first portion of the axillary artery; however, in most cases, it is preferable to divide the muscle to prevent excessive graft tension or kinking. The axillary vein is first identified and retracted caudally. Frequently, this requires the identification and ligation of crossing venous tributaries. The axillary artery is then exposed from the clavicle medially to the pectoralis minor muscle laterally and encircled with silicone vessel loops, taking care to isolate and preserve smaller branches. Given the proximity of the brachial plexus, it is best to avoid excessive use of electrocautery when exposing the axillary artery through the length of the incision.

The femoral arteries are exposed in the standard fashion with longitudinal or oblique groin incisions. This allows for the isolation and control of the superficial and profunda femoris arteries and gives the operator flexibility in the placement of the femoral anastomoses. Longitudinal incisions will facilitate adjunctive procedures such as femoral endarterectomy and/or patching when required. The femoral anastomoses are generally placed in the distal common femoral artery over the takeoff of the profunda femoris artery. Variation of the site of anastomosis is dependent on the location and degree of disease in the iliofemoral system and, if necessary, direct anastomosis to the superficial femoral or profunda femoris artery is possible. If the common, superficial, and deep femoral arteries are all occluded, direct reconstruction to the popliteal artery may be required.

Once the vessels are exposed, a long, standard tunneling device is used to create a subcutaneous tunnel between the axilla and groin. The graft should be tunneled in the midaxillary line to prevent kinking and should initially take a lateral course under the pectoralis minor that follows a gentle curve in the lateral chest wall. A countercincision can be made just below the inferior aspect of the pectoralis major on the lateral chest wall to facilitate tunneling. For patients undergoing bilateral grafts, a second suprapubic tunnel is created between the subcutaneous space over the inguinal ligaments into the exposed femoral incision using either a tunneling device or large aortic clamp.

Systemic heparin is given after graft tunneling. An externally supported polytetrafluoroethylene or Dacron graft is used as the conduit. All anastomoses are performed in an end to side fashion and are typically constructed using 5‐0 or 6‐0 polypropylene suture. The axillary anastomosis is generally performed first. It is very important to place the axillary graft anastomosis along the anterior surface of the axillary artery as medially as possible to avoid tension on the anastomosis site when the arm is abducted. It should also be performed anterior to the axillary vein to prevent compression and allow for easier access to this region should a second operation become necessary. The graft is cut in a beveled fashion and the anastomosis created at a somewhat acute angle (Fig. 1). Leaving a slight excess length of graft in the axilla has been advocated to reduce the likelihood of tension on the anastomosis. This can also be accomplished by modifying the distal course of the graft such that it travels adjacent and nearly parallel to the axillary artery for 8 to 10 cm into the axilla, and then directed to a redundant curve into the chest wall (Fig. 2). Thus, tension along the graft is concentrated along the length of the curve in the axilla instead of the anastomosis. The axillary anastomosis can be constructed with a single suture begun at the mid posterior point of the anastomosis or with two sutures beginning at the heel and toe. Femoral anastomoses initially at the heel and toe and are sutured on each side of the artery toward the center of the arteriotomy.

The distal anastomosis is conventionally performed in an end to side fashion to the appropriate artery in the groin. Confirmation of the patient's pulse status in both upper and lower extremities should be performed prior to closure. This can be done with continuous wave Doppler. In the case of axillofemoral bypass, multiple graft configurations are possible. Typically, the femorofemoral graft may be placed with the distal anastomotic limb of the axillofemoral graft. Conversely, the femorofemoral graft may be placed first and the distal anastomosis of the axillofemoral graft may be attached to the ipsilateral femorofemoral graft anastomotic limb. In obese patients, tension on the femoral anastomosis can be alleviated by adopting a ripple knee configuration (Fig. 3). The anastomosis is created with the heel caudal to the toe, thus the graft initially takes a caudal course before heading cephalad and crossing the midline. In this configuration the tension is transferred from the anastomosis to the fingertip point of the graft, reducing the risk of anastomotic disruption. There are no objective data that suggest superiority of any bypass configuration. Prefabricated grafts are also available that mitigate the need for a graft to graft anastomosis altogether.

RESULTS

Reported patency rates with axillofemoral bypass have varied widely over the past several decades, from as low as 59% to as high as 85% at 3 years. This variability was due in part to changing patient selection and indications over the past several decades, as well as status of the patient's arterial outflow. Patients undergoing axillofemoral bypass for emergent acute lower extremity ischemia tended to suffer more perioperative complications and poorer outcomes on the basis of their presenting pathology and comorbidities. Patients undergoing bypass

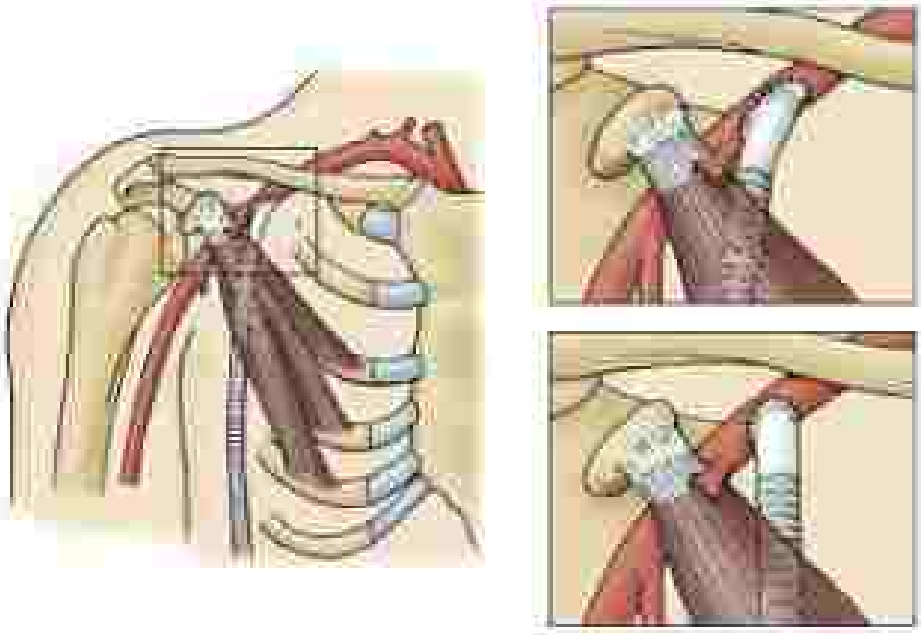

FIG. 1 Operative findings in cases of graft disruption. Femur-producing disruptions occurs with arm abduction/extension as illustrated. Top inset, Common disruption with "hood" of graft scar and scarce pulling out of "cone" of graft. Bottom inset, Complete circumferential graft disruption adjacent to anastomosis. Blaisdell and [illegible] in their initial description of the procedure, carefully recommend placing the axillary anastomosis on the first portion of the axillary artery to avoid undue tension with arm movement. (From Dyke I M, Porth H, [illegible] of Acute Disruption of Polytetrafluoroethylene Grafts Used for Axillo-[illegible] Anastomosis: A Complication of Axillofemoral Grafting. J Vasc Surg. 1994;20(1):120.)

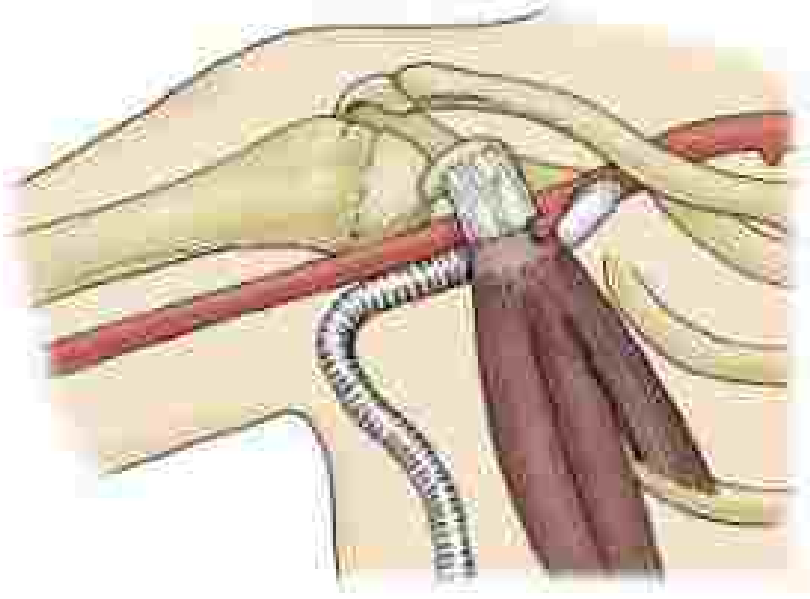

FIG. 2 Modified technique of axillofemoral graft proximal anastomosis. Graft is anastomosed to end-to-side fashion to first portion of axillary artery and evasion parallel and adjacent to artery beneath pectoralis minor for 8–10 cm before being directed in gentle and redundant curve to axilla to lie against chest wall in subcutaneous position. (From Dyke I M, Porth H, [illegible] of Acute Disruption of Polytetrafluoroethylene Grafts Used for Axillo-[illegible] Anastomosis: A Complication of Axillofemoral Grafting. J Vasc Surg. 1994;20(1):120.)

for claudication tended to have superior results, both in symptomatic improvement and patency compared to patients with critical limb ischemia likely due to significantly worse outflow disease in the latter group. However, axillofemoral bypass offers fair to excellent limb salvage rates in those presenting with CLI, with 3 year limb salvage estimates ranging from 69% to 80%. The overall perioperative mortality of axillofemoral bypass ranges from 3% to 12%, and estimated survival following axillofemoral bypass may be as low as 63% at 28 months and 35% at 3 years, although rates may be rising because of improved medical management of cardiopulmonary comorbidities.

Axillofemoral bypass is generally performed in lieu of axillofemoral bypass for reasons noted previously. Although there are no randomized comparisons of axillofemoral and axillofemoral bypass, there have been several retrospective case control studies comparing the two procedures. A recent study by Passman et al. reported a 5-year estimated patency of 74% for axillofemoral bypass versus

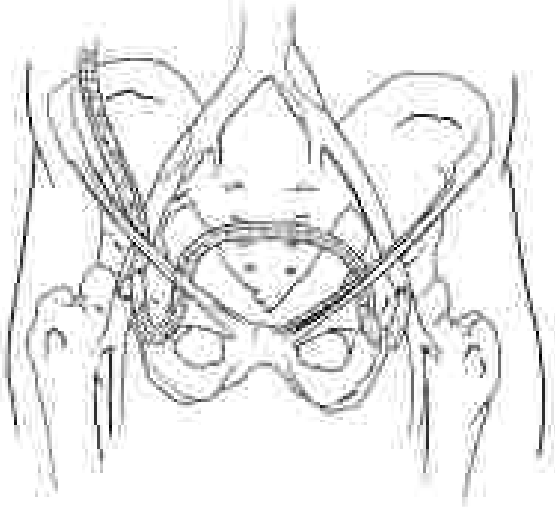

FIG. 3 Saint Mary configuration of femoral anastomosis: vessel is displaced from the anastomosis to the inferior bend of the supportive graft, which acts as a ridge, reducing the risk of disruption.

80% for aortobifemoral bypass, a difference that was not statistically significant. Although these data remain under scrutiny for patient selection, many surgeons use it as justification for offering high-risk patients extraanatomic revascularization. Not surprisingly, patients who underwent axillobifemoral bypass tended to be older, underwent surgery for limb salvage, and had higher rates of heart disease, renal failure, and prior abdominal or aortic surgery compared to those who underwent aortobifemoral bypass. Although there was no significant difference in operative mortality between the two groups, patients undergoing axillobifemoral bypass had fewer rates of postoperative complications compared to aortobifemoral bypass (9.2% vs 19.4%, respectively; $P < .05$). Although there was no difference in myocardial infarction, graft occlusion, or bleeding rates, patients who underwent aortobifemoral bypass had higher rates of pulmonary failure, acute renal failure, and stroke. There was no significant difference in patency and limb salvage rates at 5 years, although patients who underwent axillobifemoral bypass had lower overall survival.

Although much as been theorized about the potential difference in a bifemoral versus bifemoral configuration may place on graft flow rates and thus, long term patency, there has been no significant difference in a retrospective study seen between axillobifemoral and axillobifemoral grafts. There have been no significant differences associated with graft diameter nor or the presence of external graft support, however anecdotally, many vascular surgeons opt for an 8 mm polytetrafluoroethylene graft with external support.

When comparing reports in the literature regarding axillofemoral bypass grafts, there is considerable variability in the techniques used and the outcome measures defined, for example, primary versus secondary patency. In addition, it must be noted whether graft components are considered separately in patency calculations, as some authors may consider the axillofemoral and the femorofemoral components as distinct grafts.

COMPLICATIONS

Despite issues of graft patency, axillofemoral bypasses are generally well tolerated in patients with relatively infrequent reported complications. Axillary anastomosis disruption, while rare, is the most serious and life-threatening of all complications. Most cases can be attributed to excessive tension, and strategies to avoid such graft problems have been alluded to earlier in this chapter. A typical clinical scenario will involve the sudden onset of infraclavicular pain, swelling, or upper extremity neurologic symptoms following the extension or abduction of the ipsilateral arm. In such emergent situations, the single most important aspect of surgical intervention is obtaining proximal control before entering the disrupted region. This can be done either via supraclavicular approach to gain control of the subclavian artery, or with proximal and distal balloon occlusion under an endovascular fluoroscopic guided approach. Once proximal control is obtained, the treatment of choice is to disconnect the graft and place a patch over the anastomotic site (Dacron salvage is not possible).

Acute thrombosis of the axillary artery is often associated with a technical problem such as clamp injury or kinking of the native axillary artery and can be remedied with thrombectomy with patch angioplasty. Graft thrombosis is typically a result of low flow, typically because of increased resistance from progression of outflow disease rather than proximal inflow atherosclerosis. Graft salvage can be performed either with immediate operative thrombectomy or catheter based thrombolytic therapy. In either case, the underlying outflow problem should be diagnosed and addressed following initial treatment. In the event of graft thrombosis, patency can frequently be reestablished with thrombectomy performed under local anesthesia. We prefer to perform these procedures under direct fluoroscopic guidance for several reasons. First, the chance of injury to the native vessel is reduced by preventing overdistention of the balloon thrombectomy catheters. Second, it allows the surgeon to identify and possibly treat any underlying inflow or outflow lesions with and endovascular approach. Finally, should a revision be required, and angiogram defining the patient's anatomy can be obtained. In patients suffering from thromboembolism of the brachial artery resulting from steno syndrome with graft occlusion, open thrombectomy of the brachial artery with flush ligation of the axillofemoral graft at the anastomosis or occlusion of the occluded graft using a stent is the recommended approach.

Upper extremity steal syndromes is rare, but often associated with proximal subclavian disease, which can be treated with transfemoral or transbrachial balloon angioplasty with or without stent. Although the presence of inflow disease should have been evident in preoperative testing, atherosclerotic disease progression can lead to significant proximal stenosis years after initial bypass.

Fortunately, the incidence of graft infection for axillofemoral bypass is low, despite the higher risk patient population. However, when performed in situations of intraabdominal graft infection, rates of graft contamination have been reported as high as 27%. The treatment is removal of infected graft and establishment of inflow from the contralateral axillary artery. Secondary tunneling of the femorofemoral segment requires avoiding the previously infected field, and in some cases necessitates tunneling underneath the anterior abdominal musculature fascia. In rare cases of severe bilateral groin infections, bilateral axillofemoral bypass grafting should be considered. For those patients with noninfected asymptomatic perigraft seroma, the standard approach is to allow such collections to resolve spontaneously without intervention. If the seroma does not resolve after several months, it should be drained in the operating room under sterile conditions.

POSTOPERATIVE MANAGEMENT

Patients are placed on single or dual antiplatelet therapy with formal anticoagulation reserved largely for patients with a known hypercoagulable state, or in whom a secondary procedure was required to reestablish patency. As in all patients with peripheral artery disease the use of a statin is recommended. Graft surveillance is performed according to standard protocols generally every three months for the first year, every 6 months for the second year, and yearly thereafter. The need for a subsequent intervention or other abnormal findings on duplex may necessitate more frequent surveillance.

CONCLUSIONS

Axillofemoral bypass is an important and valuable option in the treatment of patients with aortoiliac occlusive disease. For many reasons, it is the preferred or only viable option for patients with significant anatomic or medical comorbidities, which preclude standard bypass options. Axillofemoral bypass can be performed with

acceptable morbidity, mortality, and long-term results, even in high-risk patients. For these reasons, surgeons should be familiar with the indications and application of these techniques.

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Management of Peripheral Arterial Thromboembolism

Colby J. Swayngim, DO, and Thomas H. Cogbill, MD, FACS

The incidence of noncerebral systemic embolic events has decreased significantly with earlier diagnosis of atrial fibrillation and use of oral anticoagulation. However, embolism to the extremities may still result in severe morbidity and mortality if not diagnosed early and managed expeditiously. Various sources of emboli have been described; cardiac causes are most common, including atrial fibrillation (AF), acute myocardial infarction, left ventricular dysfunction, and prosthetic heart valves with inadequate anticoagulation. Anatomically, arterial emboli to the extremities often lodge at bifurcations; lower extremities are affected more frequently than upper extremities (Table 1).

The overall incidence of lower extremity thromboembolism in an adult referral population decreased from 7.9 per 100,000 in 2000 to 3.5 per 100,000 in 2014. Approximately 0.5% of patients with AF will experience clinically significant noncerebral systemic embolic events, with an incidence in contemporary reviews of 0.24 per 100 patient-years. Approximately two thirds of these events affect the extremities and one third affect the visceral mesenteric circulation. Risks are significantly higher among patients with permanent rather than paroxysmal AF and with AF of longer duration (>2 years). In these patients, anticoagulation use has been associated with a lower incidence of systemic emboli, with direct oral anticoagulants being at least as effective as vitamin K antagonists. Over the past decade, the use of antiplatelet or antithrombotic medication has remained 2.3% per year. Thirty-day mortality in this patient population after a systemic embolic event is 12% to 25% and has changed little over the past 3 decades. Major adverse cardiac events within 1 year of a lower extremity thromboembolic event is about 18%. In patients with prosthetic valves the risk of a thromboembolic event is between 0.6% and 2.3% per patient-year. Thromboemboli originate from mitral prosthetic valves two to three times more frequently than from aortic prosthetic valves. Other cardiac sources of emboli include atrial myxomas and valvular heart disease due to rheumatic fever or endocarditis.

CLINICAL PRESENTATION

Symptoms and signs of acute peripheral artery embolism are often characterized by the "six Ps" associated with acute limb ischemia (ALI): pain, pulselessness, poikilothermia, paresthesia, pallor, and paralysis. History and physical examination help to differentiate between patients with peripheral arterial disease, and those with an acute embolic event. Symptoms that are chronic (months to years), progressive, associated with claudication, or rest pain and nonhealing wounds are most likely to be associated with peripheral arterial disease. Patients with ALI caused by embolism are more likely to have an arrhythmia or recent cardiac event. Other differential diagnoses to consider are acute aortic dissection, tubular disease, aneurysmal disease, arterial injury from recent vascular intervention, or thrombophilia.

Careful physical examination is critical in determining the severity of ALI and the level of occlusion, which then may indicate the most appropriate management pathway. The color and temperature of the skin should be noted with level of demarcation documented. Both sensory and motor neurologic examination should be performed with location of areas of diminished sensation or complete anesthesia and muscle weakness or paralysis. One should compare the ipsilateral vascular exam to the contralateral side, checking for presence and character of all pulses, Doppler signals, and segmental pressures. Absence of the femoral pulse or a "water hammer" femoral pulse on one side suggests a unilateral embolus lodged at or near the femoral bifurcation. Absence of both femoral pulses suggests an aortic or aortoiliac embolus. Presence of a strong, normal, femoral pulse with inaudible Doppler flow or absence of pulses to the ipsilateral pedal arteries usually indicates thromboembolism to more distal vessels in the leg. Based on physical findings, the severity of ALI can be stratified into four classes (Table 1).

PREINTERVENTION IMAGING

Patients with a classic history (acute onset of ischemic symptoms, presence of atrial fibrillation, and no previous arterial disease) and physical findings (signs of ischemia, ipsilateral loss of pulses and Doppler flow compared with normal vascular exam on contralateral limb) require no imaging to confirm the diagnosis. Delaying therapy may exacerbate the muscle and nerve damage associated with prolonged ischemia. Additionally, the cost and morbidity of imaging can be avoided.

Preintervention imaging is helpful if the diagnosis is not clear or if there is a history of preexisting atherosclerotic disease or vascular interventions. Ultrasound may be used to identify arterial emboli, aneurysmal disease, or to exclude deep vein thrombosis as a cause for symptoms. Computed tomographic angiography (CTA) of the chest, abdomen, pelvis, and lower extremity runoffs may establish or exclude differential diagnoses such as arterial dissections, tumor-based aneurysms, and atherosclerotic disease. In cases in which an embolism is identified by ultrasound or CTA, these images may assist in operative planning. Finally, conventional angiography in a hybrid operating room or interventional radiology suite may be performed as a prelude to open or endovascular procedures in patients with a previous history of atherosclerotic vessel disease, previous vascular

acceptable morbidity, mortality, and long-term results, even in high-risk patients. For these reasons, surgeons should be familiar with the indications and application of these techniques.

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The overall incidence of lower extremity thromboembolism in an adult referral population decreased from 7.9 per 100,000 in 2000 to 3.5 per 100,000 in 2014. Approximately 0.5% of patients with AF will experience clinically significant noncerebral systemic embolic events, with an incidence in contemporary reviews of 0.24 per 100 patient-years. Approximately two thirds of these events affect the extremities and one third affect the visceral mesenteric circulation. Risks are significantly higher among patients with permanent rather than paroxysmal AF and with AF of longer duration (>2 years). In these patients, anticoagulation use has been associated with a lower incidence of systemic emboli, with direct oral anticoagulants being at least as effective as vitamin K antagonists. Over the past decade, the use of antiplatelet or antithrombotic medication has remained 2.3% per year. Thirty-day mortality in this patient population after a systemic embolic event is 17% to 25% and has changed little over the past 3 decades. Major adverse cardiac events within 1 year of a lower extremity thromboembolic event is about 18%. In patients with prosthetic valves the risk of a thromboembolic event is between 0.6% and 2.3% per patient-year. Thromboemboli originate from mitral prosthetic valves two to three times more frequently than from aortic prosthetic valves. Other cardiac sources of emboli include atrial myxomas and valvular heart disease due to rheumatic fever or endocarditis.

CLINICAL PRESENTATION

Symptoms and signs of acute peripheral artery embolism are often characterized by the "six Ps" associated with acute limb ischemia (ALI): pain, pulselessness, poikilothermia, paresthesia, pallor, and paralysis. History and physical examination help to differentiate between patients with peripheral arterial disease, and those with an acute embolic event. Symptoms that are chronic (months to years), progressive, associated with claudication, or rest pain and nonhealing wounds are most likely to be associated with peripheral arterial disease. Patients with ALI caused by embolism are more likely to have an arrhythmia or recent cardiac event. Other differential diagnoses to consider are acute aortic dissection, valvular disease, aneurysmal disease, arterial injury from recent vascular intervention, or thrombophilia.

Careful physical examination is critical in determining the severity of ALI and the level of occlusion, which then may indicate the most appropriate management pathway. The color and temperature of the skin should be noted with level of demarcation documented. Both sensory and motor neurologic examination should be performed with location of areas of diminished sensation or complete anesthesia and muscle weakness or paralysis. One should compare the ipsilateral vascular exam to the contralateral side, checking for presence and character of all pulses, Doppler signals, and segmental pressures. Absence of the femoral pulse or a "water hammer" femoral pulse on one side suggests a unilateral embolus lodged at or near the femoral bifurcation. Absence of both femoral pulses suggests an aortic or aortoiliac embolus. Presence of a strong, normal, femoral pulse with inaudible Doppler flow or absence of pulses to the ipsilateral pedal arteries usually indicates thromboembolism to more distal vessels in the leg. Based on physical findings, the severity of ALI can be stratified into four classes (Table 1).

PREINTERVENTION IMAGING

Patients with a classic history (acute onset of ischemic symptoms, presence of atrial fibrillation, and no previous arterial disease) and physical findings (signs of ischemia, ipsilateral loss of pulses and Doppler flow compared with normal vascular exam on contralateral limb) require no imaging to confirm the diagnosis. Delaying therapy may exacerbate the muscle and nerve damage associated with prolonged ischemia. Additionally, the cost and morbidity of imaging can be avoided.

Preintervention imaging is helpful if the diagnosis is not clear or if there is a history of preexisting atherosclerotic disease or vascular interventions. Ultrasound may be used to identify arterial emboli, aneurysmal disease, or to exclude deep vein thrombosis as a cause for symptoms. Computed tomographic angiography (CTA) of the chest, abdomen, pelvis, and lower extremity runoffs may establish or exclude differential diagnoses such as arterial dissections, thrombosed aneurysms, and atherosclerotic disease. In cases in which an embolism is identified by ultrasound or CTA, these images may assist in operative planning. Finally, conventional angiography in a hybrid operating room or interventional radiology suite may be performed as a prelude to open or endovascular procedures in patients with a previous history of atherosclerotic vessel disease, previous vascular

interventions, or thromboembolism with a distal distribution of occlusions in the presence of intact proximal (femoral or brachial) pulses but loss of distal pulses and/or Doppler flow.

THROMBOEMBOLISM MANAGEMENT STRATEGY

The goals of therapy are to prevent further propagation of thrombus and to reestablish perfusion to the affected limb(s) as quickly as possible. When a peripheral artery embolism is suspected, initial management includes intravenous limb resuscitation with normal saline and anticoagulation with intravenous heparin using a loading bolus of 75 to 100 U/kg followed by a 15 U/kg per hour infusion to achieve an activated partial thromboplastin time (aPTT) goal of 60 to 80 seconds. Patients who are intolerant to heparin should receive a direct thrombin inhibitor such as lepirudin or argatroban with a similar aPTT goal. A 12-lead electrocardiogram should be obtained. Baseline laboratory tests should include complete blood count, serum creatinine, glucose, electrolytes, creatine phosphokinase (CPK), lactate, and a blood bank sample for type and screen. Anticoagulation and serial evaluation are sufficient for the small number of arterial embolism patients with class I ALI because the limb is not immediately threatened in these situations.

The two primary approaches for treatment of class II ALI resulting from peripheral artery embolism are open surgical thromboembolectomy and endovascular therapy consisting of percutaneous mechanical thrombectomy and/or catheter directed thrombolysis. There was a 4% increase per year in the number of endovascular procedures used for peripheral artery thromboembolism from 2003 to 2014. A Cochrane meta-analysis of five prospective, randomized controlled trials of patients with ALI compared catheter directed thrombolysis with tissue plasminogen activator (tPA) or urokinase to surgical thromboembolectomy. Death and amputation rates within 1 year were similar for each treatment modality; however, the rates of stroke (1.3% vs 0%), major bleeding (0.8% vs 3.3%), and distal embolization (12.3% vs 0%) were significantly higher following thrombolysis. Current methods of percutaneous mechanical thrombectomy were not evaluated in this meta-analysis. A recent single-center study found similar technical success and amputation rates for open thromboembolectomy versus endovascular techniques, including percutaneous mechanical thrombectomy. Open surgical and endovascular techniques are not mutually exclusive options. Increasingly, these two approaches are utilized in tandem (hybrid approach) to achieve optimal extremity reperfusion. In a small number of cases, extremity perfusion remains insufficient after open and/or endovascular interventions. Completion angiography may demonstrate persistent acute or chronic occlusive disease that requires vascular bypass grafting for limb salvage.

Factors to be considered in making therapeutic decisions include equivalence of clinical outcomes, comparative costs, length of time to reperfusion, procedural risks, and speed of recovery. Contraindications to pharmacologic thrombolysis include active hemorrhage, stroke, recent trauma, severe hypertension, intracranial tumor, or a recent surgical procedure. Risk of contrast induced nephropathy must also be evaluated whenever angiographic imaging is one component of a therapeutic modality. Regardless of the therapeutic modality selected, patients and their families should be counseled on the procedure related complications as well as the advantages and disadvantages when compared with alternative approaches.

In an effort to balance the previously mentioned considerations, we developed a treatment algorithm that can be used as a guide for management of lower extremity artery embolism with class II ALI (Fig. 1). In patients with an absent or "water hammer" ipsilateral femoral pulse and normal pulses on the contralateral limb, open femoral thromboembolectomy is favored based on ease and speed of establishing reperfusion and fewer procedure related complications. A single bolus of thrombolytic solution such as tPA can be flushed into the distal vasculature just before closure of the arteriotomy.

Patients with acute ischemia and absence of both femoral pulses in whom an aortic or aortoiliac embolus is suspected are best managed by bilateral femoral thromboembolectomies based on speed of reestablishing perfusion and effective removal of significant clot burden. These procedures should be performed in a hybrid operating room because completion angiography and adjunctive endovascular or open procedures may be necessary in these patients.

Patients with acute ischemia and a normal ipsilateral femoral pulse but absent ipsilateral distal pulses and normal contralateral pulses should undergo initial angiography with a plan for percutaneous mechanical thrombectomy and/or catheter-directed thrombolysis (Fig. 1). This approach is much more likely to achieve effective reperfusion of the smaller distal vessels involved with this distribution of thromboembolism. Angiography can better identify the site

TABLE 1 Distribution of Extremity Arterial Emboli

Site of Embolism	Approximate Frequency
Lower Extremity	84.0%
Aortoiliac	29.7%
Common Femoral	34.0%
Superficial Femoral	4.5%
Popliteal	10.5%
Tibial	5.0%
Upper Extremity	16.0%
Brachial	8.1%
Axillary	4.5%
Radial and ulnar	2.4%

TABLE 2 Classification of Acute Limb Ischemia

Class	Sensory Loss	Muscle Weakness	Arterial Doppler
I. Viable limb	None	None	Audible
IIA. Marginally threatened limb	Toes or none	None	Often inaudible
IIB. Immediately threatened limb	More than toes; Rest pain	Mild or moderate	Usually inaudible
III. Irreversible	Profound; anesthetic	Profound; paralysis	Inaudible

From Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26(3):517–538.

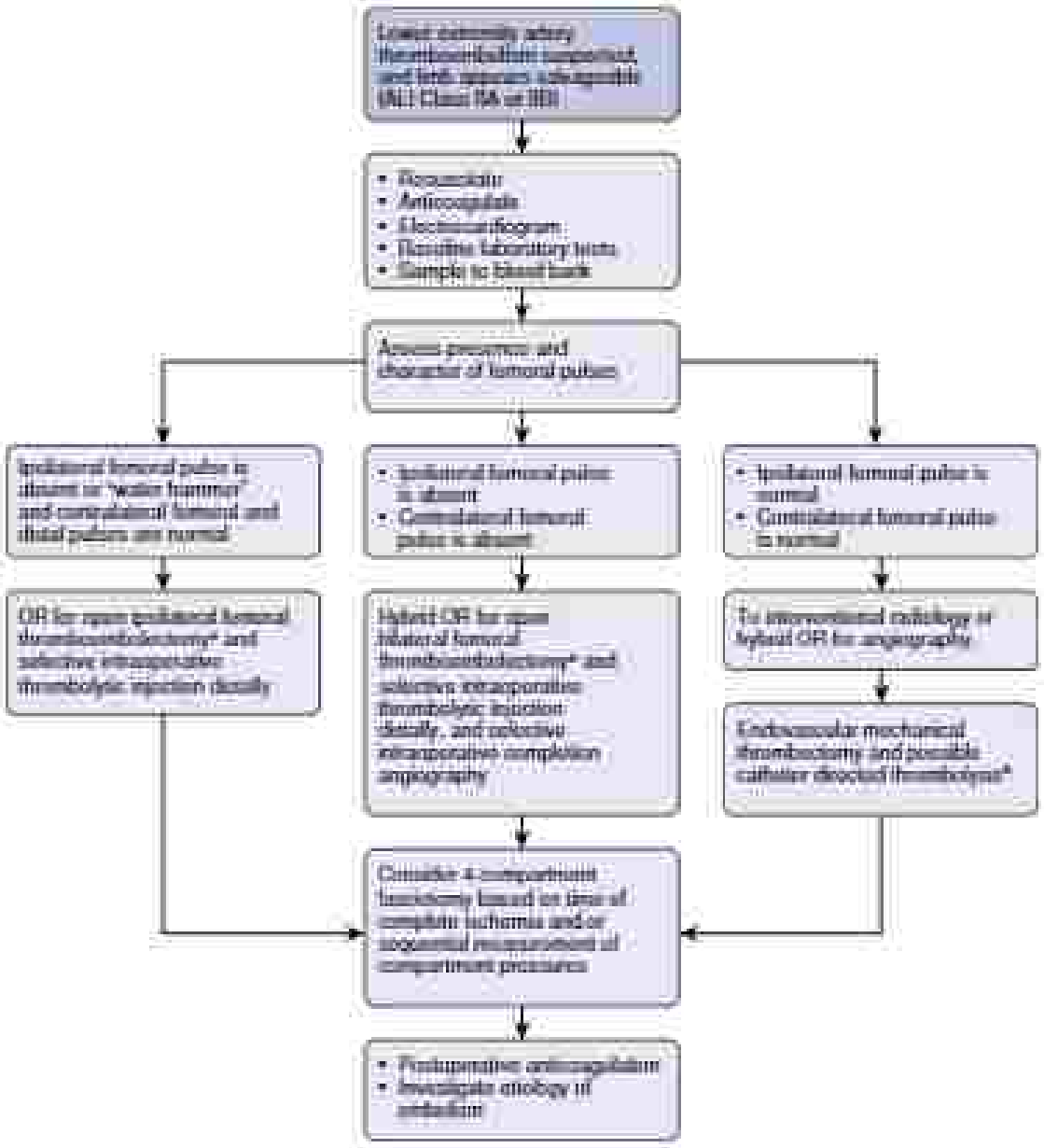

FIG. 1 Treatment algorithm for patients with class IIA and IIB acute lower extremity ischemia due to arterial thromboembolism. OR, operating room. *Open surgical and endovascular techniques may be used in tandem (hybrid approach) to achieve adequate extremity perfusion. Vascular surgical bypass may occasionally be necessary for limb salvage in the presence of a persistent acute or chronic arterial occlusion.

of embolization and thrombolysis therapy can be delivered by catheter directly into the thromboembolus. Additionally, identification of concomitant arteriosclerotic lesions may dictate the best method for revascularization.

For upper extremity emboli, we favor open brachial thromboembolectomy based on small vessel size, ease and speed of reestablishing perfusion, and fewer procedure related complications.

In the rare patient who presents with prolonged (>12 hours) class III A1I with complete loss of motor and sensory neurologic function as well as changes of livedo reticularis, revascularization of a nonviable limb may cause life threatening physiologic changes with little chance of limb salvage. A primary amputation in this setting is preferable to avoid multiple system organ failure and death.

OPEN SURGICAL TREATMENT

Femoral Thromboembolectomy

This procedure can often be performed with a local anesthetic and maintained anesthesia care. The common femoral, superficial femoral, and profunda femoris arteries are dissected and surrounded with vessel loops. A transverse arteriotomy is placed on the distal common femoral artery if there is no evidence of atherosclerotic disease so that the artery is not narrowed during closure. In patients with atherosclerotic plaque a longitudinal arteriotomy can be performed allowing for endarterectomy if necessary and closure with a patch to prevent arterial narrowing. A balloon tipped catheter is passed proximally and distally beyond the occlusion, with subsequent balloon inflation and

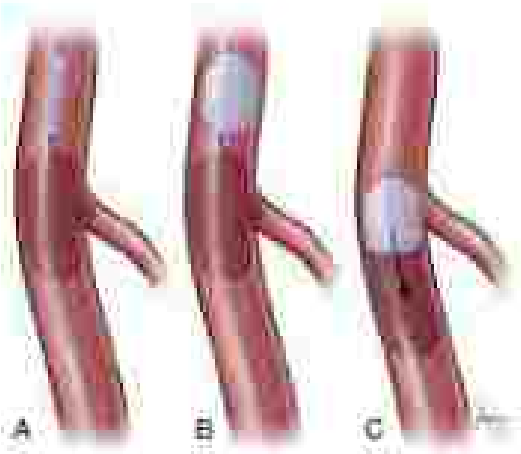

FIG. 2. Technique of balloon thromboembolectomy. (A) Pass a balloon-tipped catheter via arteriotomy through the embolus into the vessel distal to the area of occlusion. (B) Inflate the balloon while slowly withdrawing the catheter to prevent damage to the arterial wall. (C) Withdraw the inflated balloon catheter and remove thromboembolic material through the arteriotomy. (Courtesy Cleveland Clinic Center for Medical Art & Photography. Copyright 2009. All rights reserved.)

withdrawal leading to removal of the thromboembolus (Fig. 2). We recommend balloon inflation while slowly withdrawing the catheter to prevent arterial injury. Although resistance to balloon withdrawal may be related to the presence of an embolus, it also may be related to the presence of an atherosclerotic plaque, and a degree of balloon deflation may be required to avoid arterial injury. Likewise, overinflation of an inappropriately large balloon or inadvertent passage of the catheter into a branch vessel can cause arterial dissection or rupture. Two to three additional passes of an embolectomy catheter without retrieval of additional embolic material is usually sufficient. Qualitative assessment of adequate inflow can be performed by loosening the proximal vessel loop or releasing the proximal clamp. Submission of the thrombus for pathologic examination may be considered should myxoma or tumor thrombus be a possibility. The availability of over-the-wire Fogarty catheters allows the catheter to be passed into all major runoff vessels of an extremity under fluoroscopic guidance. If a standard Fogarty catheter has been used, an intraoperative completion angiogram may be considered, as the presence of backbleeding alone may not confirm complete thrombus retrieval. Should there be concern for residual thrombus, a single bolus of thrombolytic solution such as tPA can be flushed into the distal arterial bed prior to arterial closure. Intraoperative angiography is mandatory should audible Doppler signals at the dorsalis pedis or posterior tibial arteries not be restored.

AORTIC THROMBOEMBOLECTOMY

When an aortic bifurcation embolus is suspected, open surgery in a hybrid operating room is preferred. Bilateral groin cutdowns should be performed and the common, superficial, and deep femoral arteries exposed in order to obtain proximal and distal control. After systemic heparinization, a 4Fr or 5Fr embolectomy catheter is passed cranially, approximately 25 cm into the infrarenal aorta through transverse arteriotomies in each common femoral artery. The contralateral femoral artery should be occluded during each passage of the balloon catheter to minimize inadvertent embolization from the aorta down the opposite limb. After achieving appropriate prograde flow, distal thromboembolectomy of the superficial femoral and popliteal arteries is performed using a 3Fr or 4Fr catheter, followed by thromboembolectomy of the profunda femoris artery with a 3Fr catheter. If attempts to clear the distal circulation are unsuccessful, arteriography is recommended to guide endovascular thrombectomy or thrombolytic therapy. We do not recommend surgical embolectomy below the popliteal artery.

BRACHIAL THROMBOEMBOLECTOMY

Surgical thromboembolectomy is recommended over endovascular therapies for upper extremity emboli due to small vessel size and ease of surgical exposure. Upper extremity thromboembolectomy is typically performed through a transverse arteriotomy to the brachial artery. The distal brachial artery may be exposed through a transverse incision just above the elbow or, if needed, an S-shaped incision may be extended across the antecubital fossa to expose the proximal radial and ulnar arteries. Once proximal and distal control is obtained, a 4Fr catheter can be passed proximally into the subclavian artery and a 3Fr catheter subsequently passed distally through the radial and ulnar arteries. Some caution is required, as loosened subclavian thrombus may be embolized inadvertently into the cerebral circulation if the catheter is passed into the aortic arch. The Fogarty catheter can be measured externally against the patient's chest and arm and marked to help estimate the position of the subclavian artery to prevent passage of the catheter proximal to the subclavian artery origin. Should there be concern for residual distal thrombus, a single bolus of thrombolytic solution such as tPA can be flushed into the distal arterial bed prior to arterial closure.

PERCUTANEOUS ENDOVASCULAR THERAPY

Catheter-Directed Pharmacologic Thrombolysis

Ultrasound-guided access to the contralateral femoral artery is obtained initially, and a diagnostic angiogram is performed as a guide for further therapy. In addition to providing a more complete view of the arterial inflow, obtaining access remote from the embolus decreases the risk of bleeding complications because of the proximity of the puncture site to the delivery of the thrombolytic agent. Once the embolic occlusion is identified on arteriography, a sheath of appropriate length is inserted, and a hydrophilic-coated angled guidewire is passed through the thromboembolus. If the guidewire is unable to traverse the occlusion, diagnosis of acute thrombosis at the site of preexisting atherosclerotic plaque should be considered. Once the thromboembolus has been traversed by the guidewire, a multiple sidehole catheter is advanced over the guidewire and thrombolytic agent is delivered directly into the thromboembolus. Although streptokinase and urokinase continue to be used worldwide, the current lytic agent of choice in the United States is tPA. A pulse-spray bolus of 10 mg of thrombolytic agent is delivered into the thromboembolus, followed by continuous infusion at approximately 0.5 mg/hr. Heparin is administered through the side port of the sheath at 500 units/hr to prevent catheter-associated thrombosis. Every 4 to 8 hours aPTT and fibrinogen levels are checked to monitor for systemic thrombolysis. Infusion is held if fibrinogen level drops below 100 mg/dL or by more than 50% from baseline. Because low-dose heparin is administered to prevent catheter-associated thrombotic complications, the aPTT is titrated to 30 to 50 seconds. Reimaging is performed in 12 to 24 hours to assess thromboembolus dissolution. Close monitoring of the access site is imperative; this is best done in a critical care unit. Patients may report increase in distal extremity pain because of embolization of thrombus that has been lysed by tPA. Continued thrombolytic infusion and analgesia are recommended with close monitoring; these symptoms should eventually improve.

PERCUTANEOUS MECHANICAL THROMBECTOMY

Percutaneous mechanical thrombectomy was introduced to decrease the need for prolonged infusion times and reduce the number of procedures required for successful catheter-directed thrombolysis.

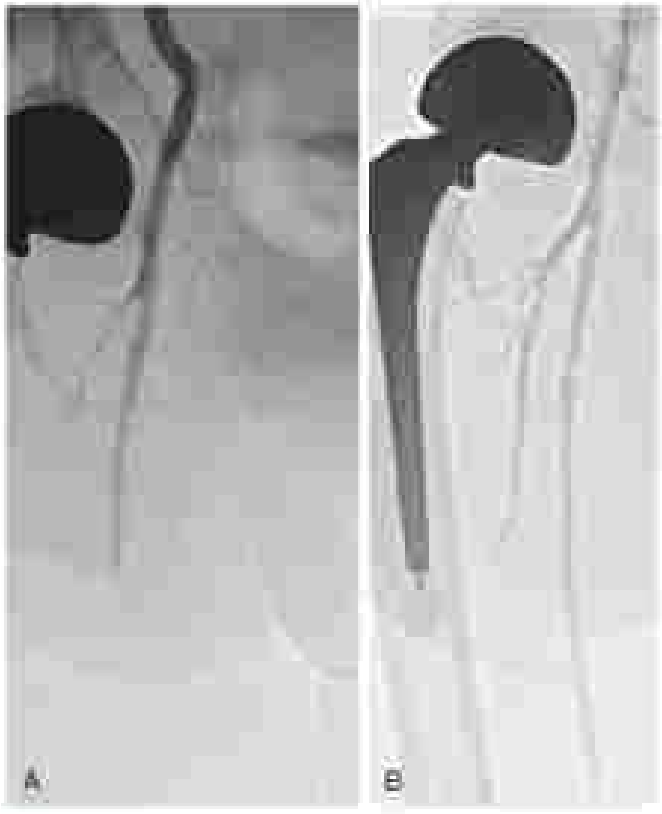

FIG 3. (A) Right femoral arteriogram obtained in a patient with atrial fibrillation, normal right femoral pulse, and cool, pale limb. Ischemia demonstrating thromboembolic occlusion of the superficial femoral artery. (B) Repeat right femoral arteriogram following pulse spray of tissue plasminogen activator and Angiojet percutaneous arterial thrombectomy demonstrating dissolution of the thromboembolism and free flow of contrast throughout superficial femoral artery.

Under ideal circumstances, percutaneous mechanical thrombectomy expeditiously reduces overall clot burden and increases the surface area of exposed clot to enable more effective pharmacologic lysis. Various devices have been designed to use suction, rotational infusion, ultrasound, or a high velocity thrombolytic jet to achieve mechanical thrombectomy. Femoral artery access is obtained in a similar manner to that described above for catheter-directed thrombolysis. Pharmacomechanical thrombolysis refers to using the percutaneous device to first face the thrombus with a pulse spray bolus of thrombolytic agent, which after a brief dwell time is followed by mechanical thrombectomy. The Angiojet Thrombectomy System (Boston Scientific) is a popular rheolytic device that works on the premise of Bernoulli's principle. Circumferentially oriented pressurized saline jets fragment the thrombus with creation of a low pressure zone, which facilitates the removal of the resultant thrombotic debris through catheter side holes. In a large multicenter registry, successful outcome was obtained in 83% of patients without adjunctive catheter-directed thrombolysis needed in 52% of patients.

POSTPROCEDURE MANAGEMENT

Hemodynamic monitoring, routine laboratory analysis with correction of acidosis or electrolyte imbalance, and serial neuromuscular examinations are necessary. Despite successful revascularization, limb loss may occur from development of acute compartment syndrome. In patients with a history of prolonged ischemia (>6 hours), a prophylactic fasciotomy should be considered. Fasciotomy is performed through medial and lateral lower extremity incisions or dorsal and volar upper extremity incisions. For patients who have not undergone prophylactic fasciotomy, the diagnosis of compartment syndrome should be considered in the presence of a tensely swollen extremity with pain on passive motion. Elevated CPK levels and myoglobinuria are late markers of tissue destruction and should not be used to establish the diagnosis. Direct compartment pressure measurements can be obtained, and fasciotomy considered if pressures are elevated (>30 mm Hg), but even in the presence of normal compartment pressures, fasciotomies should be performed if there is clinical suspicion. The wound should be left open and a vacuum assisted closure device applied in the postoperative period to reduce muscle edema. Systemic effects of muscle ischemia include rhabdomyolysis, which may cause acute tubular necrosis and renal failure. Aggressive resuscitation with intravenous fluids is the main treatment modality. This may require 1 to 2 L of normal saline per hour until diuresis is provoked and then titrating to urine output greater than 300 to 500 mL/hr until CPK drops below 5000 U/L.

Nearly all patients will require long term systemic anticoagulation to decrease the chance of a recurrent thromboembolic event. In the initial postoperative period, this is achieved with heparin or a direct thrombin inhibitor, such as lepirudin or argatroban, until bridging to an oral vitamin K antagonist is complete. Once the acute ischemic episode and its sequelae have been managed, the underlying embolic etiology should be investigated. For patients without atrial fibrillation, this approach includes transesophageal echocardiogram to evaluate the heart for vegetations, thrombus, or the presence of right to left shunt, CTA of the chest, abdomen, and pelvis with bilateral lower extremity runoff to evaluate for the presence of an aneurysm, atherosclerotic lesion or ulcer, a hypercoagulable workup, and bilateral lower extremity ultrasonography to assess for deep venous thrombosis if paradoxical embolism is suspected.

CONCLUSIONS

The incidence of acute limb ischemia secondary to arterial embolism has decreased over the past 15 years, in part from improved treatment of atrial fibrillation. However, emboli to the extremities are still responsible for limb-threatening ischemia, which requires prompt recognition and expeditious intervention. Optimal management of peripheral arterial emboli depends on the location of the embolus, the severity of ischemia, and the duration of symptoms. Contemporary treatment relies on both open surgical thromboembolectomy and endovascular techniques including percutaneous mechanical thrombectomy and catheter-directed thrombolysis. A hybrid approach to using these techniques to increasingly used to achieve limb salvage. Early limb salvage rates following treatment for peripheral arterial thromboembolism approach 90%; the amputation rate is 25% within 1 year. The 1 year overall survival rate in these patients ranges from 80% to 85% and the 5 year survival rate is less than 50%.

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Acute Peripheral Arterial and Bypass Graft Occlusion: Thrombolytic Therapy

Kelvin Hong, MD, and Robert P. Liddell, MD

Acute limb ischemia (ALI) is a vascular emergency caused by arterial embolism or thrombosis of native vessels or bypass grafts. Timely management of ALI requires expedited clinical evaluation, diagnostic workup, and initiation of appropriate treatment. Today, advances in thrombolytic agents, infusion catheters and endovascular techniques have led to catheter directed thrombolysis (CDT) becoming the treatment of choice for patients with relatively mild ALI. Patients with severe ALI need emergent surgical revascularization; however, CDT should be considered if the relative risks compared with primary operation are favorable. This chapter describes how to select the appropriate therapy for ALI, with an emphasis on the role of CDT.

PATIENT PRESENTATION AND WORKUP

Clinical Assessment

The clinical assessment of a patient with ALI should begin with a thorough history, focusing on the patient's presenting symptoms and current overall health. A history of rest pain, claudication, myocardial infarction, stroke, hypertension, diabetes mellitus, atrial fibrillation, aneurysmal disease, smoking, high cholesterol, vasculitis, and prior vascular or endovascular surgery is important to obtain. The initial physical examination should assess for the dominant clinical signs and symptoms of ALI, which traditionally include the six P's: pain, pulselessness, pallor, poikilothermy, paresthesias, and paralysis. The presence of one or more of these findings and the abruptness of their onset may also aid in determining the underlying etiology. Obvious neurologic deficits suggest an advanced state of ischemia, with sensory deficits preceding motor deficits. Frank mottling of the skin with muscle necrosis and induration implies irreversible limb ischemia (Fig. 1).

A formal stratification system has been developed to help guide the evaluation and management of ALI, while defining prognosis (Table 1). Acutely ischemic limbs should be described as viable, threatened, or irreversibly ischemic. Threatened limbs are reversibly ischemic and are salvageable with appropriate, timely intervention, whereas irreversibly ischemic limbs require amputation because major myoneuronal damage has occurred and is not reversible with surgical or endovascular revascularization.

The severity of ischemia is determined by a number of factors, including the etiology of the obstruction, the level of obstruction, the adequacy of collateral circulation, the extent of thrombus propagation, the patients underlying peripheral vascular disease and cardiac output. Although variable based on the network of existing collaterals, a period of 6 hours is generally accepted as the window in which revascularization is absolutely necessary for ALI. In practice, the degree of ischemia is more important than the absolute duration of ischemia, therefore patients must be assessed on an individual basis and in a timely fashion.

IMAGING ASSESSMENT

Imaging is done to evaluate the extent of blood flow compromise, localize culprit flow limiting lesions, and identify other sequelae of peripheral vascular disease (dissection, aneurysmal disease, thrombophilia). An acutely ischemic limb may be imaged with Doppler ultrasound (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA) before treatment. When choosing an imaging modality for native vessel disease, clinicians should take into account whether the patient has underlying renal insufficiency, diabetes, or implanted metal devices. For patients who have *normal* renal function and are not diabetic, initial evaluation with either CTA or MRA is reasonable based on their similar excellent diagnostic capabilities. Overall, DUS is a less sensitive technique for imaging native vessel stenosis than CTA or MRA; however, DUS is more ideally suited for post-lower extremity arterial bypass surgery surveillance. Asymptomatic vein graft stenosis can result in acute thrombosis and ultimately graft failure if not detected early. In contrast, DUS is not well established for evaluating long term patency of synthetic conduit bypass grafts.

DSA remains the gold standard for imaging of patients with acute limb ischemia. The chief benefit of DSA is that endovascular therapies may be initiated in the same setting as diagnostic angiography because arterial access is already achieved. Although DSA is a more invasive technique when compared with MRA and CTA, the risks associated with arterial access are minimal. Moreover, MRA and CTA are limited in assessing smaller tibial arteries and in such cases lower extremity angiography is preferred.

SELECTION OF THERAPY

The clinical and imaging assessment of a patient with ALI should be completed as quickly and efficiently as possible. Once the diagnosis of ALI is made, treatment should be initiated as soon as possible. Regardless of the etiology, all patients without contraindications should receive intravenous (IV) fluids, supplemental oxygen, an IV drip dose of aspirin, and a 100 U/kg bolus of IV heparin followed by a continuous infusion to keep the partial thromboplastin time at 2.0 to 2.5 times normal. As described earlier, the length of time a limb can endure ischemia varies with the cause and severity. The Society of Vascular Surgery/ISCVC classification based on sensory motor and Doppler evaluation, is used to triage initial limb treatments. Level I patients should be treated with heparin and observation, followed by more definitive therapy once comorbidities, functional status, and activity level are determined. Level II patients should be treated soon (Ila) or immediately (IIb) after imaging. Endovascular or operative interventions are equally efficacious in these patients, the choice being contingent on the skill and availability of the interventional radiologist or vascular surgeon. Patients with more severe ischemia (III) had traditionally been sent to surgery, but the recent advent of fast acting lytic drugs, spray pulse infusion techniques, and pharmacomechanical thrombolysis allow endovascular techniques to have a wider application. Level III patients who seek care shortly after symptom onset are candidates for surgical revascularization and fasciotomy; those presenting some time after symptom onset require amputation. Attempts to revascularize ischemic limbs late in the progression of disease are not only likely to fail but frequently result in severe pain, hyperkalemia, renal failure, and sepsis.

Recommended Interventions for Disease in Native Arteries

Catheter directed thrombolysis was first described by Dotter in 1974. When compared with high dose systemic intravenous thrombolysis CDT, resulted in significantly better outcomes with significantly lower adverse bleeding events. During the mid 1990s, a number of randomized, multicenter trials compared CDT with surgery for ALI. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial showed that CDT produces outcomes similar to surgery when used to treat thrombosed native arteries presenting within 2 weeks of the onset of symptoms. In patients

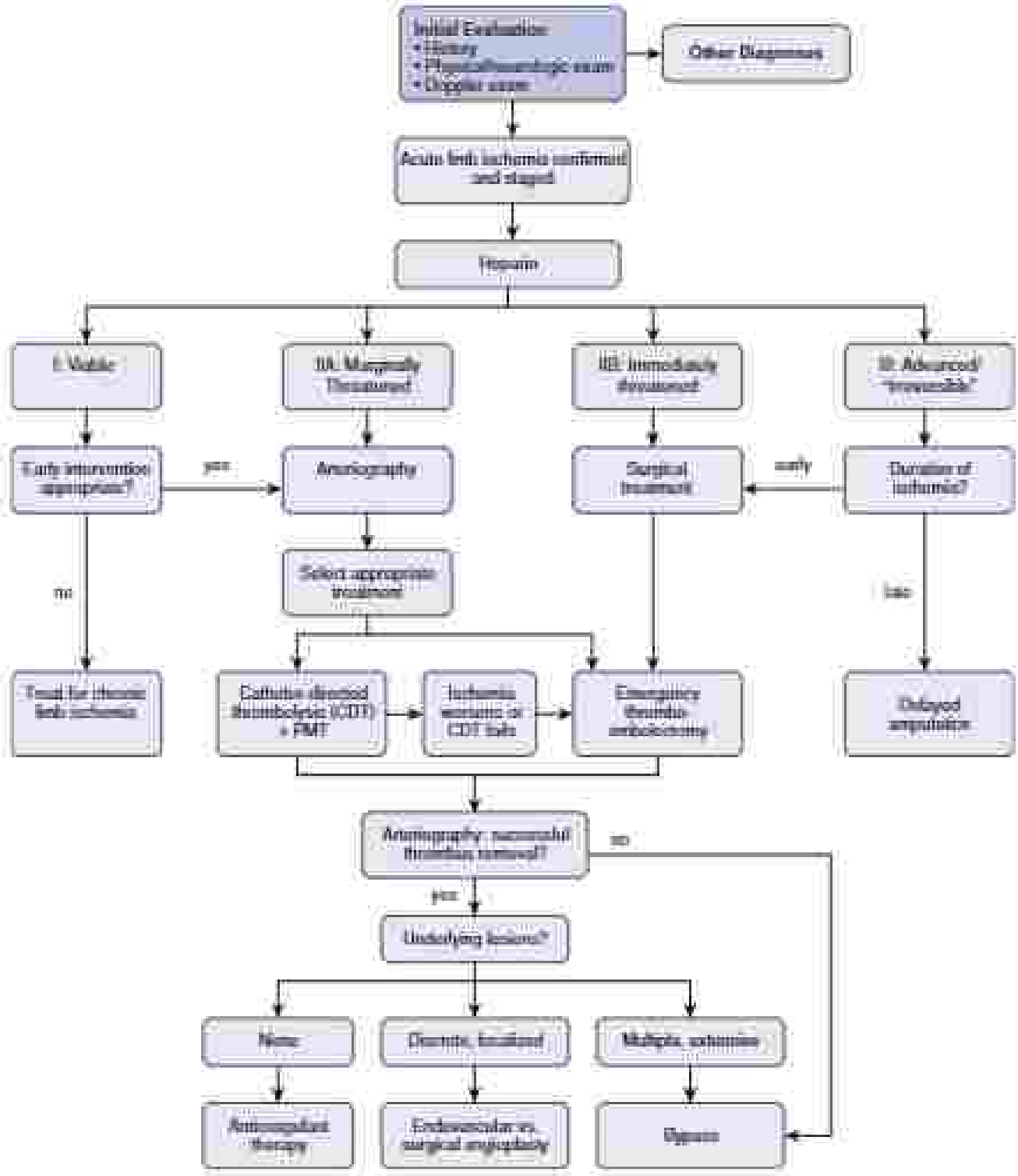

FIG. 1. Algorithm for management of acute limb ischemia. (From Rutherford RB, Acute limb ischemia. In: Rutherford RB, ed. Vascular Surgery. Philadelphia: WB Saunders; 1977. p. 1–21.)

presenting greater than 2 weeks from the onset of symptoms, surgery showed better outcomes. The STILE trial also showed that surgical interventions had better outcomes for native thrombotic or femoropopliteal disease. The Thrombolysis or Peripheral Arterial Surgery trial showed that CDT may be attempted, and then abandoned when unsuccessful in favor of more localized surgery, without increasing mortality or amputation rate. A number of retrospective studies have also demonstrated that performing CDT and angioplasty before attempting surgery can reduce the number of patients who will ultimately require surgical bypass or amputation. Although these studies do not provide definitive answers to a preferred treatment in all cases, they do suggest that CDT may improve outcomes without compromising the efficacy of subsequent surgery. Therefore, if readily available, CDT should be the first line therapy for acute native artery occlusion, with endovascular or surgical intervention to treat underlying disease once unmasked.

TABLE 1 Clinical Categories of Acute Limb Ischemia

Category	Description/Prognosis	Findings		Doppler Signals	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthesia	Profound, paralysis (rigor)	Inaudible	Inaudible

Before initiating CDT, one should assess the extent of disease in the affected limb, not only the thrombosed segment, but also in the vasculature proximal and distal to the occlusion. The assessment of distal runoff is sometimes hindered by the fact that outflow distal to an occlusion is often significantly limited. If prior studies are available, their review is often helpful in identifying possible causative underlying stenoses as well as defining distal runoff. If prior studies are not available, it is important to attempt to cross the occlusion and directly assess distal runoff without causing distal embolization. According to the Trans Atlantic Inter Society Consensus Document on Management of Peripheral Vascular Disease II guidelines, focal stenoses are best treated with percutaneous balloon angioplasty (PTA) and stenting once the native artery is opened with CDT. In contrast, long segment stenosis, diffuse disease, or limited runoff limit the affected vessel should dissuade one from initiating CDT. In diffusely diseased vessels, thrombolysis serves to only consume time while exposing the patient to potential bleeding complications. Therefore, these patients often will be triaged directly to surgical bypass.

In patients with native vessel occlusions resulting from embolic disease, lack of well developed collaterals often results in dramatic, poorly tolerated symptoms very early in the course of ischemia. When initial assessments suggest minimal baseline atherosclerotic disease, or when history points to an embolic occlusion, these patients should undergo surgical embolectomy. CDT in combination with mechanical or aspiration embolectomy is also an option. These endovascular techniques are especially efficacious below the knee, where angiographic guidance allows for evaluation and selective interventions in small arteries.

RECOMMENDED INTERVENTIONS FOR DISEASE IN BYPASS GRAFTS

The STILE trial demonstrated lower amputation rates with CDT compared with surgery for thrombotic occlusions of bypass grafts. In patients with thrombosed bypass grafts, timing of the graft failure determines the appropriate treatment. If the patient presents within the first 30 days after bypass, graft failure is most often a result of technical problems with the graft; assuming the patient is not hypercoagulable. If the bypass is partially open, imaging usually reveals the causative lesion; the most common finding is a distal anastomosis stenosis. In native vessel conduits, one will occasionally see a stenosis that results from the use of too small a caliber venous conduit, or even more uncommonly, a perivascular hematoma, resulting from improper vein preparation. Patients with early bypass failure should undergo surgical revision. An endovascular approach is only recommended in the rare case of an isolated unfavorable lesion that appears amenable to PTA. More often, thrombolysis alone serves only to open the bypass temporarily. The underlying technical problem quickly reasserts itself, and the limb once again becomes ischemic.

If the bypass goes down beyond the 30-day perioperative period, one should first consider the severity of the ischemia and the indications for the original surgery. If the ischemia does not threaten the viability of the limb, as it did in 30% of the patients in the STILE trial, and the original bypass was performed to treat life-threatening ischemia, a watch and wait approach may be warranted. It is unlikely that any revision of the graft will provide long term improvement in limb perfusion, but it is possible that further surgery could make things worse. In these cases, noninvasive imaging and DSA are appropriate to assess whether distal target vessels are available for the secondary bypass and to assess whether endovascular treatments could improve outflow from the poorly functioning bypass.

In cases of life threatening ischemia occurring beyond the 30 day perioperative window, the most common causative lesion is focal intimal hyperplasia, typically at a valve or anastomosis. CDT is the treatment of choice in these instances because it allows for identification of the treatable lesion. CDT also restores flow through the thrombosed collaterals, thus reperfusing the threatened limb. Thrombolysis should be followed by PTA once the focal lesion is identified. If a causative lesion can be identified and treated, the 1 year patency is more favorable than if there had been no lesion. Grafts maintained exclusively by CDT and PTA have been found to have excellent long-term patency rates, especially if ABIs immediately after treatment are high. There are, however, two caveats: first, the outcomes (particularly the rate of amputation free survival) of thrombolysis are generally much better in venous grafts than in synthetic grafts; second, the beneficial effect of CDT is short lived in diabetic patients, with 1 year patencies being very low. In these patients, if imaging reveals suitable distal target vessel, secondary bypasses are a superior treatment choice because of their higher patency rates.

Patients with vein grafts more than 1 year old are excellent candidates for CDT because the mature conduit has proven itself once time. The failure is usually a result of progressive atherosclerotic disease in the inflow or outflow vessels. CDT will often unmask a stenosis supporting graft with poor inflow or outflow vessels, which themselves can be treated via endovascular means to maintain graft function.

CATHETER-DIRECTED THROMBOLYSIS

Over the past 20 years, CDT has completely supplanted systemic intravenous thrombolysis. The role of CDT is to (1) restore flow, (2) reveal and underlying causative lesion, and (3) improve perfusion of the outflow vessels. The unmasked lesion should then be treated via endovascular or open surgery.

Preoperative Planning

If CDT is to be used as part of the ischemic limb treatment plan, the preprocedural consent should describe the risk of hemorrhage, limb loss, renal failure, anaphylaxis, stroke, and death. Bleeding is the most frequent significant complication associated with CDT. Intracranial hemorrhage can often be devastating, but is fortunately rare, having been reported in 1.2% (STILE) to 2.1% (Thrombolysis or Peripheral

Arterial Surgery 1) of patients undergoing CDT. Absolute contraindications to CDT include active/life-threatening bleeding, aortic dissection, recent intracranial or intraspinal surgery or trauma, and intracranial arteriovenous malformations or aneurysms. Relative contraindications include major surgery within the past 4 weeks, uncontrolled hypertension, gastric ulcers, recent eye surgery, recent stroke, recent neurosurgery, ongoing bleeding diathesis, pregnancy or the first 10 days postpartum, and intracranial neoplasms.

Technique

Patients should be given aspirin and heparin as they are being worked up for CDT. Any previous noninvasive imaging should be made available and reviewed. Pulses in both limbs should be documented, and an operating room suite should be available in the event of that conversion to open surgery be necessary. Iso-osmolar contrast should be used throughout, and the procedure should be performed under conscious sedation.

Retrograde contralateral access should be obtained with arterial puncture occurring over the femoral head. Ultrasound guided 21-gauge micropuncture access is recommended to minimize the risk of hematoma and dissection. A 5Fr vascular sheath should then be placed. A 5Fr Omni flush (AngioDynamics) or pigtail catheter should then be advanced to the level of the renal arteries. An aortogram and bilateral lower extremity runoff should then be performed.

Once the thrombosed vascular segment is identified, the wire-catheter combination should be advanced up and over the iliac bifurcation to the levels of the contralateral (affected side) external iliac artery. After a wire is placed in the contralateral external iliac artery the access catheter and 5Fr sheath should be exchanged for a 6–7Fr up-and-over sheath such as a Flexor Ballvin (Cook Medical) into the contralateral common iliac or external iliac artery. A heparin bolus is then usually administered (100 U/kg) and an activated clotting time is checked (goal activated clotting time >250 seconds).

An attempt should then be made to cross the thrombosed segment. I prefer a combination of a 45° straight or 30° angle taper Glide catheter (Terumo) and a hydrophilic guidewire (e.g., Glidewire [Terumo], Roadrunner [Cook]). This combination imparts excellent maneuverability and easily crosses most occlusions. In cases with significant underlying atherosclerotic disease, a combination of a 45° straight Glide catheter and a Bowen wire (Cook) can be used to traverse the thrombus. This combination ensures that the bent tip of the wire leads as the lumen of the diseased vessel, minimizing the risk of dissection. Use gentle, controlled attempts to cross the thrombus, with injections of dilute contrast whenever the wire-catheter combination does not easily advance. The goal is to carefully advance through the soft thrombus, avoiding embolization while staying intraluminal. Rarely, a microwire (<0.018 inch) and microcatheter (<3 Fr) may be advanced coaxially to aid in successful crossing thrombus in heavily diseased vessels with tight stenoses.

Once the thrombosed segment is crossed, the length of the occlusion should be defined and measured. An appropriate multiple side hole infusion catheter (Pulse Spray Infusion System [AngioDynamics Inc.], Katana Infusion Wire [Boston Scientific]) should then be advanced over the wire through the occlusion. The infusion length should be as close to possible to the length of the occlusion, erring on the side of a shorter infusion length. If some side holes are outside the thrombus, the infused drug will take the path of least resistance and will escape out the holes in the patent artery. After the infusion catheter is in position, the guidewire is removed and the end hole of the infusion catheter is plugged with an occlusion wire (Pulse Spray Infusion System) or infusion wire (Katana Infusion Wire). The sheath and catheter are secured to the skin, whereas the infusion catheter is secured to the sheath with Steri-Strips and sutures to prevent catheter displacement, before the patient leaves the angiography suite. I use a 150–300 U/hr intra-arterial infusion of heparin via the tip and over the sheath to prevent thrombus from forming on the tip of the sheath or along the unobstructed portion of the infusion catheter.

Infusion

Very limited data are available that compares the efficacy of thrombolytic agents for use in CDT. In the United States, streptokinase, anistreplase, alteplase (recombinant tissue plasminogen activator [tPA]), reteplase, and tenecteplase are available. A systematic review suggests that intra-arterial recombinant tPA is more effective than intra-arterial streptokinase in improving vessel patency. Lysis and bleeding rates are comparable among the various agents, with very few direct comparison trials available and no clear-cut evidence of superiority of one agent over another for CDT.

There are a number of different thrombolysis techniques described in the literature. The simplest and most often used technique is continuous infusion. In this technique, thrombolysis is performed via an infusion catheter placed after diagnostic angiography. The patient subsequently returns for follow-up angiography until a procedure endpoint (successful lysis) is reached. The bolus method involves delivery of a single, highly concentrated dose of thrombolytic agent throughout the occlusion and then initiation of continuous infusion. The pulse spray technique refers to repeated forceful injection of small aliquots of thrombolytic, thus distributing the thrombolytic agent rapidly throughout the thrombus as well as mechanically disrupting the thrombus. Pulse spray is initiated and continued in the angiography suite until antegrade flow is restored. In the graded infusion technique, the rate of drug infusion is diminished over time. Step-wise infusion differs from the other methods in that it uses an end hole catheter that is embedded in the proximal portion of the thrombus. There is no evidence of significant differences in amputation-free survival between these methods. Continuous infusion requires the least procedure time and is an appropriate choice for relatively mild ALI. If an infusion is begun late in the day, the infusion rate can be set relatively low for a 12- to 15-hour overnight infusion. However, studies have shown faster thrombolysis times when bolus or pulse spray methods are combined with continuous infusion. Therefore, bolus and pulse spray methods are often used when time is limited for reestablishing antegrade flow, which is often the case in ALI. Some reports, however, show an increased risk of bleeding complications compared with continuous infusion, whereas others do not. There is concern with both bolus and pulse spray infusion techniques that there may be an increase in distal embolization resulting from thrombus fragmentation.

I typically lace the thrombus with an initial 5–10 g bolus of tPA then initiate a 0.5–1.0 mg/hr continuous infusion (10 mg tPA in 1 L of normal saline, infused at a rate of 50–100 ml/hr). A recent study has shown similar positive results using an ultra-high dose infusion CDT protocol. The ultra-high dose technique used an initial pulse spray technique delivering 1 mg/min for 15 minutes, followed by an infusion of 15 mg over 2 hours. An angiogram is then performed and if there was residual thrombus present a further 10 mg of alteplase is infused over an additional 2 hours. Another recent study has shown that accelerated CDT protocol with an initial dose of 10 mg recombinant tPA for 30 minutes followed by a 3 hour course of a continuous intra-arterial 10 mg/hr infusion showed positive outcomes.

Patients should be admitted to a monitored bed where checks of the treated limb, Doppler pulses, groin checks, and neurologic checks should be performed at regularly prescribed intervals (every 2 hours). Fibrinogen, hematocrit, hemoglobin, platelets, and partial thromboplastin time should be checked at baseline and every 8 to 4 hours, with the tPA infusion rate halved for when the fibrinogen level falls below 150 mg/dL. If the fibrinogen level falls below 100 mg/dL infusion should be discontinued because of the increased of bleeding demonstrated in the STILE 1 trial. However, there is no prospective evidence that this practice lowers bleeding risk, and consequently, many other practices do not monitor fibrinogen levels. Alternatively, cryoprecipitate can be given to raise the fibrinogen level and allow for continued infusion of tPA.

Increased pain in the treated limb may indicate successful thrombolysis, with pain occurring as a result of distal emboli showering and washout of cytokines. Other clinical variables such as temperature,

color, pulse, and capillary refill should all point toward improving perfusion. If at any point the treated limb appears to be more ischemic, the infusion setup and catheter position should be checked. If the limb becomes critically ischemic, CDT should be aborted and surgical revascularization should be attempted. If the limb ischemia is stable or improving, revaluation with angiography is indicated every 6 to 24 hours until flow is restored.

A number of devices have been developed in an effort to accelerate the thrombolytic process, therefore decreasing the risk of hemorrhage and other complications. Pulse-spray catheters, mechanical lysis catheters, aspiration catheters, rheolytic catheters, and ultrasound-accelerated devices are all currently available. These devices have been developed to facilitate disruption and penetration of the thrombus by the thrombolytic agent. In theory, this allows less thrombolytic to be used and shortens the infusion time necessary to achieve thrombolysis. A recent study showed that there was a significant improvement in complete thrombolysis, lower 30-day amputation rate and fewer bleeding complications with ultrasound-accelerated CDT (EKOS [Bothell, WA]) when compared with standard CDT. The study also reported a significant decrease in thrombolysis time and volume of lytic agent required for successful thrombolysis in native arteries and bypass grafts.

Patients requiring more than 3 thrombolysis days are likely to have chronic thrombotic components underlying their acute presentation and could be resistant to fibrinolytic therapy. In these patients, it is possible that despite infusion of fibrinolytics, the thrombus is not lysed and they may be at risk for adverse complications of continuous fibrinolytic therapy.

ADJUNCTIVE PHARMACEUTICALS

The addition of glycoprotein IIb/IIIa platelet receptor inhibitors reduce platelet aggregation and reduce thrombolytic resistance of platelet-bound fibrin. There are several drugs in clinical use that bind glycoprotein IIb/IIIa receptors. These include abciximab (ReoPro; Lantus Biotech), a monoclonal antibody fragment; eptifibatide (Integrilin; Shering Plough); and tirofiban (Aggrastat; Merck). Studies comparing adjunctive use of abciximab during peripheral arterial CDT with CDT alone have shown no difference in technical success (Post Myocardial Infarction Remodeling Prevention Therapy and AIMAT trials). Infusion time was either shorter or equivalent. The frequency of bleeding was either equivalent or higher. Experience with tirofiban and eptifibatide is limited. Use of these agents in peripheral arterial CDT has not been widely adopted given the clinical results so far.

FOLLOW-UP

The goal of CDT is to provide timely, safe, effective, and durable revascularization of the affected limb. After successful revascularization, the patient should be placed on an 81 mg daily dose of aspirin for life. Underlying vascular risk factors should be addressed with antihypertensives, glycemic control, statins, and smoking cessation. Additional antithrombotic drugs may be administered, depending on the nature of the revascularization procedure. The value of dual antiplatelet therapy comprising aspirin plus clopidogrel or ticlopidine, which is well established in coronary stenting, remains controversial in peripheral revascularizations, and evidence-based guidelines do not recommend routine use. ABIs should be used to monitored patency after revascularization. If the ABI decreases by more than 0.2, angiography or noninvasive imaging is indicated.

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MANAGEMENT OF INFECTED GRAFTS

Melanie Nichols, MD, and Matthew R. Smeds, MD, FACS

Graft infection is a constant concern when a prosthetic material is used as a conduit in vascular surgery procedures, and a devastating complication when it occurs. Its occurrence often results in significant morbidity, high rates of limb loss, and portends a significant mortality risk. Infection rates vary depending on the anatomical location of the graft material as well as the pathology being treated as well as presence of intervening systemic infections or contaminated initial procedures. Open aortic graft implantations have infection rates ranging between 1% and 3%, which interestingly mirrors that of endovascular stent grafts, which demonstrate an infection rate of 0.2% to 1% despite the minimally invasive approach to this pathology. Lower extremity grafts have similar infection rates with up to 4.3% to 6% with higher rates associated with those in the groin. As expected, infections in grafts placed for dialysis access occur at higher rates due to the repeated manipulations, occurring in 5% to 20% of the patients. Regardless of the location of the graft or pathology being treated, the key to a good clinical outcome is early diagnosis and treatment with removal of all infected graft material, debridement to healthy tissue, and coverage of any exposed vessels.

DIAGNOSIS

The diagnosis of graft infection can be as obvious as observing exposure of part of the graft in a wound or as subtle as identifying a small amount of fluid around the graft on imaging (Fig. 1). Once there is suspicion for a graft infection, a good history and physical concentrating on fever or chills, malaise, and constitutional symptoms and examining the suspicious area for any erythema, cellulitis, swelling,

color, pulse, and capillary refill should all point toward improving perfusion. If at any point the treated limb appears to be more ischemic, the infusion setup and catheter position should be checked. If the limb becomes critically ischemic, CDT should be aborted and surgical revascularization should be attempted. If the limb ischemia is stable or improving, revaluation with angiography is indicated every 6 to 24 hours until flow is restored.

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MANAGEMENT OF INFECTED GRAFTS

Melanie Niekola, MD, and Matthew R. Smeds, MD, FACS

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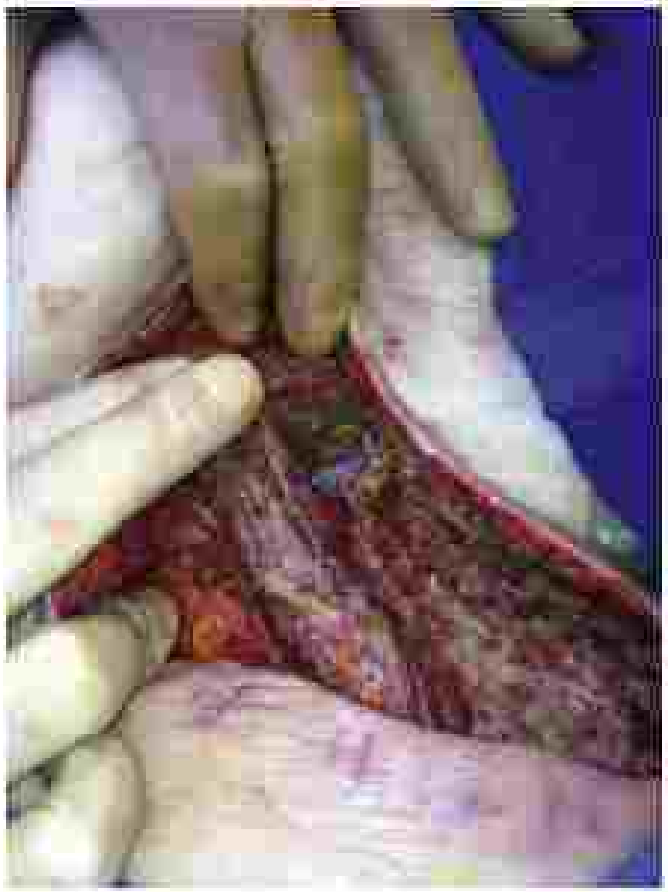

FIG. 1 Exposed femoral-femoral bypass graft with sartorius muscle flap for coverage. *(From Abramowitz JT, Jimenez JM, editors. Endovascular Surgery. 4th ed. Philadelphia: Elsevier; 2019.)*

or drainage is the first step. When infection is suspected and not obvious, then imaging modalities will be the next step for making the diagnosis. During this time, the patient should be resuscitated, a complete blood count and blood cultures should be obtained from the patient, and the patient should be started on empiric broad-spectrum antibiotics. Markers of inflammation such as the erythrocyte sedimentation rate or C-reactive protein may also be obtained in patients with graft infection and can be obtained with initial labs as well. The surgeon should begin to consider all surgical and medical management options once the diagnosis becomes clear as timely management is crucial to this disease process.

Imaging

Computed tomography (CT) scanning is the current gold standard imaging modality for making the diagnosis of graft infection (Figs. 2 and 3). Key findings on this imaging may include periprosthetic fluid or soft tissue changes, fat stranding or loss of tissue planes, ectopic gas, and pseudoaneurysm. Because these are findings that suggest infection and much greater sensitivity in the later stages of infection, a high index of suspicion is necessary. This should be the modality of choice in all suspected intracavitary graft infections (abdominal and thoracic aortic) unless contraindicated. Findings are best appreciated with intravenous contrast. Use of CT is limited when contrast cannot be used or there is artifact from previous metal implants.

Ultrasound is the initial test of choice for suspected extracavitary graft infections. It is a modality that is usually readily available, is noninvasive, and can be performed at the bedside if necessary. Findings include periprosthetic fluid and color flow can easily eliminate intraluminal extravascular fluid. It is also able to show pseudoaneurysm, hematoma, and soft tissue masses as well as assess graft patency. It is limited by being dependent on the skill of the technician and its use for intracavitary grafts is limited due to anatomic issues.

Magnetic resonance imaging (MRI) is able to distinguish similar features as CT scan for graft infections and it has the added advantage of being able to distinguish periprosthetic fluid from chronic inflammation such as fibrosis or chronic hematoma via T1- and T2-weighted images. There is no radiation exposure and contrast is not required, but gadolinium does help delineate the vasculature. Limitations of MRI include expense, length of time for image acquisition, and nephrogenic systemic fibrosis in renal patients who are given the contrast agent.

Tagged white blood cell scans and positron emission tomography scanning are also used often in diagnosis of graft infection. Tagged white blood cell scanning is a nuclear medicine test that aims to show abnormal accumulation of leukocytes in periprosthetic tissue. This test will not delineate the vasculature but can be used in conjunction with CT or MRI to determine the presumed location of the increased uptake as it correlates to graft location. This is a very sensitive test but is not useful in the early postoperative period given there is increased uptake resulting from the normal healing process during this time. This test also takes some time to complete, often with multiple trips to the nuclear medicine division. Positron emission tomography is a newer diagnostic modality and has good sensitivity due to the increased uptake of fluorodeoxyglucose in the inflammatory cells. As with the tagged white cell scan, this test can have a high false positive rate since normal healing will also increase the uptake.

Finally, endoscopy is a modality used for very specific infections which would result in a graft to enteric fistula. It should be considered in a patient with previous aortic graft placement that presents with an upper GI bleed. Ideally the technician will visualize the entire esophagus, stomach and duodenum to look for any sign of fistulation as well as other causes of bleeding. While it is a limited role, it is not a modality to discount in these situations (Fig. 4).

TREATMENT

The basic considerations for graft infection is to eradicate the infection and preserve perfusion. There are many options for accomplishing this, and the treatment modalities need to be individualized to the patient as well as abiding to basic surgical principles. The basic approach to graft infection falls into essentially one of three categories: (1) graft excision with revascularization, (2) graft excision without revascularization, or (3) graft preservation. Within these broad categories, there are multiple options for repair; however, not all these options are useable in every case and each technique may be suitable for specific circumstances. In all cases, coverage of the repair with autologous tissue (muscle flaps, omentum, etc.) may be used to decrease rates of future reinfection and deep cultures should be done to allow speciation of the infectious agent and better select antimicrobial therapy.

Graft Excision With Revascularization

Graft excision with revascularization is an option that is required if preserved in line arterial flow is necessary for limb or bowel tissue perfusion. This may include infected aortic grafts placed for occlusive or aneurysmal disease or in extracavitary grafts if the initial procedure was performed for critical limb ischemia. The goal is to remove all infected graft material and debride tissue to healthy viable deep tissue and reconstruct the arterial system in a way that is less prone to reinfection.

Extraanatomic Bypass

Extraanatomic bypass with excision of all prosthetic material for infected intracavitary abdominal grafts has traditionally been the gold standard for repair. This ensures all the infected material is

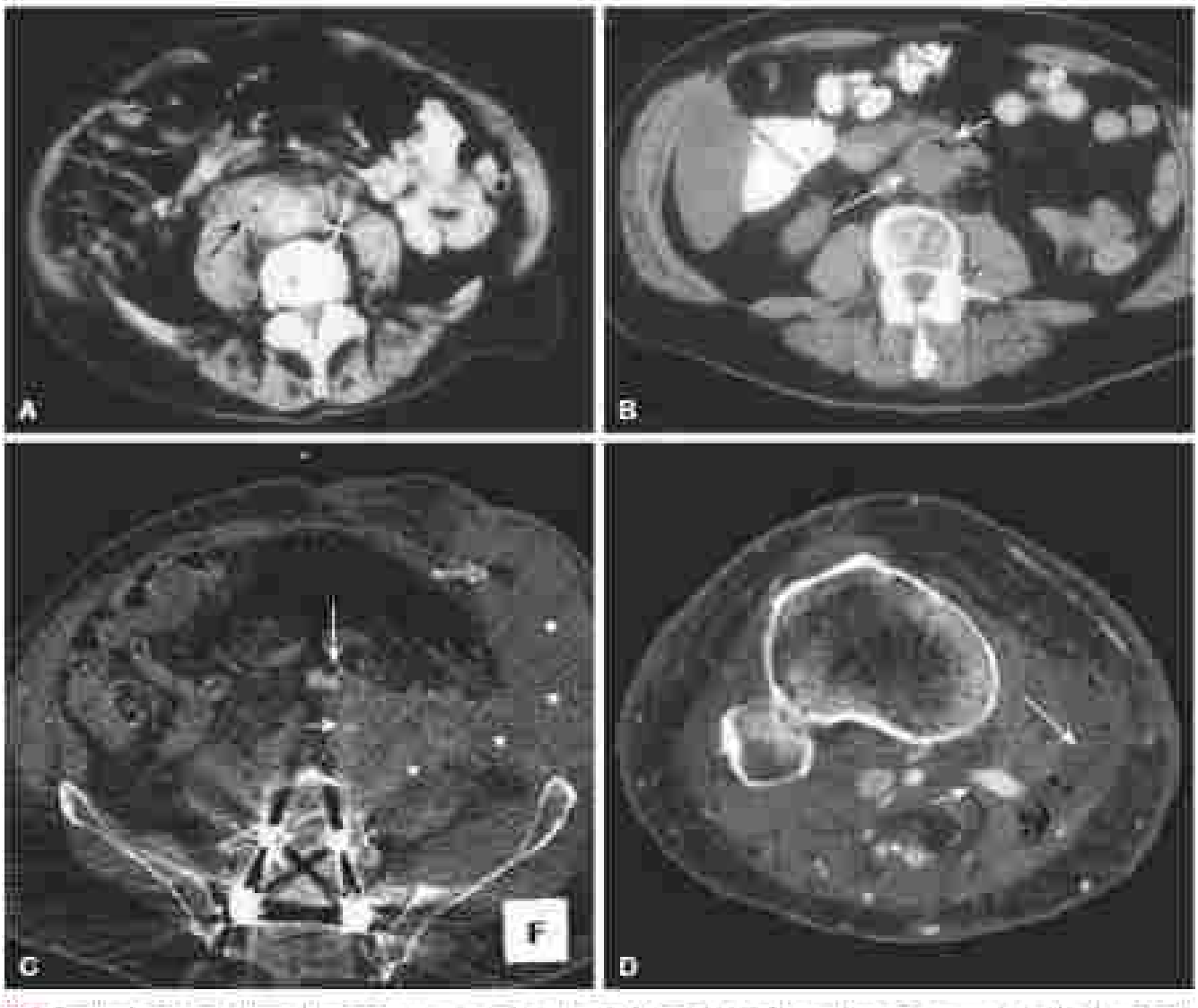

FIG. 1. Computed tomography images demonstrating vascular graft infection. (A) Polygraft field. (B) Thickened perigraft stranding and air within the graft and perigraft tissue. (C) Proximal anastomosis of graft limb anastomosis. (D) Air and abscess at the infragenicular level (large arrow), patent graft size abscess. (From Hollis JW, Mills JT, Jr, Henke PK, et al. Comprehensive vascular and endovascular surgery. 3rd ed. Elsevier; 2009.)

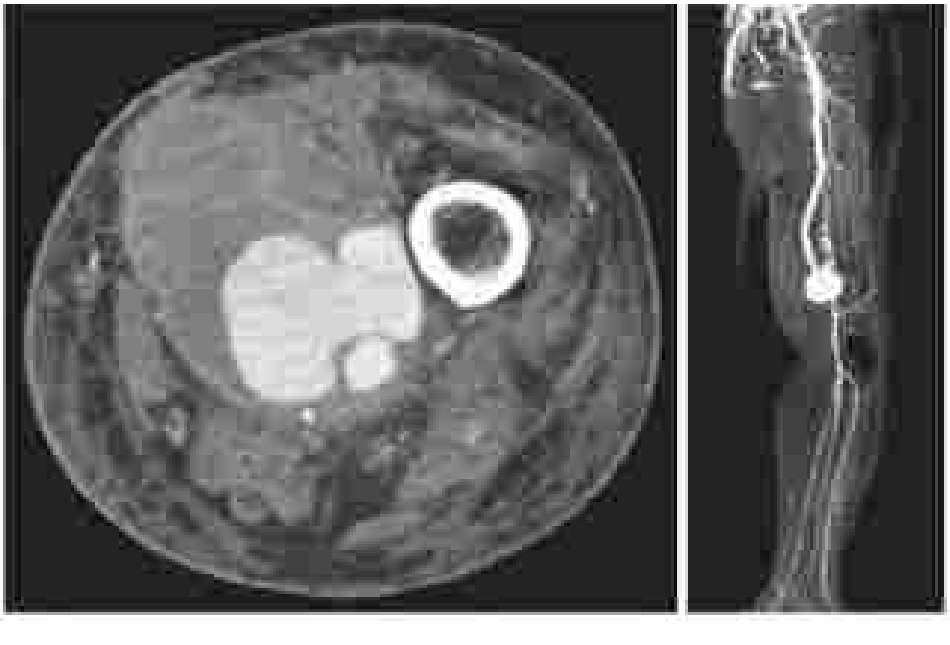

FIG. 2. Computed tomography angiogram reveals pseudoaneurysm arising from distal anastomosis of femoral-femoral to popliteal artery bypass graft. (Courtesy Allen Ing, MD.)

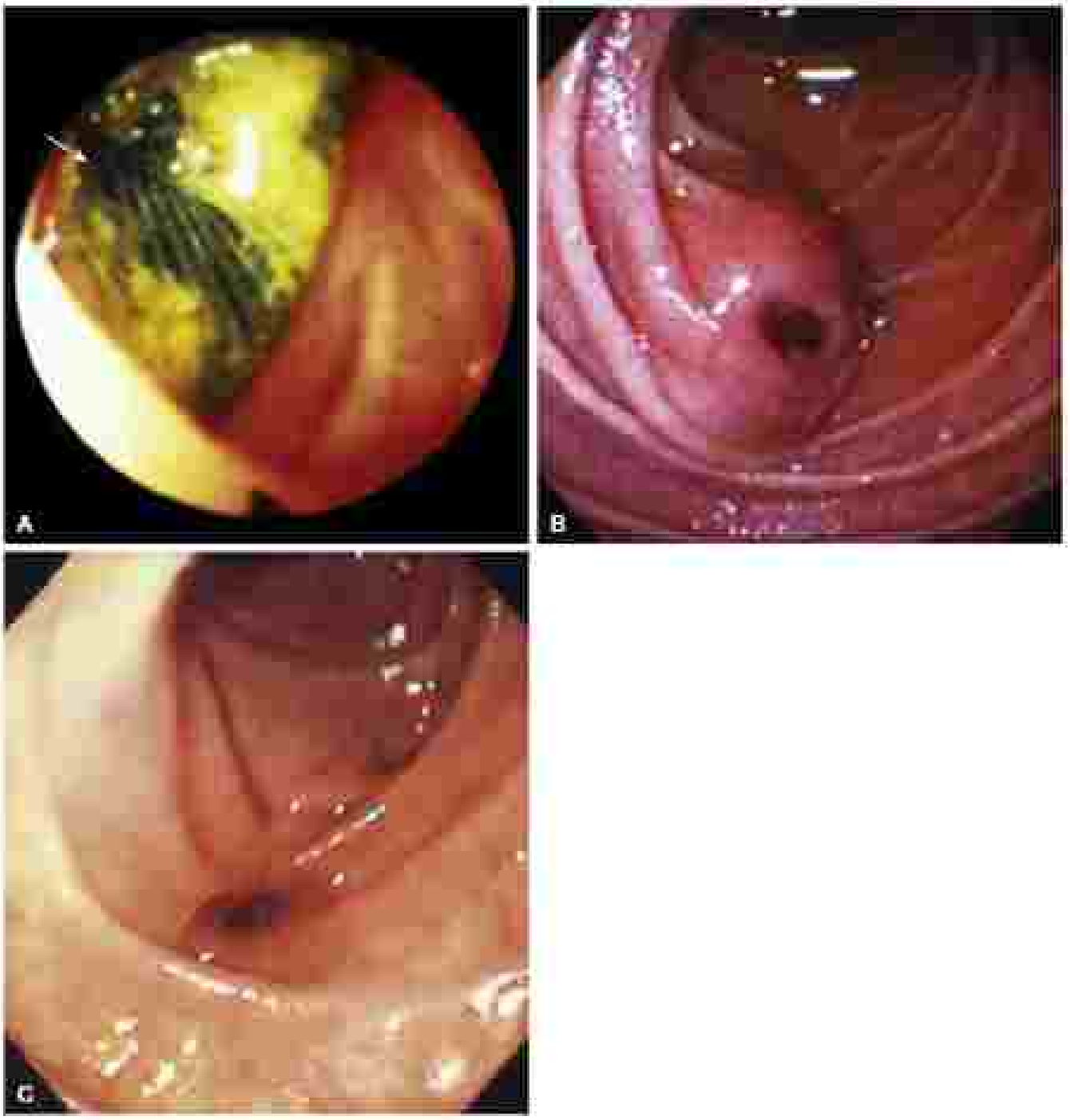

FIG. 4. Specimens of esophagogastroduodenoscopy findings in patients with aortic involvement by a prosthetic vascular graft. (A) Classic fistula of vascular graft within to duodenal lumen. (B) Pure secondary to anastomotic false aneurysm distorting duodenal wall. (C) Small stem-like duodenal lesion without actual distal mass or within graft material. (From Hollier PA, Harris EJ Jr, et al. Comprehensive Vascular and Endovascular Surgery. 3rd ed. Elsevier; 2009.)

removed and that a new conduit is placed through healthy, uninfected tissue planes. The most common procedure performed is an axillofemoral graft with a femoral femoral bypass or an axillofemoral bypass using expanded polytetrafluoroethylene as conduit (Fig. 5). The inflow anastomosis often lines the axillary artery and the outflow is to the common femoral arteries if there is no groin infection. In the setting of infection to the common femoral region, the anastomosis can be to any distal vessel not affected, usually either the superficial femoral artery or the profunda, depending on patency. If the superficial femoral artery or profunda is used as the outflow vessel, the approach to these vessels should be lateral to the sartorius muscle to avoid contamination from the femoral triangle.

If there is a need for revascularization of the contralateral limb, this can be achieved via femoral femoral bypass with prosthetic if there is no groin infection, or can be done by an iliofiac bypass if the iliac vessels are not in a contaminated field. If a groin infection is present and a femoral-femoral bypass is necessary, then use of a saphenous vein or cryopreserved vein or artery conduit may be considered, or the outflow vessel to the contralateral limb can be distal (profunda femoris or superficial femoral artery). Once the lower extremities are

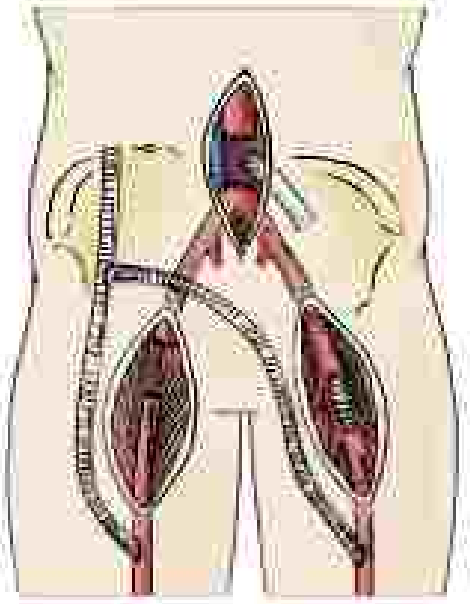

FIG. 3 Axillary artery to bilateral superficial femoral artery with ligation of aorta and excision of infected graft. (From Calligaro KD, Ferraro NA, Veluz AA, Dougherty MJ: Vascular Surgery 19th ed. Chicago: 2013.)

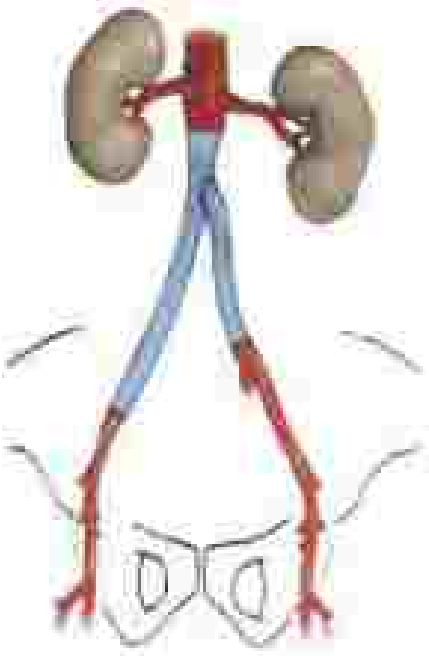

FIG. 4 Neoaortoiliac system procedure with replacement of the aorta with bilateral popliteal vein segments. (From Jackson MR, et al.: Aortic and subaortic revascularization of an infected aortic bifurcation graft treating the aortic duodenal fistulae. Vasc Surg 2002;36:627.)

reconstructed, the infected graft is completely excised, infected tissue is debrided and tissue coverage can be entertained. The approach to the infected graft is either transperitoneal by laparotomy or via a retroperitoneal approach, which can avoid intraabdominal adhesions from previous procedures. The suprarenal aorta is often needed for proximal control depending on the extent of the infected field and inflammation. Distal control of the bilateral iliac arteries should be obtained, and ureters should be identified and protected. The infrarenal aorta should be debrided to healthy tissue and the proximal portion should be oversewn in a double layer fashion with nonabsorbable monofilament suture. The same closure should be done for the distal aorta or iliac arteries. All prosthetic material should be removed and sent for culture and the unhealthy tissue should be debrided along with irrigation. The aorta stump should be covered with omentum and the retroperitoneum should be widely drained.

Complications of extraanatomic bypasses with graft explantation include anastomotic (3%–37%), early mortality, limb loss (3%–17%), and the dreaded aorta stump blow out with life-threatening hemorrhage (3%–29%). Additionally, the procedure often requires a lengthy operative time, frequently over two procedures, and the patency rates of the ultimate revascularization are not as robust as those of anatomic bypasses.

In Situ Antibiotic Impregnated Graft Replacement

In situ prosthetic graft replacement with antibiotic impregnated or antimicrobial grafts is acceptable for many patients, particularly those with low virulence pathogens, antibiotics, fistula, or erosion with impending hemorrhagic catastrophe. The procedure includes gaining proximal and distal control, excision of all graft material, debridement of infected tissue, irrigation with antibiotic solution, and immediate replacement with a new prosthetic graft. When possible, the graft material should be tunneled through a new route and all should be covered with omentum or tissue coverage, including muscle flap coverage with either the sartorius or gracilis muscle to the groin. The prosthetic materials most commonly used are Dacron soaked in rifampin or silver impregnated prosthetic grafts. Post-procedure, the patient will need to be maintained on intravenous antibiotics for 4 to 8 weeks and in some lifelong suppressive oral antibiotics after that. Use of this technique has demonstrated short operating times, excellent patency/durability, and low amputation and mortality rates, and it can be used in emergency settings in which the surgeon does not have adequate time to harvest autologous vein or thaw cryopreserved tissue. Its use in more aggressive microbial infections (drug resistant or *Pseudomonas*) is called in to question, and there is a potential for developing rifampin resistant organisms over time.

In Situ Cryopreserved Allograft Replacement

In situ arterial allograft is another alternative that consists of removing all infected graft material, debridement of tissues, antibiotic irrigation and new conduit placement with cryopreserved aorta. Again, the patient will receive 6 to 8 weeks of antibiotics postoperatively. Similar to the antibiotic impregnated grafts, the advantage of this technique is a one stage procedure, but this technique uses autologous material rather than prosthetic to decrease reinfection rate. The disadvantage of this procedure is lack of availability and cost as well as the time necessary for implantation, which requires thawing the frozen product before use. There is also concern for aneurysmal degeneration over time and need for continued surveillance of the graft and its use in aggressive microbial infections (drug resistant or *Pseudomonas*) is questioned. Long-term patency rates of this graft are less than that of prosthetic material but better than extraanatomic bypasses. Amputation rates are low (less than 8%) and mortality varies widely (9%–34%).

In Situ Venous Autograft

In situ venous autograft is a procedure also known as neo-aortoiliac system (NAIS) and consists of reconstructing the aortoiliac system using femoral popliteal vein as conduit (Fig. 4). Preoperative venous duplex of the bilateral lower extremities is necessary for this procedure because of the long length of saphenous vein that is needed as well as to ensure patency of the veins. It is unlikely that the saphenous vein will be of good caliber for use but in the event that it is (7–8 mm), then one of the deep veins can be preserved in each leg. Longitudinal thigh incisions lateral to the sartorius muscle are made to harvest the deep vein, the adductor hiatus is divided to expose the superficial femoral vein and its branches. The branches are ligated and the vein is

harvested from the level of the profunda femoris to as far proximally on the popliteal as needed for adequate length. Care is taken to preserve the profunda femoris vein and the superficial femoral vein is taken flush at its origin to ensure no deep venous thrombosis occurs. Once the vein is obtained the incisions are closed, preferably over drains. Authors have described staging the NAIS procedure. Vein is harvested with side branches ligated and left in situ and the patient is brought back the next day for the aortic portion of the case. This makes the operation much less arduous on the surgeon and has similar patency rates.

After the clean vein harvest is complete, the procedure continues with exposure of the infected graft. This includes gaining proximal and distal control, excision of all graft material, debridement of infected tissue, and irrigation with antibiotic solution. Once this is done the femoral vein is attached to the proximal aorta in a similar reversed fashion for appropriate size match. If the size mismatch is too great, then other techniques may be necessary. Two segments of superficial femoral vein can be anastomosed to each other, making a pantaloon configuration. The composite ends are then sewn end to end to the aorta (Fig. 7). Alternatively, if the mismatch is too great then the aortic stump can be oversewn and the vein graft can be anastomosed to the anterior surface of the aorta in an end to side fashion. The vein graft can then tunneled through the peritoneal tunnels and constructed to the femoral artery in an anterolateral fashion. The contralateral limb is then revascularized by creating an anastomosis with the second vein segment at the midpoint of the aortofemoral graft and then passing this to the contralateral groin where the distal anastomosis is made. The groin is closed, usually with muscle flap coverage.

The advantages of this procedure are autograft being used, in this case, complete removal of infected endograft, no concerns for immunogenicity of the conduit, and likely eradication of the infection. The disadvantages are procedure length and the complications that come with deep vein harvest, notably leg swelling and potential venous compartment syndrome that may require fasciotomies. Long term reinfection rates are close to 0% and mortality rates following the NAIS procedure range from 0% to 33%.

In situ venous allograft replacement is a procedure with similar construction to the NAIS but using cryopreserved vein. This is done to avoid the deep vein harvest and the complications that go along with it as well as to remove all infected graft material. The CryoVein is anastomosed to the aorta in an end to end fashion and the graft can then be tunneled to the femoral arteries in an anterolateral bypass fashion. As discussed, the original tunnels can be used for this procedure and muscle flaps to close the groins. CryoVein is more readily available than the CryoAorta or arterial grafts in many institutions, making this an easier conduit to obtain. However, the procedure remains lengthy, and although the conduit used is autologous, its use in aggressive microbial infections is still questioned.

Graft Excision Without Revascularization

Graft excision without revascularization can be considered in cases where the initial procedure was done for claudication or in a case where the graft is thrombosed and the patient does not have critical limb ischemia. Although the goal in most infected graft procedures is to remove graft material and maintain flow, this may not be necessary because the location of the graft or reasons for its placement. The technique in this case is to preserve as many branches as possible to maintain collateral flow. The arteriotomy left with the graft removal is repaired, commonly with a vein patch to not narrow the vessel. In some cases, a small cuff of graft is left behind and oversewn. This still not narrow the artery but may pose a future problem with continued graft material in this infected field. The patient is at risk of limb loss even if their initial procedure was not for critical limb ischemia. Their native vessel may have progressed with calcific disease and the nature of the graft removal may disrupt any collateral vessels feeding the outflow, so monitoring of the limb closely postoperatively is crucial.

FIG. 7 Nonanatomic aortic replacement of infected aortic graft with harvested femoral popliteal vein. Patient's head is picture right, vein is anastomosed in end-to-end fashion with aorta on right of picture with end-to-side anastomosis of vein to vein to create bifurcation in the middle of the image. (*Courtesy Kevin Ni, MD.*)

Graft Preservation

A final option for graft infection is graft preservation with wide local wound debridement. Infected prosthetic material is left behind, and this technique should be reserved for limited circumstances. Patent grafts with a short segment involved with low virulent infections are a prime example of one where preservation can be considered. Infections limited to the periprosthetic tissue, nonvirulent species and no systemic signs are criteria necessary before preservation is attempted. Once a patient fit into this category then the next step is debridement of all infected tissue with washout of the area. This may need to be done several times to ensure there is healthy uninfected tissue. Repeat cultures of the area are also necessary to continue to guide treatment. Once there are negative cultures and healthy tissue, the wound can be closed or covered. If the tissue in the surrounding area is healthy, then muscle flap coverage is a good option. The wound may require negative pressure vacuum-assisted closure therapy as well as possible need for skin graft. Authors have described the use of antibiotic beads placed at the site of infected grafts that cannot be explanted or a period of antibiotic instillation and drainage of drains can be placed near the abscessed graft. Conservative management of intracavitary graft infections in these manners can be done, but it is exceedingly more difficult to preserve graft material without persistent or recurrent infection. Partial graft preservation is also sometimes entertained, particularly in patients with isolated infections of a limb of a prosthetic graft. The infected limb is removed, culturally tissue is debrided, and it is replaced with autogenous, autologous, or antibiotic soaked Dacron. This new conduit is often tunneled through clear tissue planes, with some surgeons using the obturator canal. Graft preservation is difficult and may ultimately fail, but the features to increase success are: low virulence organisms, absence of periprosthetic abscess or sepsis, and early appearing infection (Figs. 8 and 9).

INFECTED STENT-GRAFTS

Aortic stent graft infection is a rare problem at this time but clearly poses a large concern for morbidity and mortality in these patients, and given the increasing extent of endovascular management of vascular diseases, this issue promises to become much more prevalent. Additionally, as we have become more adventuresome with repairing large vascular problems with this minimally invasive approach,

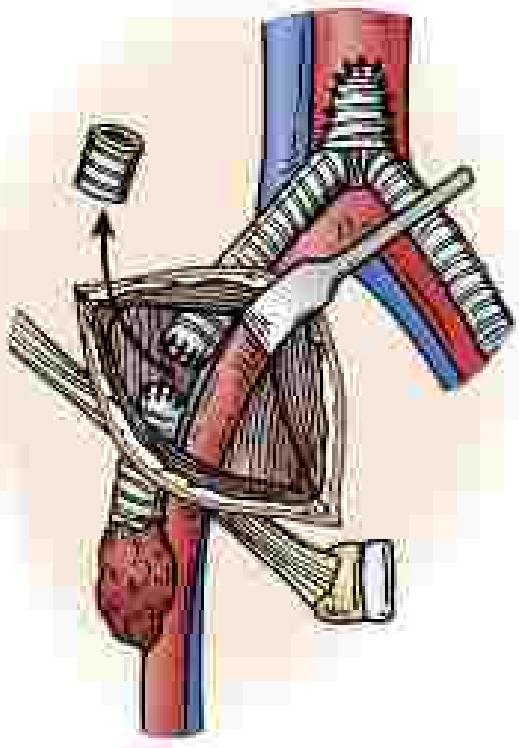

FIG. 8 Retroperitoneal exposure of aortobifemoral graft limb through obturator plane. (From Crawford JL, Johnson WC, Salam AA, Kahaku EK, Hallett JW Jr. Aortic reconstruction through the obturator plane. Surgery. 1985;98:1000–1008.)

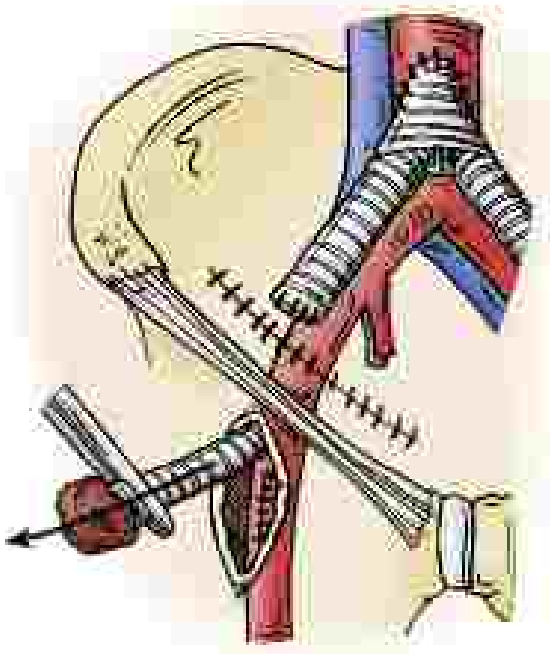

FIG. 9 Removal of infected graft portion from the groin. Replacement with vein, cryopreserved artery or rifampin-soaked Dacron graft is performed for revascularization if needed. (From Crawford JL, Johnson WC, Salam AA, Kahaku EK, Hallett JW Jr. Aortic reconstruction through the obturator plane. Surgery. 1985;98:1000–1008.)

patients are now being offered endovascular repairs while not being candidates for open repairs. Infections in this older and sicker population can thus be challenging. Currently, 0.2% to 5% of abdominal or thoracic stent grafts get infected. The source of infection is thought to be due to systemic bacteremia resulting in seeding of stent graft and every device is equally susceptible. This bacteremia may be the result of internal known systemic infections, chronic infections, placement of the stent graft in an infected field, or in patients who have had repeated interventions performed after their initial procedure. Time to diagnosis is usually within 22 months of surgery.

Patients may be asymptomatic but usually will present with pain, bronchitis, development of an endoleak, fistula, or rupture. Diagnosis is largely made by CT angiogram but can also be made via other modalities discussed earlier (Fig. 10). In patients with presumed infection, blood cultures should be taken and the patient should be started on broad spectrum antibiotics. The determination is then made if the patient will be able to withstand a major procedure to remove the infected stent graft.

If the patient is able to withstand an open operation, then preparation should be the same as for the intracavitary infected grafts. The options for removal of the infected material and maintaining flow are the same as for the infected aortic grafts. After the abdomen is opened and infected tissue debrided, proximal and distal control is obtained on the aorta. The proximal control may need to be supraceliac or even in the thoracic aorta. The aorta is opened and the stent graft is removed. This could pose a challenge particularly in grafts with suprarenal fixation. Once the graft is removed then aortic reconstruction is accomplished by in situ prosthetic graft placement, in situ arterial allograft, in situ venous autograft or in situ venous allograft. The other option would be to do an extra anatomic bypass with removal of all infected material and over sewing of the aorta. These procedures were discussed earlier. Long term, these patients have fairly high morbidity and mortality, with up to 50% having a perioperative complication and an overall 5-year survival of 50%.

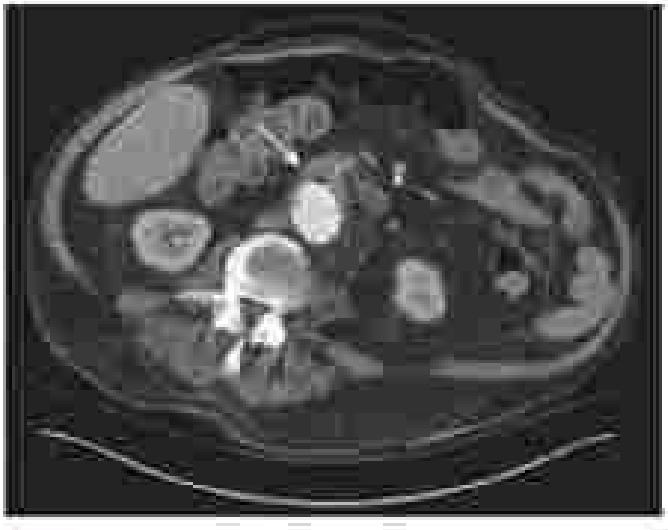

FIG. 10 Computed tomography angiogram reveals air and fluid around abdominal aortic graft. Arrow points to duodenum looping over the top of the graft with an accompanying fistula. (Courtesy Michael Williams, MD.)

Patients with infected thoracic endovascular aortic repairs do worse than those with infected endovascular aortic repairs and use of autologous or autogenous material as conduit has been demonstrated to be superior.

INFECTED DIALYSIS ACCESS GRAFTS

Prosthetic arteriovenous access is used for a large number of renal patients on dialysis. These grafts can essentially be anastomosed to any artery and vein that are in close proximity including access in the

area, groin, and chest wall. Because this graft is repeatedly punctured for dialysis as well as the location of some of the access sites, there is a relatively high rate of infection ranging from 9% to 20%.

These graft infections can present like any other graft infection, but with the repeated use, there is a high chance of developing a pseudoaneurysm or hemorrhage in these patients. Patients often present with malaise, fevers, and evidence of erythema or purulent drainage from previous access sites. Once graft infection is suspected, blood cultures should be taken and the patient should be placed on empiric antibiotics. If there is a high enough index of suspicion, then no imaging is necessary; however, some of the infections can take a more indolent course and ultrasound or tagged white blood cell scan can aid in diagnosis.

As described previously, all infected material should be removed. An incision should be made over the area of the anastomosis and control should be both proximal and distal on the artery and the vein. Once this is done, then the graft can be removed. This may require a combination of several depending on how well the graft is incorporated. Once the graft is removed, the venotomy can be closed primarily. A vein patch obtained from either saphenous vein or a nearby vein if able should be used to close the artery to prevent narrowing. Tissue or muscle is then used to close the area over the vein and artery. If there is evidence of significant infection, such as purulent drainage, the skin should be left open to heal by secondary intent or a wound vacuum assisted closure device placed. The patient may then need a temporary dialysis line until the infection is cleared at which time a more permanent access can be entertained.

CONCLUSIONS

Although prosthetic graft infection is a diagnosis no surgeon wants to make, the key to a good outcome is early diagnosis and intervention. The patient will need control of sepsis, broad-spectrum and then targeted antibiotics, debridement of the infected tissue, removal of all graft material when able, and revascularization as needed. With careful patient selection and timely repair, salvage of these patients is possible via a number of surgical options.

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ATHEROSCLEROTIC RENAL ARTERY STENOSIS

Joseph S. Giglia, MD

Atherosclerosis is the most common cause of renal artery stenosis (RAS), accounting for 90% of cases. Atherosclerotic RAS has been implicated as a significant contributor to systemic hypertension and impaired renal function. It is important to understand that RAS is rarely the sole cause of hypertension or renal dysfunction. Although the incidence of RAS may be as high as 45% in certain high-risk groups, there are no data to justify prophylactic treatment of asymptomatic patients. The majority of patients with symptomatic RAS should be managed medically with invasive intervention reserved for only a select subset of patients. As in other areas of vascular intervention, the explosion of catheter-based endovascular interventions has increased the number of procedures for RAS often without regard for the natural history or the clinical outcomes. Open surgical reconstruction is still indicated in a limited number of situations with very specific indications.

INCIDENCE

The incidence of atherosclerotic RAS in approximately 5.4% in patients with resistant hypertension, and it may affect as many as 6.8% of adults older than 65 years of age. It is even more prevalent in those with vascular disease, with estimates between 22% and 49%. Risk factors associated with atherosclerotic RAS include advanced age, hypercholesterolemia, peripheral arterial disease (PAD), cerebrovascular disease (CVD), and coronary artery disease (CAD), with the severity of atherosclerotic RAS often paralleling the severity of CCAD.

NATURAL HISTORY

Although RAS often is implicated as a cause of systemic hypertension and worsening renal function, it is most frequently discovered as an incidental finding on abdominal ultrasound, computed tomography angiography, magnetic resonance angiography, or random angiography performed for another reason. In studies using sequential angiography, atherosclerotic RAS lesions progressed in 11% to 44% of subjects. Progression to complete occlusion occurred in only 10% to 16% of patients with more than 60% stenosis. In patients studied by ultrasound, complete occlusion occurred in only 7% of patients with a stenosis greater than 60%. Progression of these lesions may be even less common, as a significant increase in RAS was seen annually in only 0.5% of patients with cardiovascular risk factors. Recently, these observations have led to a shift in the paradigm of RAS treatment.

The underlying pathophysiology is complex but likely related to a combination of renal ischemia and activation of the renin-angiotensin-aldosterone (RAA) system. Activation of the renin-angiotensin-aldosterone system results in the release of the vasopressor angiotensin II and plasma expansion via the effects of aldosterone. In most cases, the resultant hypertension can and should be managed medically. The ultimate endpoint of the disease process is hypertension resistant to medical therapy and progressive renal dysfunction resulting from ischemia, with renal atrophy being documented in 5.5%, 11.7%, and 29.8% of patients with normal renal arteries, renal arteries with less than 60% stenosis, and renal arteries with more than 60% stenosis, respectively. A critical issue is whether the renal parenchyma has already undergone permanent irreversible changes that will not be altered by intervention on a proximal main renal artery.

EVALUATION

Symptomatic RAS patients have resistant hypertension (uncontrolled hypertension on three medications) or progressive renal failure. Current guidelines suggest screening for RAS as part of a secondary hypertension etiology workup for those with resistant hypertension, severe hypertension (systolic blood pressure higher than 180 mm Hg, diastolic blood pressure greater than 110 mm Hg), elevated nighttime blood pressures during 24-hour monitoring, malignant hypertension, onset of hypertension at age younger than 30 years, sudden worsening of previously well-controlled hypertension, or discrepant kidney length on imaging. Patients with sudden worsening of renal function

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Atherosclerotic Renal Artery Stenosis

Joseph S. Giglia, MD

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or recurrent flash pulmonary edema should also undergo evaluation for RAS. Individuals in whom renal function acutely worsens after the initiation of an angiotensin converting enzyme (ACE) inhibitor have an increased incidence of bilateral RAS.

Duplex ultrasound is the initial method of choice for RAS screening. The degree of stenosis is best determined by measurement of each renal artery peak systolic velocity (PSV). Normal renal arteries have a PSV of 60 to 180 cm/s. Renal artery PSV greater than 180 cm/s is indicative of RAS greater than 60%. The ratio of renal artery PSV to aortic PSV, also is calculated, with a value higher than 3.5 being indicative of RAS with luminal stenosis greater than 60%. The ratio of renal artery PSV to aortic PSV is invalid if the aortic PSV is greater than 100 cm/s, suggesting severe aortic disease. The other signs of RAS include intrarenal vascular tardus parvus and renal atrophy. A critical portion of the examination is calculation of the resistive indices within the kidney. Elevated risk indices indicate permanent irreversible renal parenchymal damage that would not be expected to be altered by renal artery intervention.

Computed tomography angiography and magnetic resonance angiography are more sensitive and specific modalities for delineating the precise anatomy and degree of RAS. Conventional arteriography remains highly accurate for identification and quantification of RAS but should only be undertaken if therapeutic intervention is planned.

Patients with RAS often have concomitant CAD, PAD, and CVD and should undergo evaluation as indicated by history and physical examination. Baseline serum creatinine, hemoglobin, lipid panel, and glucose are checked routinely.

TREATMENT

Although atherosclerotic RAS is associated with increased cardiovascular morbidity and mortality, there is no current evidence to support revascularization of asymptomatic patients or patients with well-controlled hypertension. Numerous randomized controlled studies, including the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial comparing the results of endovascular intervention versus medical management, have demonstrated no benefit of stenting in patients with atherosclerotic RAS who are treated with antiplatelet therapy, statins, and blood pressure control with an ACE inhibitor or angiotensin receptor blocker (ARB).

Revascularization of patients with atherosclerotic RAS currently is reserved for refractory hypertension that is not responsive to maximal medical therapy and for patients with worsening coronary renal function. Young patients in whom flash pulmonary edema is caused by atherosclerotic RAS also may benefit from revascularization.

Medical Therapy

All patients with atherosclerotic RAS are at increased risk for cardiovascular morbidity and mortality, therefore hypertension and factors known to be associated with progression of atherosclerosis should be controlled aggressively.

Hypertension Control

Hypertension control should start with an ACE inhibitor or ARB. Calcium channel blockers, β-blockers, chlorothiazide, or hydralazine may be added for better control. There is good evidence that ACE inhibition and ARBs are helpful in patients with underlying cardiac disease and nephropathy. Most patients are able to tolerate ACE inhibitor or ARB therapy. However, ACE inhibition can decrease glomerular filtration rate (GFR) by blocking efferent arteriolar constriction, and therapy must be monitored closely to ensure that the decrease in GFR is minimal.

Lipid-Lowering Agents

Hyperlipidemia should be treated with a statin. Statin therapy decreases rates of myocardial infarction, prevents progression of CAD, PAD, and CVD, and decreases cardiovascular mortality. Although few studies have directly correlated statin use to outcomes in patients with RAS, reduction in angiographic progression of RAS has been demonstrated.

Antiplatelet Therapy

Although no study has focused specifically on patients with atherosclerotic RAS, antiplatelet therapy with aspirin or clopidogrel has been associated with decreased adverse cardiovascular events and mortality in patients with CAD, PAD, and CVD. Antiplatelet therapy is also an important adjunct after endovascular RAS revascularization. Patients who receive renal artery stents are treated with clopidogrel for at least 30 days, followed by low dose aspirin indefinitely. Antiplatelet therapy in these instances is meant to reduce early thrombotic complications as well as to reduce the chance of restenosis.

Smoking Cessation

As in all patients with atherosclerosis, smoking cessation is essential. Smoking has been implicated in arterial endothelial cell damage, increased levels of low density lipoprotein cholesterol, and increased platelet aggregation. Smoking also causes vasoconstriction, increased heart rate, and increased blood pressure. Smoking cessation has been shown to improve survival in patients with CAD and PAD. Patients who are able to quit smoking enjoy a 13% reduction in all cause mortality.

Glycemic Control

Patients with diabetes and concomitant atherosclerosis are at increased risk for progression of vascular disease. Good glycemic control (hemoglobin A_1 <7.0%) should be attained via either oral hypoglycemic agents or insulin therapy to prevent microvascular complications.

Renal Artery Stenosis Surveillance and Follow-Up

Although there are no quality data on RAS surveillance, I recommend duplex ultrasound initially every 6 to 12 months for patients with RAS greater than 60% to assess for progression of stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier restaging of the renal arteries.

Revascularization

Based on the results of the Angioplasty and Stenting for Renal Artery Lesions and CORAL trials, revascularization for atherosclerotic RAS currently is reserved for patients with recalcitrant hypertension or worsening kidney function despite optimal medical management and young patients with flash pulmonary edema caused by RAS. Entry criteria for these studies excluded patients most likely to benefit from revascularization. For example, during the CORAL trial, enrollment was broadened to include patients with well-controlled hypertension, and patients with a recent history of congestive heart failure were excluded.

Revascularization can be accomplished by endovascular procedures or by open surgery. Endovascular approaches are preferred in most cases because of their minimally invasive nature, excellent early results, and lower perioperative morbidity and mortality when compared with open surgery. Angioplasty alone has lower success rates than angioplasty with stent placement. Open renal artery surgery is reserved for urgent salvage of endovascular technical failures resulting in hemorrhage or renal ischemia, revascularization of renal artery branches that are not amenable to endovascular repairs, and renal artery revascularization in combination with elective aortic reconstructions that require an open approach. Open renal artery

revascularization may also be required in select patients with aortic aneurysms or dissections treated with endovascular techniques.

Endovascular Therapy

The endovascular approach typically begins with standard percutaneous femoral artery access using the Seldinger technique. A diagnostic

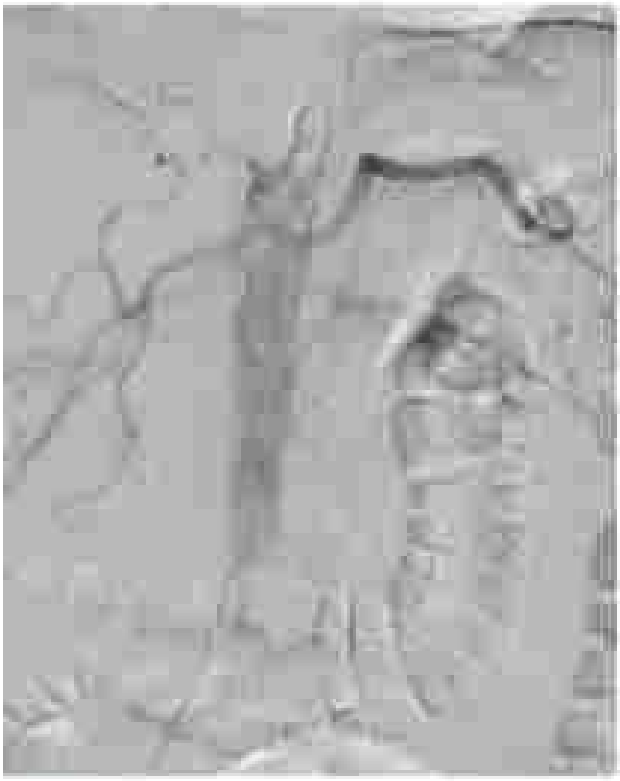

FIG. 1 Aortogram displaying a proximal left renal artery stenosis.

catheter is inserted into the aorta, and an aortogram is obtained (Fig. 1). The brachial or radial arteries can be used if the renal artery is steeply angled or the patient has unfavorable aortoiliac anatomy (Fig. 2). A weight-based dose of unfractionated heparin is administered intravenously after the appropriate size sheath is in place. A wire is introduced into the diseased renal artery using an end-hole selective catheter (Fig. 3). Percutaneous balloon angioplasty is then performed with an appropriate size balloon-expandable stent (Fig. 4). It is important to place the stent extending 1 to 3 mm into the aorta, however, as the renal ostium is often composed with aortic wall plaque (Fig. 5). The proximal end of the stent is then flared with a slightly

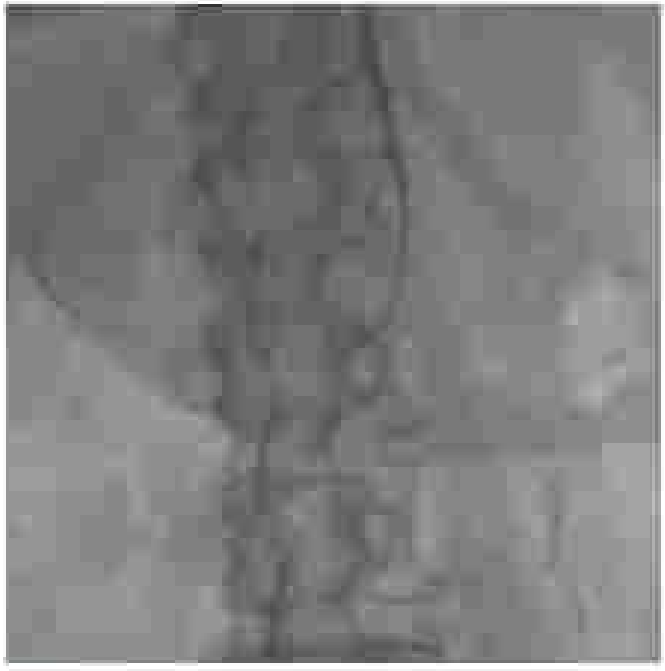

FIG. 3 Right renal artery has been catheterized and a wire advanced distally.

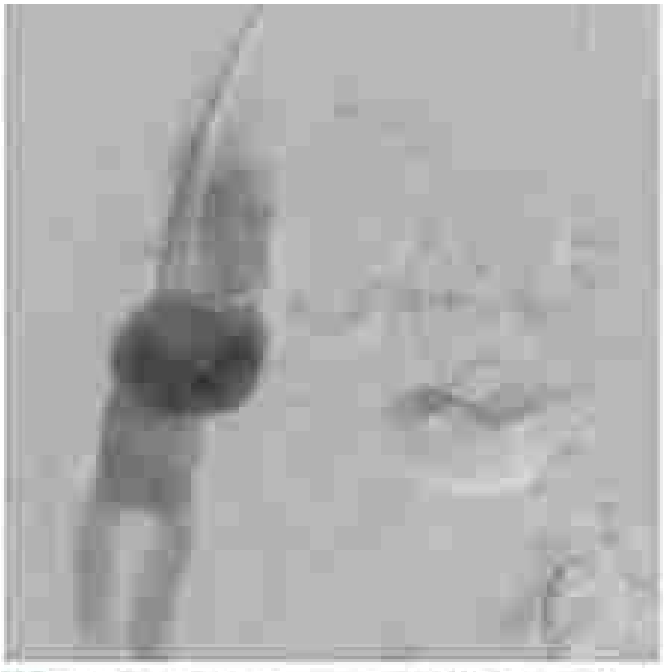

FIG. 2 A left brachial or radial approach is used if there is unfavorable aortoiliac anatomy.

FIG. 4 Left renal artery stenosis treated with an appropriately sized balloon expandable stent from a femoral artery approach.

larger balloon. Repeat selective renal angiography is performed before removing the guidewire to confirm patency. Completion angiography is then performed after the wire is removed over-the-end hole catheter. Control of the access site may be accomplished with a closure device or simple removal of the sheath followed by manual pressure after the activated clotting time has decreased below 180 seconds. Open femoral artery repair may be selected in patients with small arteries or if there was increased risk for hemorrhage or thrombosis.

Medical Management After Revascularization

Clopidogrel is prescribed for at least 30 days after intervention and low-dose aspirin therapy is continued indefinitely. The patient returns in 2 weeks to assess the access site, renal function and blood pressure.

Complications

Complications include rapid postintervention decline in renal function, which can result from atheromatous embolization or contrast-induced nephropathy. Contrast-induced nephropathy is seldom an issue as the procedure can be performed with minimal dilute dye or carbon dioxide. Pre- and postprocedure hydration is routinely performed for patients not at risk for congestive heart failure.

Renal artery rupture is a rare but serious complication during percutaneous balloon dilation and stent deployment. It is critical to maintain wire access of the vessel until satisfied with post-intervention anatomy. In the event of rupture of the renal artery, a covered stent may be deployed to control the site of perforation. Endovascular access to a ruptured vessel may be exceedingly difficult or impossible if wire selection is lost before repair. An urgent open salvage procedure that is rarely successful secondary to the duration of warm ischemia.

Renal capsule perforation with hemorrhage can occur if a wire extends distally through the kidney. It is critical to maintain control of a hydrophilic wire while it is in the renal artery and to maintain visualization of the tip with fluoroscopy at all times. It may be necessary to use an angled hydrophilic wire to cross a severely stenotic lesion, but it should be exchanged for a braided 3 tip (3 mm) wire before proceeding with the intervention.

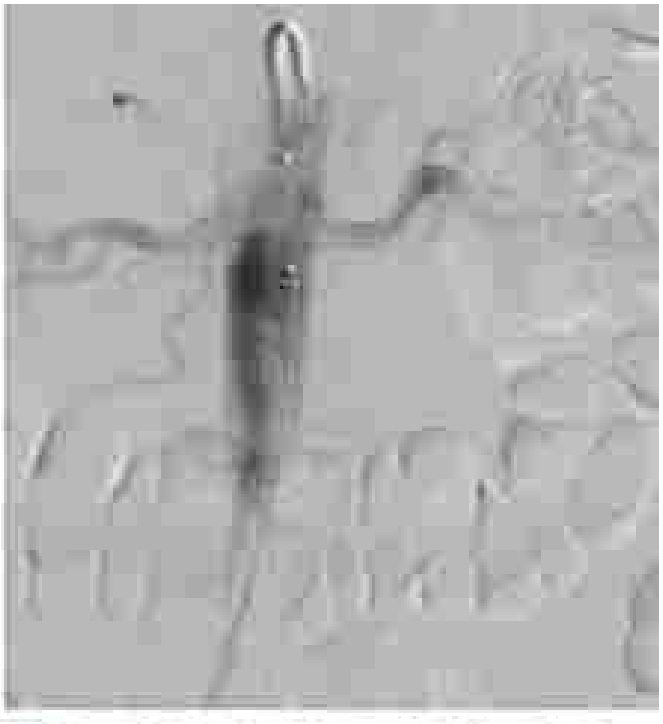

FIG. 5 Proximal end of the stent is positioned into the aortic lumen because the renal artery plaque is often continuous with aortic disease.

Renal artery dissection can occur when traversing tight calcified lesions. In addition, branch vessels may be compromised with treatment of a proximal lesion. Occasionally, a dual-wire configuration is needed to maintain access to both branches (Fig. 6).

Access site complications, including femoral pseudoaneurysm, hematoma with potentially significant blood loss, lymphatic leak, and femoral artery dissection, are possible. It is mandatory to use ultrasound guidance to locate appropriate access site in the common femoral artery to minimize access site complications. In addition, fluoroscopy should be used to localize the femoral head to enhance the ability to control hemorrhage with manual compression following femoral sheath removal.

Outcomes

Control of hypertension, measured by number of antihypertensive medications, has been demonstrated to improve in up to 80% of RAS patients treated by angioplasty and stenting. Renal dysfunction, measured by serum creatinine or estimated GFR, has been shown to stabilize or improve in 60% of RAS patients.

Surveillance and Follow-up

Although there are no quality data on RAS surveillance after angioplasty and stenting, we recommend a duplex ultrasound within 1 month after the procedure to document the postprocedural change in renal artery PSV and in the renal artery PSV to aorta PSV ratio. Several additional duplex ultrasounds are performed every 6 to 12 months to assess for recurrent stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier imaging of the renal vasculature.

Endovascular Management of Restenosis

Restenosis rates are as high as 50% at 12 months and 67% at 18 months. Unfortunately, the impact of restenosis has been addressed poorly in the randomized controlled trials comparing stenting and medical management. Postintervention statins and antiplatelet medications are beneficial for prevention of restenosis. Patients with progressively worsening restenosis on follow-up duplex studies and all symptomatic patients with worsening renal function or blood pressure control who have imaging evidence of restenosis should undergo reintervention if no contraindications exist. Endovascular reintervention had only modest success with a 47% rate of hypertension improvement in several small studies.

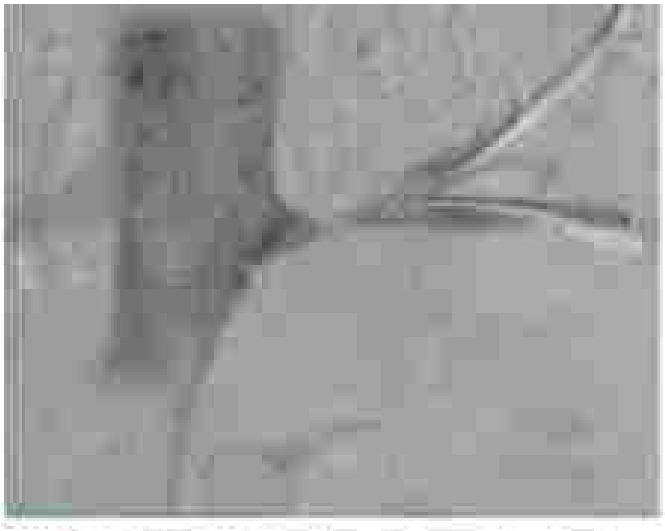

FIG. 6 Dual-wire technique is used to maintain access to both renal artery branches in this situation with a proximal left renal artery stenosis and an early bifurcation.

Open Surgical Repairs

Open surgical repair may be considered in patients with symptomatic atherosclerotic RAS who are undergoing elective open surgery for aortic disease. These individuals with significant renal artery branch disease also should be considered candidates for open repair, as stenting may not be feasible in these patients.

For elective open renal artery revascularization, careful preoperative risk assessment is essential. RAS is a marker for generalized atherosclerosis, and these patients must be screened for CAD, PAD, and CVD. Preoperative cardiac and pulmonary assessments are paramount to assess perioperative risk and initiate therapy to mitigate risk.

Aortorenal Artery Bypass

The patient should be positioned with the umbilicus at the level of the bed break, with the table angled at 15 degrees. The most versatile approach for open repair is the midline incision from xiphoid to pubis in the event that other procedures are indicated. However, a transverse supraumbilical incision provides better exposure of the paraaortal aorta and proximal renal arteries. Traditionally, the small bowel is retracted to the right side of the abdomen, the retroperitoneum is incised to expose the aorta, and the duodenum is subsequently reflected to the patient's right. Alternatively, full mobilization of the left colon and splenic flexure provides the best exposure of the paraaortal aorta and proximal renal arteries. It is easily performed and may be associated with decreased postoperative ileus (Fig. 7). The left renal vein is retracted cephalad to expose the underlying aorta and the left renal artery. Left renal vein branches (gonadal, adrenal, lumbar) may be divided to improve mobilization; it is necessary for the surgeon to decide if division of the left renal vein will be necessary before division of these important renal vein collaterals.

The proximal right renal artery can be accessed through previously mentioned exposure; however, if access to the distal right renal artery is required, it is best accomplished by medial mobilization of the right colon and duodenum. Mannitol (12.5 g) may help to prevent the development of acute renal failure by renal vasodilation, flushing of renal tubules, and scavenging free radicals. The patient is systemically heparinized before clamping the arteries. Consideration should be given to perfusion with cold preservation solution if the renal ischemia time is expected to be more than 1 hour.

Saphenous vein or synthetic grafts are used to create the aortorenal artery bypass. An atraumatic vascular clamp is applied to a suitable soft portion of the aorta. An arteriotomy is made with a No. 11 blade or an aortic punch. An end to side anastomosis is then fashioned using running 5-0 polypropylene sutures. The graft is distended with arterial pressure before being cut to length. Appropriate graft length is important to avoid undue tension or redundancy. The stump of the proximal end of the renal artery is oversewn with running 6-0 polypropylene suture. The distal end of the graft and the distal end of the renal artery are spatulated. An end to end anastomosis is then fashioned using 6-0 polypropylene suture. After completion of the anastomosis flow within the distal renal artery is interrogated with handheld continuous wave Doppler ultrasound and/or an ultrasonic flow probe.

Extraanatomic Renal Artery Bypass

When the aorta is heavily diseased with calcific atherosclerotic plaque and an aortorenal bypass is not feasible, there are several options for an extraanatomic bypass. The left renal artery may be revascularized using the transected distal splenic artery. The retroperitoneal exposure described earlier is carried cephalad, and the pancreas is mobilized anteriorly to expose and mobilize the splenic artery. Intravenous unfractionated heparin is administered, and the splenic artery is controlled proximally with an atraumatic vascular clamp and ligated and divided as distally as possible. The left renal artery is then controlled proximally and distally with vascular clamps and transected close to its aortic origin. The proximal stump is closed with 4-0 polypropylene suture at the aorta. The transected end of the splenic artery is then mobilized and anastomosed to a distal, free portion of the transected left renal artery using 6-0 polypropylene suture (Fig. 8). An extensive endarterectomy of the proximal left renal artery can be performed if additional length of the vessel is required for a tension-free anastomosis. The spleen is left in situ if collateral circulation is intact and there is no evidence of a capsular tear. Splenectomy should be performed if there is any indication of capsular injury secondary to the risk of postoperative hemorrhage.

The right renal artery may be revascularized using the common hepatic artery as the inflow source. The right colon is mobilized and

FIG. 7 Retrorenal exposure instead of the standard intraperitoneal approach provides excellent access to the paraaortal aorta and bilateral renal arteries as seen in this intraoperative image.

FIG. 8 Completed splenorenal bypass. Note the left renal artery is mobilized, cephalad and anastomosed to the transected splenic artery. The left renal vein is being retracted with a Penrose drain to expose the aorta.

FIG. 9 Proximal anastomosis of a right hepatorenal bypass with with the saphenous vein graft is seen to the common hepatic artery at the site of origin of the gastroduodenal artery. Metzenbaum scissor is used to mark the vein to assist with proper orientation.

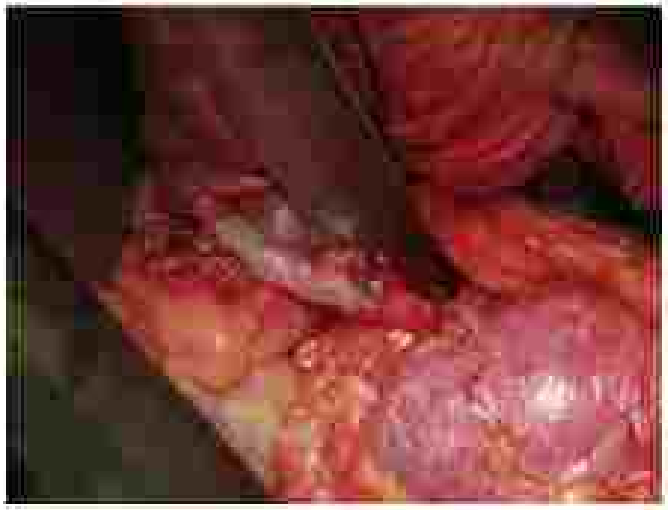

FIG. 10 Distal anastomosis of a right hepatorenal bypass with a saphenous vein graft in this case it was performed in an end-to-end configuration to prevent retrograde flow into the false lumen of an aortic dissection.

the right renal artery is identified as it courses distal to the inferior vena cava. The common hepatic artery is located and dissected until the gastroduodenal artery is exposed. The common hepatic artery is left intact and a saphenous vein interposition graft is anastomosed at the origin of the transected gastroduodenal artery (Fig. 9). The vein graft is then anastomosed to the right renal artery either in an end-to-side or an end-to-end configuration. An end-to-side configuration may be used for proximal stenosis without evidence of distal embolization and an end-to-end configuration is necessary if the proximal renal artery requires ligation (Fig. 10).

The left and right renal arteries also may be revascularized with PTFE or vein interposition grafts originating from the iliac arteries. Whenever a graft is used, appropriate graft length is critical to ensure that there is no tension or redundancy.

Aortorenal Endarterectomy

A midline incision is made and the retroperitoneum is opened overlying the infrarenal aorta, with exposure obtained as outlined previously. The left and right renal arteries are dissected free, and vascular loops are placed around each of the renal arteries. The aorta is circumferentially freed above and below the renal artery origins. Intravenous unfractionated heparin is administered. Vascular loops are used to control the renal arteries. The suprarenal and infrarenal aorta is controlled with atraumatic vascular clamps. Aortorenal endarterectomy can be accomplished via transverse arteriotomy extending onto the renal arteries. Atheromatous plaque is removed carefully with a vascular knife to achieve tapered endpoints. Occasionally, a small distal shelf will require placement of a 7-0 polypropylene tacking suture. The aortotomy is closed with a patch angioplasty.

Complications

Cardiovascular and pulmonary complications are common after open renal artery revascularization. Dialysis-dependent renal failure occurs in only 1% of patients. The perioperative mortality rate is between 2% and 4%. Thirty-day mortality has been associated with increasing age, chronic renal failure, and history of congestive heart failure.

Results

Approximately 80% of patients experience blood pressure improvement or cure postoperatively. Renal function improves or stabilizes in approximately 60% of patients who undergo open repair. As many as 70% of selected patients who recently started dialysis may no longer require dialysis after open renal artery revascularization. Early postoperative thrombosis occurs in only 1% to 2% of patients.

Surveillance and Follow-up

Although there are no quality data on RAS surveillance after bypass or endarterectomy, I recommend a duplex ultrasound 30 days after the procedure to interrogate the graft and flow to the renal arteries. Several additional duplex ultrasounds are performed every 6 to 12 months to assess for recurrent stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier restaging of the renal vasculature.

SUMMARY

Atherosclerotic RAS may cause systemic hypertension or impaired renal function. The vast majority of patients with symptomatic RAS are managed successfully by careful control of hypertension and risk factors associated with the progression of atherosclerosis. Revascularization is recommended for RAS patients with renovascular hypertension that is not responsive to maximal medical therapy, those with worsening excretory renal function, and young individuals in whom flash pulmonary edema is caused by RAS. Revascularization by renal artery angioplasty and stenting has largely supplanted open renal artery surgery because of its minimally invasive nature, excellent early renal artery patency, and decreased periprocedural morbidity and mortality. Open renal artery bypass and endarterectomy currently are reserved for urgent salvage after technical endovascular failures and procedures in combination with elective aortic reconstructions that require an open approach. Open extraanatomic renal artery bypass operations may be helpful when treating patients with aortic aneurysm or dissections when using aortic endografts.

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Raynaud's Phenomenon

Nasim Nasiri, MD, and Alan Dardik, MD, PhD

First described by Maurice Raynaud in 1862, Raynaud's phenomenon (RP) has been characterized by pathologic, paroxysmal, reversible vasoconstriction of acral arteries and arterioles in response to sympathomimetic stimuli (cold, provocative emotional or pharmacologic stimuli, etc.). The classic triphasic presentation involves progression from a period of pallor secondary to intense vasospasm, to cyanosis related to pooling of deoxygenated blood, and finally to rebound hyperemia due to gradual vasodilatation. The overall prevalence in the general population has been estimated to be 3% to 5%. The nomenclature used to describe this condition, including Raynaud's syndrome, Raynaud's disease, Raynaud's phenomenon, primary Raynaud's, and secondary Raynaud's, has been confusing, misleading, and often erroneously applied. Coined by Hutchinson, RP was a term designed to suggest the variable etiologic mechanisms underlying this condition.

In 1992, Leflon and Medsger addressed the issue and proposed the following solution, primary RP refers to the characteristic findings without evidence of an underlying medical or surgical condition (but to an idiopathic condition). Secondary RP describes the characteristic findings related to an underlying medical or surgical condition. This chapter follows the language suggested by Leflon and Medsger.

PRIMARY

Primary RP is seen worldwide, with higher incidence in colder climates. The median age at onset of primary RP is 14 years; only 27% of cases begin at the age of 40 or later. Symmetric events involving both hands or feet are common. Tissue loss or gangrene is not associated with primary RP. Given the idiopathic nature of this subtype, diagnostic tests aimed at identifying underlying contributory causes, such as nail fold capillaroscopy, erythrocyte sedimentation rate, and serologic markers, are, by definition, normal (Fig. 1 and Table 1). A positive family history in first-degree relatives is not uncommon, suggesting a yet to be identified genetic correlation of unknown penetrance.

SECONDARY

Secondary RP is more commonly seen after the age of 30 years. Unlike primary RP, secondary RP is associated with severe attacks that may be isolated to one extremity. Gangrene and ischemic ulceration are possible. Common systemic diseases associated with secondary RP include certain connective tissue, rheumatologic, autoimmune, endocrine, and hematologic disorders. The disorder most commonly associated with secondary RP is scleroderma. Given the asymmetrical patterns of distribution, a thorough workup evaluating for thromboembolic, atherosclerotic, degenerative, and/or compressive arterial etiologies is advisable (Box 1).

PATHOGENESIS

The pathogenesis of RP involves a highly localized process with unimpeded, augmented sympathomimetic tone and subsequent vasoconstrictive mechanisms affecting acral arteries, arterioles, and thermoregulatory arteriovenous connections. This has been attributed to overexpression or hyperactivity of postsynaptic alpha-2 receptors, decreased endothelial nitric oxide and prostacyclin production, and altered metabolism of endothelin-1 and angiotensin II. Disrupted capillary flow caused by endothelial dysfunction occurs in severe cases of secondary RP leading to tissue loss and/or gangrene. A chronic inflammatory state from recurring episodes can lead to vascular structural changes such as intimal fibrosis. In addition, imbalances between coagulation and fibrinolysis have been observed in both primary and secondary RP.

DIAGNOSIS

The diagnosis of RP remains primarily clinical. It is critical to differentiate between primary and secondary RP to correctly manage and treat patients as management is considerably different for the two conditions. A detailed clinical history with special emphasis on the location, severity, and frequency of symptoms is required. Seasonal variation and association with stressful situations are important to elicit. A detailed social history focusing on past or present tobacco and/or illicit drug use as well as a thorough review of active medications and supplements is critical. The physical examination should include a thorough pulse examination.

A screening diagnostic test is usually a noninvasive arterial study to rule out obstructive pathology (Fig. 2). The study should include evaluation of bilateral extremities with segmental pressures, Doppler waveforms, and wrist/ankle brachial indices. Plain radiographs are of limited utility, but they may demonstrate heterotopic calcification or cervical ribs suggesting upstream etiologies for secondary RP. Digital plethysmography can be performed. Obstructive lesions will demonstrate blunted, dampened waveforms on pulse volume analysis, whereas vasoconstrictive processes have a pathognomonic peaked dome at the apex of the waveform. Cold immersion testing is a highly sensitive but nonspecific adjunctive diagnostic measure. Computed tomography angiography or magnetic resonance angiography are helpful in screening for upstream or thromboembolic arterial disease. Selective, catheter-directed, digital subtraction angiography is reserved for those cases in which noninvasive testing has been inconclusive or has suggested the presence of disease amenable to endovascular therapy.

Serologic tests are appropriate when secondary RP is suspected. This is especially true when systemic symptoms such as myalgias, arthralgias, fever, weakness, and rash are present. A complete blood count, routine blood chemistry panel, antinuclear antibodies test, rheumatoid factor, and complement levels should be drawn (Box 1).

MANAGEMENT

Nonpharmacologic

Conservative, nonoperative, nonpharmacologic measurements aimed at avoidance of triggers are the cornerstone of therapy for most patients with RP. Cold exposure should be minimized and hands' first warming measures, such as mittens, applied as often as necessary. Caffeine, cigarette smoking, and other culprit agents should be avoided. The severity and frequency of symptoms determines how drastic the lifestyle modification is required.

Pharmacologic

Patients whose symptoms remain refractory to conservative measures are considered for vasodilatory pharmacotherapy with a number of agents available for off-label use. These medications are prescribed at the lowest possible dose that allows a satisfactory decrease in the frequency and severity of the vasospastic episodes.

The typical first-line pharmacologic agent for RP is a dihydropyridine class, long-acting calcium channel blocker such as nifedipine, nicardipine, or amlodipine. Sustained-release nifedipine, for example, is titrated at a dose of 10 to 30 mg daily to three times daily. Side effects include hypotension, headaches, weight gain, dizziness, or lightheadedness. Other doses and types of calcium channel blockers are available and have been used with variable success rates. Phosphodiesterase inhibitors (e.g., sildenafil, tadalafil) may be tried if calcium channel blockers are ineffective. There are multiple

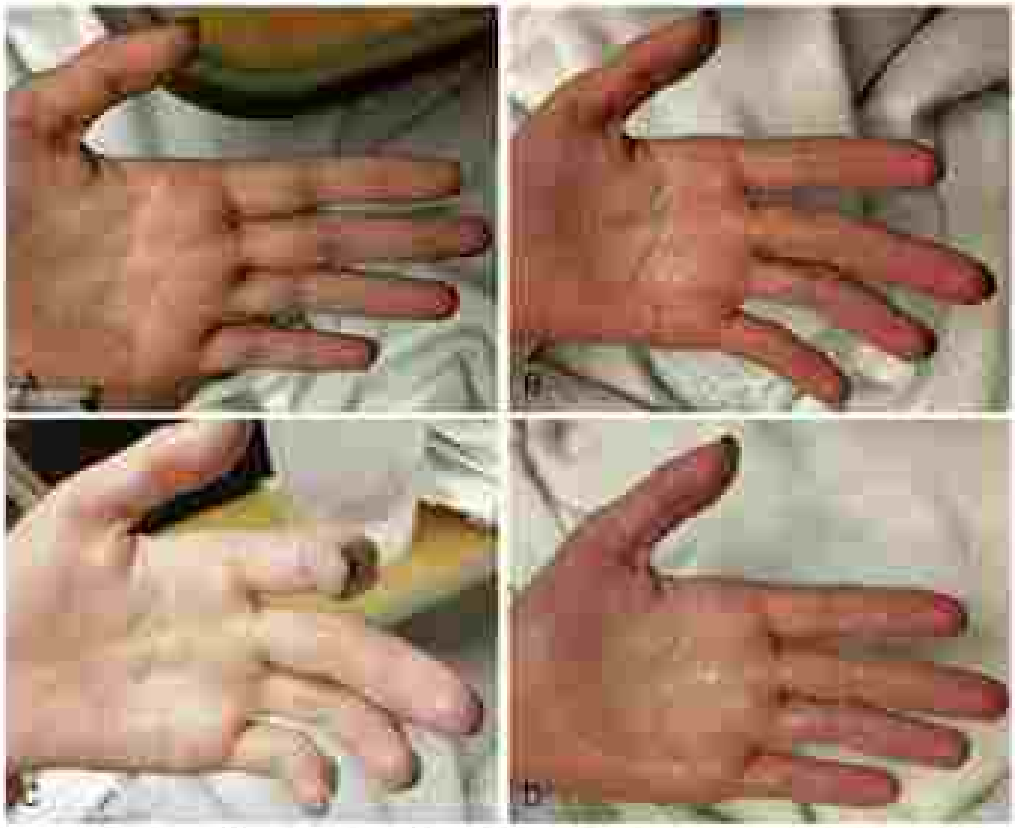

FIG. 1 Raynaud's phenomenon in a patient with Ehlers-Danlos syndrome as illustrates the color changes associated with cerebral stimuli. (A) Normal-appearing hand. (B) After cold stimuli, the pallor from vasoconstriction can be seen. (C) After 30 seconds the hypothenar eminence appears in digital with blood hyperfusion. (D) Hand after 3 minutes exposure to normal.

TABLE 1 Characteristics of Primary and Secondary Raynaud's Phenomenon

	Primary	Secondary
Age	Younger (<30 years)	Older (>30 years)
Gender preference	Female	Male (depending on secondary cause)
Incidence	Most common	Less common
Familial predisposition	Yes	Yes
Combination with other disease	No, idiopathic	Associated with systemic disease
Vascular defect	Functional dysregulation of autonomic nervous system	Structural changes to connective tissue or vessels
Associated signs	None	Arthritis, sclerodactyly, cardiopulmonary abnormality, rash
Frequency	Precipitated by stimuli	Periodic and stimuli trigger
Severity of symptoms	Long history of mild attacks	Severe and disabling pain
Distribution	Symmetric	Asymmetric
Duration	Self-limited	Need for additional treatment (pharmacologic, surgery)
Critical complications	None	Ischemia and ulcers
Capillaroscopy	Normal (symmetric, slim, and uniform)	Abnormal (dilated, irregular, elongated, and tortuous vessel)
Vascular examination	Normal pulses	Abnormal pulses
Erythrocyte sedimentation rate	Normal	Elevated
Serologic studies	Negative	Autoantibody antibody, autoantibodies
C-reactive protein	Normal	Elevated

BOX 1 Secondary Causes of Raynaud's Phenomenon

Rheumatologic
- Systemic sclerosis (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome)
- Sjögren's syndrome
- Systemic lupus erythematosus
- Ehlers-Danlos syndrome
- Rheumatoid arthritis
- Dermatomyositis
- Polymyositis
- Mixed connective tissue disease

Autoimmune
- Raynaud's syndrome
- Vasculitis (polyarteritis nodosa, Henoch-Schönlein purpura)
- Antiphospholipid syndrome
- Primary pulmonary hypertension

Endocrine
- Hypothyroidism
- Pheochromocytoma
- Carcinoid

Infections
- Hepatitis B and C infection
- *Mycoplasma pneumoniae*

Medications
- Cyclosporine
- Ergotamine
- β-blockers
- Cytotoxic chemotherapeutic agents (bleomycin)
- Bromocriptine
- Nicotine
- Cocaine
- Sulfonylureas
- Interferon-α and interferon-β
- Clonidine
- Sympathomimetics
- Estrogen in oral contraceptives
- Caffeine

Occlusive Vascular
- Atherosclerosis
- Vascular trauma (hypothenar hammer syndrome)
- Buerger's disease
- Thoracic outlet syndrome
- Thromboembolism

Hematologic Proliferative
- Leukemia
- Lymphoma
- Polycythemia vera
- Multiple myeloma
- Dysproteinemia (intravascular coagulation)
- Cryoglobulinemia
- Cold agglutinin disease

Neurologic
- Migraines
- Carpal tunnel syndrome
- Polyneuropathy

Environmental
- Emotional stress
- Tobacco
- Repetitive trauma or injuries to hand

Malignancy
- Lung, stomach, small bowel
- Paraneoplastic syndrome
- Neurofibromatosis

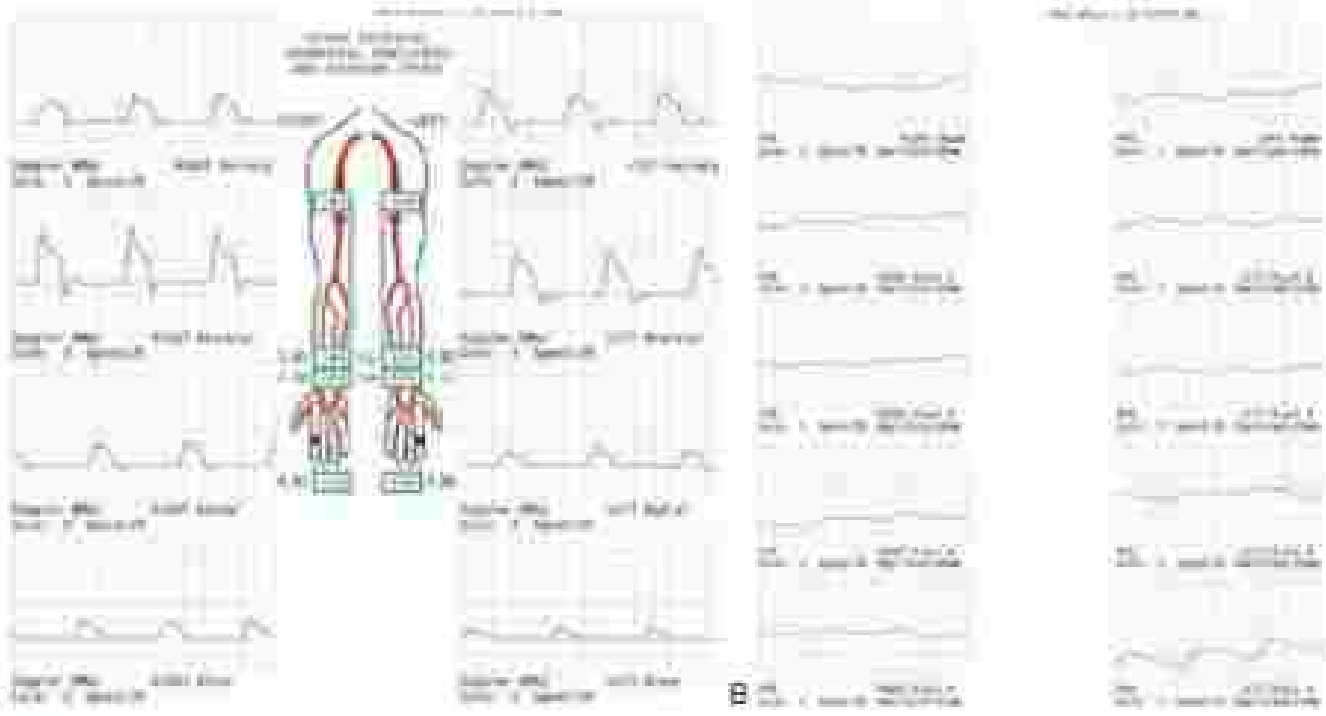

FIG. 1 (A, B) Example of an abnormal upper extremity noninvasive arterial study focus the thumb waveforms proximally and the the digital brachial

second-line agents for the treatment of RP, including prazosin, losartan, and prostaglandins. These drugs are reserved for recalcitrant cases and usually are used by subspecialists in the field. Topical nitroglycerin at 0.1 mg of gel up to 4 times a day can be used alone or in combination with oral agents. Close monitoring of side effects and vital signs is important in cases of polypharmacy.

Surgical Treatment

Surgical treatment for secondary RP is indicated to treat any identified underlying obstructive pathology (Box 1). Local wound care is initiated with serial debridement of necrotic tissue and dressing changes. Limited digital amputation may be required with the treatment goal of alleviating pain and preserving function. Cervical or lumbar sympathectomy (chemical or surgical) can provide temporary relief of pain and ulcer healing but long-term results are variable. A thoracoscopic approach has nearly replaced open procedures for cervical sympathectomy. Other proposed techniques are characterized by anecdotal results, variable success and complication rates, significant placebo effect, and limited long-term data; these techniques include adventitial stripping of digital arteries, regional sympathetic blocks, digital botulinum toxin injections, and spinal cord stimulation.

SUMMARY

RP encompasses two broad categories of disease depending on the etiology, location, and severity of symptoms. Primary RP is a more benign, idiopathic condition with a more symmetric distribution affecting the bilateral hands and/or feet. Its diagnosis is mainly clinical with adjunctive noninvasive studies that can help rule out upstream pathology and/or rule in provoked vasospasm. Lifestyle modifications and avoidance of provocative stimuli remain the cornerstone of therapy. Refractory cases can be treated with a variety of off-label pharmacologic agents, most commonly long-acting calcium channel blockers. Secondary RP is a more severe form of disease most commonly associated with scleroderma. Other contributing causes include upstream obstructive pathologies, compression-related syndromes, thromboembolic phenomena, and systemic inflammatory conditions. Treatment is aimed at addressing the underlying cause and attenuating symptoms. Less responsive to pharmacotherapy, Secondary RP has also been treated with a variety of adjunctive surgical/interventional maneuvers that have yielded equivocal short- to mid-term outcomes. Further research into the behavioral and alternative therapeutic modalities is ongoing.

SUGGESTED READINGS

Chikura B, Moore T, Manning J, Taiel A, Patrick AL. Thumb involvement in Raynaud's phenomenon as an indicator of underlying connective tissue disease. *J Rheumatol*. 2010;37:2061–2065.

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THORACIC OUTLET SYNDROME

Timothy R. Williams, MD, and Julie A. Freischlag, MD

Thoracic outlet syndrome (TOS) represents several distinct entities with a constellation of signs and symptoms depending on the anatomic structures involved. The underlying pathophysiology of these disorders is compression of the neurovascular structures of the upper extremity where they emerge from the chest, the region known as the thoracic outlet. Estimates of incidence range from 3 to 80 per 1000 in the population. In general, there are three forms of TOS described, namely neurogenic, venous, and arterial. Neurogenic TOS (nTOS) is by far the most common form, accounting for 95% of all cases. This occurs from compression of the brachial plexus within the interscalene triangle, which is bordered by the first rib, the anterior scalene muscle, and the middle scalene muscle (Fig. 1). The second most common is venous TOS (vTOS), which accounts for approximately 4%. vTOS arises from compression of the axillosubclavian vein within the costoclavicular space, which is bound by the first rib, clavicle, and anterior scalene muscle. The subclavius muscle and tendon, which connects the first rib and the clavicle, frequently contributes the vein in this region (Fig. 1). Finally, arterial TOS (aTOS) occurs in about 1% of all cases and develops from compression of the axillosubclavian artery within the interscalene triangle. This disorder commonly occurs in association with a cervical rib. Aside from being rare, arterial TOS is frequently insidious in its evolution, making it a challenge to diagnose. It frequently manifests with evidence of limb ischemia resulting from distal embolization from aneurysmal degeneration or from vessel occlusion. Although these three disorders are all defined as thoracic outlet syndrome, the presentation, diagnosis, and management vary significantly.

DIAGNOSIS AND TREATMENT

nTOS

TOS is largely a clinical diagnosis that is established based on a careful history and physical examination. Unfortunately, there exists no gold standard diagnostic modality to either confirm or exclude the diagnosis; however, select tests can be used that influence the strength of the diagnosis. TOS can develop from acquired factors such as trauma to the shoulder and chest wall, from repetitive overhead activity, or from certain congenital anatomic predispositions such as a cervical rib or anomalous fibrous bands. Common presenting symptoms include upper extremity paresthesias and pain within the C8-T1 dermatome, as well as arm weakness. These symptoms are typically exacerbated by arm abduction (raising the arms overhead) and are alleviated by adduction (arm at the side). nTOS occurs most commonly in women, with a ratio of nearly 3:1. Additional symptoms include anterior neck, back, and shoulder pain of varying degrees, making this disorder difficult to distinguish from other pathologic conditions.

Several physical examination maneuvers can be used to support the diagnosis. Many patients will experience tenderness to palpation over the anterior scalene muscle to the low anterior neck. Classically, Adson's maneuver has been used to assess for TOS, with ablation of pulses at the wrist representing a positive test; however, this and other

second-line agents for the treatment of RP, including prazosin, losartan, and prostaglandins. These drugs are reserved for recalcitrant cases and usually are used by subspecialists in the field. Topical nitroglycerin at 0.1 mg of gel up to 4 times a day can be used alone or in combination with oral agents. Close monitoring of side effects and vital signs is important in cases of polypharmacy.

Surgical Treatment

Surgical treatment for secondary RP is indicated to treat any identified underlying obstructive pathology (Box 1). Local wound care is initiated with serial debridement of necrotic tissue and dressing changes. Limited digital amputation may be required with the treatment goal of alleviating pain and preserving function. Cervical or lumbar sympathectomy (chemical or surgical) can provide temporary relief of pain and ulcer healing but long-term results are variable. A thoracoscopic approach has nearly replaced open procedures for cervical sympathectomy. Other proposed techniques are characterized by anecdotal results, variable success and complication rates, significant placebo effect, and limited long-term data; these techniques include adventitial stripping of digital arteries, regional sympathetic blocks, digital botulinum toxin injections, and spinal cord stimulation.

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Suggested Readings

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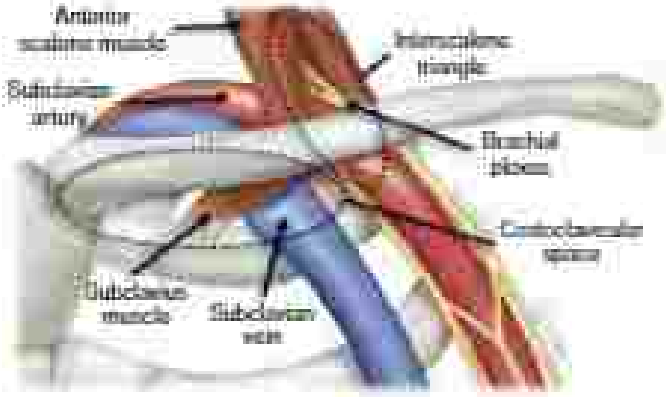

FIG. 1 Anatomy of the thoracic outlet. Key structures within the thoracic outlet, from left to right: the costoclavicular ligament, subclavius muscle, subclavian vein, anterior scalene muscle, subclavian artery, and the brachial plexus. The two key anatomic spaces exposed across the costoclavicular space and the interscalene triangle. (Courtesy I.A. Crim.)

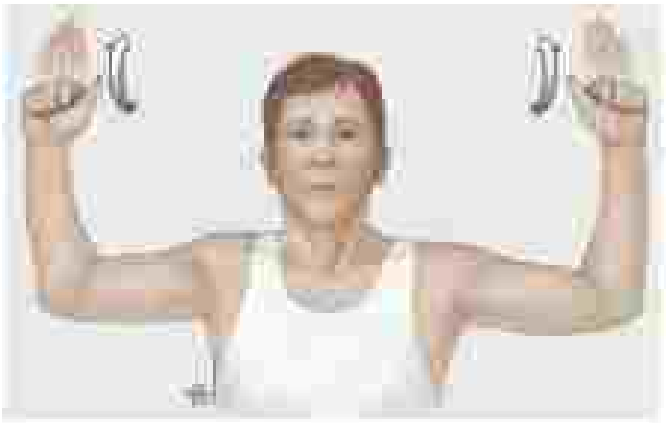

FIG. 2 The elevated arm stress test. The arms are held at 90 degrees of abduction and external rotation with the elbows at 90 degrees of flexion to narrow the costoclavicular triangle. Hands are rapidly opened and closed to elicit the patient's symptoms, which is suggestive of neurogenic thoracic outlet syndrome. (Courtesy Mayo Foundation for Medical Education and Research.)

similar arm abduction tests can be positive in upwards of 20% of healthy, asymptomatic individuals and should therefore not be used to support the diagnosis. The clinical test that has proven most beneficial is the elevated arm stress test, where the arms are positioned in the hold up position (90 degrees of shoulder abduction, external rotation, and elbow flexion) (Fig. 2). Patients are instructed to continuously open and close their hands for 3 minutes, with reproduction of their symptoms defined as a positive test. A chest radiograph should be performed to assess for evidence of a cervical rib (Fig. 3A) or rudimentary first rib (Fig. 3B), as well as other bony abnormalities including previous clavicular fractures. Duplex ultrasonography is commonly performed to assess for arterial and venous compression, which can serve as indirect evidence of compression within the thoracic outlet. Other diagnostic modalities such as computed tomography (CT), magnetic resonance imaging, and electromyography are costly and add little to the diagnosis of nTOS and therefore should not be routinely performed. Select centers have used magnetic resonance imaging with provocative maneuvers to evaluate for nerve compression within the interscalene triangle; however, this test requires local expertise that may not be present at all institutions. Additionally, maximal positioning required for these studies may result in significant

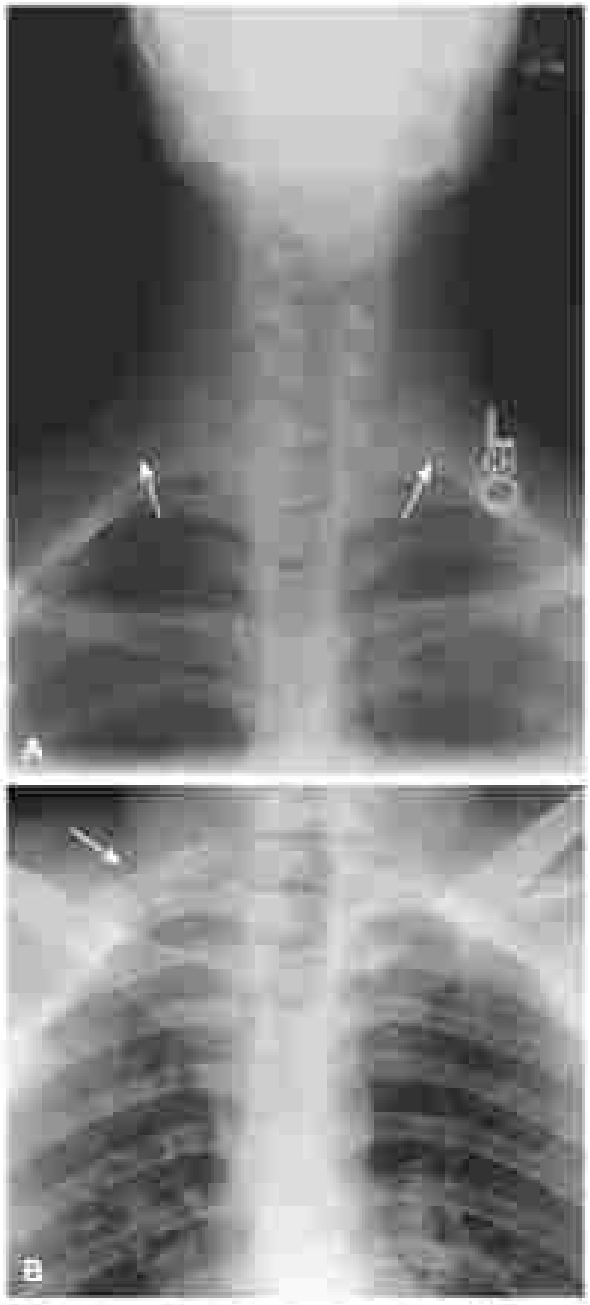

FIG. 3 Bony abnormalities in thoracic outlet syndrome. (A) Chest radiograph demonstrating bilateral cervical ribs. (B) Chest radiograph demonstrating a rudimentary first rib. Such bony abnormalities can predispose individuals to neurogenic and arterial thoracic outlet syndrome. (A, Modified from Kliewer MA, Hertzberg BS, Dubose-Ellis J, et al. Cervical rib: radiographic prevalence and significance. Radiology. 1998;208:645–648.)

symptom exacerbation, so should be used with caution. In select patient populations with atypical symptoms or suspicion for alternate pathologies, these tests may play an important role.

When the diagnosis remains equivocal, an anterior scalene muscle block can be performed, which is widely accepted as a useful diagnostic adjunct for suspected nTOS. This involves the injection of a short acting local anesthetic directly into the anterior scalene muscle using ultrasound or CT guidance. The block is meant to induce muscle relaxation, thereby simulating decompression of the thoracic outlet. A positive block is one that effectively reduces the patient's symptoms

and has been shown to correlate with symptomatic improvement following surgery. Beyond serving as a diagnostic modality, anterior scalene muscle block will frequently provide short-term symptom relief. When botulinum toxin (Botox) is used, longer-term symptom relief can be achieved, with reported durations of up to 3 months. This can be used as a bridge to surgical decompression but should not be used as primary therapy because repeated injections can increase the risk of scar formation, thereby complicating future surgery.

Although the presentation of nTOS may vary across patients, consensus-based diagnostic criteria have been developed by experts in the field (Consortium for Outcomes Research and Education on Thoracic Outlet Syndrome) in an effort to standardize the approach to this challenging patient population. The symptoms and physical examination findings felt to most strongly correlate with the diagnosis of nTOS include the following: local tenderness with palpation over the scalene triangle, reproduction of hand/digit paresthesias with palpation over the scalene triangle, symptom exacerbation with overhead arm use, thenar/hypothenar muscle atrophy, a positive supraclavicular Tinel's sign, weakness of handgrip, paresthesias in the supraclavicular space, paresthesias in digits 4 and 5, and a positive 1-minute elevated arm stress test, among others. Additionally, the following diagnostic tests have been deemed to most strongly correlate with the diagnosis: symptom improvement with scalene and/or pectoralis minor muscle block, the presence of a cervical rib or prominent C7 transverse process, and improvement following first rib resection and scalenectomy (FRSS) for contralateral disease.

Preoperative management centers around physical and/or occupational therapy, activity modification/restrictions, and pharmacotherapy. In general, a minimum of 2 to 3 months of physical therapy should be performed because many patients with nTOS will experience significant improvements and may not require surgery when activity modifications or postural changes have proven beneficial. Muscle relaxants, nonsteroidal antiinflammatory drugs and analgesic agents are commonly used as an adjunct to management.

For those patients with history, physical examination, and diagnostic findings to support the diagnosis of nTOS, along with a suboptimal improvement following a reasonable trial of physical therapy, surgical intervention should be strongly considered. In general, a lower threshold for surgical intervention should be considered in those patients with a compelling diagnosis confirmed with focal bony abnormality such as a cervical or rudimentary first rib.

vTOS

vTOS represents the second most common form of TOS and involves compression of the subclavian vein within the costoclavicular space. Most commonly, this stems from acquired anatomic changes such as hypertrophy of the anterior scalene and subclavius muscles or from trauma to the anterior chest, particularly to the context of a clavicular fracture. It is frequently seen in young, otherwise healthy adults or adolescents, in athletes, and those who are exposed to occupational conditions that demand repetitive overhead use of the arms. Over time, this repetitive mechanical injury to the vein can lead to progressive scarring, inflammation, narrowing and ultimately thrombosis (Paget-Schroetter's syndrome). Common presenting signs and symptoms include arm swelling, pressure, fatigue, cyanosis, and a sensation of heaviness. In contrast to nTOS, patients do not typically experience debilitating pain, but may experience discomfort from tense edema. In those with a subacute or late presentation, evidence of venous collaterals along the chest wall may be apparent. Patients with venous compression in the absence of prior thrombosis or occlusion may experience similar symptoms, but these tend to be milder and relieved by arm rest (McElhenny's syndrome).

The diagnosis can be suspected based on history and physical examination findings, however, it is definitively established with duplex ultrasound, CT venography, or conventional venogram. Typically, duplex ultrasound is the standard initial diagnostic modality. Findings supporting the diagnosis of vTOS include loss of flow on color Doppler in the distal subclavian vein and a continuous venous waveform (lack of phasicity) within the axillary vein. In the absence of complete occlusion, venous compression can be elicited with the arm in varying degrees of abduction, resulting in an ablation of flow. Chest radiographs should be routinely performed to assess for bony abnormalities.

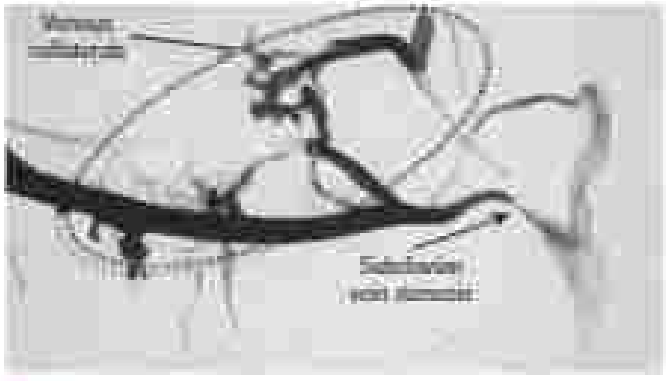

FIG. 4 Venogram in a patient with venous thoracic outlet syndrome. Venogram performed following transaxillary first rib resection and scalenectomy shows the venous stenosis within the costoclavicular space, which resulted in abundant collateral vessels providing venous drainage of the arm.

Perioperative management is centered around anticoagulation. For patients with a severe, acute presentation (onset <14 days), catheter-directed thrombolysis can be considered, although this remains controversial. Venography characteristically demonstrates abundant collateral vessels and stenosis/occlusion of the subclavian vein at the costoclavicular junction (Fig. 4). In general, angioplasty should be avoided before surgical decompression because this seldom rectifies the underlying extrinsic compression of the vessel and results in further injury. For subacute or chronic presentations, thrombolysis plays no role in management.

In patients without secondary causes for venous thrombosis of the subclavian vein (i.e., central venous catheters, documented hypercoagulable state), surgery is typically indicated. The timing of surgery remains an area of controversy, with some advocating for early surgical decompression and others promoting an upfront period of anticoagulation (weeks to months) prior to surgery. It is the author's stance to perform early decompression (within 1 week) for acute presentations in an effort to minimize the inflammatory cascade produced by acute thrombosis, with a more protracted approach for patients with a chronic presentation (≥ 4 weeks).

aTOS

aTOS is the rarest form of TOS, representing approximately 0.5% of patients overall. As with vTOS, it tends to occur in younger patients and most commonly occurs in patients with bony anomalies such as a cervical or rudimentary first rib. The underlying pathology of this disorder is repetitive trauma to the subclavian artery, which leads to progressive vessel stenosis, occlusion, or aneurysmal degeneration with distal embolization. Presenting symptoms commonly include arm or hand claudication. Patients may also experience typical signs or symptoms of acute limb ischemia, including paresthesias, poikilothermia, paralysis, pallor, and pulselessness. Because distal embolization may cause variable degrees of ischemia, patients may experience an insidious progression of the disease and present late, with abrupt episodes of exacerbation punctuated by intervals of improvement. In advanced disease, patients may experience tissue loss or even digit gangrene.

Initial assessment should include duplex ultrasonography along with upper extremity segmental blood pressure measurements. It is important to obtain bilateral upper extremity blood pressure

measurements to assess for a discrepancy. Duplex ultrasound can reliably detect axillosubclavian stenosis and/or aneurysmal degeneration, as well as downstream occlusion of the brachial artery or forearm vessels from distal embolization. As with other forms of TOS, a chest x-ray should be performed to evaluate for bony anomalies. CT angiography should be considered to further delineate the patient's anatomy; however, conventional angiography may be necessary to aid in surgical decision making.

Unlike other forms of TOS, aTOS universally requires surgical intervention and frequently mandates surgery beyond thoracic outlet decompression. Although surgical decompression of the thoracic outlet remains a fundamental tenant of management in these patients, aTOS requires a tailored surgical approach based on the patient's specific anatomic abnormalities. This may include reconstruction of the axillosubclavian artery, thrombolysis, endarterectomy, and/or distal bypass depending on the extent and level of disease.

SURGICAL MANAGEMENT

Although certain aspects of surgical management may vary based on the specific form of TOS, the unifying aspect of all interventions involves surgical decompression of the thoracic outlet. This can be performed using a supraclavicular, transaxillary, infraclavicular, or paraclavicular (infraclavicular and supraclavicular) approach depending the form of TOS and the patient's unique anatomic characteristics. It is our preference to use the transaxillary approach for the majority of neurogenic and venous TOS cases, which represents approximately 80% of all cases. aTOS, because it frequently requires vascular reconstruction to varying degrees, is typically managed from a paraclavicular approach, as it frequently requires vascular reconstruction, either bypass or interposition grafting.

Transaxillary Approach

The transaxillary approach provides excellent surgical exposure of the interscalene triangle and the costoclavicular space, making it ideally suited for the surgical management of both nTOS and vTOS. Because this technique uses a lateral surgical approach rather than anterior, the first rib can be exposed widely. This exposure also provides excellent visualization of the brachial plexus, subclavian vein, and subclavian artery. Additionally, this exposure provides excellent control for comparison to alternative exposures.

Patients undergo general anesthesia routinely, along with a short acting nondepolarizing muscle blockade. Long acting neuromuscular blockade should be avoided to enable nerve stimulation and corresponding muscle contraction during exposure and dissection, thereby minimizing the risk for iatrogenic nerve injury. Following anesthesia induction, the patient is positioned in the lateral decubitus position with support from an axillary roll and a bean bag. The body is further padded with foam at pressure points and pillows are placed between the legs. The arm, axilla and chest wall are widely prepped. The arm is then suspended within the Mathieder retractor, which holds the arm in 90 degrees of abduction and the elbow at 90 degrees of flexion (Fig. 5). Not only does this retractor hold the arm in a stable position, but it facilitates lateral retraction of the arm to open the axillary space and provide adequate visualization during the dissection. The arm is appropriately padded to prevent neurovascular injury during positioning and retraction.

A transverse incision approximately 8 to 10 cm in length is made within the axilla at the lower border of the axillary hair line, between the pectoralis major muscle anteriorly and the latissimus dorsi muscle posteriorly. Following incision, dissection proceeds with electrocautery down to the chest wall, being vigilant to avoid injury to the long thoracic and thoracodorsal nerves. Upon reaching the chest wall, the arm is retracted laterally, and blunt dissection ensues within this avascular plane using finger dissection, Kitner dissectors, and/or peanuts. The first rib can be palpated deep in the dissection bed. Additional blunt dissection is performed to identify the subclavian vein anteriorly, the first rib inferiorly and the subclavian artery and brachial plexus posteriorly (Fig. 6A).

FIG. 5 Positioning for the transaxillary approach. The patient is in the lateral decubitus position with the arm suspended within the Mathieder retractor which affords excellent exposure and maintains stable arm positioning. The joint of the retractor is raised and lowered throughout the procedure to enhance exposure and to minimize traction injury. (Image courtesy of Jeffrey S.A. Carter.)

Next, soft tissue attachments and the intercostal muscle bridging the first and second rib are cleared from the lateral superior border of the first rib using a periosteal elevator or blunt dissection. The subclavian muscle and tendon are identified anteriorly and carefully lysed with Metzenbaum scissors, being mindful to not injure the adjacent subclavian vein. The inner table or surface of the rib is then carefully separated from the underlying parietal pleural of the chest using a spatula or small periosteal elevator. On the lateral and flat outer surface of the rib, fibers of the middle scalenus muscle are pushed posteriorly to create a plane between the brachial plexus and the rib. It is important to not transect this muscle sharply as inadvertent transection of the long thoracic nerve may occur, which passes through the belly of the middle scalene muscle in this region.

A plane is then developed bluntly between the anterior scalene muscle and the subclavian artery using a Kitner to facilitate safe division of the anterior scalene muscle. Division of the anterior scalenus is performed in several steps, using a right angle clamp to spread and laterally retract a portion of muscle followed by meticulous transection using Metzenbaum scissors (Fig. 6B). Additional passes are performed until the entirety of the muscle has been divided. The rib is then divided with a bone cutter anteriorly within the costal cartilage, being mindful to not injure the subclavian vein. The right angle is then passed along the inner border of the first rib to remove any additional fibers of the anterior scalene muscle that remain. Next, the rib is transected posteriorly, while avoiding injury to the brachial plexus (Fig. 6C). In the presence of a cervical rib, removal of both the first and cervical rib is typically required but poses unique challenges. Often, the nerve is anteriorly displaced by the cervical rib, making it difficult to achieve a safe plane for bone transection. Furthermore, the cervical rib or rudimentary rib frequently has a bony attachment to the rib below. Resection frequently requires this bone removed using a rongeur, but ultimately a tailored approach based on the patient's specific anatomic characteristics is required. Following removal of the rib, a rongeur is used to excise any residual bone to avoid sharp edges.

Major complications are rare, with the risk of significant nerve or vascular injury being less than 1%. In the event of an arterial and/or venous injury, it is challenging, if not impossible, to definitively repair from the transaxillary exposure, requiring an urgent anterior approach for vascular control. Assurance for a pneumothorax is achieved by filling the surgical field with saline before closure and

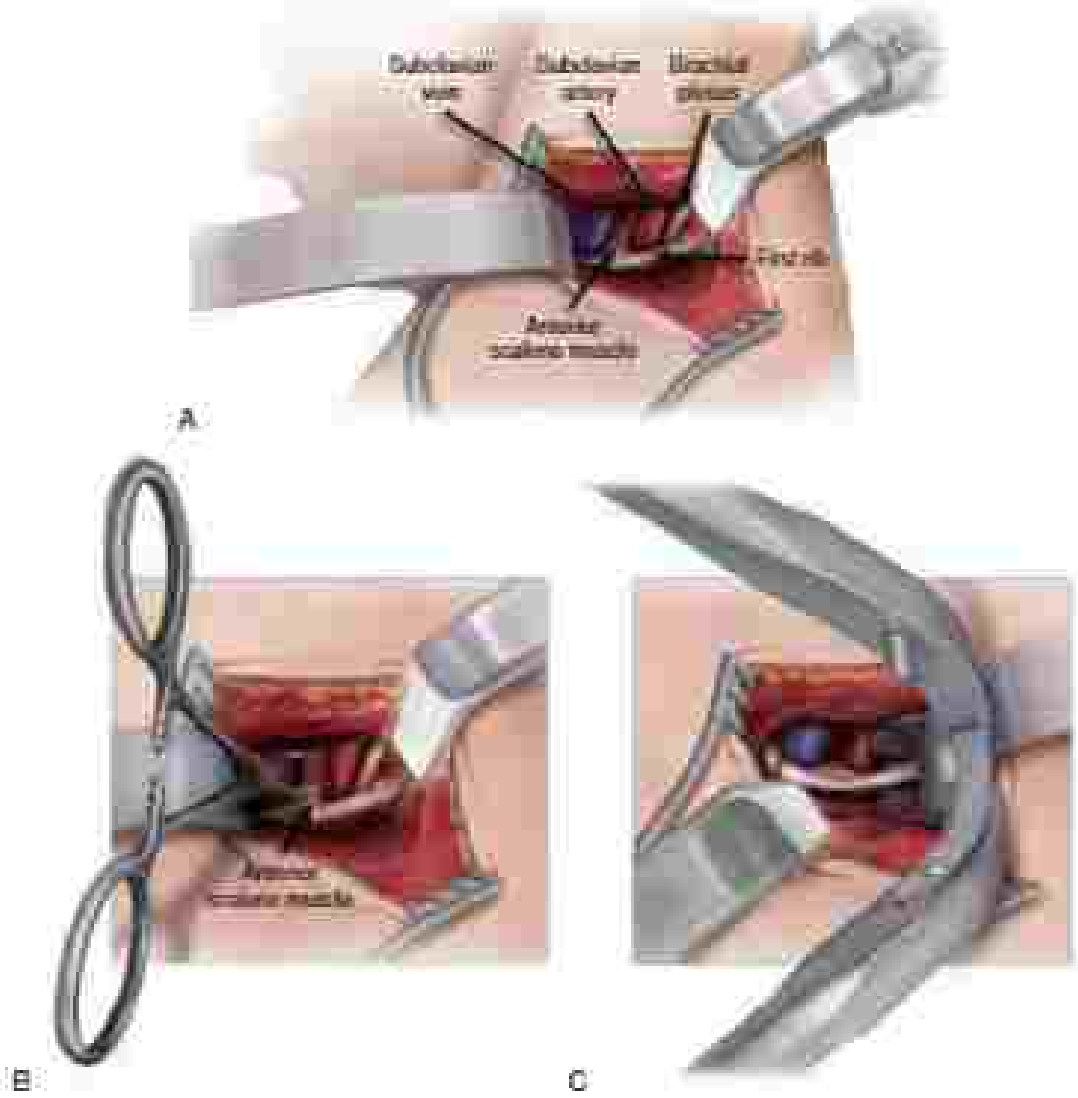

FIG. 6 Infraclavicular approach for first rib resection and scalenectomy. (A) Anatomic relationships as viewed from the infraclavicular approach. A rigid retractor is used to enhance visualization and combined with a Deaver to provide superior and posterior retraction. (B) Division of the anterior scalene muscle is performed with the use of a long right-angle clamp and Metzenbaum scissors. (C) Division of the rib first performed anteriorly then posteriorly (courtesy S.A. Sanders).

performing a Valsalva maneuver, with loss of fluid volume and/or bubbling of air serving as evidence of a pleural defect. This rarely requires placement of a chest tube. Rather, the pneumothorax can be evacuated during closing through application of suction to a red rubber catheter placed within the pleural space, which is removed before final skin closure. The skin and subcutaneous tissue are then closed in standard fashion. A routine postoperative chest x-ray is not required even when a pneumothorax is detected intraoperatively because it does not change management, provided the patient remains asymptomatic.

Supraclavicular Approach

An alternative and widely used exposure is the supraclavicular approach, which is commonly used for all forms of TOS (Fig. 7). This is our preferred exposure for the management of arterial TOS, enabling both arterial reconstruction and first rib resection. This is also our preferred approach for redo operations following prior, non-transaxillary exposure, given the increased potential for vascular complications resulting from scarring. For patients with either aTOS or vTOS, the supraclavicular approach can be combined with an infraclavicular approach (paraclavicular) to better facilitate vessel exposure, lysis, and/or reconstruction.

Patients are positioned supine with a shoulder roll to allow for neck extension. The head is rotated contralateral to the affected side. The chest wall, axilla, and ipsilateral upper extremity are included in the operative field. A skin incision in the supraclavicular fossa is made 1 to 2 cm cephalad and parallel to the clavicle, extending from the clavicular head of the sternocleidomastoid muscle laterally for approximately 10 cm. The scalene fat pad is divided inferiorly and medially between ties or with electrocautery to facilitate superolateral retraction. Care should be taken to avoid injury to the phrenic nerve as it emerges through anterior surface of the anterior scalene muscle. A nerve stimulator can be used to aid in identification. Next, the anterior scalene muscle is divided sharply, being mindful to avoid injuring the subclavian artery found deep to the muscle. Some authors suggest full excision of the muscle from its insertion on the transverse process to provide the greatest decompression of the space, which is an advantage afforded by this anterior approach. However, this places the phrenic nerve at risk and has not been conclusively shown to minimize recurrence.

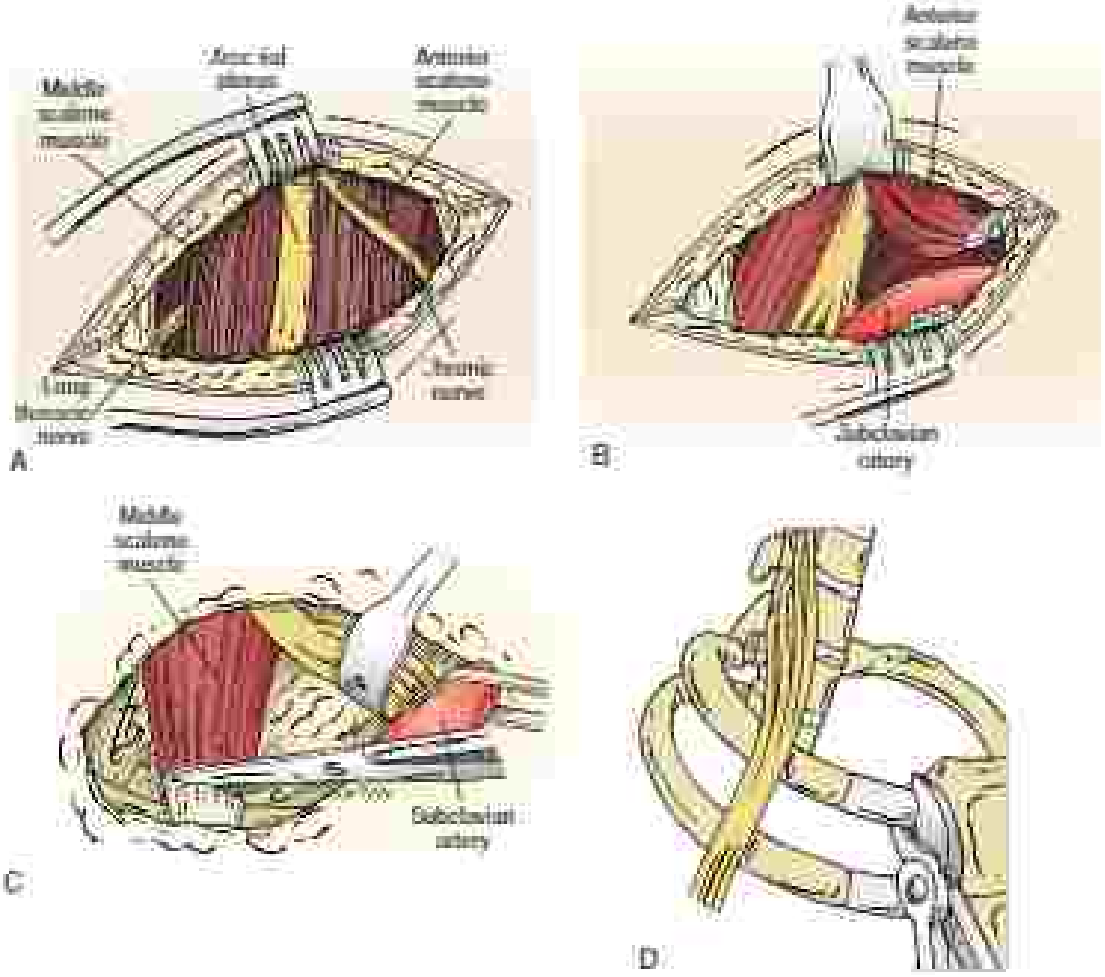

FIG. 1 (A-D) Supraclavicular approach for first rib resection (left side). See text for details.

Posterior to the brachial plexus is the middle scalene muscle, which must be cleared from the first rib to facilitate posterior transection of the rib. The long thoracic nerve can be found exiting the middle scalene muscle along its lateral border and should be protected; injury to this nerve can result in significant disability, causing a winged scapula and impairing anterior arm elevation. The middle scalene muscle is bluntly cleared from the rib using a periosteal elevator. Sharp division of the muscle close to the rib can be entertained, provided the long thoracic nerve has been identified and protected. Anterior slips of the muscle may be found coursing beneath the plexus, which may require epifascial retraction on the nerves to fully detach the muscle from the rib.

Intercostal muscle between the first and second ribs is dissected away anteriorly and posteriorly. The parietal pleura is then bluntly dissected away from the inner surface of the rib above and below, being careful to not enter the pleural space. Small branches of the subclavian artery may require ligation to facilitate elevation of the artery before transection of the rib. Any residual attachments between the rib and the brachial plexus are then cleared. While anteriorly retracting the pleura, a bone cutter is positioned posteriorly around the rib and the rib is divided. Next, the subclavian vein and artery are elevated and retracted posteriorly to facilitate anterior division of the rib, anterior to the insertion of the anterior scalene muscle. Unlike the transaxillary approach, transection of the rib at the costrovertebral junction can seldom be achieved from this exposure, but it should be divided as far anterior as possible. Residual bone can then be excised using a rongeur.

Infraclavicular Approach

The infraclavicular approach is an alternative for patients with venous TOS, providing access to the costoclavicular space and allowing for more complete anterior resection of the first rib. It also provides excellent exposure of the axillosubclavian vein, allowing for venous reconstruction either with patch angioplasty or interposition grafting, a strategy advocated by some surgeons for competitive athletes. However, there is not a uniform consensus on the need to perform venous reconstruction in the majority of vTOS cases and should therefore be performed in a very selective fashion. As mentioned previously, this approach is frequently combined with a supraclavicular exposure, what has been called the panclavicular approach, enabling both venous and arterial reconstruction, as well as sufficient posterior exposure for complete rib resection.

Patients are positioned and prepped as described for the supraclavicular approach. A transverse skin incision should be made 1 to 2 cm caudal to the clavicle approximately 10 cm in length, beginning at the medial one third of the clavicle and extending laterally. The pectoralis major muscle will be encountered and is spread to expose the clavipectoral fascia. The pectoralis minor is retracted laterally or can be divided to enable more distal exposure of the subclavian artery and vein, thereby facilitating vascular reconstruction. The subclavius muscle and tendon medially are divided sharply to provide adequate decompression of the vein. The rib can be divided far anteriorly at the costosternal junction.

SURGICAL OUTCOMES

CONCLUSION

SUGGESTED READINGS

THE DIABETIC FOOT

David W. Schuchhman, MD

The prevalence of diabetes and its associated complications has continued to rise in the United States and worldwide. There are an estimated 30 million people in the United States with diabetes. Of these patients, up to 25% will develop a diabetic foot ulcer during their lifetime. Diabetic foot ulcers and infections are the long-term complication of diabetes responsible for the most hospital admissions and account for nearly one half of all diabetes-related hospital bed days. The financial burden is significant as well with the mean adjusted cost of care for a diabetic foot ulcer at more than $9000 per admission, costing $13 billion per year in the United States.

The primary factors for developing foot ulcers are peripheral neuropathy, peripheral arterial disease, reduced immune function, and altered foot architecture. Although 15% to 40% of diabetic foot ulcers are primarily neuropathic in nature, 50% to 60% are secondary to both neuropathy and ischemia. The cornerstone of care for the diabetic foot ulcer is prevention. This is done with a combination of foot inspections, foot hygiene, offloading shoes, and education on when to seek medical care. If an ulcer does occur, the early identification and determination if complicated by infection is crucial. Care for these patients is best accomplished in a multidisciplinary setting including medicine, surgery, wound care, diabetes education, and rehabilitation team.

PATHOPHYSIOLOGY

Diabetic foot ulcers occur in the setting of a physical trauma, which is often minor, in the altered tissue physiology secondary to diabetes. Complications of diabetes that affect the foot include peripheral

SURGICAL OUTCOMES

Outcomes following surgery for TOS are inherently linked to the type of TOS being treated. With respect to nTOS, symptomatic improvement following surgery ranges from 60% to greater than 90% across various studies. A recent report from the Johns Hopkins Hospital reviewed their experience with FRRS for nTOS over a 10-year period, during which 286 patients underwent 308 FRRS. They reported symptomatic improvement in 89% of patients during the first 5-year period, which increased to 92.8% in the second period. These improved outcomes were attributed to improved patient selection, a higher percentage of patients with a positive muscle block and a younger patient cohort. Another study recently published evaluated outcomes in the subset of patients in whom cervical ribs were present and demonstrated sustained symptomatic improvement or resolution in 92%. However, early symptomatic improvement does not guarantee sustained results, with recurrence rates as high as 30% reported. Multiple factors are believed to influence this, including scar tissue, chronic nerve injury, and/or incomplete resection/decompression. Moreover, some patients will fail to have significant symptomatic improvement at all. In a study of 102 consecutive first rib resections (141 patients) for nTOS, 13% of patients were found to have marginal or no improvement in symptoms following surgery. Contributing factors included a poor response to scalenus muscle block, the presence of chronic pain syndromes, preoperative opioid use, active smoking, and older age (mean age 45 vs 38, $P = 0.02$). Additionally, the duration of preoperative symptoms also predicted postoperative outcomes, with an average 96 months of preoperative symptoms in those experiencing unresolved symptoms postoperatively compared with 48 months in those with resolution of symptoms. In this context, it is important to consider alternative diagnoses because of the frequent nonspecific symptoms in this patient population.

For patients with vTOS or aTOS, outcomes are more easily defined on basis of objective testing. Arterial and venous patency rates are reported to be greater than 90% after thoracic outlet decompression and vascular intervention, either open reconstruction or endovascular treatment. The authors' standard approach for vTOS is to continue routine systemic anticoagulation preoperatively to vTOS patients for several months, with duration predicated on vessel patency and the need for percutaneous intervention. A routine venogram is performed 2 weeks postoperatively, with approximately 80% to 90% either having a widely patent vein or undergoing successful venoplasty for the presence of residual stenosis. When venoplasty is required, anticoagulation is continued, and a subsequent follow-up ultrasound is performed at 1 month, at which time anticoagulation is discontinued if the vein is widely patent without residual thrombus. A minority of patients will have complete occlusion of the axillosubclavian vein found during the 2-week postoperative venogram and therefore not undergo venoplasty, which justifies continued anticoagulation for up to 6 months. Nonetheless, most of these vessels will either recanalize over time or the patient will develop collaterals sufficient to produce sustained symptomatic relief.

CONCLUSION

The diagnosis and decision making in neurogenic TOS is frequently challenging with the subjective nature of its presentation. Conversely, vascular forms frequently represent a straightforward diagnosis based on history and supported by objective vascular testing. With respect to surgical management however, nTOS infrequently involves more than first rib resection and scalenectomy, whereas vascular forms frequently require a more nuanced approach involving adjunctive procedures such as vascular reconstruction or endovascular therapies. For neurogenic patients, excellent results can be achieved with careful patient selection, being mindful to exclude alternate diagnoses for which TOS surgery will afford no benefit. The management of aTOS is driven by the distribution and extent of arterial thrombosis, rarely adhering to a standardized approach. Finally, a procedure-based approach to vTOS produces durable results regardless of the surgical approach and rarely requires extensive vascular reconstruction. Further consensus is needed to determine best practices for diagnosis and management for this group of low-frequency disorders.

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THE DIABETIC FOOT

David W. Schuchhman, MD, and Brandon W. Peppper, MD, FACS, RPVI

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PATHOPHYSIOLOGY

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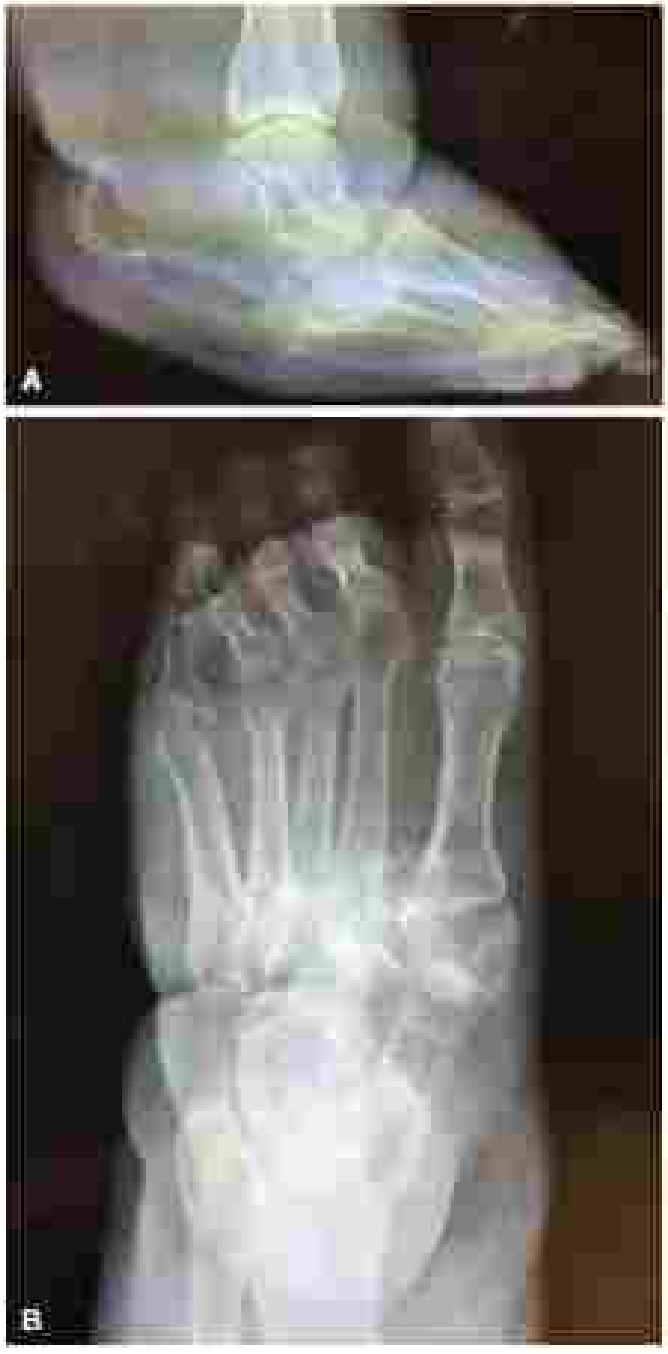

FIG. 1 Plain films of Charcot's foot.

neuropathy, microvascular and macrovascular disease, changes in architecture, and altered response to infection. Peripheral neuropathy affects up to 60% of patients with diabetes and is present in more than 90% of patients who develop a diabetic ulcer. Diabetes affects both large and small nerve fibers, resulting in altered sensation of pain, temperature, touch, and vibration as well as impaired autonomic function. There is a loss of protective sensation that may result in delayed detection of injuries. Loss of sweat gland function leads to drying of the skin and formation of cracks that can predispose patients to infection. Motor neuropathy can also lead to an imbalance between flexor and extensor muscles in the foot. This results in the clawing of the toes and prominence of metatarsal heads contributing to altered pattern of mechanical stress and pressure on the foot. This is commonly referred to as Charcot's foot (Fig. 1).

The peripheral arterial disease seen in diabetic patients affects both macro- and microvascular circulation. In diabetics, the macrovascular arterial impairment includes diffuse tibial and proximal arterial disease. Long segment stenosis of these vessels is often seen. In general, the aorto-iliac and femoral systems are spared from early diabetic changes making surgery the key to treatment. As with the general patient population, large vessel disease is often exacerbated by hypertension and cigarette smoking. The addition of aorto-iliac or femoral disease from smoking creates additional risk for limb loss as collateral pathways are impaired. Additionally, diabetic patients have a microvascular disease component. This is characterized by microarterial dysfunction with loss of autoregulatory control leading to increased flow, endothelial damage, arteriovenous shunting, edema, impaired leukocyte migration, and decreased oxygen diffusion. All these factors not only increase risk for development of an ulcer, but additionally play an important role in impairing wound healing.

Evaluation

Patients may seek care for any number of diabetic foot complaints, this can be a spectrum that extends from asymptomatic break in the skin incidentally noted on exam to shock from overwhelming infection. The chronicity of the ulcer, a history of healed ulcers, or presence of additional ulcers in the same or other foot provides additional insight to underlying pathology. A recurrent ulcer that has healed in the past likely has adequate blood supply to heal and is likely from pressure or recurrent trauma. Physical examination may reveal Charcot arthropathy, which is joint and bone destruction seen in the neuropathic foot. It is characterized by an acute phase that is manifest by edema, localized warmth, erythema, and joint crepitus. This phase may be misdiagnosed as gout, osteomyelitis, deep venous thrombosis, or cellulitis. ...gnetic resonance imaging can be useful to detail the nature of bone damage and determine between these conditions. The chronic phase begins after the acute inflammation has improved. It is a prolonged phase of healing and remodeling.

The initial decision point is to determine if an infection is present and whether this an acute infection versus chronic colonization in ischemic tissue. This is based on a thorough history and physical examination. Infection should be suspected if there is evidence of inflammation including redness, warmth, swelling, tenderness, or pain. Fever, purulent secretions, and foul odor may also be evidence of acute infection. Severe necrotizing infections will often present with cutaneous blisters, subcutaneous emphysema, skin discoloration, or foul smelling odor. This may be accompanied by altered mental status and shock, but this is a late finding. It is important to remember that pain may not be present even in these more severe infections if a sensory neuropathy is present. In the acute setting, evaluation must immediately focus on mapping the spread of infection and debridement and preserving options for limb salvage. On physical examination, palpation of the plantar aspect of the foot remains an important aspect of the evaluation. Pain with plantar pressure should prompt consideration for a deep space infection. This type of infection tracks along the tendons to either the dorsal or plantar aspect and can track toward the proximal foot. ...hen present, limb salvage is difficult and aggressive treatment and surgical evaluation are required.

Chronic infections may present with tuberous tissue, and necrotic tissue without signs of acute infection. ...gested bone is often encountered and can be seen in both acute and chronic settings. If infection is suspected patients should have glucose, complete blood count with differential, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin drawn. Persistent hyperglycemia despite a normal antihyperglycemic regimen is a sensitive sign of infection in the acute setting.

VASCULAR EVALUATION

The presence of peripheral arterial disease should be assessed. A physical examination should be performed with Doppler signal

assessment. Ankle brachial index (ABI) can be falsely elevated in this patient population because of arterial calcification leading to incompressible vessels. ABI should still be attempted and toe pressures and toe brachial index should be obtained if available. Additional studies that can be helpful include pulse volume recordings and transcutaneous oxygen measurement but are not easily available in most settings. In the acute setting, vascular intervention usually follows source control. In contrast, for chronic changes, vascular intervention should precede surgical debridement to get best results for limb healing and minimize amputation level. A toe pressure less than 40 mm Hg indicates critical ischemia or toe brachial index of less than 0.3 are an indication of critical ischemia, whereas a toe pressure greater than 55 mm Hg has been correlated with the ability to heal a foot ulcer. An alternative test is transcutaneous measurement of partial oxygen pressure. A value of less than 10 mm Hg suggests the tissue is completely compromised, and less than 35 mm Hg significantly suggests hypoxia at rest and need for revascularization. The goal of revascularization is restoration of plantar arch flow to meet the metabolic demands of healing. It is important to note, that more flow is required for the healing process than for maintenance once healed and this principle should guide revascularization.

Decision for Revascularization

Vascular surgeons have the options for revascularization including bypass, transluminal interventions with or without stent placement, or a combination of both. The factors that will affect the selection intervention will be the nature of the disease with short or long segment stenosis, patient's overall health, accessibility of proximal inflow and a distal vessel that will support adequate outflow to maintain patency. The surgeon must assess what flow is needed for healing. A simple toe amputation (low wound burden) will require less flow than that required to heal a transmetatarsal amputation (TMA; large wound burden). Therapy should be guided to supply adequate flow to heal. Although restoration of a palpable pulse is ideal, this is often unattainable and therapy needs to focus on an increase in ABI or toe pressure as a best commensurate with healing.

Medical Therapy and Treatment

The routine culture of clinically uninfected wounds is not recommended. If clinical evidence of infection is present, a culture of deep tissue may be collected during debridement after the wound has been cleansed and debrided. However, if infection is mild, the patient has not recently been on antibiotics, and is immunocompetent, a culture is likely unnecessary. Diabetic foot ulcers are almost universally colonized and swab specimens or tissue before debridement will not provide accurate results. In the acute setting, after the culture is performed, and initiation of broad spectrum antibiotics should not be delayed. Therapy should cover for methicillin resistant *Staphylococcus aureus* if this patient has a history of methicillin resistant *Staphylococcus aureus*, it is prevalent in the region, or if severe infection is present. Antibiotic therapy should be tailored based on culture data. Antibiotic therapy is only needed until the infection is cleared and does not need to be continued until the wound is healed. For mild infections 1 to 2 weeks is recommended and 2 to 3 weeks for moderate to severe infections assuming that infected bone and tissue has been removed.

Osteomyelitis should be suspected if there is exposed bone, a probe passes easily to bone, the wound is large, or the erythrocyte sedimentation rate is greater than 70 mm/hr. If bone is exposed or the probe passes to bone supporting imaging is not needed for diagnosis. Magnetic resonance imaging is often ordered but should only be used in cases where there is suspicion of bony infection and no physical examination findings of exposed bone. Plain x-ray may show signs of erosion, but some of these findings can be seen with chronic diabetic foot changes.

Treatment

A multidisciplinary team has been shown to improve outcomes among patients with diabetic foot wounds. These teams vary by institution but often include an endocrinologist, surgeon, wound care, nutritionist, occupational therapist, and podiatrist. Goals of management should be to optimize glucose control with a target hemoglobin A1c of less than 7%, insure creation, restoring inline flow to the foot, optimizing comorbid conditions, and offloading the wound. It is important to remember that patients presenting with critical ischemia of the leg have a 35% 1-year mortality. Additionally, 33% will be alive but have progressed to limb loss, and only 33% will be alive with an intact limb. Even with successful revascularization, patients can suffer delayed complications weeks to months later, with heart attack remaining the primary cause of death. Regardless of therapy chosen, the mortality and complication profile is set, and therapy is focused on preservation of limb salvage and mitigating cardiac events.

ACUTE DIABETIC INFECTION

A surgeon should be involved early in the care of these patients because early debridement is important for infection control. Patients that present with signs of ascending infection or sepsis should be started on broad spectrum antibiotics. Additionally, plans for surgical drainage should be expedited. The key to initial management is source control. Debridement of nonviable tissue and distal drainage is the surrounding principle of the initial operation. The surgeon should ensure the patient understands the possibility of amputation and at which level. For patients that have toxic sepsis and infection tracking up to the ankle, a guillotine-style amputation of the lower leg may be required. We advise against limited closure and manual amputation at the initial surgery because often more tissue is salvageable than initially believed. Life over limb mentality must be considered to ensure sepsis is controlled. For nonsepsis, but clearly infected foot infections, distal drainage through open TMA or open ray excision is a good first step to gain source control. Once infection is controlled, full vascular workup and revascularization options should be considered (discussed more in the following section). Preservation of viable plantar skin and dorsal drainage are ideal when able. Subsequent operations require focus on removal of all infected bone and soft tissue coverage of the distal foot.

Treatment of Chronic Diabetic Infection

Chronic wounds are common in the diabetic population. Treatment for these wounds focuses on gaining substantial information before surgery. A full vascular evaluation should be done and include noninvasive and invasive imaging as needed. A multidisciplinary discussion should occur with regard to proposed surgical needs. Our preference is TMA and revascularization options should be based off this. For diabetics with distal tibial vessel bypass targets, open bypass has been shown to be superior to angioplasty if the patient has a two year life expectancy. However, many patients are poor bypass candidates secondary to severe cardiac disease, limited conduit, unfavorable anatomy, or a host of other limiting factors. Endovascular revascularization remains the most common intervention performed for lower extremity revascularization. The surgeon should remember that bypass performed after endovascular intervention carries a higher risk of failure for patients who have both options available, bypass should be strongly considered.

For chronic patients that present with diabetic foot changes, but no frank ulceration, additional consideration is recommended. These patients typically present with critical ABI of 0.3 or less. In these cases, durability is more important because failed intervention will return the patient to this baseline status. Initial revascularization should focus on restoration of inflow as increasing ABI and toe brachial index even minimally can often move a patient out of the critical category.

Ultimately, the goal of therapy for chronic lesions is achieving soft tissue healing over the distal site and preservation of limb function.

One area that requires special discussion is the treatment of chronic osteomyelitis. When a patient is known to have bony infection, clearance remains challenging. Surgical removal of the bone offers the best potential at avoiding future infection. Culturing the remaining clean bone can be helpful ensuring that the final distal bone is free from disease. Antibiotic therapy for osteomyelitis is lengthy and relies heavily on the ability to deliver antibiotics to the diseased area. The silver vascath home central access for delivery of antibiotics, which carries a different set of possible risks. If this route is selected, palpable inline flow, which means flow that creates a palpable pedal pulse (or pulse in the area of infection), needs to be the end result of surgical therapy. In our practice, we favor removal of distal infected bone in the diabetic patient because the microvascular circulation is compromised and restoration of flow in the distal macrovascular circulation should be undertaken.

Although the majority of diabetic foot infections present with compromised flow, there are some patients who have intact dorsalis pedis or posterior tibial flow that is palpable. These ulcers are almost always on the plantar foot over the first metatarsal head. They are the result of improper feedback secondary to neuropathy. The ulcer itself is a pressure ulcer. Although the same principles apply as previously described, offloading of the foot alone can be enough for treatment of superficial wounds.

LEVELS OF AMPUTATIONS

Of unique consideration are patients that present acutely and require source control while on full anticoagulation. Removal of some medications is still not readily available, but we recommend against delayed source control. The "bloodless" amputation remains important for these patients. This principle involves amputation through the joint level so that named vessels can be ligated and muscular dissection is minimized. Key levels include the through ankle and through knee amputation for lower extremity bloodless amputations.

For patients that are functional and ambulatory and require lower extremity amputation, attempts to preserve a below knee amputation (BKA) should be made. This includes revascularization of inflow vessels or opening femoral and popliteal vessels. In general, inline popliteal flow is needed for predictable healing of a functional BKA; however, when this is not possible (DFA popliteal occlusion), it is reasonable to try a BKA, disclosing to the patient the risk of future failure. Following BKA, it is important to use knee immobilizers, splints, and physical therapy to prevent contracture and distal stump rubbing and breakdown.

For nonambulatory patients and bed bound patients, above knee amputation (AKA) may be preferred because there is less chance of stump breakdown from rubbing. Patent inguinal inflow and a patent profunda femoris artery are needed for successful healing of an AKA. Hip disarticulation carries an overall high risk of mortality and revascularization attempts should be made to save an AKA.

CONCLUSION

The management of the diabetic foot presents a clinical challenge. The work of a multidisciplinary team to optimize healing potential by controlling diabetes, managing hypertension, smoking cessation, controlling infection, and offloading wounds is important to achieve the goal of limb preservation.

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GANGRENE OF THE FOOT

Rebecca Scully, MD, MHA, and Samir Lee Sin Sneh, MD, MPH

Gangrene, or localized tissue death most typically from ischemia or infection, has been a long recognized entity. Hippocrates described gangrene and noted the importance of dividing living and dead tissue, or amputation, as an important treatment modality. Today, management of gangrene is often divided into two types: dry and wet. Both dry and wet gangrene can be visible evidence of many insidious disease processes, including peripheral vascular disease and diabetes. As such, their management must address both the acute wound and the chronic process underlying it. Although wet gangrene, or wounds with an infectious component, often represent a surgical emergency, the treatment of dry gangrene, or tissue death or loss attributed to ischemia without signs of secondary infection, is often more urgent than emergent.

EPIDEMIOLOGY

An estimated 10 to 12 million individuals in the United States, and as many as 200 million individuals worldwide, have peripheral arterial disease (PAD) with the incidence of disease increasing with age, with as many as 20% of individuals older than age 80 having some degree of PAD. The overall annual incidence in the United States is approximately 2.3%, with an incidence of critical limb ischemia, defined as rest pain or tissue loss, of 0.35%. Although historically PAD was thought to be slightly more common among men than women, more recent evidence suggests that PAD is equally common among both genders, however, men are more likely to be symptomatic. In the United States, the incidence of PAD appears to be higher among African Americans compared with other racial groups. An estimated 30 million individuals in the United States have diabetes with a lifetime risk of diabetic foot infections of 15% to 25% and an annual incidence of 3% to 10%.

PATHOLOGY

Dry gangrene is an ischemic process, typically related to calcific disease in the arteries of the lower extremities leading to decreased blood flow to the lower extremities (Fig. 1). Wet gangrene can arise as superinfection of an ischemic lesion or as an ascending infection related to a diabetic foot wound. The most common pathogen in diabetic foot wounds is *Staphylococcus aureus*; however, wounds are also often polymicrobial and necrotizing soft tissue infections can also occur.

EVALUATION

History

History and examination are critical to the expeditious diagnosis of lower extremity gangrene. Risk factors including tobacco use, hypertension, hyperlipidemia, and diabetes should be identified as well as concomitant coronary artery disease and cardiopulmonary status given the need for operative intervention and the highly correlated nature of these diseases, with as many as 75% of individuals with lower extremity PAD having concomitant coronary artery disease. Individuals with new or unstable angina may require cardiac

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Rebecca Scully, MD, MPH, and Samir Kaushik Shah, MD, MPH

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History and examination are critical in the expeditious diagnosis of lower extremity gangrene. Risk factors including tobacco use, hypertension, hyperlipidemia, and diabetes should be identified as well as concomitant coronary artery disease and cardiopulmonary issues given the need for operative intervention and the highly correlated nature of these diseases, with as many as 75% of individuals with lower extremity PAD having concomitant coronary artery disease. Individuals with new or unstable angina may require cardiac

FIG. 1 Left foot dry gangrene. Patient with extensive left foot dry gangrene by staging after failure to heal a first ray amputation.

intervention before a revascularization procedure and foot edema may precipitate a cardiac event.

The time course of the patient's wound is important to note as is an antecedent history of rest pain or claudication. Infectious symptoms including fever, malaise, or rigors should be elicited, as well as drainage from the wound or a new odor. Pain in the foot can often be classified by a history of neuropathy to diabetics and can be a marker of wet gangrene. A thorough surgical history is also critical with a particular focus on prior debridement as well as prior endovascular and vascular procedures. Worsening hyperglycemia is also a potential warning sign that can often be associated with ongoing infection, particularly in diabetics.

In addition to medical and surgical history, it is important to get a sense of the patient's current level of activity, both in terms of assessing their perioperative risk of complications, as well as to better inform decisions surrounding the level of amputation. For example, below knee amputations (BKAs) are generally preferred over above-knee amputations (AKAs) because of the decreased energy required for ambulation. Nevertheless, an individual who is noncambulatory or unlikely to be ambulatory after a BKA will benefit from an AKA to reduce the risk of postoperative complications such as flexion contractures and stump ulcers.

In addition to PAD and diabetes, atherosclerotic events from aneurysmal disease within the thorax or abdominal aorta or the popliteal arteries may also lead to lower extremity digital ischemia; however, this is rare. Although this is often called blue toe syndrome, gangrene is actually a more common finding at presentation, occurring in approximately one-third of patients. Trauma, medication side effects, particularly vasopressors, frostbite, malignancies, granulomatous diseases, and vasculitis are also on the differential and can often be elucidated by the history.

Physical Examination

A thorough vascular examination is critical to the evaluation of patients with gangrene, including a full pulse examination. Absent pulses in the extremity in question suggest underlying vascular disease that will need to be addressed, occasionally before debridement in the case of dry gangrene, or in the case of wet gangrene, following adequate source control. The presence or absence of pulses speaks to the extent of underlying disease proximal to the point of examination, possible revascularization options, and need for further vascular imaging. A Doppler probe is helpful to identifying nonpalpable flow. However, the absence of palpable pulses, even in the presence of audible Doppler signals, is often abnormal and suggests underlying occlusive vascular disease; medial calcific disease without luminal compromise is a common exception occurring in diabetics and those with renal failure. Examination of the wound in question should include evaluation of its extent as well as for any signs of an infectious process. Discoloration, erythema, purulent discharge, fluctuance, odor, and crepitus are all concerning signs. Altered or diminished mental status, tachycardia, tachypnea, and hypotension suggest a more systemic process.

Laboratory Values

A full set of laboratory tests should be checked including complete blood count, basic metabolic panel, and coagulation studies. In the case of dry gangrene, the most important element of the laboratory workup is evaluation of renal function because of its implications for use of contrast imaging. In wet gangrene, a leukocytosis can be present on complete blood count. Hyperglycemia can also often be seen. A metabolic acidosis may be present and lactate levels may be helpful in guiding resuscitation. Hyponatremia should raise concern for a necrotizing process. C-reactive protein and erythrocyte sedimentation rate may be helpful if there is concern for osteomyelitis not apparent on examination. Coagulation studies should be checked as many patients may be coagulopathic secondary to illness or to medications. Nutritional studies including albumin and prealbumin may also help to guide decisions making regarding amputation and a need for nutritional supplementation.

IMAGING

Noninvasive Studies

Ankle Brachial Index

Discussed since the 1950s, the ankle brachial index (ABI) can be evaluated by the clinician at the bedside and may give additional information regarding the degree of underlying vascular disease (Fig. 2). To measure an ABI, the patient should be placed supine and a manual blood pressure cuff should be used to measure first the systolic blood pressure in both the left and right arms. This should be repeated in the lower extremities by placing the cuff immediately proximal to the malleoli and identifying the systolic pressure at which the dorsalis pedis and posterior tibial signals reappear after they are extinguished by progressive pressure elevation. The ABI is then the ratio of the higher pressure in each foot over the highest upper extremity pressure. An ABI of 0.9 to 1.3 is considered normal. An ABI above 1.3 suggests noncompressible vessels, as is often seen in patients with diabetes and renal failure. ABIs of 0.4 to 0.9 suggest moderate vascular disease, typically producing claudication. ABIs less than 0.4 most often occur in patients with critical limb ischemia, which includes rest pain and tissue loss (Table 1).

Toe Brachial Index

Measured in a similar fashion to ABIs, toe brachial index (TBI) can often give more accurate assessment of underlying disease in diabetics and can also be used in individuals with wounds that preclude evaluation at the ankle. A normal range for TBI is greater than 0.7, given the expected decrease in pressure between the ankle and the toe. Absolute toe pressures can also be reported, with a toe pressure of greater than 30 mm Hg required for wound healing.

Pulse Volume Recordings

Pulse volume recordings are performed in the vascular laboratory and are often performed in conjunction with ABI or TBI measurements and segmental limb pressures (Fig. 3). It is a form of air plethysmography resistant to noncompressibility artifact related to medial

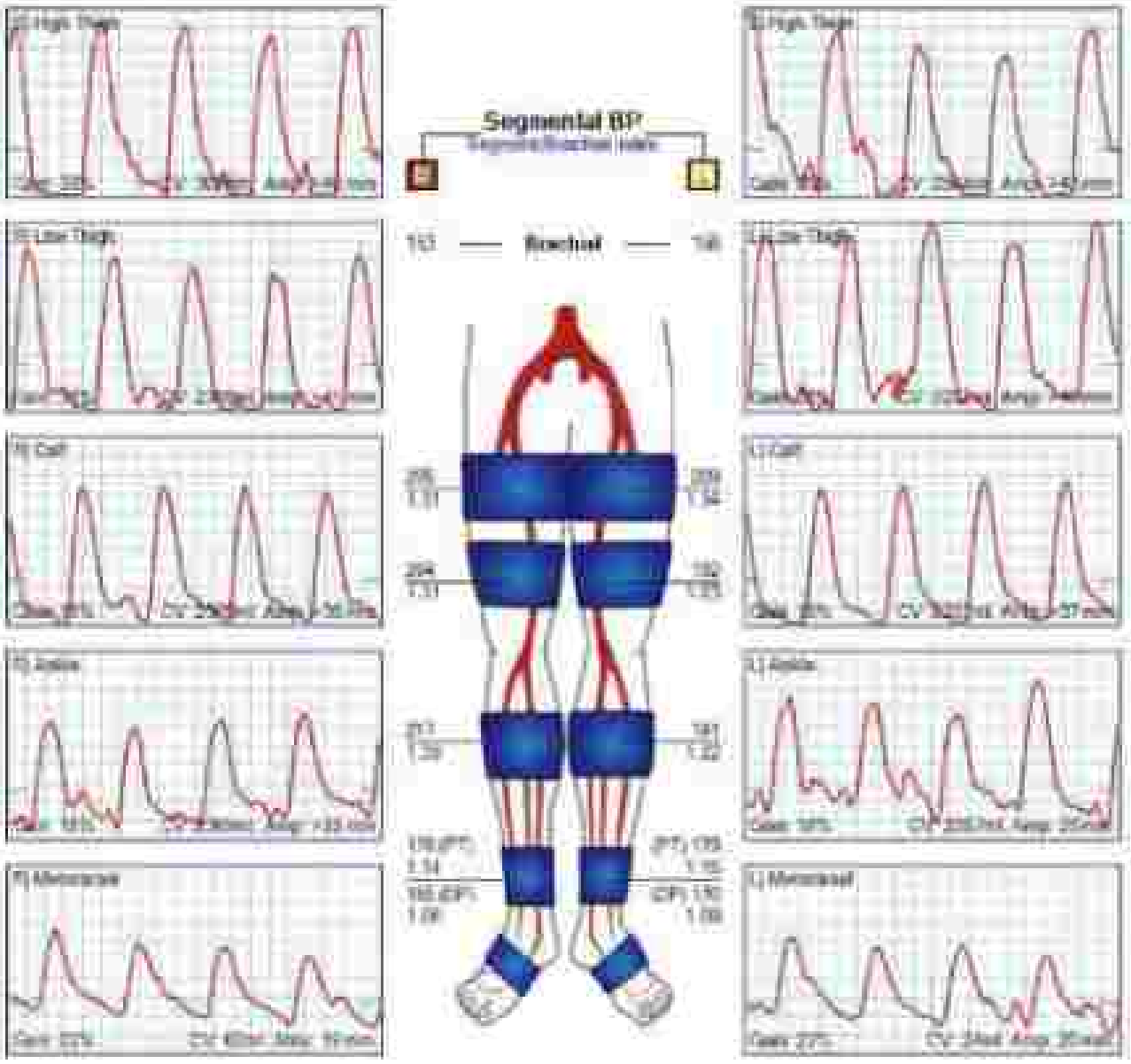

FIG. 2 Ankle-brachial index, pulse volume recordings, and segmental limb pressures. A normal study demonstrating three standard methods of arterial disease: ankle-brachial index (bottom), pulse volu e recordings (waveforms on either side), and segmental limb pressures.

TABLE 1 Ankle-Brachial Index Interpretation

Index	Interpretation
>1.3	Calcified vessels, unable to interpret
0.4–0.9	Mild moderate arterial disease, usually producing claudication
<0.4	Severe arterial disease, usually producing critical limb ischemia

calcification and can be a useful adjunct to diagnose and localize arterial disease. Segmental limb pressures are performed at three or four standardized locations across the lower extremity; gradients greater than 20 mm Hg between consecutive stations suggest the presence of a clinically significant lesion.

Imaging

Plain Films

Films of the foot or leg are useful to look for gas within the tissues, which is concerning for necrotizing infections. Although plain films are not sensitive for early changes of osteomyelitis, radiographs may show more advanced osteomyelitis. Although x-ray imaging offers no information on arterial anatomy, it can be obtained rapidly and is a useful adjunct to delineate the extent of a rapidly spreading infection.

Computed Tomography Angiography

Computed tomography angiography (CTA) has become the workhorse imaging modality for lower extremity vascular disease. Angiography can give a wealth of information regarding anatomy and burden of disease for a patient, helping in both diagnosis and operative planning. Although the accuracy of CTA varies slightly by the level of disease, CTA is 95% sensitive and 94% specific for diagnosing

lesions with greater than 50% stenosis. Kidney injury secondary to iodinated contrast loads has also been a concern. Although 5% to 10% of patients develop acute kidney injury following contrast load, the majority of patients recover with only 2% showing persistent impairment or need for dialysis at 90 days. There also does not appear to be a role for periprocedural sodium bicarbonate or acetylcysteine in renal protection when compared to intravenous hydration with normal saline though the evidence continues to evolve.

MRA

Magnetic resonance angiography is an additional imaging option in this patient population and, like CTA, can be quite sensitive and specific. Magnetic resonance angiography is used somewhat less frequently, given both the time and expense of the study but also given the risk of nephrogenic systemic fibrosis with the use of gadolinium contrast agents in individuals with renal insufficiency. Although rare, nephrogenic systemic fibrosis is a devastating, often fatal complication involving progressive fibrosis of the skin, lungs, liver, and musculature, including the heart. Renal contrast agents and noncontrast imaging modalities continue to evolve but are not yet universally available.

Angiography

Digital subtraction angiography can be both diagnostic and, when paired with endovascular interventions, a therapeutic option in the management of lower extremity gangrene. As CTA improves, the role for purely diagnostic angiography has become somewhat more limited; however, it can provide a more nuanced view of the vasculature particularly for distal disease, in cases of severe disease, and in highly calcified vessels.

MANAGEMENT

The essential first step in the management of wet gangrene is source control. In the case of foot sepsis, the patient should be taken urgently or emergently to the operating room for debridement. The initial procedure should be limited to debridement or open guillotine amputation, with the knowledge that the patient will require subsequent revision to a formal amputation. Definitive amputation at the same setting is associated with worse outcomes and is not recommended. To that end, efforts should be made to preserve as much tissue as possible while also achieving adequate drainage of any sepsis that is present.

Debridement

Debridement of devitalized or infected tissue can be performed rapidly with a goal of removing dead tissue while preserving options for future revisions. Guillotine or open amputation describes an open amputation at a level sufficient to remove any infected or necrotic tissue. Similar to formal amputation, the patient is positioned supine and, if possible, infected tissue can be excluded from the field using a sterile bag or towel. The soft tissue at the level of the amputation can be divided sharply; vessels should be ligated as they are identified. A circular incision is made and flaps are not raised, the fibrotomy of the bone can be slightly offset from the skin edge because the skin can retract over time. Length should be preserved whenever possible. It is a means of rapid source control, minimizes operating room time for individuals who are systemically ill, and can be performed under peripheral block for individuals who cannot tolerate general anesthesia. Although it may be tempting to perform a formal amputation, the risk of primary closure in wound infection or breakdown and with that, the need for revision of an amputation to a higher level. In one study following below knee guillotine amputation, up to 93% of individuals were able to achieve primary healing after revision to formal BKA compared with only 79% of individuals who were closed primarily. A further 11% of the group that was closed primarily required revision to an AKA. The use of guillotine amputation was formalized during World War I, where the risk of wound progression following primary closure was so feared that it was banned by the surgeon general. Joint disarticulation can be also performed very rapidly and can be accomplished without the use of a saw. It can be performed at any level, from the interphalangeal joints to the hips and can often be performed under a nerve block, which can be particularly useful in patients who cannot tolerate general anesthesia. Operation under tourniquet control may be a useful adjunct to reduce blood loss.

Postoperatively, open wounds can be managed with wet to dry dressings, particularly if there is concern for remaining infection that would benefit from frequent evaluation. Vacuum dressings are also commonly used and may be more comfortable for some patients. The affected extremity should be elevated above the level of the heart as much as possible and can be wrapped with a gentle compression dressing to minimize tissue edema before formal revision.

Antibiotics

Although the goal of debridement is to remove infected tissue, adjunctive antibiotics are used and may require a prolonged course if there is concern for osteomyelitis. For diabetic patients, infections are often polymicrobial in nature and require broad spectrum antibiotic coverage. For individuals who have been frequently hospitalized or are on dialysis, antibiotic resistant infections, particularly methicillin-resistant *Staphylococcus aureus*, are frequently seen and should be empirically covered pending culture data.

Amputation

The goal of amputation is to eliminate infected or ischemic tissue but also to do so at a level that the patient will be able to heal based on their underlying vascular anatomy and that will allow for rehabilitation, including the use of prosthetics to otherwise functional individuals. Prosthetic use carries with it an increase in energy demand that may not be achievable for some patients. Ambulation following BKA and AKA increases energy expenditure 10% to 40% and 40% to 70%, respectively. Approximately 15% to 25% of BKAs go on to require revision to AKA, which should be kept in mind in counseling patients as well as in planning level of amputation. Although there are certain general principles that apply to all amputations (Box 1), there are procedure specific considerations that will covered below.

BOX 1 General Principles of Amputation Surgery

- Assess arterial perfusion and bone architecture
- Balance ischemia with amputation technique
- Excise all nonviable or infected tissue
- Avoid tension on closure
- Use sharp dissection to minimize tissue damage
- Preserve as much length as possible
- Maintain skin integrity
- Avoid skin edges over bony prominences
- Create a stump that is amenable to prosthetic fitting
- Use proximal joint level amputation when possible to preserve energy expenditure for ambulation
- Avoid flexion contracture of joints proximal to amputation
- Use appropriate postoperative dressing to control edema and promote healing

Modified from Hak DJ, Sabiqunnaqvi VR. Techniques and results in amputation. In: Johnson W, editor. *Rob and Smith's vascular surgery*. 5th ed. Philadelphia: Elsevier; 2010. p. 772–776.

Toe Amputation

For progress isolated to the toe, a toe amputation can be performed, with the level based on the patient's examination and extent of disease. The amputation preserving the metatarsal head is preferable if possible. A fish mouth incision can be used, particularly for partial amputations, as well as a racquet incision, which may be more effective for complete toe amputations. Care should be taken to minimize trauma to the surrounding skin. The flexor and extensor tendons should be divided sharply, typically with bone scissors, and allowed to retract back under the skin edge. A rongeur can be used to shape the bone or, if possible, a joint disarticulation can be performed using a scalpel or cautery. The articular cartilage should be removed, typically using a rongeur, to improve granulation and healing. Any sharp or protruding edges from the bone should be smoothed as well. For infected wounds, the amputation site should be packed wet to dry and can be allowed to heal secondarily or can be revised at a later date. If perfusion is adequate and there is no evidence of infection, the amputation site can be closed, typically using absorbable sutures to reapproximate the tissue followed by interrupted nonabsorbable monofilament sutures such as nylon in the skin in vertical mattress or simple fashion.

Ray Amputation

Amputation of the toe including the metatarsal bone is defined as ray amputation and is useful in the management of more proximal toe infection or osteomyelitis involving the metatarsal head (Fig. 3). When concern exists for osteomyelitis, it is useful to send proximal bone margins for pathology and also for culture to guide postoperative management. Although ray amputations can be performed for any toe, multiple ray amputations can affect the stability of the forefoot and may lead to pressure alteration. Given this a transmetatarsal amputation (TMA) may be preferable. A first toe ray amputation can affect foot mechanics and can be difficult to off load. Given this, some surgeons do recommend a TMA instead of an isolated first toe ray amputation, but this is controversial. Nearly one third of toe amputations fail to heal and require revision to a more proximal level.

TMA

A TMA can be effective in the management of forefoot wounds that are otherwise not amenable to ray amputation (Fig. 4). TMA preserves limb length, allows for ambulation, and has better healing rates than ray amputation. The dorsal incision should be placed at the level of the metatarsal heads with the plantar incision placed more distally to allow for closure. Skin flaps should be raised and the extensor tendons divided to expose the metatarsal bones. These can then be divided using a saw. The forefoot can then be used to retract the distal foot and expose the flexor tendons, which should also be divided with caution to preserve a long plantar flap to allow for the metatarsal heads to be covered and the closure to lie over the dorsal aspect of the foot. The incision is then closed with interrupted nonabsorbable monofilament sutures.

Negative pressure dressings followed by skin grafting can sometimes be used to salvage an open TMA and allow for preservation of limb length.

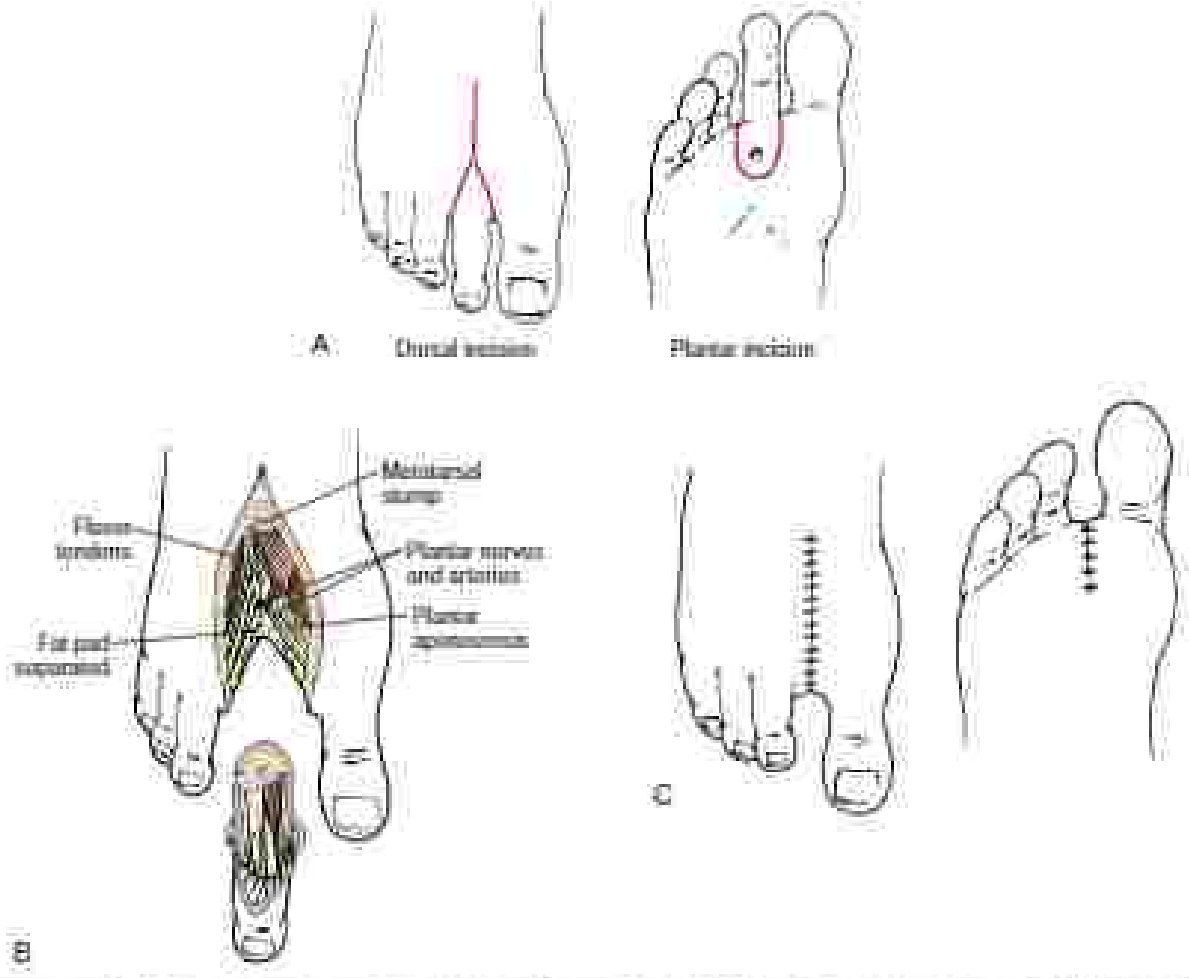

FIG. 3 Ray amputation. (A) Ray amputation incision. (B) Transection of metatarsal shaft. (C) Closure with nonabsorbable sutures under no tension. (From Attinger CE, Steinberg JS, Bulan E, et al. Amputations and revisions in the diabetic foot: Johnson JE, editor. Surgery of the foot and ankle. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 1–19.)

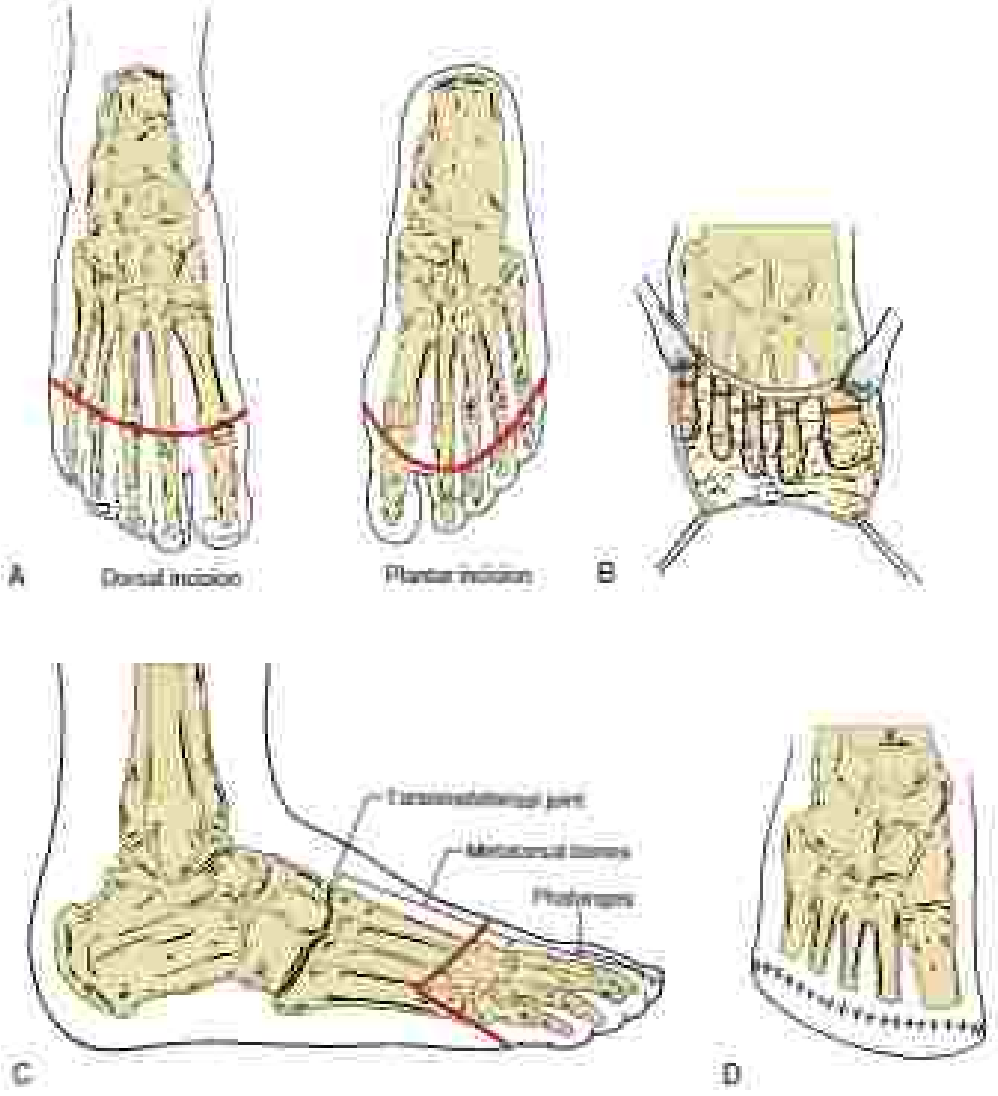

FIG. 4 Transmetatarsal amputation technique of transmetatarsal amputation. (A) Dorsal and plantar incisions, with disarticulation of the metatarsophalangeal joints. (B) Level of bone transection. (C) Closure with monofilament sutures. [illegible] (From Holt JF, Kalisher A: Site, technique and results in [illegible] In: Rutherford RB, editor: Vascular Surgery, ed 2. Philadelphia, WB Saunders Co, 1980.)

Midfoot and Hindfoot Amputations

Most proximal foot amputations include Lisfranc, or tarsometatarsal amputation, and Chopart, or an amputation at the level of the talocalcaneonavicular and calcaneocuboid joints. A Syme's amputation is performed at the ankle and involves ankle disarticulation and division of the distal tibia and fibula at the level of the malleoli. The heel fat pad is then tacked to the tibia. Although each of these procedures preserves limb length, they have a significant effect on foot biomechanics and as such are less durable than a TMA.

BKA

Transtibial, or below-knee, amputation is one of the two procedures typically considered a major amputation. There are five typical incisions: small posterior, fish mouth, sagittal, skew, and medial. Each has its own benefits and contraindications. The posterior flap is the most common and for many is the approach of choice (Fig. 5). The tibia is divided 10 to 12 cm below the tibial tuberosity if possible based on the patient's examination. The anterior skin incision should be slightly more distal to allow for soft tissue coverage of the bone and should be two thirds of the circumference of the leg at the level of the amputation. The length of the posterior flap should be created distally at a distance equal to one third of the circumference of the calf at the level of amputation. This can be marked out using a suture to measure circumference. A tourniquet can be quite useful in the performance of a BKA; however, the lower extremity should not be exsanguinated in the case of sepsis. The skin is divided sharply and the anterior and lateral compartments are then divided, typically with cautery. Having multiple cautery devices can be helpful in expediting the procedure. The periosteum of the tibia is then elevated proximally and a reciprocating saw is used to divide the tibia. It can be done from an anterior or medial approach with the advantage of the medial approach being that it can minimize inadvertent division of the posterior tibial artery prior to ligation. The fibula is also divided 1 to 2 cm proximal to the end of the tibia. The anterior edge of the tibia should be beveled using the saw or a rasp. The posterior flap should then be completed using cautery or an amputation knife. Following release of a tourniquet, if it is used, hemostasis should be assured and can be aided by suture ligatures, which minimizes cautery to the flaps. Nerve bundles should be divided sharply and allowed to retract. Following meticulous hemostasis the fascial layer of the flaps can be approximated using absorbable sutures with care made to make a posterior flap sufficient to create a stump that will accept a prosthesis without leaving too

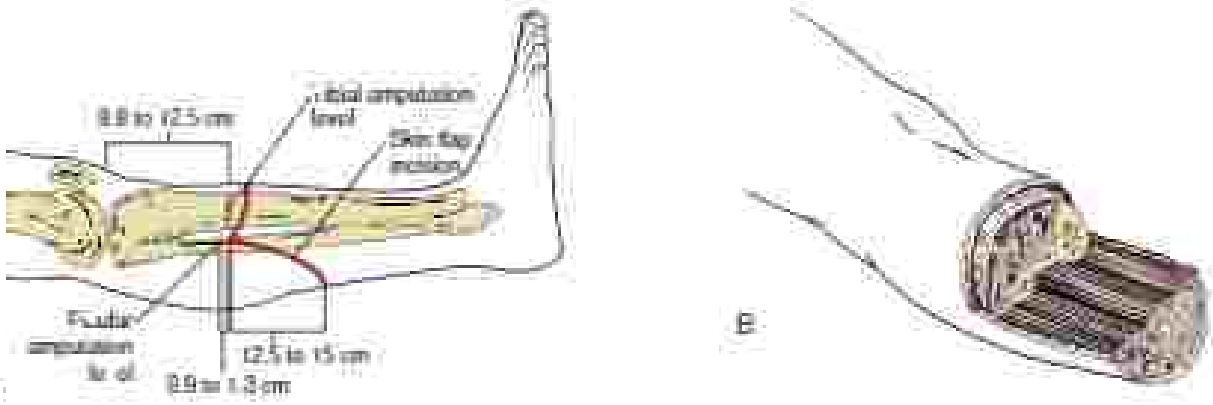

FIG. 7 Below-knee amputation. (From Hill JB, Rutherford RB: Techniques and results in lower extremity amputation. In Rutherford RB, editor: Vascular surgery, ed 8, Philadelphia, 2014, Saunders.)

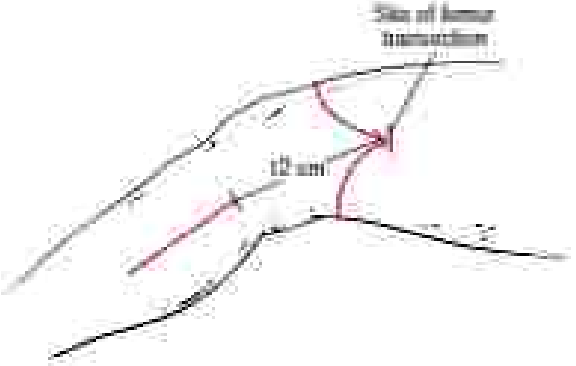

FIG. 8 Above-knee amputation. (From Hill JB, Rutherford RB: Techniques and results in lower extremity amputation. In Rutherford RB, editor: Vascular surgery, ed 8, Philadelphia, 2014, Saunders.)

much or too little bulk. Dog-ears should also be avoided. The skin is then closed, typically with nonabsorbable monofilament sutures, staples, or a combination of the two.

Sagittal incisions involve the creation of medial and lateral flaps of equal length. Skew flaps are anteromedial and posterolateral flaps. A fish mouth incision is similar to that used to more distal amputations but is suboptimal given that the incision is then placed over the load-bearing surface of the limb. Creation of a long medial and short lateral flap can also be performed, bringing the closure to the lateral aspect of the leg.

Many surgeons use a knee immobilizer postoperatively; however, care must be taken to avoid pressure ulceration to the limb. Physical therapy is also important to avoid contractures, which can render the limb unusable. Again, similar to TMA, approximately 30% of BKA wounds have issues with primary wound healing, with 15% to 25% of patients requiring revision to AKA.

AKA

For an AKA, the femur is divided at one third of the length from the knee to the hip (Fig. 6). A fish mouth or circular incision can be used. Again, a tourniquet can be helpful, skin should be protected, major vessels controlled with suture ligation, and nerves divided sharply. The femur is divided with a reciprocating saw and sharp edges should be smoothed with a reciprocating saw or rasp. Hemostasis and hematoma should be obtained and drains can be left if there is concern for hematoma or seroma formation. As with BKAs, the fascia is reapproximated with absorbable sutures and the skin with staples, nonabsorbable monofilament sutures, or both. Ace wraps are more challenging to place following AKAs compared with after BKAs; an minimal wound vac or large adherent dressing may be more effective ways to protect the incision.

Amputation carries with it a relatively high risk of perioperative and long-term mortality that varies with the level of amputation. Thirty-day mortality ranges from 3.6% to 12% following BKA and 13.3% to 17% for AKA. At 1 year, mortality is approximately 30% for BKA and 50% for AKA.

REVASCULARIZATION

Gangrene is often a manifestation of arterial insufficiency. As such, intervention to allow required to restore distal blood flow to allow for wound healing. The restoration of pedestal flow to the foot is the ideal goal when addressing critical limb ischemia, preferably with inline flow via at least one vessel.

Revascularization should be performed in the setting of critical limb ischemia (CLI) when at all possible to minimize tissue loss and risk of major amputation. With any revascularization procedure, inflow, outflow, and conduit should be considered. Inflow is the most distal vessel without a proximal flow limiting lesion and outflow is the most proximal vessel without a distal flow limiting lesion.

Open, endovascular, and hybrid options exist to the management of CLI and lower extremity gangrene. At this point, data comparing treatment approaches are sparse. The Bypass vs Angioplasty in Severe Ischemia of the Leg (BASIL) trial compared open versus endovascular approaches to revascularization in critical limb ischemia and is thus far the only substantial randomized study to do so. Although the BASIL trial had a number of limitations that affect its generalizability and endovascular intervention was limited to angioplasty rather than stent placement, it did find that for individuals who survived for more than 2 years, open surgery showed superior amputation-free survival. Larger trials to delineate the roles of endovascular and open therapy are ongoing.

Although open surgical bypass has been the historical gold standard and is associated with excellent limb salvage rates and durability, an endovascular first approach has been adopted by many. Retrospective data suggest that for suitable patients, an endovascular first approach for individuals with infrapopliteal vascular disease does lower perioperative morbidity but does so at the cost of increased need for subsequent procedures, specifically in individuals with critical limb ischemia rather than claudication. Data have also suggested that for failed initial endovascular intervention for CLI, limb salvage rates following subsequent open or repeat endovascular revascularization procedures are comparable for those undergoing an open initial approach. This suggests that options are not lost by attempting endovascular approach first; however, this remains controversial and the potential for patient selection and confounding by indication cannot be understated.

The BASIL II and the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia trials, both currently under way, are each designed to fully address the question of endovascular versus open revascularization for individuals with critical limb ischemia where equipoise exists between the two treatment modalities. Both will randomize patients and both will address quality of life and cost effectiveness as well as clinical outcomes.

With regard to conduit selection for open bypass, autogenous vein has been shown to be preferable to prosthetic, particularly for infrapopliteal bypass; however, in individuals in whom an endovascular approach has failed and without autogenous options, prosthetic material can be effective.

POSTOPERATIVE MANAGEMENT

Postoperative pain management can be quite difficult. Nerve blocks and peripheral nerve catheters can be useful, as can adjuncts alongside acetaminophen and gabapentin. Nutrition should be maximized to aid in wound healing and the addition of nutritional supplements can be useful. Postoperative evaluation by physical therapy should be performed for all patients, particularly given issues of altered weightbearing status. Elevation of the limb while the patient is recovering is also useful. Many patients will require postdischarge admission to a rehabilitation center. Following major amputation, patients remain nonambulatory for 4 to 6 weeks before their prosthesis is fitted. For some younger patients, immediate postoperative prosthesis may be preferable and can help to improve primary healing rates and lessen the psychological impact of amputation.

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BUERGER'S DISEASE (THROMBOANGIITIS OBLITERANS)

Nav Vash Gop a, MD, FACS, Ca l M. Wahl pha, MD, PhD, All stir adeh, M , FACS, and Bruce c. Gewe . , MD, F CS

Thromboangiitis obliterans (TAO), or Buerger's disease, is a non-atherosclerotic, segmental, occlusive inflammatory disease that affects the small- and medium-sized arteries and veins of the extremities. Patients are usually young male tobacco smokers who present with distal extremity ischemia, ischemic ulcers, or gangrene. TAO has a worldwide distribution, but it is most prevalent in the Mediterranean, the Middle East, and Asia. The prevalence of disease in the United States, Europe, and Japan appears to be declining and may partly be due to a decline in smoking as well as adoption of more uniform and stricter diagnostic criteria. The incidence in women has increased and may be as high as 30%. This relative rise in incidence is probably multifactorial and may in large part be due to the increase in tobacco use among women.

Although the etiology of TAO is unknown, the condition is strongly associated with heavy tobacco use, including cigarettes, cigars, and smokeless forms such as chewing tobacco and snuff. Smoking is considered by most to be an absolute requirement for diagnosis and progression is closely linked to continued use. However, a causal relationship has not been conclusively demonstrated. The disease is classified pathologically as a vasculitis. Features that distinguish TAO from other types of vasculitis include highly inflammatory thrombus with relative sparing of the blood vessel wall, normal acute phase reactants and no serum markers of immunoactivation.

CLINICAL PRESENTATION

Buerger's disease typically begins with involvement of the distal small arteries and veins. More proximal arteries may be involved when the disease progresses, but involvement of large arteries is unusual. The onset of symptoms usually occurs before the age of 40 (a 45 years. Patients may present with claudication of the feet, legs, hands, or arms. Two or more limbs are always involved, all four limbs are affected in about 80% of patients. Intermittent symptoms are initially localized to the forefoot or the pedal arch because of the distal nature of the disease, as opposed to patients with peripheral atherosclerotic disease who first experience calf claudication symptoms. Progression of the inflammatory disease leads to development of ischemic rest pain and ulcerations to the distal portion of toes or fingers. In most series, about three-quarters of patients present with ischemic ulcers (Fig. 1). Raynaud's phenomenon and superficial migratory thrombophlebitis are manifestations that are commonly encountered.

Although TAO predominantly affects the vessels of the extremities, a few instances of aortic, cerebral, coronary, mesenteric, pulmonary, and renal involvement have been reported in the literature. Moreover, Buerger's disease, although extremely rare, is associated with a poor prognosis. Patients with known Buerger's disease presenting with gastrointestinal manifestations should be urgently evaluated for bowel ischemia; early surgical intervention is recommended.

DIAGNOSIS

TAO is often a diagnosis of exclusion. Several criteria have been proposed to help establish the diagnosis. The common clinical criteria can be summarized as:

- Age <45 years
- Current or recent history of tobacco use
- Distal extremity ischemia documented by noninvasive vascular testing

The BASIL II and the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia trials, both currently under way, are each designed to fully address the question of endovascular versus open revascularization for individuals with critical limb ischemia where equipoise exists between the two treatment modalities. Both will randomize patients and both will address quality of life and cost effectiveness as well as clinical outcomes.

With regard to conduit selection for open bypass, autogenous vein has been shown to be preferable to prosthetic, particularly for infrapopliteal bypass; however, in individuals in whom an endovascular approach has failed and without autogenous options, prosthetic material can be effective.

POSTOPERATIVE MANAGEMENT

Postoperative pain management can be quite difficult. Nerve blocks and peripheral nerve catheters can be useful, as can adjuncts alongside acetaminophen and gabapentin. Nutrition should be maximized to aid in wound healing and the addition of nutritional supplements can be useful. Postoperative evaluation by physical therapy should be performed for all patients, particularly given issues of altered weightbearing status. Elevation of the limb while the patient is recovering is also useful. Many patients will require postdischarge admission to a rehabilitation center. Following major amputation, patients remain nonambulatory for 4 to 6 weeks before their prosthesis is fitted. For some younger patients, immediate postoperative prosthesis may be preferable and can help to improve primary healing rates and lessen the psychological impact of amputation.

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BUERGER'S DISEASE (THROMBOANGIITIS OBLITERANS)

Nav Vash Gupta, MD, FACS, Carl M. Wahlgren, MD, PhD, Ali Azizzadeh, MD, FACS, and Bruce L. Gewertz, MD, FACS

Thromboangiitis obliterans (TAO), or Buerger's disease, is a non-atherosclerotic, segmental, occlusive inflammatory disease that affects the small- and medium-sized arteries and veins of the extremities. Patients are usually young male tobacco smokers who present with distal extremity ischemia, ischemic ulcers, or gangrene. TAO has a worldwide distribution, but it is more prevalent in the Mediterranean, the Middle East, and Asia. The prevalence of disease in the United States, Europe, and Japan appears to be declining and may partly be due to a decline in smoking as well as adoption of more uniform and stricter diagnostic criteria. The incidence in women has increased and may be as high as 30%. This relative rise in incidence is probably multifactorial and may in large part be due to the increase in tobacco use among women.

Although the etiology of TAO is unknown, the condition is strongly associated with heavy tobacco use, including cigarettes, cigars, and smokeless forms such as chewing tobacco and snuff. Smoking is considered by most to be an absolute requirement for diagnosis and progression is closely linked to continued use. However, a causal relationship has not been conclusively demonstrated. The disease is classified pathologically as a vasculitis. Features that distinguish TAO from other types of vasculitis include highly inflammatory thrombus with relative sparing of the blood vessel wall, normal acute phase reactants and no serum markers of immunoactivation.

CLINICAL PRESENTATION

Buerger's disease typically begins with involvement of the distal small arteries and veins. More proximal arteries may be involved when the disease progresses, but involvement of large arteries is unusual. The onset of symptoms usually occurs before the age of 40 (a–45 years. Patients may present with claudication of the feet, legs, hands, or arms. Two or more limbs are always involved, all four limbs are affected in about 80% of patients. Intermittent symptoms are initially localized to the forefoot or the pedal arch because of the distal nature of the disease, as opposed to patients with peripheral atherosclerotic disease who first experience calf claudication symptoms. Progression of the inflammatory disease leads to development of ischemic rest pain and ulcerations to the distal portion of toes or fingers. In most series, about three-quarters of patients present with ischemic ulcers (Fig. 1). Raynaud's phenomenon and superficial migratory thrombophlebitis are manifestations that are commonly encountered.

Although TAO predominantly affects the vessels of the extremities, a few instances of aortic, cerebral, coronary, mesenteric, pulmonary, and renal involvement have been reported in the literature. Moreover, Buerger's disease, although extremely rare, is associated with a poor prognosis. Patients with known Buerger's disease presenting with gastrointestinal manifestations should be urgently evaluated for bowel ischemia; early surgical intervention is recommended.

DIAGNOSIS

TAO is often a diagnosis of exclusion. Several criteria have been proposed to help establish the diagnosis. The common clinical criteria can be summarized as:

- Age <45 years
- Current or recent history of tobacco use
- Distal extremity ischemia documented by noninvasive vascular testing

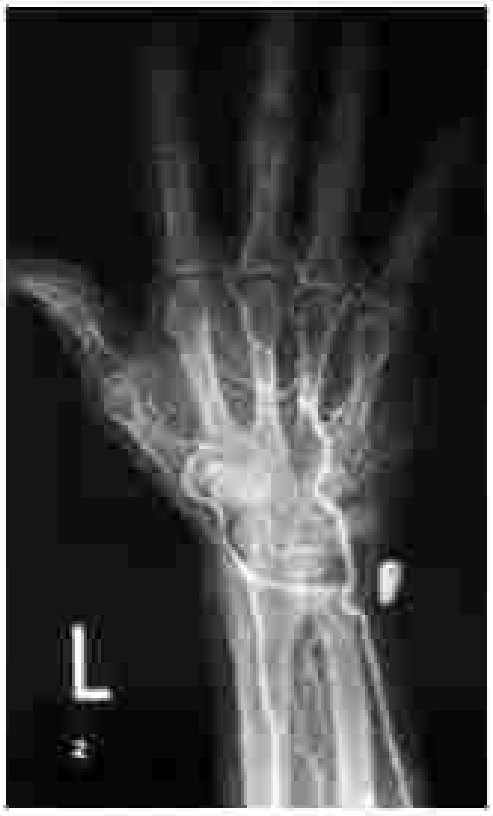

FIG. 1 Hand angiogram of patient with Buerger's disease showing involvement of the digital arteries with severe occlusions and collaterals.

- Findings suggestive of TAO on conventional angiography or magnetic resonance imaging
- Exclusion of autoimmune disease, hypercoagulable states, diabetes mellitus, proximal source of emboli, trauma, and local lesions (popliteal entrapment syndromes, adventitial cystic disease)

Physical examination often reveals cyanotic and erythematous extremities. Sensory abnormalities (burning, hypesthesia, numbness, and tingling) resulting from ischemic neuropathy are common as well as cold sensitivity that may be related to ischemia or to increased muscle sympathetic nerve activity. Absent distal pulses in the presence of normal proximal pulses are typical in patients with the disease. Ankle/brachial indices should be included in the vascular exam. Involvement of both the upper and lower extremities is common. Dry-punctuate ischemic lesions are often seen on both the hands and feet. Although nonspecific, a positive Allen test in a young smoker with digital ischemia is strongly suggestive of the disease.

Although a definitive diagnosis of TAO can only be made with tissue biopsy showing cellular thrombus and the classic acute phase lesion, physical examination and history are often classic. Hence, tissue biopsy is usually reserved for patients presenting with unusual characteristics, such as large artery involvement or those presenting at an age of more than 45 years.

No specific laboratory tests exist to confirm the diagnosis, however, several serologic tests should be included in the workup to rule out disease processes that can mimic TAO, including scleroderma, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome, mixed connective tissue disease, systemic lupus erythematosus, and hypercoagulability disorders. We routinely obtain a complete blood count with differential, electrolytes, renal and liver function tests, fasting blood glucose, urinalysis, sedimentation rate, reactive protein, and a complete hypercoagulability screen including antiphospholipid antibodies. Serologic markers that should be obtained include antinuclear antibody, rheumatoid factor, complement measurements, and urologic markers for calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome and scleroderma (SCL 70 and anticentromere antibody). Patients with giant cell arteritis or Takayasu arteritis usually present with more proximal vascular involvement and more frequently have elevations of acute phase reactants.

Standard arteriography is not essential for the diagnosis. Noninvasive imaging such as magnetic resonance angiography and computed tomographic angiography are good alternatives. Four-limb segmental arterial pressures and digital plethysmography (waveform and/or digital pressure measurement) are useful to document distal occlusive disease. When suggested by unilateral involvement, a proximal source of emboli should be excluded with echocardiography and/or computed tomographic angiography/magnetic resonance angiography.

Arteriography should be performed in those patients with threatened limb loss. Although there are a number of angiographic findings highly suggestive of TAO, there are no pathognomonic findings (Box 1). The angiographic appearance of TAO (Fig. 2) may be identical to other types of small vessel vasculitis or toxic arterial responses related to amphetamine, cannabis, or cocaine abuse. If a nonsmoking patient presents with signs consistent with TAO a toxicology screen is advisable.

Because of the relatively young age of most patients, the possibility of popliteal artery entrapment syndrome, cystic adventitial disease, or popliteal artery aneurysm should be considered in patients with lower extremity symptoms. The presence of diabetes mellitus, end-stage renal disease, or significant risk factors for atherosclerosis argue against a diagnosis of TAO.

BOX 1 Angiographic Findings in Thromboangiitis Obliterans (Buerger's Disease)

- Involvement of small and medium sized vessels
- Palmar, plantar, tibial, peroneal, radial, and ulnar arteries as well as digital arteries of fingers and toes
- Normal extremity arteries proximal to the popliteal and distal brachial levels
- Proximal atherosclerosis and vascular calcification are absent
- No source of thrombus
- Abrupt transition from a normal and smooth proximal artery to an area of occlusion
- Symmetrical and segmental arterial involvement
- Tortuous corkscrew collaterals are suggestive, but not pathognomonic, of Buerger's disease

TREATMENT

The main and most effective treatment for TAO is the total abstinence from tobacco products. Smoking is closely related to exacerbation and remission of the disease. Even smoking a few cigarettes a day or using smokeless tobacco or nicotine replacement may keep the disease active. Although smoking cessation can be a challenge, our experience showed that up to one-third of patients successfully discontinued tobacco use with proper counseling and support.

A correlation exists between continued smoking and limb amputation. If patients discontinue tobacco use, they can be reassured that the disease will often arrest and amputation can be avoided as long as ischemic ulcers have not already occurred. That said, patients with established significant occluded arterial segments may continue to experience intermittent claudication or Raynaud's phenomenon. End-stage renal disease may also be associated with disease progression and limb amputation in these patients.

In patients with disease progression despite smoking cessation, effective therapeutic options are limited (Box 2). Initial reluctance for

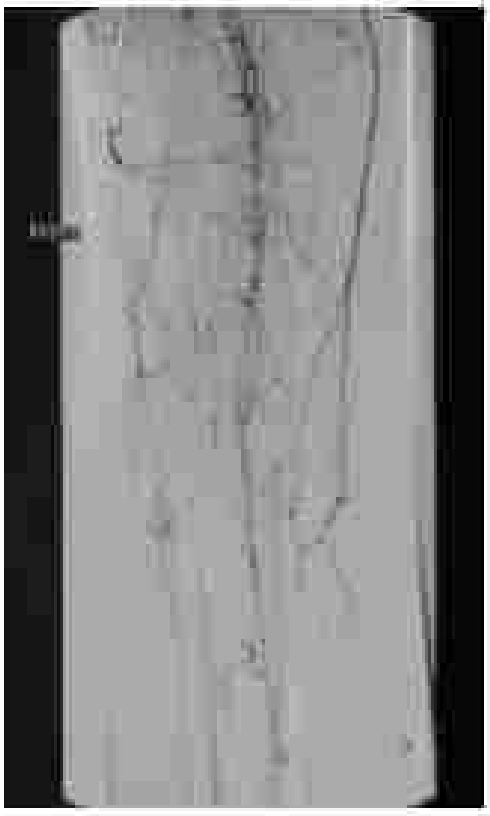

FIG. 2 Lower extremity angiography of patient with Buerger's disease showing multiple occlusions and collateral collaterals.

BOX 2 Treatment Options in Thromboangiitis Obliterans (Buerger's Disease)

Cessation of tobacco product use
Local wound care
Arterial reconstruction with vein graft
Endovascular intervention
Therapeutic options
- Prostaglandin analogue (topical or intravenous) sodium
- Cilostazol
- Hyperbaric oxygen therapy
- Calcium channel blockers (i.e., amlodipine or nifedipine, if vasospasm)
- Intermittent pneumatic compression pump
- Implantable spinal cord stimulator
- Therapeutic angiogenesis by gene- or cell based therapies

Amputation

infusion of the prostaglandin analogue iloprost has not been borne out by further trials or experience. Anticoagulants, antiplatelet drugs, and rheologic agents seem to be ineffective. Calcium channel blockers are only helpful if significant vasospasm is present. Intravenous thrombolytic therapy is not effective and has not been used in our practice. Therapeutic angiogenesis, including intramuscular gene transfer of vascular endothelial growth factor and bone marrow–derived stem cell therapy, seems promising and beneficial. Early studies with intramuscular injection of adult human bone marrow–derived mesenchymal stromal cells have shown a clinical benefit including reduced rest pain, healing of ulcers, improved hemodynamic parameters and total walking distance. Larger randomized trials are needed to further evaluate the safety and efficacy of these therapies.

Unfortunately, arterial reconstruction is usually not an attractive option because of the diffuse segmental involvement and distal nature of the disease. As well, the concomitant inflammatory venous disease often renders the saphenous vein unsatisfactory for use as conduits. However, if conservative treatment fails in patients with severe ischemia and nonhealing ischemic ulcers of the lower extremities, revascularization should be considered. The distal arteries must be thoroughly evaluated by arteriography for optimal preoperative planning and target vessel identification. If surgical exploration reveals a diminutive receiving vessel, bypass should be abandoned.

Although less invasive endovascular approaches might be attractive in this population, the diffuse, distal, and segmental involvement of the lesions limits currently available catheter-based techniques and their role is likely to be similar to that of surgery. Extended endovascular interventions down to the foot have shown to be technically feasible in a limited number of TAO patients but long-term data are lacking. Early data do support the use of endovascular recanalization in TAO patients with critical limb ischemia and no adequate distal target vessel or inadequate venous conduit for bypass. As expected, the endovascular strategy results in lower primary and secondary patency rates and higher rates of reinterventions. However, mid-term amputation-free survival rates are similar to those for patients undergoing bypass with venous conduit. More proximal femoropopliteal lesions in patients with advanced disease should be addressed to maximize inflow to collateral vessels.

As with many interventions for occlusive vascular disease, limb salvage rates usually exceed graft patencies. Although patency for distal bypass is no more than 50% even in the small number of patients with Buerger's disease who can undergo bypasses, limb salvage rates frequently exceed 70%. In these well-selected patients, even limited periods of revascularization provide a sufficient interval to heal ischemic ulcers in the feet.

Sympathectomy as a primary or adjunctive treatment option has been cited in a large number of patients with TAO without encouraging results. The lack of success reinforces the obstructive rather than vasospastic nature of the disease. Still, in some patients, spinal cord stimulation can have a salutary effect through pain reduction.

Amputations are inevitable in patients with extensive gangrene or sepsis. The goal is to remove all nonviable tissue, preserve optimal residual function, and minimize surgical morbidity. Application of these principles may result in unconventional amputation levels with a preponderance of multiple digital or distal amputations.

PROGNOSIS

In general, the prognosis for many patients with TAO is surprisingly good and depends largely on the ability to discontinue tobacco use. Despite the considerable morbidity, life expectancy for patients approaches that of an age-matched population. This could possibly be explained by the young age of presentation and the lack of coronary involvement in the disease process.

Even though ischemic ulcers are already present in the majority patients presenting for medical care, the overall limb amputation rate is less than 50%. It seems that recurrence of necrotic lesions subsides in patients older than 45 years. Still, follow-up of patients with TAO shows frequent hospitalization and surgical procedures. Major amputation and prolonged hospitalization markedly influence quality of life with many patients losing any opportunity for productive jobs.

SUMMARY

TAO is a nonatherosclerotic, segmental, and inflammatory disease. It is characterized by the development of segmental thrombotic occlusions of the medium and small arteries and veins of the extremities.

It occurs in young smokers who present with distal extremity ischemia, ulcers, or gangrene. The most important diseases to exclude are atherosclerosis, emboli, and autoimmune diseases. The only effective treatment is complete and permanent abstinence from tobacco

products. There are several medical, endovascular, and surgical therapies that are palliative and treatment should be directed toward pain relief, promoting healing of the ulcers and limb salvage. Major amputation affects the patient's quality of life and long-term outcome.

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Acute Mesenteric Ischemia

Courtenay M. Holscher, MD, and Thomas J. Ashjian, MD

Although acute mesenteric ischemia (AMI) accounts for less than 1 in 1000 hospital admissions, it remains a highly morbid and life-threatening surgical disease. Even in the modern era, mortality associated with AMI ranges from 25% to 80%. This high mortality is due to challenges in diagnosis and delays in treatment. The typical presentation of AMI is abdominal pain described as out of proportion to examination findings, which is a subjective description for a nonspecific presentation. Because the bowel cannot tolerate prolonged ischemia, a high index of suspicion is necessary to expedite the evaluation allowing prompt intervention.

Four pathologic processes can cause AMI: embolus or thrombosis of the superior mesenteric artery (SMA); nonocclusive mesenteric ischemia, or mesenteric vein thrombosis. Historically, SMA embolism was the most common presentation, accounting for nearly one-half of AMI cases. However, with an aging population and a high prevalence of atherosclerotic disease, more modern case series have found that arterial thrombosis of a diseased SMA was the most common cause of AMI. Nonocclusive mesenteric ischemia is due to a low flow state often associated with cardiogenic shock or the use of vasopressors; its management is largely supportive and nonoperative. Although selective catheterization of the SMA with intraarterial infusion of vasodilators such as papaverine may be used and laparotomy may be required for necrotic bowel, initially, mesenteric vein thrombosis should be managed nonoperatively, with full heparin anticoagulation and supportive care. Selective catheterization of the splenic artery and SMA for catheter-directed thrombolytic therapy is potentially useful but may only be used for a maximum of 48 hours. Laparotomy may be required for necrotic bowel but venous thrombectomy is not effective.

ANATOMY AND COLLATERALIZATION

The pathophysiology of AMI should be considered in the context of the visceral arteries and their collateralization. The splanchnic arterial supply consists of the celiac artery, SMA, and inferior mesenteric artery (IMA) (Fig. 1). The celiac artery supplies the foregut from the distal esophagus to the duodenum, spleen, and hepatobiliary system and collateralizes with the SMA through the gastroduodenal and pancreaticoduodenal arteries (Fig. 2). The SMA supplies the midgut from the jejunum to the transverse colon and collateralizes with the IMA through the marginal artery of Drummond and the arc of Riolan, also known as the meandering mesenteric artery. The IMA supplies the hindgut from the mid colon to the rectum. The rectal arteries serve as collaterals between the IMA and internal iliac arteries.

In the setting of chronic mesenteric ischemia, in which occlusion of one or two visceral arteries occurs over months or years, these collaterals enlarge to accommodate the metabolic demands of the bowel. However, in the setting of an acute thrombosis or embolism, visceral collaterals are insufficient to adequately perfuse the bowel in the distribution of the occluded artery, resulting in AMI.

CLINICAL PRESENTATION

Embolic Disease: Presentation and Risk Factors

The classic presentation of AMI caused by an SMA embolism (Fig. 3) is sudden onset of abdominal pain out of proportion to exam with immediate bowel evacuation. On examination, the abdomen is soft and doughy while the patient clearly appears extremely uncomfortable. Although this classic presentation should trigger prompt evaluation for AMI, other symptoms can include fever, nausea, vomiting, abdominal distension, and bloody diarrhea. A history of arrhythmia such as atrial fibrillation or cardiac events such as myocardial infarction or mural thrombus suggests an embolic etiology.

Thrombotic Disease: Presentation and Risk Factors

AMI caused by arterial thrombosis also presents with sudden onset abdominal pain, but often patients will have a history consistent with chronic mesenteric ischemia or significant atherosclerotic disease of other vascular beds (Fig. 4). A history of recent visceral endovascular intervention, which might have caused dissection or local trauma or any hypercoagulable disorder, should be elicited. Although chronic mesenteric ischemia, discussed elsewhere in this text, presents with symptoms of pain after eating that can be considered abdominal angina, we believe that there is a continuum from AMI to chronic mesenteric ischemia with an occasional patient presenting with subacute mesenteric ischemia or essentially minimal rest pain without other derangements in vital signs or laboratory findings. In our experience, patients with subacute mesenteric ischemia often present in the ambulatory setting but progress rapidly to AMI and thus should be managed urgently to avoid the need for laparotomy and bowel resection.

Evaluation

Patients with AMI might have normal vital signs or may have significantly deranged vital signs resulting from inflammation and hypovolemia secondary to bowel edema. Laboratory findings are nonspecific and can include a leukocytosis, electrolyte derangements, elevated amylase, and lactic acidosis. Although a hypercoagulable state may present as AMI, it is unusual and should be kept in mind, particularly in patients with mesenteric vein thrombosis. An electrocardiogram (ECG) and cardiac enzymes should be performed to identify arrhythmia or recent myocardial infarction.

Computed tomographic angiography (CTA) has become the standard imaging study to diagnose AMI (Fig. 5). In SMA embolism, CTA will demonstrate a nonvisceral sign with abrupt occlusion of the SMA several centimeters from the origin. In SMA thrombosis, the SMA is typically occluded at its origin and often enlarged collaterals are identified, supporting a preexisting diagnosis of chronic mesenteric

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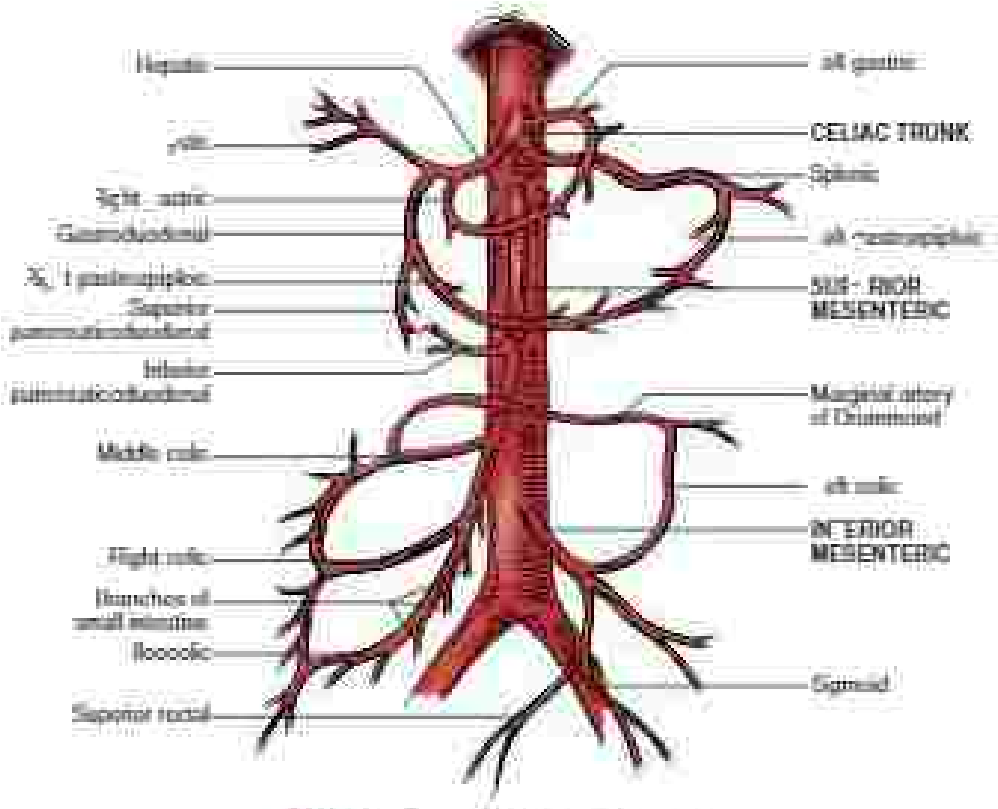

FIG. 1 Visceral arteries and their main branches.

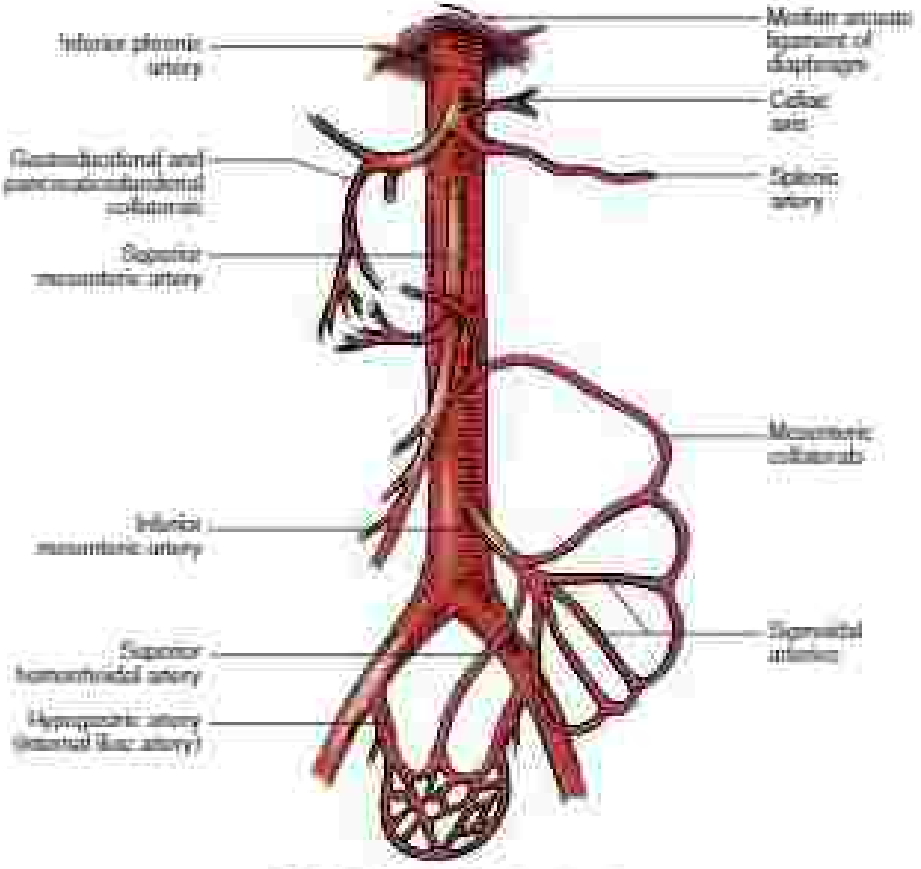

FIG. 2 Collaterals of the visceral arteries.

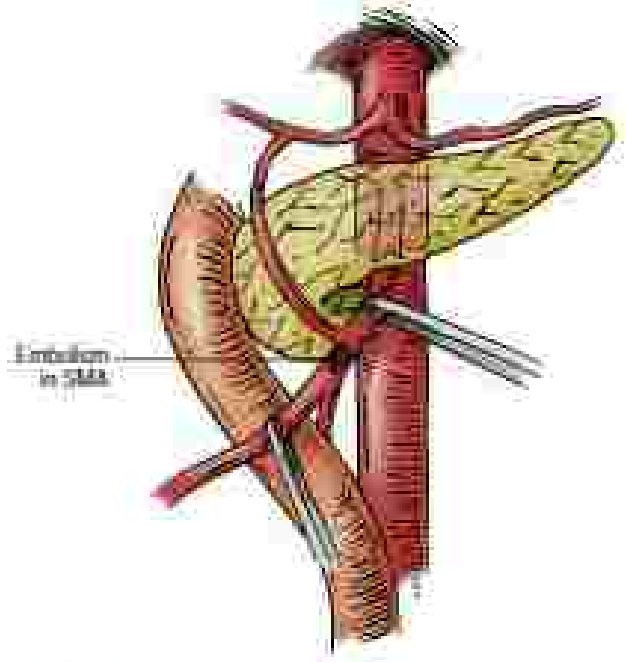

FIG. 3 Embolism of the superior mesenteric artery (SMA).

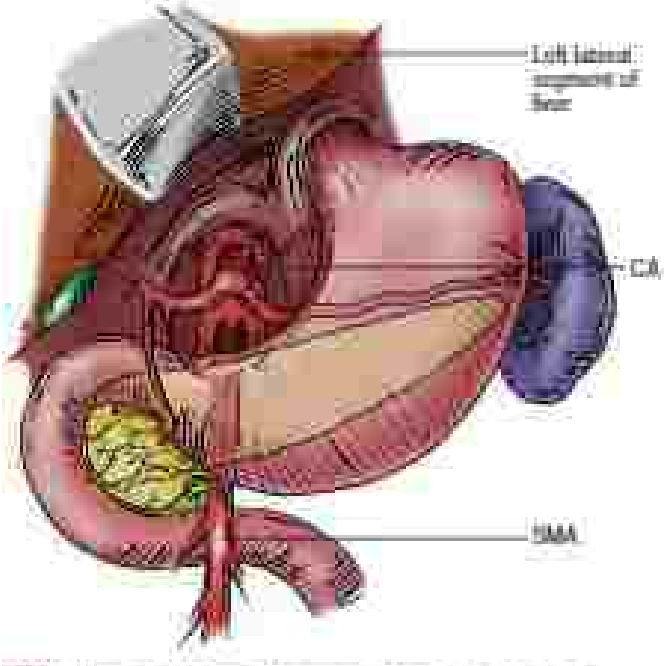

FIG. 4 Stenosis of the superior mesenteric artery (SMA) and celiac artery (CA).

ischemia. CTA can also identify other causes of mesenteric ischemia such as aortic dissection and mesenteric venous thrombosis. Digital subtraction angiography, once the gold standard, can be useful if endovascular interventions are being considered or if further details of vascular anatomy are needed for operative revascularization. Especially in the setting of a planned endovascular intervention, a hybrid operating room with endovascular capabilities can facilitate dual endovascular and open management of AMI. Other imaging studies including magnetic resonance imaging, plain radiographs, and ultrasound are of less utility and should be avoided as treatment can be expedited. Magnetic resonance angiography does not use the radiation and contrast needed for CTA but requires more time than CTA and produces images with lower resolution. Plain radiographs can show late findings of AMI such as pneumoperitoneum or portal venous gas, but do not identify the causative vascular occlusion. Although duplex ultrasound can be useful in the setting of chronic mesenteric ischemia, it is typically not useful in AMI because of overlying bowel edema and high operator dependence. Finally, although echocardiography can be helpful to delineate cardiac sources of emboli, it should not delay revascularization and is not required preoperatively.

TREATMENT

Perioperative Management

Once the diagnosis of AMI is made, revascularization should be planned without delay. Patients should be aggressively resuscitated with intravenous fluids and have correction of electrolyte abnormalities. A bolus of intravenous heparin should be given once the diagnosis is made to prevent propagation of thrombus. Unless absolutely necessary, pressor agents should be avoided. In the case of heparin-induced thrombocytopenia thrombosis, heparin should be stopped and argatroban or bivalirudin should be started. Broad-spectrum antibiotics should be given if there are any signs of bowel infarction. Arrhythmias should be managed medically or with cardioversion if the patient is hemodynamically unstable.

Operative Management

Exposure

Revascularization for AMI begins with a vertical midline laparotomy and assessment of bowel viability. Assuming that the entire small bowel is not necrotic, prompt revascularization is the first priority. The most expeditious approach to the SMA is to retract the omentum and transverse mesocolon cephalad and pack the small bowel in whatever position that exposes the root of the mesentery the best. A vertical or T-shaped incision in the peritoneum at the base of the transverse mesocolon then exposes the fatty tissue within the SMA mesentery. Although the SMA probably will not have a pulse to it at this level, it can usually be palpated as a thickening or cord deep in the root of the mesentery. Careful dissection deep through the fatty tissue heading toward the cord, while ligating all small crossing veins and visible lymphatics to avoid annoying bleeding or chyle leakage, will expose the SMA. The SMA is generally a large vessel so it should not be too difficult to locate. Once found, the vessel is circumferentially dissected out for a couple of centimeters. Cloth vessel loops are then looped (Potts' loops) around the vessel and any branches.

Embolectomy

If the SMA is soft and disease free, a transverse arteriotomy is made and a No. 3 or No. 4 Fogarty balloon catheter is passed proximally to the aorta (Fig. 5). It should pass with little resistance. The balloon is gently inflated and pulled back through the SMA. Of note, when the embolus and catheter pop out of the arteriotomy, there will be a violent jet of blood from the SMA, so an assistant must be ready to tighten the proximal vessel loop. Once normal inflow is obtained a No. 2 or No. 3 Fogarty catheter can then be gently passed distally and into any visible branches to retrieve any propagated thrombus. Thrombus might be visible in the distal artery at the arteriotomy; gently teasing it out with a small forceps can sometimes lead to the very pleasing result of a long intact string of thrombus. Once no more thrombus is returned the vessel is gently irrigated with heparinized saline and the arteriotomy is closed with 5-0 or 6-0 polypropylene suture in a running fashion.

Not uncommonly, the patient will present with a classic embolic picture of AMI, but when the vessel is dissected, there is atherosclerotic disease present. We generally still make a transverse incision

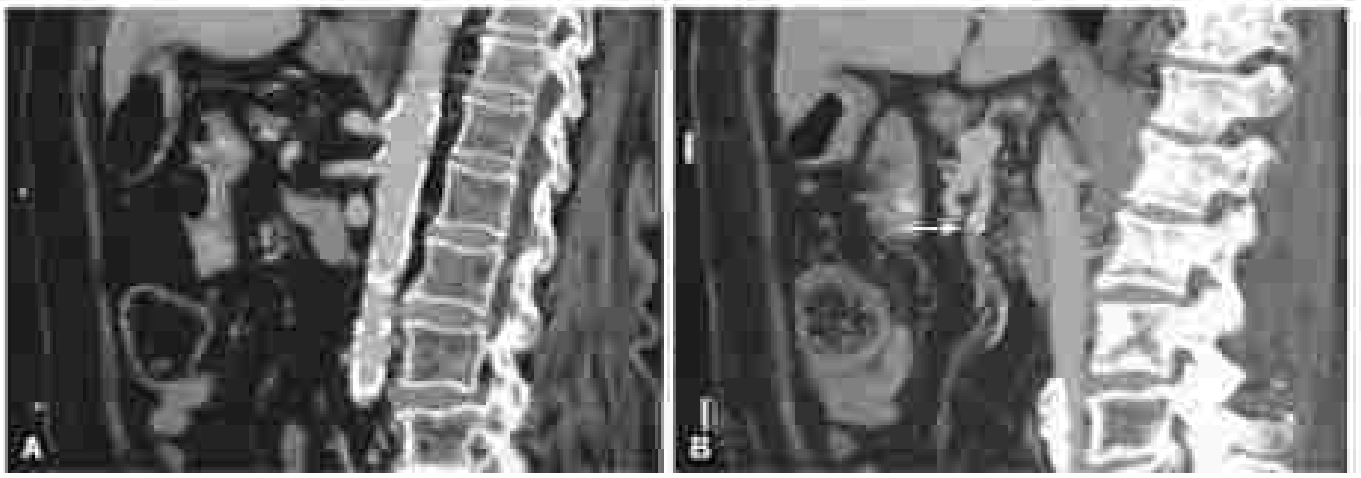

FIG. 5. Thrombus in the superior mesenteric artery (SMA), demonstrated on computed tomography. (A) Patent but diseased aorta and SMA origin. (B) Thrombosed mid-SMA just distal to atherosclerotic plaque (arrow).

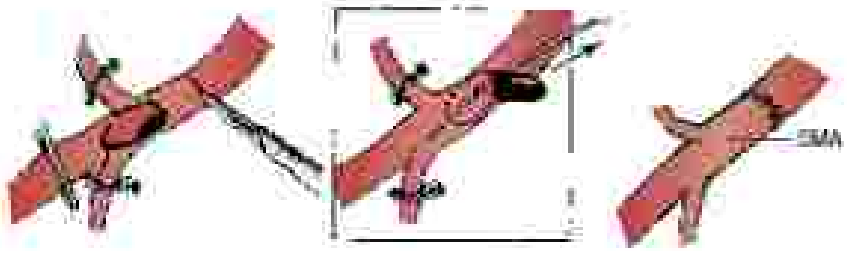

FIG. 6. Standard transverse arteriotomy for superior mesenteric artery embolectomy. (From Cronenwett, Johnston, editors: Rutherford's Vascular Surgery and Endovascular Therapy, 8th ed. Philadelphia: Elsevier; 2014.)

because it can always be converted to a longitudinal arteriotomy if the transverse closure is problematic. If a longitudinal incision is made or a transverse incision converted to a longitudinal one, it should always be closed with an autogenous vein patch.

Bypass

Revascularization for SMA thrombosis is typically undertaken in the setting of underlying atherosclerotic disease and abnormal splanchnic vessels. Because of this, the management of SMA thrombosis is more challenging and time-consuming than embolectomy. Although there might be multiple diseased visceral vessels, a single bypass graft to the SMA is adequate revascularization for AMI. Although antegrade bypass from the supraceliac aorta is associated with superior patency, the more difficult exposure of the supraceliac aorta and need for supraceliac clamping in these critically ill patients leads us to strongly recommend a retrograde bypass from the iliac arteries. Either of the common or external iliac arteries may be used for inflow and we tend to choose whichever vessel is the easiest to dissect out and has the least amount of calcification. In the standard literature, much is made about using the right common iliac artery for the inflow as the graft makes a gentle C-loop and is less likely to kink (Fig. 7). In our experience, kinking has not been a problem regardless of which iliac vessel is used. Our preferred conduit is autogenous saphenous vein, although if none is available it is reasonable to use a 6- or 8-mm prosthetic. Standard bypass techniques are used with the anastomosis to the iliac artery being performed first. Hemostasis is confirmed at the inflow, then we determine the best path for the bypass to the SMA. Not uncommonly, the bypass can be tunneled through the mesentery or retroperitoneally such that it lies nearly straight.

Endovascular Approaches

In the rare case in which there is very low suspicion for systemic bowel, such as in subacute mesenteric ischemia, an endovascular-only method can be taken. Although a totally percutaneous approach can be used, we prefer a left brachial artery cut down for access. This avoids leaving a frequently occlusive sheath in the brachial artery any longer than necessary and also avoids brachial artery complications. Although many wires and catheter combinations can be used, we use an 5F Omni Flush catheter (AngioDynamics Inc.) to assist in gaining wire access to the descending thoracic aorta and abdominal aorta. We exchange that for a 100 cm pigtail catheter to perform the diagnostic angiogram confirming the stenotic but patent SMA. After full heparinization, the brachial sheath is exchanged for a 6F or 7Fr 90 cm Shuttle Select sheath (Cook Inc.). The lesion is then crossed with an appropriate wire for the selected stent. Either a covered or uncovered balloon expandable stent may be used, although some recent preliminary data indicate that covered stents have better patency. The diameter should match the diameter of the normal artery with the length extending from a millimeter or two into the aorta to just distal to the lesion. Once the stent is deployed and confirmed to be appropriately placed, the wire and sheath are removed and the brachial artery is repaired with a 6-0 polypropylene suture. If the SMA is occluded from either atherosclerotic disease or thrombosis or is circumferentially heavily calcified, then the patient is probably best treated by an open surgical technique.

Hybrid Open and Endovascular Revascularization

Recent case series have confirmed open laparotomy with retrograde stenting of the SMA with access via a branch of the SMA. This approach

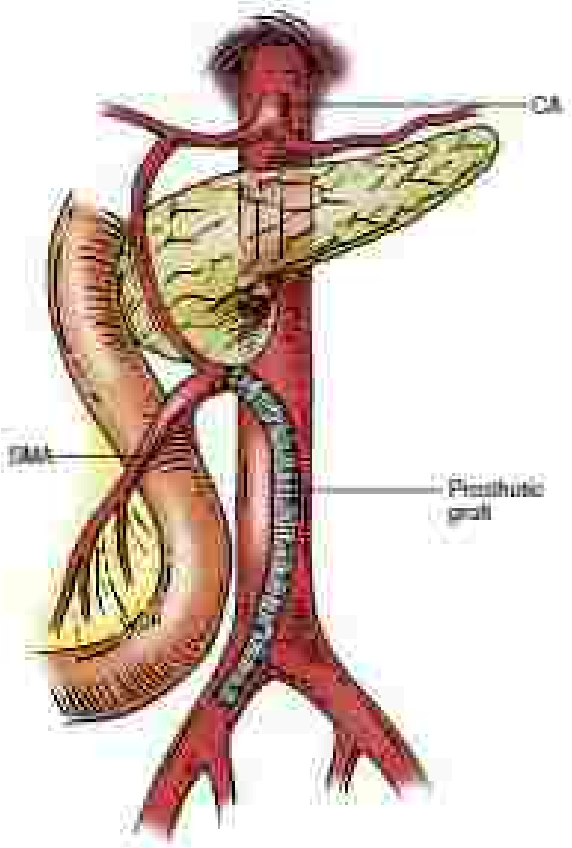

FIG. 7 Retrograde bypass from the common iliac artery (CA) to the superior mesenteric artery (SMA). SMV, Superior mesenteric vein.

avoids aortic clamping and the time required for bypass grafting but does require a hybrid operating room/endovascular suite. Illuzzi et al. reported 20% mortality and 45% primary patency in their series of 15 patients who presented with AMI and underwent retrograde open mesenteric stenting. Oderich et al. reported 8% mortality and 76% primary patency in their cohort of 48 patients. We do not have any experience with this technique and although interesting, we believe that an appropriately and expeditiously performed iliomesenteric bypass will have superior long-term patency with equal surgical time.

Management of Ischemic Bowel

In general, revascularization should precede resection of any bowel. This will allow repurfusion of any threatened areas of bowel and potentially decrease the length of bowel that must be subsequently resected. At the initial operation, frankly necrotic bowel should be resected and left in discontinuity. Questionably viable intestine should not be resected because the patient will be returned to the operating room in the next 24 to 48 hours to inspect the bowel and reestablish the discontinuous ends. Although much is made of mesenteric Doppler examination and fluorescein injection with Wood's lamp inspection after revascularization, we have not found it to be of much use because the bowel will declare itself, especially by the time of the second look operation. If after successful revascularization, all of the bowel is viable and no resection is necessary, a second look laparotomy is not mandatory.

In the rare case in which there is very low suspicion for necrotic bowel and an endovascular approach has been successful to revascularization, laparotomy can be avoided. However, a low threshold must be maintained for operative bowel evaluation. This can be done laparoscopically.

OUTCOMES

Even with revascularization, mortality in AMI is high with reported short-term mortality ranging from 22% to 90%. Factors associated with worse outcomes include older age, prolonged symptom duration, and the need for bowel resection. Although endovascular only management is associated with lower mortality rates, there is a clear selection bias to those patients who have an attempt at endovascular only management strategies. Much of the mortality in AMI can be attributed to the underlying atherosclerotic or embolic disease process, and even with successful revascularization, ongoing resuscitation and management in an intensive care unit are necessary.

POSTOPERATIVE MANAGEMENT

Following AMI, survivors should be on lifelong anticoagulation for an embolus or thrombus due to arrhythmia or hypercoagulable disorders. Aspirin is indicated for any revascularization using bypass grafting. Dual antiplatelet therapy with aspirin and clopidogrel should be used after stenting for at least the first 6 weeks then single agent therapy should be continued for life. Clopidogrel alone can be used for patients with an aspirin allergy or intolerance. Duplex ultrasound should be performed every 6 months for a year after bypass then yearly thereafter to detect graft stenosis.

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Chronic Mesenteric Ischemia

Douglas W. Jones, MD, and Alik Farber, MD

Chronic mesenteric ischemia (CMI) results from inadequate arterial perfusion of the abdominal viscera, as supplied by the celiac artery, superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and the rich collateral network between these visceral arteries. Atherosclerosis of the aorta involving the origins of the visceral arteries is the most common cause of CMI. In general, symptomatic CMI requires hemodynamically significant occlusive disease that involves at least two of the three visceral arteries and almost always involves the SMA. The most common disease pattern is involvement of the celiac artery and SMA, though concurrent SMA and IMA disease can also lead to symptomatic CMI. Atherosclerotic stenoses or occlusions often involve the visceral artery origins and may be confluent with aortic mural plaque (i.e., coral reef atherosclerosis). However, atherosclerotic lesions involving long segments of the visceral arteries are also seen. Dissection (spontaneous, posttraumatic, fibromuscular dysplasia) or arteritis (Takayasu's disease, giant cell arteritis, polyarteritis nodosa) of the visceral arteries may also cause CMI but these disorders are uncommon. Median arcuate ligament syndrome, compression of the celiac artery by the median arcuate ligament of the diaphragm, is an uncommon cause of postprandial abdominal pain caused by CMI. Although there are clearly demonstrated hemodynamic effects of median arcuate ligament syndrome, it has been argued that associated abdominal pain may be partially neurologic in origin resulting from celiac ganglion compression.

INDICATIONS FOR REVASCULARIZATION

Postprandial abdominal pain is the hallmark of CMI, also termed intestinal angina, and caused by episodic gut ischemia induced by eating. In the fasting state, gut and organ perfusion is normal, but fixed occlusive lesions limit the increase in visceral blood flow required for digestion in the postprandial state. Patients may exhibit sitophobia (fear of eating because of abdominal pain), which prevents adequate nutrition and causes progressive and potentially life-threatening weight loss. Diarrhea, constipation, nausea, and/or vomiting may also occur. Timely diagnosis and treatment of symptomatic CMI is essential because untreated CMI can lead to intestinal infarction, which is often lethal. In appropriately selected patients, revascularization successfully relieves symptoms, aids in weight gain, and most importantly, alleviates intestinal infarction.

Asymptomatic visceral artery stenoses are relatively common and given their indolent course should not be routinely treated by revascularization, which carries a risk of complications. Because of the high prevalence of asymptomatic visceral artery occlusive disease (observed in up to 20% of those older than 65 years) and ubiquity of nonspecific abdominal symptoms, it is essential to determine whether chronic and sometimes vague abdominal symptoms are convincingly attributable to occlusive lesions prior to pursuing revascularization. Gastroenterology consultation can be helpful in ruling out other causes of pain. Index of suspicion among providers should remain high, as there are some patients with atypical debilitating abdominal symptoms and demonstrable, hemodynamically significant visceral artery lesions that may benefit from revascularization. However, intervention is recommended only after other possible etiologies have been fully explored and ruled out.

When CMI is suspected, duplex ultrasound can determine whether hemodynamically significant lesions are present and which visceral arteries are affected. Duplex imaging of the visceral aorta is best performed in the morning, after an overnight fast, because the minimizes presence of bowel gas, which may preclude visualization of the visceral arteries by the vascular technologist. Diagnosis of significant visceral artery disease is based on measurements of peak systolic velocity (PSV), end diastolic velocity (EDV), and changes in the SMA velocity spectral waveform from a fasting to postprandial state (Box 1). Hemodynamically significant stenosis (>70% diameter reduction) is associated with elevated blood flow velocity across the lesion, typically demonstrated by: (1) PSV greater than 275 to 300 cm/s and (2) EDV greater than 45 to 55 cm/s (Fig. 1). The spectral waveform at and immediately distal to the stenosis demonstrates turbulence while downstream it appears dampened. A mesenteric aortic PSV ratio greater than 3 is also predictive of more than 50% stenosis. Steinkamp and colleagues reported a PSV threshold of 400 cm/s for more than 70% stenosis of the SMA (overall accuracy of 80%) and of 320 cm/s for more than 70% stenosis of the celiac artery origin (overall accuracy of 87%). Although mesenteric duplex ultrasound is technically demanding because of the depth of the visceral arteries, an interpretable study is possible in more than 80% of individuals, with excessive bowel gas being the primary reason for a suboptimal examination. Visceral duplex testing should be considered a screening diagnostic modality that complements clinical assessment of patients with suspected CMI, and when abnormal it should prompt additional imaging such as computed tomographic angiography (CTA) or magnetic resonance angiography.

CTA has high sensitivity and specificity for identifying visceral atherosclerosis and is useful for planning revascularization. It has the additional benefit of visualization of other intra-abdominal pathologies which may be contributing to symptoms. However, CTA does not provide hemodynamic information, its image quality is limited in the presence of severe calcification, and contrast load may not be tolerable for patients with chronic renal insufficiency or contrast sensitivity. Magnetic resonance angiography can be considered in some patients who cannot undergo CTA; however, its utilization in those fitted by implantable devices, patient intolerance, and variable image quality.

RECONSTRUCTION OPTIONS

Reconstruction options for visceral arterial occlusive disease take three forms: endovascular revascularization, open bypass grafting, and transaortic mesenteric endarterectomy. Anatomic disease patterns have important implications for which treatment option is most appropriate. For example, atherosclerotic lesions limited to 1 to 2 cm of a proximal visceral artery segment may be best treated by angioplasty and stenting (Fig. 2). In contrast, long occlusions, arterial dissection, and arteritis generally affect long segments involving both the main trunk and its branches and may require bypass grafting.

Endovascular Revascularization

Endovascular treatment of CMI has become increasingly common, with many centers adopting an endovascular first approach for most cases, while reserving open surgery for those patients who fail endovascular therapy. Angioplasty and stenting are best suited for the treatment of focal, ostial arterial lesions (Fig. 3). Revascularization of the SMA is the primary goal of endovascular therapy, though the celiac artery and IMA may also be treated, especially if the SMA is occluded and cannot be revascularized, and an extensive collateral network is seen (Fig. 4). Some have argued that two vessel revascularization (i.e., celiac artery and SMA) is superior to treating a single vessel; however, this remains controversial. In general, efforts should be made to revascularize the SMA first, if a severe stenosis or occlusion is present. If this is accomplished expeditiously, then it is reasonable to consider treating a diseased second visceral vessel as long as anticipated procedural risk is low.

Visceral arterial lesions, even though they may appear focal, are often caused by overflow aortic atherosclerotic thrombus. Balloon angioplasty is rarely adequate to treat calcified visceral artery lesions because of recoil and persistent stenosis after angioplasty alone. As a result, balloon-expandable stents (which have high radial force) are considered the endovascular treatment of choice. Careful attention is paid to make sure stents "flare" into the visceral aorta (Fig. 3) to prevent restenosis by extension of aortic plaque across an unstented ostium. Celiac artery stents should not be placed when uncorrected, hemodynamically significant compression by the median arcuate ligament is present, as suggested by preprocedure duplex ultrasound or CTA, as this can lead to stent deformation and vessel occlusion.

Stent grafts (stents covered by prosthetic material) are increasingly being used for CMI. Stent grafts provide protection against inadvertent visceral branch or aortic injury during the high-pressure inflation required to dilate a calcified plaque, and also trap atherosclerotic plaque against the vessel wall, limiting distal embolization. Stent grafts are also protected against restenosis due to ingrowth of hyperplastic material through stent interstices (as seen in bare metal stents). Oderich and colleagues have reported that stent grafts are associated with lower rates of restenosis and reintervention compared to bare metal stents, though this remains controversial.

Access site is an important consideration and must be planned carefully. Common femoral artery access is associated with fewer complications, but cannulation of the visceral artery origin can be challenging, especially if its origin is downgoing. These geometric disadvantages can usually be overcome with appropriate catheter selection or deflectable tip sheaths. However, tracking of a balloon-expandable stent into position for deployment may still not be possible due to acute angles and inadequate sheath support. In contrast, brachial access provides a better angle of approach to downgoing vessels. This is particularly useful when attempting to recanalize an occluded celiac artery or SMA origin, as this often requires substantial sheath support which is unattainable from a brachial access site. Advantages of brachial access must be weighed carefully against the higher access site complication rate, especially for larger sheath sizes. Radial access is increasingly used for mesenteric artery revascularization with good results.

The risk for embolization during the treatment of visceral occlusive disease, particularly when total occlusions are recanalized, has prompted some to use distal embolic protection devices (i.e., filters) to catch dislodged plaque fragments or thrombus during guidewire and catheter manipulations, although the benefit of this additional maneuver remains unclear.

In some cases, a lesion such as a flush ostial occlusion cannot be successfully treated using typical endovascular techniques. Accordingly, failure of endovascular therapy has become a common indication for open revascularization. However, some patients are poor candidates

BOX 1 Visceral Duplex Ultrasound Criteria for Normal and Stenotic Celiac Artery, SMA, and IMA Flow

Normal

Celiac: PSV 90–110 cm/s, low resistance flow pattern
SMA: PSV 95–110 cm/s, high resistance flow pattern in fasting state with EDV >5 after meal
IMA: PSV 90–180 cm/s, high resistance flow pattern

Diagnostic Testing (Fasting)

<70% Stenosis
Celiac: PSV <200 cm/s, EDV <55 cm/s; resistive index <0.75
SMA: PSV <300 cm/s, EDV <45 cm/s with diastolic flow reversal in distal SMA
IMA: PSV <200 cm/s, antegrade resistive flow (like SFA)

>70% Stenosis
Celiac: PSV >200 cm/s, EDV >55 cm/s with retrograde common hepatic artery flow with severe stenosis or celiac artery occlusion
SMA: PSV >300 cm/s, EDV >45 cm/s with loss of diastolic flow reversal
IMA: PSV >300 cm/s, antegrade flow with loss of diastolic flow reversal
Mesenteric aorta ratio >3

Velocity Spectra Changes With Test Meal

Increase in PSV in area of stenosis with dampening of distal waveform, and most frequently in assessing the significance of SMA occlusive disease

EDV, end-diastolic velocity; IMA, inferior mesenteric artery; PSV, peak systolic velocity; SFA, superficial femoral artery; SMA, superior mesenteric artery

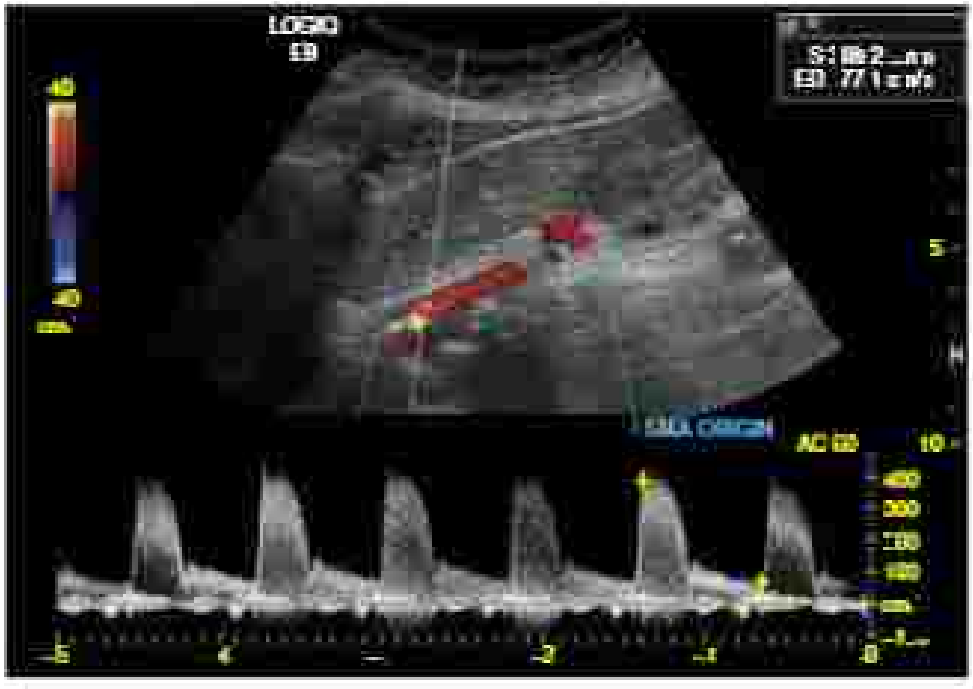

Fig. Splenic image and velocity spectra recorded from the origin of the superior mesenteric artery with a >70% diameter reducing stenosis based on a peak systolic velocity of 295 cm/s and end-diastolic velocity of 77 cm/s.

for open repair because of excessive comorbid disease, a hostile abdomen, or extensive aortoiliac calcification that would preclude clamp placement. Retrograde open mesenteric stenting, a hybrid approach that incorporates aspects of open and endovascular surgery, can be considered in such cases. A midline laparotomy is performed allowing for transabdominal exposure of the celiac artery or SMA. The vessel is directly accessed and a wire is passed through the visceral vessel into the aorta in a retrograde fashion; angioplasty and stenting can then be performed using principles described above. This technique is most commonly employed in the setting of acute mesenteric ischemia, when abdominal exploration may be a planned part of the initial procedure, facilitating access to the visceral vessels. Further, the use of prosthetic bypass in this setting may be limited by enteric contamination in the acute setting so other revascularization options may be preferred.

Arterial Bypass Grafting

The technique of bypass grafting for visceral artery occlusive disease is applicable to most disease patterns and is selected for patients with long segment stenoses or occlusions that are not amenable to endovascular revascularization. Because long-term outcomes with bypass tend to be superior to endovascular therapy, patients may be selected for primary open bypass if they are relatively young, have a low comorbidity burden, and demonstrate favorable anatomy. Bypass grafts to the mesenteric arteries can originate from a nondiseased supraceliac portion of the aorta (antegrade bypass) or from the infrarenal aorta or iliac artery (retrograde bypass).

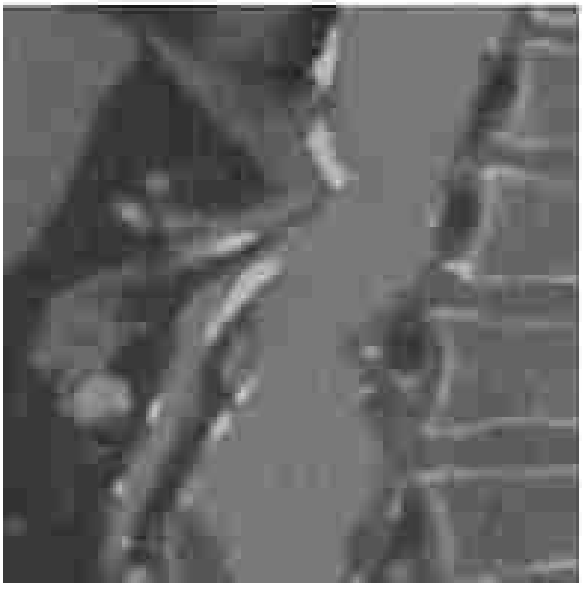

FIG. 3 Lateral angiogram of the aorta showing atherosclerotic plaque involving the origin of the celiac and superior mesenteric arteries.

Antegrade Mesenteric Bypass

Aortic exposure for antegrade bypass is achieved through a transabdominal, transcrural approach (Fig. 5) or via a medial visceral rotation from the left. The transcrural exposure of the supraceliac aorta can be performed via midline or bilateral subcostal incision. The attachment of the left lobe of the liver is divided to expose the aorta. Intraoperative division of the median arcuate ligament and dissection of the aorta and its branches. Exposure of the aorta for cross-clamping is facilitated by self-retaining retractor blade placement. Bypass grafting with either a polyester or a polytetrafluoroethylene conduit is performed with local aorta endarterectomy at the proximal anastomosis, if necessary. Unless the celiac artery is completely free of disease, a bifurcated graft is used with separate limbs targeting the celiac artery and SMA.

The proximal anastomosis of an antegrade aortomesenteric bypass should be placed in a disease-free supraceliac or distal thoracic portion of the aorta. The bifurcated graft should be fashioned with a relatively short main body. In a minimally diseased aorta, a side-biting clamp can be used to perform the proximal anastomosis without complete occlusion of the aorta. However, total aortic cross-clamping may be required, particularly if disease burden makes partial aortic clamping unreliable or unsafe. Circumferential supraceliac aortic infiltration is not performed routinely unless there is an intervening part of intercostal arteries that need to be exposed for temporary control. Once the proximal anastomosis is complete, bifurcated limb length and alignment are easy to determine. The SMA limb is tunneled to a retroperitoneal plane (Fig. 5). An end-to-end celiac or end-to-side common hepatic artery anastomosis is constructed followed by an end-to-side SMA anastomosis.

Retrograde Mesenteric Bypass

The infrarenal portion of the aorta, the iliac artery, or a previously placed prosthetic aortic or aortoiliac graft all can provide inflow for a retrograde mesenteric bypass. Exposure of the aorta is performed via a standard infrarenal approach. The infrarenal aorta or the iliac artery is often used as inflow. The inflow anastomosis is performed end-to-side and the outflow (visceral branch) anastomosis performed either as end-to-end or end-to-side (Fig. 6). In contrast to the antegrade approach, a single vessel is targeted for retrograde bypass. If the SMA is the revascularization target, it is exposed beyond the duodenal arcus

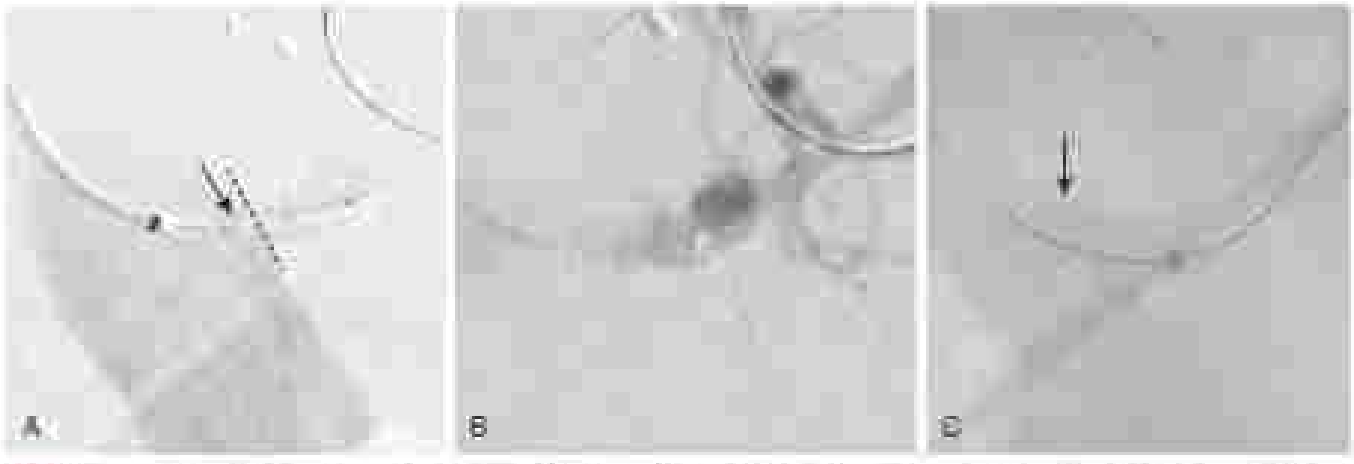

FIG. 4 Fluoroscopic images of visceral artery stent angioplasty. (A) Optimal position of the celiac stent, extending 1–2 mm into the aortic lumen. The arrow represents the proximal end of the stent. The dotted line represents the aortic wall. (B) Celiac stent after pressure-monitored deployment of a balloon-mounted stainless steel stent. (C) "Jailed" celiac stent, showing a flared proximal end (arrow). The inner white represents the location of the aortic wall.

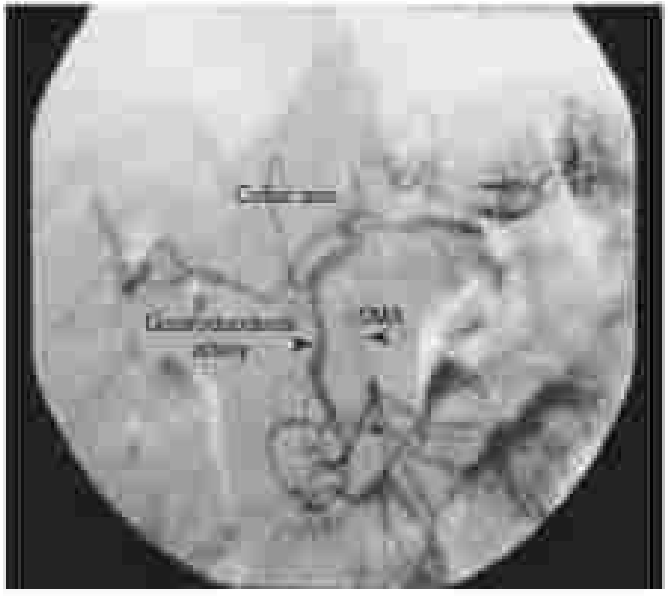

FIG. 4 Angiogram by selective contrast injection into the celiac axis with opacification of the superior mesenteric artery (SMA) via a large gastroduodenal artery in this case, reconstruction of either the celiac axis or the SMA could provide perfusion to the entire visceral circulation.

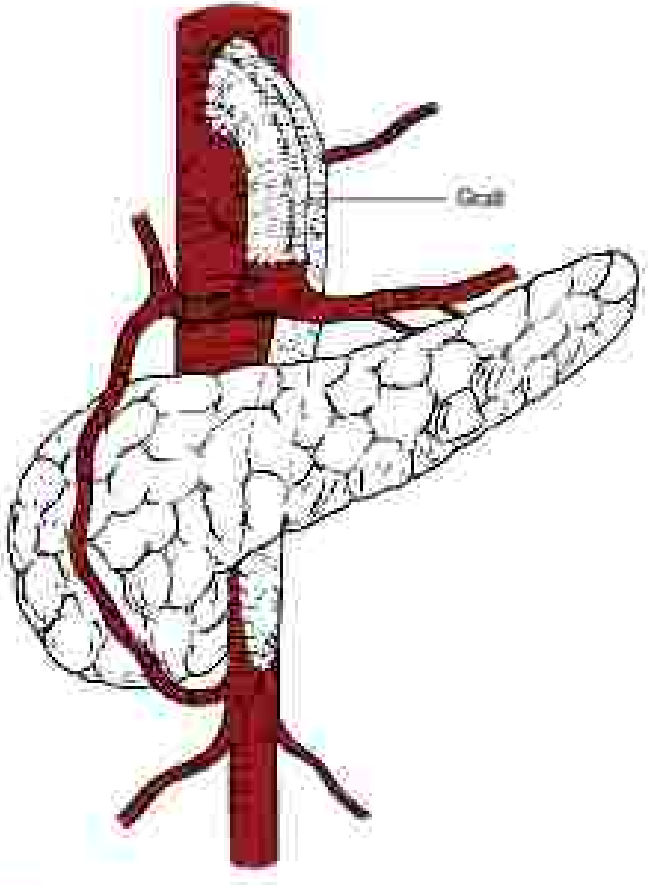

FIG. 5 Antegrade bifurcated aortomesenteric bypass. Limbs are oriented on top of each other in an anteroposterior orientation. Note end-to-end celiac artery anastomosis and end-to-side superior mesenteric artery anastomosis. (From Oderich GS, Gloviczki P, Bower TC, et al. Open surgical, endovascular, and hybrid treatment of chronic mesenteric ischemia. In: Cronenwett JL, Johnston KW, eds. *Rutherford's Vascular Surgery and Endovascular Therapy*. Philadelphia: Elsevier; 2014.)

in the root of the mesentery. For celiac artery occlusion, the common hepatic artery is usually selected as the graft target as it requires less dissection and the graft alignment is easier. To avoid graft torsion and kinking, use of a ringed polytetrafluoroethylene conduit in gentle C-shaped configuration is recommended. Autogenous vein conduit can be used, in the setting of enteric contamination; however special care needs to be taken to avoid graft kinking. In general, a retrograde bypass can be performed more quickly and obviates the need for supraceliac aortic cross-clamping in most cases.

Transaortic Mesenteric Endarterectomy

Plaque excision via an aortotomy allows endarterectomy of aortic wall plaque and each involved contiguous arterial branch using the aforementioned endarterectomy technique. Aorta exposure can be achieved via a midline abdominal incision, bilateral incision, or retroperitoneal left flank approach. For each approach, the left kidney remains in its anatomic position while the plane behind the left colon, spleen, pancreas, and stomach is developed to allow medial visceral rotation toward the midline. The diaphragmatic crus is often divided to gain further proximal exposure. If necessary, the entire aorta from the distal thoracic level to the aortic bifurcation can be exposed completely. Proximal and distal aortic clamping are required for control. A U-shaped trapdoor aortotomy circumscribes the orifices of the celiac and superior mesenteric arteries, and an eversion endarterectomy is performed to remove the aortic plaque and to circumferentially free the visceral orifices (Fig. 7). Endarterectomy is not typically extended to include the renal artery origins unless symptomatic renal artery stenosis is diagnosed preoperatively. The aortotomy is closed with running suture and often does not require a patch. Typically, the transaortic endarterectomy procedure can be completed with a visceral total ischemia time of less than 45 minutes.

Transaortic mesenteric endarterectomy has been largely supplanted by endovascular techniques and open bypass. However, it is still useful in certain situations, such as patients with multi-vessel orificial lesions that are contiguous with aortic atherosclerotic (coral reef) plaque. A limitation of endarterectomy is its ability to remove visceral artery plaque extending beyond 2 cm from the origin, which is more likely to be a challenge for the SMA. If inspection of the distal endarterectomy endpoint reveals a residual obstructing plaque, an additional longitudinal SMA arteriotomy can be performed to complete the endarterectomy, tack down distal plaque and perform standard patch closure. Alternatively, a stent can be deployed across the ostium.

OUTCOMES OF REVASCULARIZATION

The management of CMI has undergone a dramatic change in the past 2 decades. Though open bypass has traditionally been the dominant treatment modality, utilization of endovascular therapy has steadily increased, surpassing bypass in the early 2000s (in the United States). In 2014, endovascular therapy comprised close to 80% of CMI revascularization procedures. Concurrent with this trend has been the increase in overall, nationwide revascularization procedures for CMI. These trends imply that a larger number of patients are being considered eligible for revascularization given the improved perioperative safety profile of endovascular therapy.

Regarding perioperative outcomes, both endovascular and open revascularization have more than 90% rates of technical success and initial symptom relief, when performed in appropriately selected patients. Endovascular therapy is consistently associated with operative mortality rate less than 3%. Though open bypass mortality rates are variable, bypass can be performed with comparable mortality rates of 2% to 5% at high volume centers. However, nationwide mortality rates may be as high as 9% to 13% indicating that excellent perioperative results of open bypass may not be broadly applicable. In addition to potentially lower procedural mortality rates, endovascular therapy has been associated with lower morbidity rates, shorter length of stay and cost savings (at index revascularization procedure) compared to open bypass.

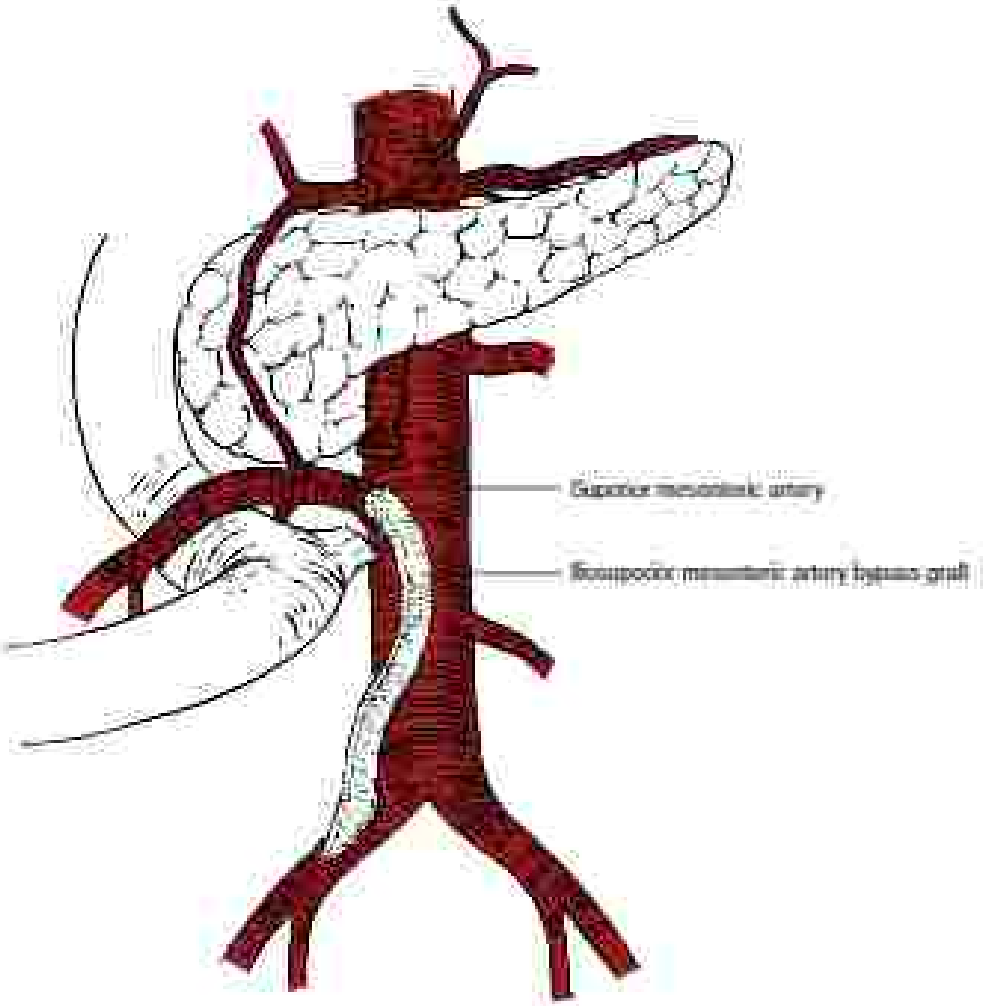

FIG. 6 Retrograde iliomesenteric bypass. Distal anastomosis can be end-to-end, as illustrated, or end-to-side. (From Chaikof, Lumsden, editors. Atlas of Vascular Surgery and Endovascular Therapy. Anatomy and Technique. Philadelphia: Saunders; 2010.)

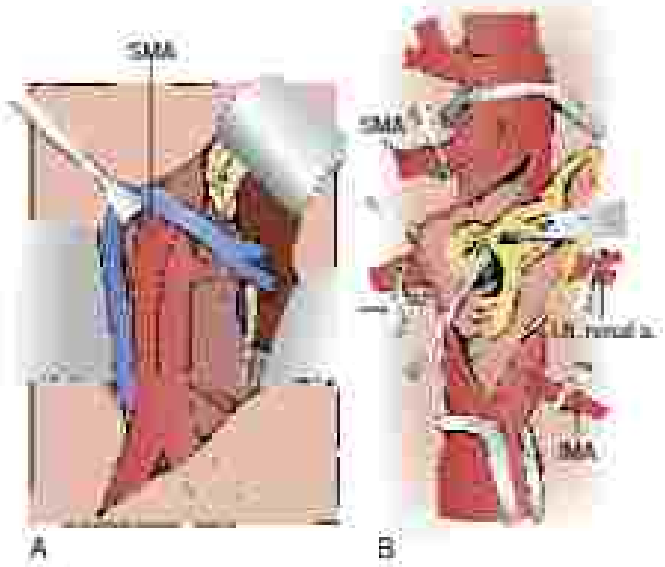

FIG. 7 Transaortic mesenteric endarterectomy. (A) Aortotomy is made to include the origins of the celiac artery and superior mesenteric artery (SMA). (B) Terminal endarterectomy of the celiac artery and SMA origins. IMA, Inferior mesenteric artery. (From Bergan JM, Yao JST, Kistner RL, Flinn WR. Techniques in visceral artery reconstruction (part I). Adv Vasc Surg. 1994;2:329–374.)

The procedural morbidity of open repair is higher than that of endovascular intervention, but endovascular interventions are less durable and treated patients require more secondary procedures for restenosis. High-quality long-term data are not available, but the patency rate of endovascular therapy has been reported to be <50% at 5 years, compared with 80% to 90% for open bypass. Rates of long-term symptom relief are also superior for open bypass.

Oderich and colleagues have reported on their experience using balloon-expandable stent grafts (61 patients) and bare-metal balloon-expandable stents (164 patients) for CMI. Primary patency at 3 years was 92% for stent grafts compared with 72% for bare metal stents ($P = .003$). Patients receiving stent grafts were also more likely to remain free of symptoms (92% vs 58%) and less likely to be reintervened on (0% vs 8%). These outcomes are promising and emphasize that developments in endovascular technology (such as stent grafts) have the potential to further improve long-term outcomes associated with endovascular therapy.

DUPLEX SURVEILLANCE AFTER MESENTERIC REVASCULARIZATION

Patients who develop recurrent CMI symptoms because of endovascular or bypass stenosis can be rendered symptom free again by repeat visceral artery intervention. This is preferentially performed with an endovascular approach, whenever possible. Resolution of a treated visceral artery may also be preserved by routine ultrasound surveillance, which may detect vessel restenosis before the development of clinical symptoms. Among reported series of mesenteric

revascularization, clinical follow-up alone inaccurately predicted graft occlusion and was associated with a sensitivity as low as 33%.

Duplex ultrasound testing is a useful technique to evaluate functional patency after visceral artery bypass grafting procedures or endovascular stent angioplasty. Repair site stenosis can be identified reliably, which assists in decision making regarding the need for reintervention to treat or prevent recurrent gut ischemia. Visceral duplex testing of a bypass graft or stent angioplasty site that shows PSV greater than 300 cm/s with EDV greater than 50 to 70 cm/s or a damped velocity spectra within a bypass graft and low PSV (<40 cm/s) should be considered for interrogation by visceral angiography to confirm or exclude severe stenosis (>70%).

The management of asymptomatic high-grade stenosis after both open and endovascular repair remains undefined. Fortunately, the embolic potential of symptomatic hyperplasia associated with surgical or endovascular reintervention is uncommon. Progressive stenosis of the original atherosclerotic lesion or restenosis/occlusion of the visceral artery remains the most common cause of recurrent symptoms among treated patients. Because recurrent symptoms are associated with intervention failure and increase the risk for gut necrosis, a more aggressive approach toward treating endovascular stent stenosis is appropriate in these patients. In asymptomatic patients, intervention should be limited to vessels showing more than 70% stenosis at the repair site as shown by duplex ultrasound, followed by confirmatory angiographic imaging with pressure gradient measurement, as necessary. Reintervention using endovascular therapy is usually successful, reduces PSV at the stenotic site, and is associated with continued relief of gut ischemia.

Suggested Readings

Abuhamad AS, Monga AK, Stone PA, et al. Duplex velocity criteria for stenosis after renovisceral vascular artery stenosis in an ideal stenosis. J Vasc Surg 2001;33:736–738.

Björck M, Koelemay M, Acosta S, et al. Editor's choice—management of the diseases of mesenteric arteries and veins: clinical practice guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;53(4):460–510.

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Hemodialysis Access Surgery

Bonnie E. Lonze, MD, PhD, and Thomas Ryan Ryder, MD

For the past decade, the overall prevalence of end-stage renal disease in the United States has increased at a rate of approximately 2% per year. An estimated 30 million Americans have a diagnosis of chronic kidney disease. In 2015, 124,111 new patients initiated dialysis treatment, bringing the total number of Americans living on dialysis to almost 500,000. For the vast majority of these patients, hemodialysis is the preferred mode of renal replacement therapy. The ability to deliver this lifesaving therapy is dependent on the creation and maintenance of adequate vascular access.

HISTORICAL NOTES

Over the course of approximately a century, end-stage renal failure went from a universally fatal illness to a tolerable chronic illness with reasonable long-term survival. In the United States a series of events involving science, medicine, and politics led to universally available and undeniable renal replacement therapy.

The concept of dialysis was introduced by the Scottish physical chemist Thomas Graham, whose experiments in the 1850s characterized the movement of water across semipermeable membranes and led to an understanding of the principle of osmosis. It was in fact Graham himself who first applied the term dialysis to describe the phenomenon of colloidal osmotic gradients to move solutes across a membrane separating two solutions.

Fifty years later, John Jacob Abel, a pharmacologist at the Johns Hopkins Hospital, first explored the application of dialysis to a clinical setting. Abel, working with Leonard Rowntree and B.B. Turner, described in 1914 the construction of the "artificial kidney," an apparatus that consisted of 37 tubes connected in series and encased in a large glass container filled with a dialysate solution. Using hirudin as an anticoagulant to prevent clotting in the tubes, they tested the invention on anesthetized animals. Using arterial cannulae to channel blood into the narrow tubes of the circuit, they demonstrated that animal blood could be dialyzed.

The first successful human use of dialysis is credited to Willem Kolff, a Dutch physician who had studied Abel's work. During the German occupation of the Netherlands in the 1940s, he designed and built, mainly from household items, a dialysis device he named the "rotating drum kidney." This device consisted of a large drum, covered with thin tubing that sat partly submerged in a large tank of dialysate. Blood passed through the series of tubes affixed to the drum that then rotated within the tank, facilitating dialysis of the blood across the tubing. Kolff's first surviving patient was a 67 year old woman with acute renal failure caused by sepsis. She endured an 11 hour dialysis session in which a measured 48 grams of urea were removed. Kolff foresaw many possible applications of hemodialysis and was astutely aware that its implementation for chronic renal failure would require durable vascular access.

The first solution to the access problem was developed by Belding Scribner at the University of Washington. Having been introduced to a newly engineered material called polytetrafluoroethylene or PTFE (Teflon) and recognizing its inert and noninflammatory properties, he conceived of using a U shaped Teflon tube to create an external arteriovenous connection that could be accessed for dialysis. On March 9, 1960, the first dialysis by way of the Scribner shunt was performed. Although this did establish an important proof of principle, Scribner shunts had unacceptably high rates of infection, thrombosis, and hemorrhage, and their functional patency rarely exceeded a few months. Seeking to improve on this, James Cimino and Michael Brescia invented the radiocephalic arteriovenous fistula and described the technique in their landmark *New England Journal of Medicine* article in 1966.

With safe and reliable vascular access technically feasible, widespread availability of hemodialysis had a final major obstacle to overcome: cost. Lobbying at local and national levels resulted in government funding for improvements in dialysis machine technology and the construction of more dialysis units. However, because of its cost, most people believed that, without federal government support, access would remain limited to the privileged few. In November 1971, a chronic dialysis patient named Shep Glazer and his nephrologist demonstrated a dialysis session before a congressional committee in Washington, DC. This had a tremendous impact on the committee

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members, which led congress to act. In October of 1972, President Nixon signed into law a bill authorizing Medicare coverage of dialysis.

In this chapter, we review and summarize our current practices for the evaluation, placement, and maintenance of hemodialysis access. In 2002, the Society for Vascular Surgery and the American Association for Vascular Surgery published recommendations for standardized reporting of dialysis access techniques, procedures, and configurations. For purposes of brevity, however, we preferentially use common nomenclature throughout the following discussion.

NATIONAL PRACTICES AND GUIDELINES

In 2009, the End-Stage Renal Disease Program alone consumed 6% of the overall Medicare budget—a total of $29 billion—and this staggering sum is rising annually. As health care cost containment has become a major national focus, there has been great motivation within the dialysis community to identify best practices that minimize costs and maximize patient benefit. Until recently, most new accesses placed had been prosthetic grafts. Certainly, some of these grafts were placed out of necessity. Unfortunately, convenience, lack of surgeon experience, and the higher reimbursement rate for prosthetic grafts undoubtedly played a role in their preferential placement. Specifically, in 1990 ePTFE grafts were placed twice as frequently as autogenous arteriovenous fistulas. According to the Centers for Disease Control and Prevention, in 1995 just over 20% of patients on dialysis were using autogenous access. Clear evidence has since emerged that autogenous fistulas are associated both with better outcomes and lower costs, and this has drawn attention to the unacceptably low proportion of patients in the United States undergoing dialysis through autogenous access. The disproportionate and often inappropriate use of prosthetic grafts fueled the National Kidney Foundation's Kidney Disease Outcomes and Quality Initiative (KDOQI). This is a comprehensive analysis of the best practices with regard to the management of end-stage renal disease. An offspring of KDOQI was the Centers for Medicare and Medicaid Services' Fistula First Breakthrough Initiative, which aimed to promote awareness among patients and physicians of the superiority of autogenous access. More recently there has been pushback from some in the vascular community who believe that there are certain patients who should preferentially have prosthetic access. This has been rebranded as Fistula First Catheter Last. Although we agree in principal, the best access remains a good arteriovenous fistula. The current national goal is to place autogenous access in at least 66% of new dialysis patients, and the effort seems to be working. In 2015 according to the United States Renal Data System's (USRDS) annual report there were nearly twice as many autogenous fistulas placed than prosthetic grafts.

Currently, the three main avenues for hemodialysis access are tunneled central venous catheters, arteriovenous prosthetic grafts, and autogenous arteriovenous fistulas. Clearly, the worst outcomes are associated with catheter usage, and therefore every effort should be made to avoid them. To this end, current KDOQI guidelines stipulate that all patients should be referred to a surgeon for the placement of autogenous access when they reach stage 4 chronic kidney disease (glomerular filtration rate <30). This allows sufficient time for fistula placement and maturation before the commencement of dialysis. The caveat to this scenario is that not all patients have a suitable vein for autogenous fistula creation. Only those with suitable veins should have them access placed far in advance of the initiation of dialysis, and this access should be an autogenous fistula. The most common cause of prosthetic graft failure is stenosis at the venous anastomosis due to neointimal hyperplasia. This worsens with time, so if a prosthetic graft is required, it should only be placed when dialysis is imminent or has already begun.

The options for dialysis access are frequently impacted by treatment options instituted years before the patient reaches end-stage renal disease. Patients and physicians alike must be aware that for those with any degree of renal dysfunction, subclavian vein central lines and ports, PICC (peripherally inserted central catheter) lines, and even forearm intravenous catheters (sparing only an distal cephalic vein) should be avoided whenever possible. PICC lines are the curse of the dialysis access surgeon. Not only do they frequently ruin a typical good access vein, the basilic vein, but they are also associated with rates of central venous stenosis or thrombosis estimated up to 65%, which renders the arm unsuitable for the most common and durable access types.

FIG. 1 Mature radiocephalic arteriovenous fistula 6 weeks after surgery.

The algorithm for selecting which fistula to place is fairly straightforward. One should begin distally and work proximally in the nondominant arm: radiocephalic (Fig. 1), brachiocephalic, then upper arm basilic transposition. We believe that the benefits of autogenous access are so great that many exceptions to the standard algorithm are permitted. Although use of the nondominant arm is preferable, frequently the veins are better in the more active dominant arm. In this circumstance, the dominant arm is used without hesitation for fistula placement. If a patient has no suitable vein for autogenous access, then a prosthetic graft may be used. A good prosthetic graft is better than a bad vein. Although prosthetic grafts may be placed between any artery with sufficient flow and any suitable vein with unobstructed outflow, it is best to begin as far distally as possible and reserve more proximal sites for the future. For example, we would consider these configurations in the following order: distal brachial artery to distal brachial vein forearm loop, distal brachial artery to proximal brachial vein or distal axillary vein straight graft, and, finally, proximal brachial artery to proximal brachial vein or distal axillary vein upper arm loop. With education and careful attention to best practices, autogenous access can be preferentially placed, and the use of prosthetic grafts can and should be limited.

PREOPERATIVE EVALUATION

End-stage renal disease is rarely an entity that exists in isolation, and dialysis patients have a higher incidence of significant comorbid conditions. According to the USRDS, among the cohort of new dialysis patients who were registered in 2006 to 2008, 84% had hypertension, 31% had coronary artery disease, 32% had congestive heart failure, 25% had insulin dependent diabetes, 14% had peripheral vascular disease, 9% had a history of previous stroke or transient ischemic attack, and 7% were unable to ambulate. Briefly stated, these patients are poor operative candidates. The preoperative evaluation involves assessing cardiopulmonary reserve and selecting the arm/limb with the least risk. At the current time most of our arm accesses are placed using supraclavicular or infraclavicular nerve blocks.

Aside from a history of events relevant to cardiopulmonary status and prior dialysis access attempts, it is imperative to inquire as to all previous venous access procedures including dialysis catheters, subclavian lines or ports, PICC lines, pacemakers, and defibrillators. Prior trauma to the upper extremities or clavicles should be noted. The physical examination should include auscultation of the heart

and lungs and an evaluation of the extremities to determine the patient's best option for dialysis access. The radial, ulnar, and brachial pulses should be palpated bilaterally. Uncommonly a radial pulse is present with an occluded brachial artery. An Allen's test to confirm adequacy of ulnar flow to the hand should be performed if a radiocephalic fistula is contemplated. It cannot be overemphasized that the preoperative physical examination is incomplete unless a venous tourniquet is used to assess the superficial veins.

Duplex ultrasound–based vein mapping before dialysis access surgery was essentially mandated by the KDOQI guidelines. We strongly disagree with this blanket recommendation. Although vein mapping at times may be helpful for operative planning, it is frequently unnecessary, adds cost, and may not always give valid information. In patients already on dialysis via a catheter we rarely request a vein map. If no suitable vein is found at surgery (see operative techniques below) then the patient will require a prosthetic graft. In patients referred before the initiation of dialysis, vein mapping may be helpful in those who are obese, intravenous drug abusers, or have had prior PICC lines. It may also be helpful in patients with normal sized arms where neither an adequate basilic nor cephalic vein is palpable with a tourniquet in place. Last, with the ubiquity of portable ultrasound machines, surgeon performed vein mapping on the OR table after nerve block anesthesia is in place frequently reveals usable veins that were deemed inadequate on preoperative imaging. This has become our routine.

Venography is an important component of successful dialysis access surgery. Its primary use is not to roadmap the arm veins but rather to confirm central vein patency. Our practice is to use it liberally in any patient with a history of arm swelling or prior central venous cannulation on the side of proposed access. In profoundly ill patients carbon dioxide may be used as a contrast agent, thereby avoiding the risks of iodinated contrast induced nephropathy. If a hybrid endovascular operative suite is available, the venogram may be obtained at the beginning of the access case, allowing for a combined procedure that is more convenient for the patient.

Last, for the safety of the surgical team, any patient with a history of intravenous drug use should have a plain radiograph of the upper extremity to evaluate for the presence of foreign bodies.

Prior to surgery, standard blood chemistries and a complete blood count are all that are necessary. The surgeon can assume that uremic platelet dysfunction will always be present, and we have found no utility in checking bleeding times pre operatively. Uncommonly arginine vasopressin at a dose of 0.3 μg/kg will be needed during surgery to control oozing. Additionally, aspirin use does not seem to impact bleeding significantly, and, considering the cardiovascular risk profile of these patients, we routinely administer a dose of 81 mg in the preoperative area. Clopidogrel does seem to increase oozing in some patients, so this should be held for 5 to 7 days, unless the patient has recently undergone coronary artery stenting. Many patients are also on warfarin. In general we do not advocate holding warfarin and feel comfortable proceeding with access surgery with an international normalized ratio up to 2.5.

OPERATIVE TECHNIQUES

The best option for anesthesia depends on the patient's comorbid conditions, the anesthesiologist, and the proposed surgery. Although local anesthesia is a viable option for many patients, it works best for patients undergoing radiocephalic or nontransposed brachiocephalic fistulas. Although we have used it successfully for upper arm basilic transpositions, it tends to be somewhat less than ideal for both patient and surgeon due to the relatively large area that must be anesthetized. Over the last several years we have gone almost exclusively to supraclavicular or infraclavicular regional nerve blocks. The blocks are placed in the preoperative area by a dedicated block team while the preceding case is underway. This helps to maximize efficiency and shorten turnover time. If the skin incision approaches the deltopectoral groove or the axilla, supplementation of the regional block with local anesthetic may be necessary particularly with an infraclavicular block. Because of this we are using supraclavicular blocks more often.

Autogenous Arm Fistulas

The patient is positioned supine with the shoulder of the operative side near the edge of the bed. The arm board should be positioned such that the arm rests in the center of the board. A standard skin preparation including the shoulder and axilla is performed. If available, an arm board drape is most convenient otherwise an extremity drape will suffice.

Radiocephalic Fistula

A 3- to 4-cm incision is placed just proximal to the wrist along the lateral or radial aspect of the arm. Once the skin is incised, the surgeon and assistant both lift the skin with Adson forceps facilitating easy identification of the cephalic vein after some gentle blunt dissection. The vein is encircled with a vessel loop and then sharply dissected out, tying all branches with 4-0 or 5-0 ties. The radial artery is dissected out circumferentially in a standard fashion and controlled with vessel loops. Any side branches are tied but not divided, which helps to maintain its orientation. The cephalic vein is divided distally, gently dilated with sequential coronary dilators, and then flushed with heparinized saline solution. After flushing the radial artery, a spatulated end-to-side anastomosis is performed using a 6.0 or 7.0 polypropylene suture. Any large proximal vein branches are ligated through separate 1-cm incisions. Closure consists of 3-0 interrupted absorbable dermal sutures and a 4-0 running absorbable subcuticular suture. On occasion the vein is so superficial that a very short skin line incision can be made over the snuffbox and the anastomosis done there just as described above. If a snuffbox anastomosis is used, then we usually ligate any large distal forearm venous branches to enhance maturation of the cephalic vein.

Upper Arm Fistula

If there is a proximally good cephalic vein, then a transverse incision is made in the antecubital crease (Fig. 2A), and the cephalic vein is identified (Fig. 2B). If of suitable size it is dissected out to its confluence with the median cubital vein, ligated distally, and divided. Sequential coronary dilators are gently passed cephalad and should easily pass if there is no intraluminal scarring. Although a sufficient length of vein can be mobilized at this point to easily reach the brachial artery, we frequently convert the incision into a hockey stick shaped incision (with the handle of the stick along the cephalic vein, Fig. 2C) and mobilize 10 to 15 cm or more of the vein (Fig. 2D and E). Not only does this allow ligation of the accessory cephalic vein and other small branches, it also allows superficial tunneling of the vein (Fig. 2F), which is necessary in all but the thinnest of arms. With the vein transposed, accessing the fistula can be performed earlier (as soon as 4 weeks depending on vein size), easier, and more commonly enabling earlier removal of dialysis catheters. Dissection of the distal brachial artery through the medial aspect of the antecubital incision is done in a standard fashion with control obtained with vessel loops. If the brachial artery appears smaller than expected, the patient most likely has a high brachial bifurcation. In these cases, the more suitable donor artery almost always is the deeper of the two vessels and should be evaluated before proceeding with the anastomosis. The vein is tunneled just beneath the skin making sure that there is no kink or twist at the most proximal site of mobilization (Fig. 2G). Once an arteriotomy is made and the artery flushed with heparinized saline solution, the vessel loops are replaced with baby bulldog clamps. This eliminates any vessel stretching and makes the end-to-side anastomosis easier to perform. Closure consists of 5-0 absorbable suture to the subcutaneous tissue and 5-0 nylon vertical mattress skin sutures (Fig. 2H). In our experience, subcuticular closures in the upper arm have been associated with postoperative wound problems

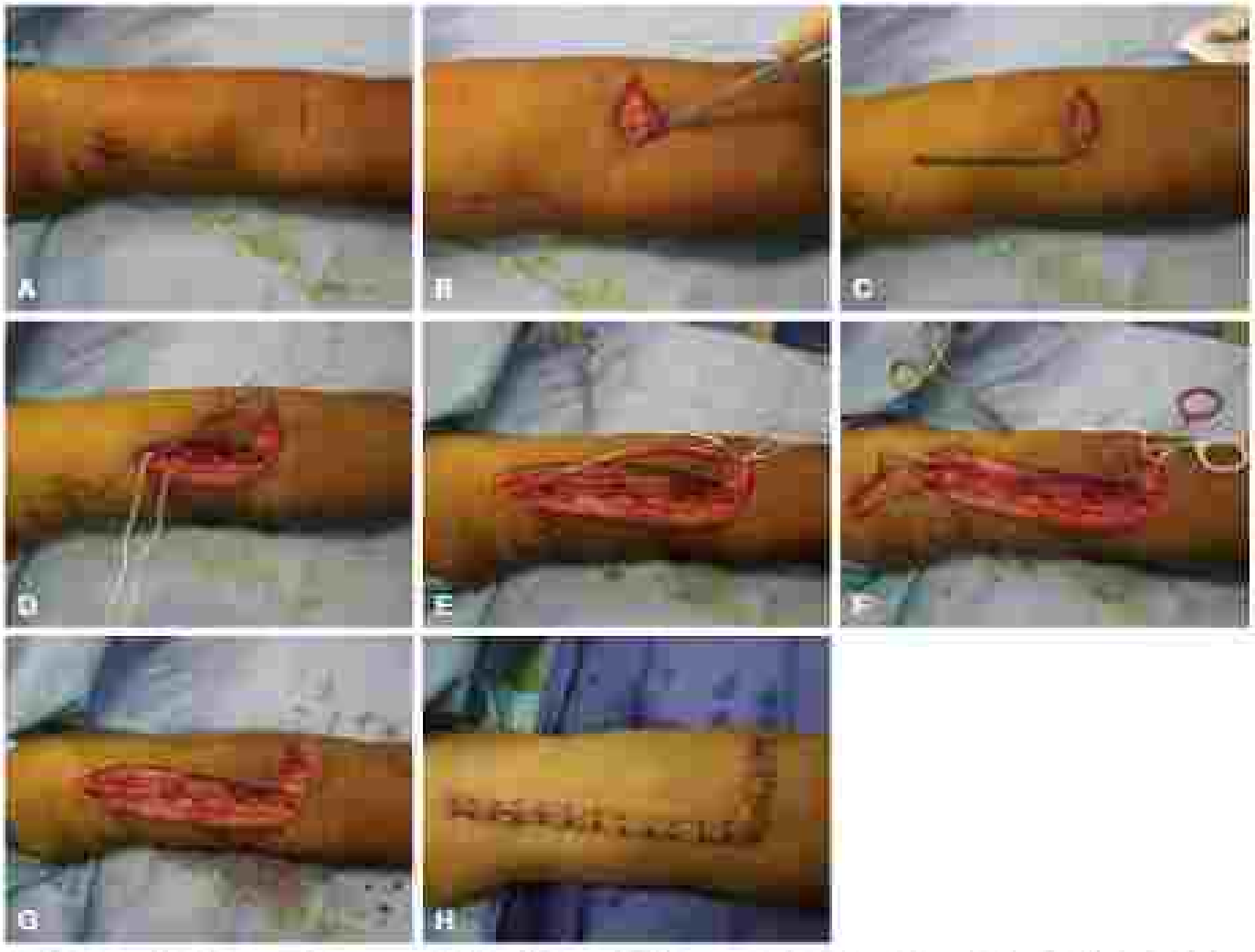

FIG. 1 Brachiocephalic arteriovenous fistula creation. (A) Anecubital incision. (B) Identification of cephalic vein in anecubital fossa. (C) Hockey-stick incision. (D) Proximal dissection of cephalic vein. (E) Ligation of cephalic vein branches, dissection of brachial artery in anecubital fossa. (F) Superficial tunneling of mobilized cephalic vein. (G) Completed arteriovenous anastomosis. (H) Closure of skin with vertical mattress nylon sutures.

much more frequently than with interrupted nylon closures. In addition, patients are much more apt to keep their follow-up appointments if they have sutures that need to be removed. If the cephalic vein is not of adequate size or quality, then the median cubital vein is identified near the medial aspect of the incision. If the median cubital vein is adequate, it is ligated distally, divided, and flushed with heparinized saline solution. We then extend the medial end of our skin incision in a hockey-stick fashion along the medial aspect of the arm nearly to the axilla. The vein is dissected circumferentially over its course toward the axilla as it joins the basilic vein, which subsequently joins the proximal brachial vein. If the median cubital vein is not adequate, then the basilic vein is used. In this instance we place two surgical towels under the upper arm to improve positioning and then make a new incision just anterior to the medial epicondyle of the humerus. Once the basilic vein is identified and found to be of appropriate size and quality, the incision is extended proximal and distally until enough vein for a transposition has been exposed. The brachial artery is then dissected out in the antecubital fossa either through a separate incision or through the medial aspect of the antecubital incision if that incision had already been made to inspect the cephalic vein. The vein is then tunneled and the anastomosis prepared and performed as described above. The fascia and subcutaneous layers are reapproximated with running 3-0 absorbable suture. The skin is closed with interrupted 3-0 nylon vertical mattress sutures. At the end of the case there should be a palpable thrill in the fistula. If there not), then there is a technical problem, and the incision should be reopened. Of note, if intraoperative vein mapping is used, then the initial incision should be over the most suitable vein as described above.

Prosthetic Arteriovenous Grafts

If there is no suitable vein then a prosthetic graft must be placed. Although the most commonly used graft is 6-mm ePTFE, bovine carotid artery, bovine mesenteric vein, and polyurethane urea (Vectra) grafts may also be used. A transverse incision is made over the brachial artery in the antecubital fossa. The brachial artery and vein (if at least 5 mm in diameter) are isolated and controlled with vessel loops. The vein should be generously dissected out to allow a long venous anastomosis. A second smaller counterincision is made on the lateral volar surface of the mid forearm on the radial side. Placement of the counterincision in this fashion draws the graft toward the radial aspect of the forearm, and this allows the patient's arm to be in a comfortable position during a dialysis session. The venous anastomosis is performed first (when using ePTFE, however, if using a biologic graft, the arterial anastomosis is performed first), particularly if the graft has a pretunneled flared end. The graft is tunneled in a gentle arc in the counterincision and then back to the anticubital fossa. Tunneling is best accomplished with a Kelly-Wick tunneler

(IMPBA), although an aortic clamp may be used. The arterial anastomosis is then performed, and the incisions are closed. If the brachial vein is too small at the antecubital fossa then a second incision is made on the proximal medial aspect of the upper arm and the proximal brachial or distal axillary vein is used for the venous outflow. Whereas this describes the two most common graft configurations, in reality any suitable artery and vein may be used. We strongly believe in limbs first and therefore do not agree with the use of forearm grafts to help mature upper arm cephalic or basilic veins.

OPTIONS FOR NONCONVENTIONAL ACCESSES

Not uncommonly patients present for dialysis access after many months of catheter usage and have developed upper extremity central vein occlusion or stenosis (Fig. 3). Placing brachial artery–based access ipsilateral to this problem will lead to significant arm edema and an unusable access. Long standing dialysis patients with central vein stenosis or thromboses pose a particular challenge. Options must be carefully considered in these cases, and there is no room for error. Failure to establish access can quickly turn into a life threatening situation.

HeRO

The HeRO graft (hemodialysis reliable outflow) is an option for upper extremity access in the setting of central vein stenosis that uses the right atrium for venous outflow. The HeRO consists of a standard ePTFE graft and a reinforced single lumen venous outflow catheter. This device requires that wire access across the stenotic segment of central vein can be achieved. Once stiff guidewire access to the right atrium is obtained, then the venous outflow catheter is placed over the wire and positioned in the right atrium. The other end of the catheter is then tunneled laterally in the deltopectoral groove and attached to the standard ePTFE graft via a manufacturer supplied alloy connector. The ePTFE graft is then tunneled like any other graft and the opposite end is sewn to the brachial artery in the standard fashion. The HeRO can also be used to create unimpeded venous outflow to salvage a functioning autogenous arm access in the event that a central vein stenosis or occlusion has developed. After the HeRO catheter has been placed and tunneled to the upper arm, it is connected to the venous end of the fistula using a small cuff of the ePTFE with the attached alloy connector. Last, one can modify the HeRO by replacing the graft with an early puncture graft (Access or Thru-Vent) and then attaching it to the HeRO catheter using the recently available Super HeRO adapter. This allows one to gain vein access to the right atrium using the patient's dialysis catheter. Obviously, there is no catheter for postoperative dialysis, so these patients should be admitted until there is confirmation that dialysis can performed using the early puncture graft. Although the HeRO obviates the need to move the access to the leg, it comes with all the problems that are associated with nonautogenous access, including graft infection and thrombosis. Long term warfarin anticoagulation should be strongly considered to all patients being dialyzed via a HeRO.

Low-Volume Access

Radial or ulnar artery–based accesses have lower volume flows than those based off of the brachial artery. Not uncommonly we have seen patients with failed upper arm grafts and ipsilateral central vein occlusion who mysteriously have a usable cephalic or basilic vein. Using forearm artery inflow creates a usable but low volume flow access and generally doesn't lead to significant arm swelling in spite of the central venous issues. Admittedly this doesn't always work, and we have had to ligate the accesses of several patients because of massive arm swelling.

Leg Access

In general, the leg is only used for access once all upper extremity options have been exhausted. However, young women and pumpkin may prefer a primary thigh access, the former to avoid the obvious arm scarring and the latter because they depend on their arms for mobility. The most common leg access is a thigh loop of ePTFE, although autogenous options exist including saphenous and femoral vein fistulas. Although we have extensive experience using the femoral vein and find it particularly useful when translocated to the upper extremity for home hemodialysis patients, its use for a thigh fistula should be carefully planned and works best in thin legs. The saphenous vein may also be used as a thigh fistula (tunneled anteriorly as a straight fistula and anastomosed to the distal superficial femoral artery), but if the vein is not generous in size (at least 5 mm) failure to mature into a useful access is common. For a prosthetic thigh graft, an oblique skin line incision is made just distal to the groin crease and either the deep femoral or proximal superficial femoral artery is used for arterial inflow. Through the medial aspect of that incision, the proximal saphenous vein or saphenofemoral junction is preferentially used for venous outflow. The proximal femoral vein may be used but the dissection is somewhat more difficult.

COMPLICATIONS AND MANAGEMENT

Infection is the most frequent complication of hemodialysis access and is a major cause of morbidity and mortality in the dialysis population (Table 1). Up to 20% of all deaths in dialysis patients are due to infections, and most come from vascular access sites. Compared with autogenous fistulas, the relative risk of infection related death is 10 times greater in those dialyzing through catheters and 1.3 times

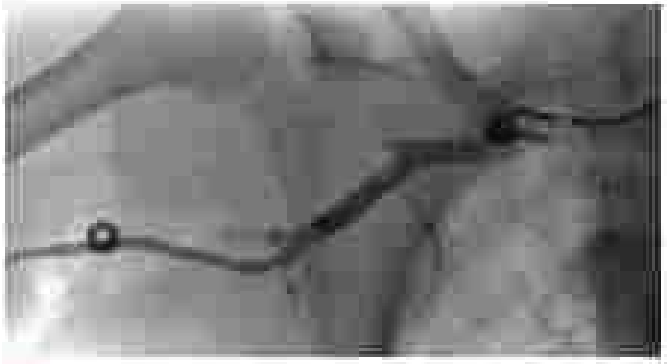

FIG. 3 Superior vena cava occlusion as demonstrated by upper extremity venogram in a dialysis patient with history of multiple prior dialysis catheters and failed upper extremity accesses.

TABLE 1 Relative Frequencies of Dialysis Access–Derived Infections in a Single-Center Study of 1574 Consecutive Dialysis Access Surgery Patients

Overall incidence of infection, n (%)	132 (8.5%)
Category of infection, n (%)	
Dialysis center derived infection (>30 days after surgery)	66 (50%)
Spontaneous infection in nonfunctional graft	30 (22.7%)
Infection in remaining stump of partly excised graft	22 (16.7%)
Operative site infection (<30 days after surgery)	6 (4.5%)
Postinterventional radiology thrombectomy	8 (6.0%)

greater in those draining through prosthetic grafts. The cumulative probability of developing a catheter-related infection is greater than 50% after 2 months of dialysis through a catheter. Diabetes and human immunodeficiency virus are also independent risk factors for greater infection rates among all access types. Staphylococcal species are the most frequently isolated organisms. Access-derived infections other than 5% rate for arm access infections and 15% for leg access) lead to metastatic infectious complications including bacterial endocarditis, osteomyelitis, septic emboli, and septic arthritis. For catheter-related bacteremia, management consists of culture-directed parenteral antibiotics and removal or exchange of the infected catheter. For infected ePTFE grafts, management must be guided by an attempt to balance the benefits of preserving a functioning access with the severity of infection. Some localized infections can be successfully treated with aggressive intravenous antibiotic therapy combined with resection and replacement through clean tissue of a portion of the graft, though recurrent infection is not uncommon. There is a lower recurrent infection rate when the entirety of the graft is removed, but the operations tend to be more difficult and access is lost.

The risk of access failure due to thrombosis is more common in prosthetic grafts than in autogenous fistulas. Early failure is generally due to technical factors but can also be related to hypercoagulability, low flow states, or use of inadequate vein. In mature accesses most problems will be detected by the dialysis unit. High venous pressures, poor arterial inflow, recirculation, and diminishing effectiveness of the dialysis all indicate access problems. The anatomic location of the problem usually can be ascertained by physical examination. The lack of bruit and thrill indicates thrombosis. A weak thrill or bruit suggests inflow problems. Pulsatility in a fistula generally indicates an outflow venous problem. Early intervention can often salvage an otherwise threatened fistula or graft. A duplex scan can further pinpoint the area of the problem but is frequently unnecessary. In general, the diagnostic test of choice is fistulography, at which time therapeutic interventions including thrombectomy, angioplasty, and stenting can be carried out. Occasionally open revision is necessary with many options available to improve either arterial inflow or to relieve venous outflow obstructions.

Almost all arm accesses create a steal syndrome, but significant steal occurs less than 15% of the time, with brachial artery–based accesses presenting the highest risk. Loss of a palpable distal pulse at the time of fistula creation indicates that a significant steal syndrome could develop. Manual compression of the fistula should result in restoration of the distal pulse. Options for improving distal perfusion include ligation, plication, banding, proximalization or distalization of the arterial inflow, and the DRIL (distal revascularization with interval ligation) procedure. The DRIL has the benefit of leaving the functioning fistula undisturbed and alleviates the physiologic pathway for the steal and restores downstream perfusion. We do not routinely perform arm angiography before performing a DRIL, but, if the patient has demonstrable atherosclerotic disease in other areas, then this should be considered. Lastly, although the use of saphenous vein for the bypass portion of the DRIL is standard, we have frequently used the fistula vein without consequence.

Other complications that occur with varying frequencies and degrees of morbidity include edema due to venous hypertension, seromas, wound problems, and carpal tunnel syndrome. Aneurysmal dilation of mature grafts or fistulas generally does not need to be addressed with surgery unless there is overlying skin breakdown or impending breakdown as demonstrated by thin, stretched, shiny skin. In general, having a low threshold to investigate and intervene on a fistula that is not performing optimally will minimize the need for repeated access surgeries.

CONCLUSIONS

- Assume dialysis is forever, so when performing access surgery, do not jeopardize future options.
- Try to avoid all catheters and if possible prosthetic materials; that is, use fistula first.
- Fistula dysfunction mandates prompt investigation and intervention to maximize chances of fistula salvage.
- Dialysis access performed properly will be rewarding for the patient, as well as the surgeon.

SUGGESTED READINGS

Fistula First National Vascular Access Improvement Initiative. www.fistulafirst.org.

Gutchelf CW, Porter SR. History of the science of dialysis. Am J Nephrol 1997;17:289–298.

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VENOUS THROMBOEMBOLISM: PREVENTION, DIAGNOSIS, AND TREATMENT

Jonathan A. Cardella, MSc, MD, FRCS, and Rowena S. Amarasekara, MD, MSc, FACS

Venous thromboembolism (VTE) is a condition in which thrombi form inappropriately in the venous circulation. VTE has been commonly been subcategorized to comprise deep venous thrombosis (DVT) and pulmonary embolism (PE) and has been recognized as a significant health issue representing the third leading vascular-based diagnosis after myocardial infarction and stroke. Despite significant improvement in prophylaxis and treatment of VTE, the incidence has not changed over the past 3 decades. The cost to the US healthcare system for acute treatment of venous thrombosis is in the billions of dollars per year. The sequelae of postthrombotic syndrome and chronic thromboembolic pulmonary hypertension are sources of morbidity, loss of functional status, and diminished quality of life. Therefore, identifying the patients at risk for VTE, strategies to mitigate VTE, and prompt diagnosis of DVT/PE are important considerations in the care of the surgical patient. This issue reached national importance in the late 2000s, which resulted in the US Surgeon General's Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism. This initiative, along with the Agency for Healthcare Research and Quality, deemed VTE prevention as an important priority to improve patient safety.

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VENOUS THROMBOEMBOLISM: PREVENTION, DIAGNOSIS, AND TREATMENT

Jonathan A. Cardella, MSc, MD, FRCSC, and Rwamu S. Amankwah, MD, MSc, FACS

Venous thromboembolism (VTE) is a condition in which thrombi form inappropriately in the venous circulation. VTE has been commonly been subcategorized to comprise deep venous thrombosis (DVT) and pulmonary embolism (PE) and has been recognized as a significant health issue representing the third leading vascular-based diagnosis after myocardial infarction and stroke. Despite significant improvement in prophylaxis and treatment of VTE, the incidence has not changed over the past 3 decades. The cost to the US healthcare system for acute treatment of venous thrombosis is in the billions of dollars per year. The sequelae of postthrombotic syndrome and chronic thromboembolic pulmonary hypertension are sources of morbidity, loss of functional status, and diminished quality of life. Therefore, identifying the patients at risk for VTE, strategies to mitigate VTE, and prompt diagnosis of DVT/PE are important considerations in the care of the surgical patient. This issue reached national importance in the late 2000s, which resulted in the US Surgeon General's Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism. This initiative, along with the Agency for Healthcare Research and Quality, defined VTE prevention as an important priority to improve patient safety.

EPIDEMIOLOGY OF VTE

VTE represents a significant impact on US healthcare with respect to prevention, treatment, and expenditure. Clinically, patients with VTE may present with DVT, PE, or both. Roughly two-thirds of patients will be treated for DVT and one-third for PE, which is the principal cause of mortality associated with VTE. Sudden death represents the first symptom in 25% of individuals who have a PE. VTE is recognized as a complex (multifactorial) disease involving both environmental exposures (clinical risk factors), genetic, and environmental interactions.

Incidence

Presently, there is no national surveillance program for VTE; therefore, the calculated prevalence and incidence is theoretically underestimated. Additionally, the rates of VTE for minority populations is unknown and unaccounted for in current estimates. Information from clinical organizational databases as well as hospital and community-based studies estimate the overall incidence in the United States to be approximately 1 to 2 per 1000 of the population, or 300,000 to 600,000 cases.

When examining the incidence by age, race, and gender, there are differences (Table 1). The overall rate of VTE is highest in African Americans and lowest in Asians. VTE is predominantly a disease of older age. In the absence of thrombophilia or a central venous catheter, it is rare prior to late adolescence. The occurrence of VTE is increased in both men and women with age; however, age adjusted incidence is higher for men (120 per 100,000) than women (108 per 100,000) although, women have a higher incidence during their childbearing years. PE accounts for an increasing proportion of VTE with increasing age for both sexes. The incidence of idiopathic VTE are estimated at 25% to 50%.

Recurrence

Although early diagnosis and the individualized course of anticoagulation (range 3–6 months) for VTE in the surgical patient setting is decreasing the immediate morbidity and mortality, about 30% of patients develop recurrence within the next 10 years. The highest risk occurs within the first 6 to 12 months with the risk decreasing successively but never falling to zero. Utilization of secondary prophylaxis (beyond the 3- to 6-month period) is beneficial in preventing recurrence; however, the duration of the acute management does not affect the rate of recurrence after 3 months of adequate anticoagulation has been fulfilled, which suggests that VTE is a chronic disease with episodic recurrence.

There are several independent predictors for recurrence (Box 1). Among patients with cancer, the risk of recurrence is increased in those individuals with lung, gastrointestinal, or genitourinary disease. Men have been reported to have a higher risk of recurrent VTE than women. When adjusting for sex specific risk factors gender is not an independent predictor for recurrence. Persistent elevated D-dimer in patients with idiopathic VTE and potentially residual vein thrombosis have also been described as a risk factor for relapse, therefore, secondary chemoprophylaxis should be considered in this cohort of individuals.

The reported risk of recurrence by incident event type, PE or DVT alone, varies in the literature. Patients with recurrence are more likely to be afflicted by the same event type as the primary incident event. Therefore, DVT begets DVT and PE begets PE. Provided with the information that the 7 day survival is greater for DVT (96%) than for PE (71%), secondary prophylaxis should be continued beyond the standard 3- to 6-month regimen for patients with PE although consideration of patient and thrombosis factors should be considered. This should be particularly considered in those patients with PE and decreased cardiopulmonary reserve because these individuals are more likely to die from a recurrent PE.

Survival, Morbidity, and Mortality

Our ability to diagnose DVT and PE has improved tremendously over the past several decades; however, the incidence of VTE and the long term survival after VTE has not changed despite aggressive treatment protocols. The mortality rate in the United States has been estimated between 100,000 and 180,000 deaths annually. The probability of early mortality within 1 month is approximately 6% in individuals with a DVT and 10% of those with a PE. The mortality rate for PE has been estimated to be 30% in investigations that included autopsy-based PE diagnosis, which demonstrates that many PE are not clinically recognized before death. Mortality rates are lower among patients with idiopathic venous thrombosis and higher among those whose thrombosis occurs in the setting of cancer. Other factors that predict reduced survival after VTE are increasing age, male gender, lower body mass index, confinement to a hospital or nursing home at the onset of VTE, congestive heart failure, chronic lung disease, and serious neurologic disease.

Morbidity such as postthrombotic syndrome (PTS), venous insufficiency, recurrent thromboembolic events, and chronic pulmonary hypertension are reported after the first episode of VTE. Thirty to 50% of patients with lower extremity DVT develop PTS and chronic

TABLE 1 Estimated Incidence of Venous Thromboembolism by Age, Race, and Gender

Characteristics	Annual Incidence per 1000
RACE/ETHNICITY	
Black	0.77–1.43
White	1–1.7
Hispanic	0.61
Asian	0.39
AGE (Y)	
<15	<0.5
15–44	1.09
45–79	1.02
>80	5–6
GENDER	
Male	1.3
Female	1.1
Overall	1–2

From Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public concern. Am J Prev Med. 2010;38(4Suppl):S495–501.

BOX 1 Predictors of Recurrence

- Increasing age
- Body mass index
- Neurologic disease with leg paresis
- Active cancer
- Lupus anticoagulant
- Antiphospholipid antibody
- Antithrombin deficiency
- Protein C and S deficiency
- Hyperhomocysteinemia
- Inflammatory bowel disease

venous insufficiency. These lifelong conditions are characterized by pain, swelling, skin necrosis, and ulceration. Quality of life (QOL) is adversely affect up to 4 months after DVT with further declining QOL in those individuals with PTS. Patients perceive the diagnosis of VTE as a reduction in their QOL, compounded with the potential morbidity and limitations placed by therapeutic anticoagulation are taken into consideration.

Risk Factors

The pathophysiology of VTE is based on the postulation, in the mid-nineteenth century by Rudolph Virchow, that thrombosis was the result of at least one of a triad of factors that comprise endothelial injury, hypercoagulability, and stasis of flow. This hypothesis has been validated by numerous studies, with greater than 90% of patients diagnosed with VTE having at least one of the three risk factors. It is clear that VTE is a multifactorial condition that involves inherited (genetic) and both continuous and transitory acquired risk factors (Table 2), which can be stratified, based on their risk (Table 3). Although not fully elucidated, a threshold seems to exist in the presence of one risk factor does not portend disease status; however, an interactive effect of several prothrombotic events can lead to clot formation. It is estimated that 10% of cases are idiopathic, with no acquired risk factor identified while in another 10% to 20% there is no identifiable acquired or inherited risk factor determined. This exposes our understanding that there are still undescribed inherited and/or acquired risk factors.

An impression exists that the risk factors for DVT and PE are quite different from risk factors for coronary artery disease. There is evidence to demonstrate that VTE is a cardiovascular disease and that risk factors for arterial and venous thrombosis may be similar. This was outlined in a study that demonstrated an association between asymptomatic carotid disease and DVT development. Furthermore, it has been determined that there is a fivefold increase in subsequent myocardial infarction in the decade following an unprovoked DVT when compared with controlled subjects. Although there appears to be a relationship between arterial disease and venous thrombosis, a cause and effect remains intangible. There have been suggestions that some cardiovascular risks (obesity, hypertension, diabetes, high cholesterol, and smoking) that are modifiable may reduce the development of potential VTE in the future; however, this concept requires further corroboration and has been challenged. The risk factor that appears agreed on that can be modified is smoking.

Often when considering risk factors, the surgeon is focused on the hospitalized patient. The surgeon must keep in mind that three of four VTE events occur outside the hospital setting. There is an association between a hospital stay or surgical procedure within the preceding 90 days and development of an acute DVT and/or PE. A population-based cohort study in Olmsted County, Minnesota, found that the independent risk factors for VTE included: surgery, trauma, hospital stay, placement in a nursing home, and cancer. In the Worcester Venous Thromboembolism Study, three-quarters of the VTE events occurred after the period of hospitalization. During the preceding 3 months, 23% had undergone surgery and 36% had been hospitalized. Among these patients, two-thirds experienced VTE within 1 month of their hospital discharge and more than one half of these events occurred in individuals 65 years of age or older. There was also noted a significant increase in major bleeding episodes in this age group. Therefore, when abstracting risk factors for VTE, it is imperative that the surgeon consider the entire continuum of care and treat individuals accordingly.

TABLE 2 Risk Factors for Venous Thromboembolism

Genetic	Acquired	Transient/Acquired
Family history of thrombophilia	Advance age	Pregnancy
Factor V Leiden	Antiphospholipid antibodies	Oral contraceptives
Prothrombin G20210A	Cancer	Hormone therapy
Protein C deficiency	Chronic disease	Hospitalization
Protein S deficiency	Obesity	Surgery
Antithrombin deficiency		Trauma
Sickle cell trait		Immobilization

From Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public concern. Am J Prev Med. 2010;38(4S):S495–S501.

PREVENTION AND PROPHYLAXIS OF VTE

The initiative by the Agency for Healthcare Research and Quality, the American Public Health Association, the Centers for Disease Control and Prevention, the National Quality Forum, the Centers for Medicare and Medicaid Services, the US Congress, and the US Surgeon General were started to raise public awareness and improve patient safety and quality related to VTE. Despite these measures and acknowledgment that VTE prophylaxis is an important patient safety measure, adoption of this measure was initially inadequate. The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting study of more than 68,000 hospitalized patients in 32 countries noted only 58.2% of surgical patients and 39.5% medical patients received American College of Chest Physicians (ACCP) guideline–appropriate VTE

TABLE 3 Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

	DVT (%)		PE (%)	
Level of Risk	Calf	Proximal	Clinical	Fatal
Low risk: age <40 yr and uncomplicated surgery no risk factors	2	0.4	0.2	<0.01
Moderate risk: age >40 yr; minor, prolonged, or complicated surgery with risk factors	10–20	2–4	1–2	0.1–0.4
High risk: age 40–60 yr or >60 yr; major surgery additional risk factors (prior VTE, CA, hypercoagulability	20–40	4–8	2–4	0.4–1
Highest risk: Surgery in patient with multiple risk factors (i.e, prior VTE); hip, knee surgery, trauma	40–80	10–20	4–10	0.2–5

Modified from: Geerts WH, Graham ID, Tolli JA, et al. Prevention of venous thromboembolism. The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. 8th ed. American College of Chest Physicians evidence-based clinical practical guidelines. Chest. 2008;133(6):381S–453S.
CA, cancer; DVT, deep vein thrombosis; PE, pulmonary thromboembolism.

prophylaxis. A 2005 audit of the surgical services at Johns Hopkins found only 33% of 522 randomly selected patients were prescribed prophylaxis in line with ACCP guidelines. The steps in achieving VTE prevention requires attention to each stage of the process: (1) assessment of both VTE and bleeding risk, (2) selecting risk appropriate VTE prophylaxis, and (3) administration of risk appropriate VTE prophylaxis (Fig. 1). Evidence-based guidelines from the ACCP are published and updated regularly to address the subject of VTE prevention, prophylaxis, and management in medical and surgical patients. Other organizations such as the Eastern Association for the Surgery of Trauma and the American Academy of Orthopedic Surgeons also issue evidence-based guidelines for this subgroup of patients.

Assessment of VTE and Bleeding Risk

There are several risk assessments that have been developed for medical, orthopedic, and nonorthopedic surgery patients. These use the risk factors previous described. Currently, there is not one single model that is collectively accepted by the medical community; however, a model that is applied frequently is the Modified Caprini Risk Assessment Model (Table 4). Patients are separated according to their estimated VTE risk (VTEr) in the absence of pharmacologic or mechanical prophylaxis. Therefore, a very low risk score (Caprini score = 0) represents a VTEr less than 0.5%. In contrast, a high risk score (Caprini score ≥6) would correspond to a VTEr of at least 6%. This assessment model has been validated and has been used to assess patients undergoing general (breast, thyroid, and parathyroid), abdominal and pelvic surgery (gastrointestinal, urologic, and gynecologic), and critically ill patients. Presently, there are few data regarding vascular and bariatric patients; however, the model performs appropriately for these groups.

Despite the many scoring systems available, for the surgical patient that requires VTE prophylaxis an assessment of the risk for major bleeding commences with a full evaluation of the patient's history and

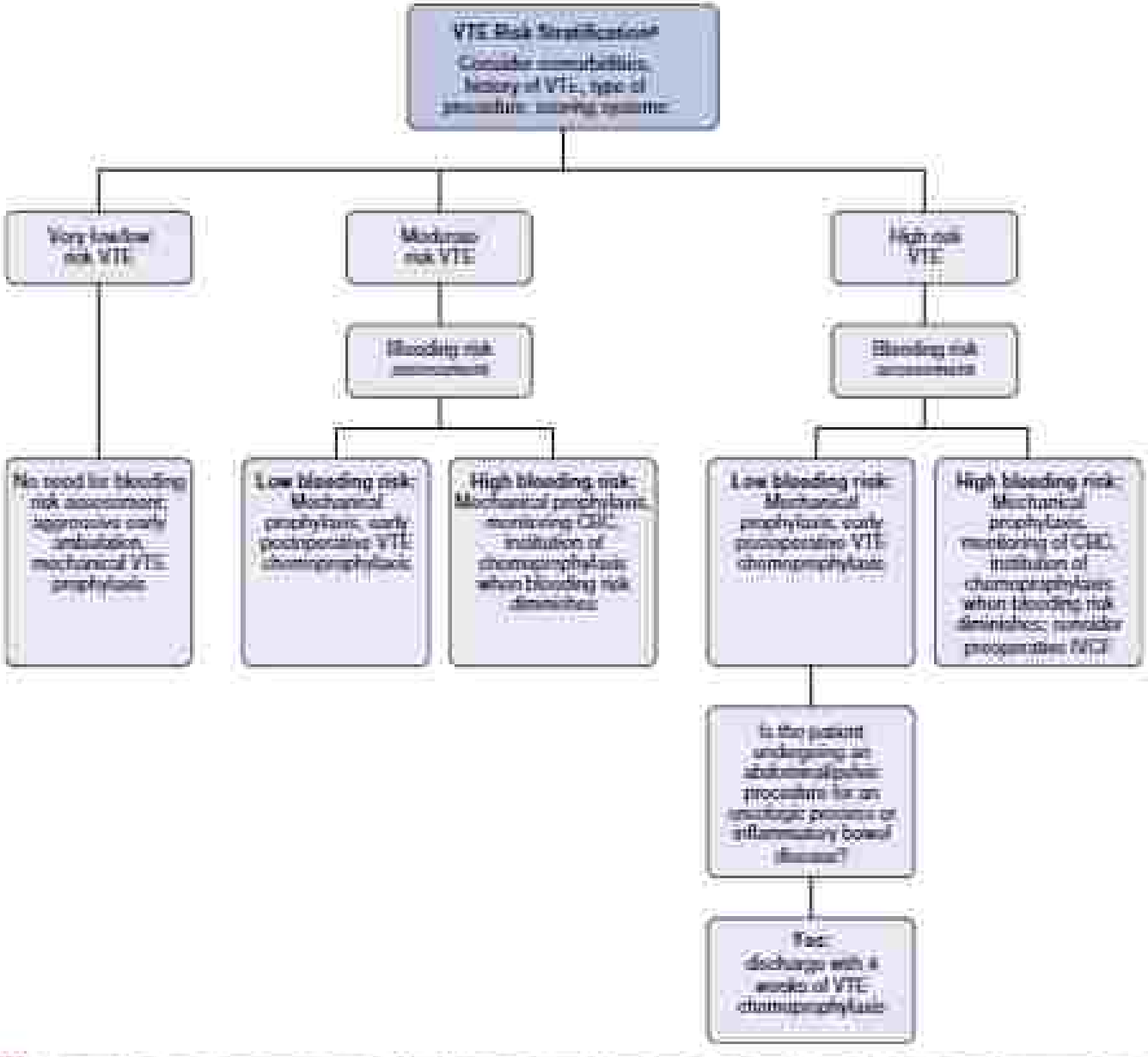

FIG. 1 Perioperative venous thromboembolism prophylaxis guidelines, adapted in part from the American College of Chest Physicians recommendations. CBC, complete blood count; IVCF, inferior vena cava filter; VTE, venous thromboembolism. *For patients undergoing general, vascular, gastrointestinal, urologic, bariatric, gynecologic, or plastic reconstructive surgery.

TABLE 4 Modified Caprini Risk Assessment Model for VTE in General Surgical Patients

1 Point	2 Points	3 Points	5 Points
Age 41–60 yr	Age 61–74 yr	Age ≥75 yr	Stroke (<1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m²	Major open surgery (>45 min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	Factor V Leiden	Acute spinal cord injury (<1 month)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (>72 hr)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (<1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Interpretation

Surgical Risk Category	Score	Estimated VTE Risk in the Absence of Pharmacologic or Mechanical Prophylaxis (%)
Very low	0	<0.5
Low	1–2	1.5
Moderate	3–4	3.0
High	≥5	6.0

The table is applicable only to general, abdominal pelvic, bariatric, vascular, and plastic and reconstructive surgery. Use zero for other types of surgery (e.g., cancer surgery).

BMI, body mass index; VTE, venous thromboembolism.

From Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e227S.

an examination. Major bleeding is usually defined as fatal bleeding, symptomatic bleeding in an organ or critical area, bleeding which causes a drop in the hemoglobin of 2 g/dL or greater or requiring a transfusion of two or more units of whole blood or red cells. Bleeding related to VTE prophylaxis differs among the types of patients. A study looking at 33 randomized controlled trials with 33,813 patients undergoing general surgery evaluated pharmacologic prophylaxis and calculated the bleeding complications. Minor complications found were injection site bruising (6.9%), wound hematoma (5.2%), drain site bleeding (2.0%), and hematuria (1.4%) were most common. Major bleeding complications, such as gastrointestinal tract (0.2%) or retroperitoneal (<0.1%) bleeding, were infrequent. Discontinuation of prophylaxis occurred in 2.0% of patients and less than 1% of patients required subsequent operation. Analysis of the use of high versus low dose unfractionated heparin demonstrated that the use of the lower dose had a reduced rate of discontinuation and subsequent operation. The baseline risk for bleeding has not been fully investigated; however, The American College of Chest Physicians have outlined risk stratifications and estimated the bleeding risk based on review of several studies. They have determined the baseline risk for being less than 1.0% for general (abdominal and pelvic), bariatric, thoracic, neurosurgery (craniotomy and spinal), plastic and reconstructive surgery. There is a higher risk of bleeding (>2%) in patients undergoing Cardiac surgery or involved in a trauma or requiring emergent surgery for trauma. Bleeding must also be examined by the surgeon regarding the potential for low and high bleeding risk. This will be based on individual risk factors for bleeding. These risk factors can include those with active bleeding, patients suffering from intracranial hemorrhage, patients with moderate to severe coagulopathy or patients with a genetic hematologic disorder or thrombocytopenia. The surgeon must be cognizant of these components to reduce potential injury to their patient.

Selecting Risk Appropriate VTE Prophylaxis and Administration

The rate of thrombosis reported in patients undergoing a general surgical procedure without prophylaxis has been reported between

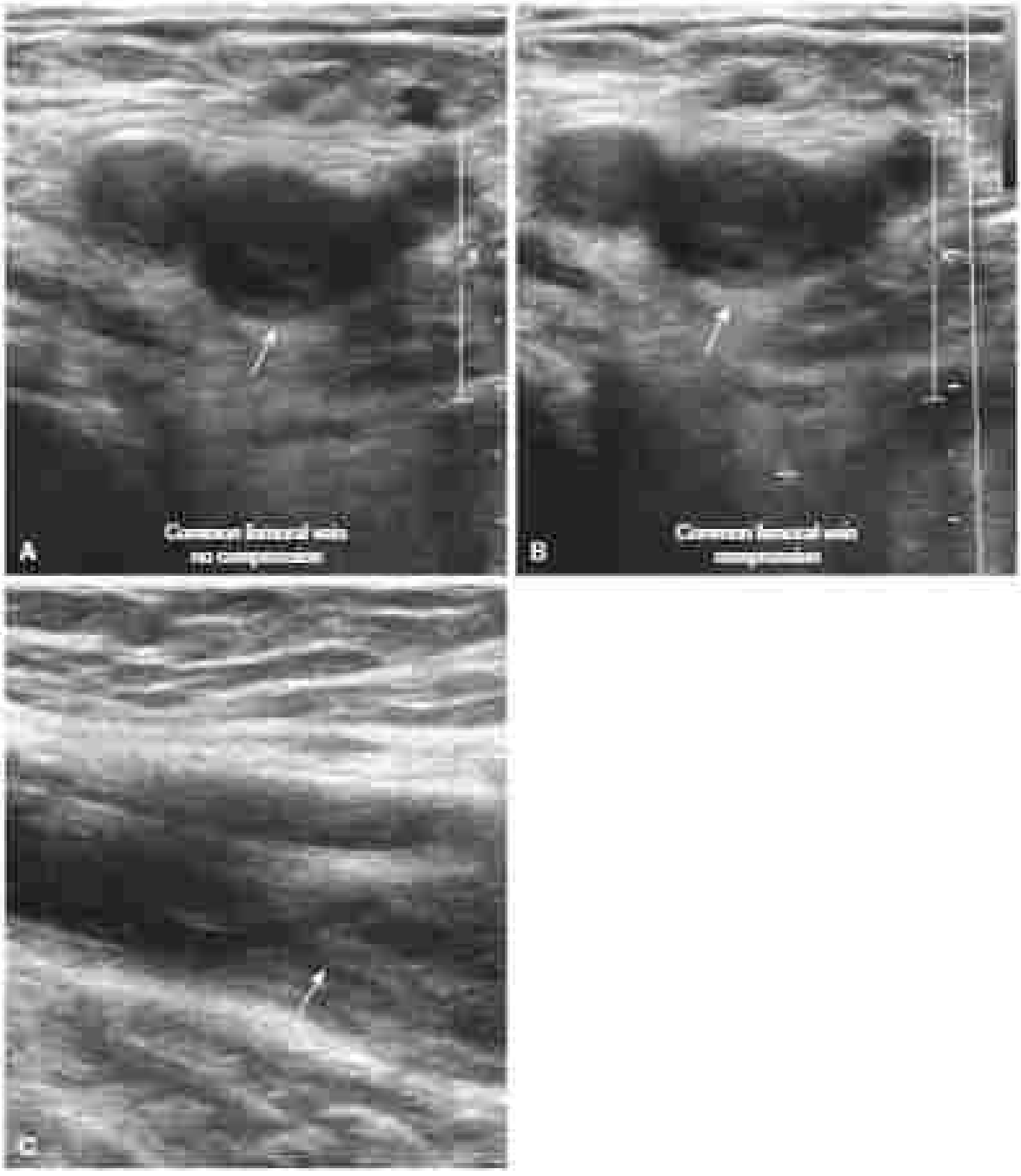

FIG. 3 (A) Cross-sectional venous ultrasound image showing noncompressibility and hyperechoic thrombus (arrow). (B) Compression view. (C) Longitudinal ultrasound image of the common femoral vein with nonhomogenous thrombus (arrow).

15% in 30%, with PE ranging between 0.2% and 5% and fatal PE < 0.002% (Table 3). Hospital initiatives of early mobilization of the patient post operatively, shorter hospital stay, utilization of perioperative antibiotics and greater use of thromboprophylaxis have demonstrated a significant impact in the reduction of VTE in the surgical patient. Selecting the appropriate thromboprophylaxis will be based on assessment of the risk of VTE and the risk of bleeding (Fig. 1). Methods for VTE prophylaxis include pharmacological, mechanical and a combination of both. The goal is to prevent VTE while reducing bleeding risk.

Mechanical methods of prophylaxis include graded compression stockings (GCS) and pneumatic compression device (PCD) which often are applied together. They are designed to eliminate stasis or interrupt thrombus development. None of these mechanical methods have been as rigorously investigated compared to pharmacological methods for reducing DVT. No trials to date have demonstrated mechanical devices alone are able to reduce the frequency of fatal PE. Utilization of GCS in isolation is not supported except in patients with high risk for bleeding. There are data to support a reduced incidence in DVT when used compared to controls. Additionally, when implemented in conjunction with low dose unfractionated heparin (LDUH) there is a 75% rate reduction in DVT compared to those patients treated with only LDUH. Pneumatic compression devices used with GCS have shown to be beneficial in reducing DVT. The PCD as stated above, is based on increasing lower extremity blood flow and as an adjunct to increasing native fibrinolytic activities.

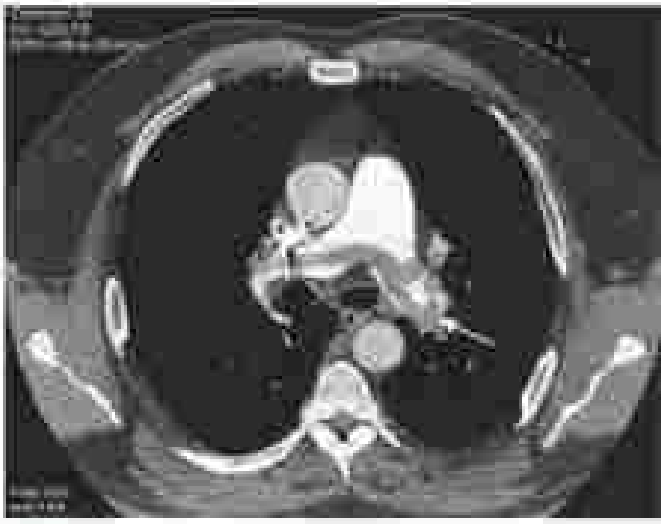

FIG. 3 Computed tomography scan demonstrating pulmonary embolism (PE).

Studies demonstrate its efficacy, however, compliance tends to be the concerning issue and particular clinical situations prevent its use. When applied with LDUH it can be effective. In a randomized trial of cardiac surgical patients, the combination of PCD and LDUH was shown to reduce the rate of symptomatic PE from 4% to 1.5% when compared to the use of LDUH alone. In the surgical patient with multiple risk factors and high risk for VTE a combination of pharmacological and mechanical prophylaxis with GCS and/or IPC should be used.

The most prevalent methods for the prevention of VTE in moderate to high risk patients is LDUH, low molecular weight heparin (LMWH), Warfarin and fondaparinux. It was the International Multicenter Trial published in 1975 that randomized 4121 patients over 40 undergoing major surgeries to either a control group or to receive LDUH. This study led to the discovery that employing heparin decreased the frequency of fatal PE and that heparin based thromboprophylaxis prevented DVT. This investigation made a significant contribution to our understanding of preventative management and significantly changed patient outcomes. Since that investigation there have been numerous studies and guidelines that have continued to provide supportive evidence in terms of both efficacy and safety using these pharmacological agents for the prevention of VTE in the perioperative period.

Conventionally, systemic intravenous LDUH (loading dose 80 U/kg and the infusion then adjusted to achieve a partial thromboplastin time 2 to 2.5 times normal) has been administered for several days during which time an oral anticoagulation has been initiated. LMWH is administered subcutaneously and weight based adjusted (1 mg/kg to 100 mg/kg twice a day). The advantage of this treatment is that it does not require monitoring. Circumstances that dictate monitoring are in patients who are obese, pregnant or in renal failure. This form of treatment can be easily continued in the outpatient setting. Fondaparinux is a weight based administered medication (5 mg/kg for body weight <50 kg; 7.5 mg/kg body weight for 50 to 100 kg; 10 mg/kg body weight for >100 kg) for the treatment of DVT as well as PE. The recommendation is treatment for at least five days with concurrent administration of oral anticoagulation. It has also been suggested as an anticoagulant when the patient has been diagnosed with heparin induced thrombocytopenia (HIT). Warfarin is one of the earliest oral anticoagulants. Typical dosing is 5 mg/day till the predetermined therapeutic level is reached, which is usually an INR between 2 and 3. When the INR level is achieved close monitoring will allow the dose regimen to be appropriately adjusted to stay within that range. This medication is started after anticoagulation has been initiated for several days to prevent warfarin skin necrosis. This occurs as a result of a transient hypercoagulable period where warfarin inhibits Protein C and S prior to other coagulation factors. Other pharmacological agents are Factor Xa inhibitors (apixaban, rivaroxaban) and direct thrombin inhibitors (dabigatran), which are first choice oral anticoagulants for long term anticoagulation.

COMPLICATIONS

One of the most formidable complications that a surgeon will confront with anticoagulation is bleeding. The first 5 days of anticoagulation with LDUH it has been reported that 10% of patients will experience some form of bleeding. The report incidence of major bleeding with Warfarin and an INR of 2 to 3 is roughly 6% per year. When encountered the proper management is administration of protamine for the reversal of heparin and the initiation of vitamin K and/or fresh frozen plasma to correct the INR.

The other complication associated with anticoagulation using LMWH or LDUH is heparin induced thrombocytopenia (HIT). This is a result when heparin dependent antibody immunoglobulin binds to activate platelets. The ensuing interaction causes thrombosis and thrombocytopenia. This is typically seen 5 to 14 days after the initiation of anticoagulation with LMWH or LDUH. It can occur earlier if the patient has had any prior exposure to heparin. Close monitoring of the hematocrit, hemoglobin and platelets after the commencement of anticoagulation will allow the surgeon to recognize any acute change and act accordingly.

HIT occurs in 0.6 to 30% of patients exposed to heparin. The diagnosis should be suspected when there is a drop of greater than 50% in the platelet count, a drop in the platelet count below 100,000/μl, or there is unexpected thrombosis while the patient is on heparin. Laboratory assay testing must be carried out to make the diagnosis. Once diagnosed or if there is a high index of suspicion of HIT, heparin must be stopped immediately. Direct thrombin inhibitors hirudin, lepirudin and argatroban are the treatments of choice. The surgeon treating their patients should know that lepirudin is excreted by the kidneys and argatroban is excreted by the liver and will need to be prescribed correctly when dealing with liver and renal failure patients.

DIAGNOSIS

Clinical suspicion for VTE should prompt rapid diagnosis and treatment as the consequences of untreated DVT can lead to PE, which can be fatal. Initially, a careful history and physical can help guide diagnostic testing and management when the diagnosis of DVT or PE is considered. VTE should be considered in any patient with presenting complaints of leg swelling and shortness of breath. On history, patients may have had prior surgery, active cancer, recent surgery or a family or personal history of hypercoagulability, to name a few. Presenting signs and symptoms of DVT can include erythema, swelling, pain, dilated superficial veins as well as skin changes. Infrequent but serious sequelae of DVT that can lead to a surgical emergency are phlegmasia cerulea dolens or phlegmasia alba dolens. These conditions represent a continuum of worsening (cerulea) and ultimate occlusion (alba) of venous outflow resulting in an ischemic limb that requires immediate surgical attention. Patients presenting with PE may complain of pleuritic, chest pain, shortness of breath and hemoptysis. Signs and symptoms can range from tachycardia, a new onset of atrial fibrillation or complete cardiopulmonary collapse.

The role of serum based testing in VTE is debatable. The D-dimer test is a marker of endogenous fibrinolysis and has been used in two main scenarios, whole blood agglutination and Enzyme Linked Immunosorbent Assay (ELISA) tests. The reported sensitivity of these tests is 85% and 95%, respectively. Both tests are plagued by low specificity. While not useful as a screening tool for VTE they may provide an adjunct in medical patients, as the false positive rate is exceedingly high in the post surgical patients. Evaluation of blood or genetic tests for the diagnosis of hypercoagulable states is not useful

in the acute setting and should not delay treatment. However, obtaining these tests can be useful in the long term, with respect to the management of anticoagulation.

The diagnosis of DVT is primarily made by duplex ultrasound (Fig. 2). The advantage of this imaging modality is its availability, high resolution and lack of radiation, which make it an attractive diagnostic choice. Limitations to venous duplex ultrasound utilization are the body habitus of patient, intra-operator variability as well as patient sensitivity or pain precluding compression by the ultrasound probe. Furthermore, venous duplex does not routinely directly image the iliofemoral system. Therefore, adjuncts such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning with the addition of intravenous contrast dye timed to the venous phase may be of utility. In unusual circumstances, catheter based venography can be used to aid in diagnosis, but it is more frequently used in treatment of deep femoral or caval pathology.

The gold standard for the diagnosis of PE is CT scan (Fig. 3). This technology is readily available at most hospitals and with the adjunct of intravenous (IV) contrast it can provide rapid, high resolution images to allow evaluation of pulmonary anatomy and the identification of filling defects within the pulmonary arterial tree suggestive of pulmonary emboli or thrombus. The drawback to this type of imaging is its use of IV contrast and radiation. The use of IV contrast may be prohibitive in patients with renal insufficiency or patients with a dye allergy. The use of radiation can pose a health risk to patients who require recurrent scans for other medical issues due to the cumulative dose associated with recurrent radiation exposure. An alternative option is ventilation–perfusion (V/Q) scanning. The test is highly specific (97.7%) for the diagnosis of PE but not particularly sensitive (77.4%) as other pulmonary pathology can result in a positive V/Q scan. Despite this, V/Q scanning remains a choice when CT scanning is not preferred.

Application of echocardiography has similarly assisted in the diagnosis of PE. Either transthoracic or transesophageal echo can be utilized to demonstrate right ventricular strain or overload and occasionally can visualize thrombus within the right heart. Its main utility is in patients who are too critically ill to be moved to the CT scanner. Also, echocardiography is valuable in the operating room in patients who have decompensated acutely without obvious cause. Although considered beneficial in three scenarios, a CT with contrast should be sought when the patient is stable to confirm diagnosis.

Other imaging modalities for PE such as MRI have not gained widespread use. While conventional catheter based angiography can be useful its role is usually reserved for those patients undergoing therapy for PE. Plain film imaging, while able to demonstrate some findings associated with PE, should not be solely used for definitive diagnosis.

TREATMENT

Treatment goals of VTE are directed at elucidating the underlying cause of the thrombosis as well as preventing clot propagation, PE or future thrombotic events. Furthermore, efforts may be directed at preventing long term sequelae of VTE, such as post thrombotic syndrome (PTS).

Superficial Venous Thrombophlebitis

Superficial venous thrombophlebitis (SVT) typically presents as a painful, palpable cord that may be associated with some erythema or local edema. While generally benign, SVT is more common than DVT and can present as a concomitant finding with DVT. In fact, some studies estimate that SVT presents concomitantly with DVT in up to 25% of patients. When, SVT encroaches the junction with the deep venous system, the risk for a subsequent DVT can be as high as 18%. While there are no consensus treatment guidelines for SVT initial workup should include a duplex ultrasound to look for DVT as well as clot proximity to the deep venous system. While not entirely evidence based, treatment consists primarily of nonsteroidal anti-inflammatory drugs (NSAIDs) as well as treatment of local symptoms and when used in combination with low molecular weight heparin (LMWH) or fondaparinux for 45 days can reduce extension of SVT. For cases of SVT that encroach on the deep venous system surgical ligation of the phlebitic vein can be considered as an anticoagulation.

Deep Venous Thrombosis

The initial phase of DVT treatment is focused toward the etiologic causes of the thrombotic event as well as medical management of the thrombosis with therapeutic anticoagulation. Consideration should be given to patient factors such as risk of bleeding, recent surgery, history of GI or other major bleeding events. Furthermore, an understanding of the situation that has led to the thrombotic event should be evaluated, that is, provoked vs. unprovoked, underlying malignancy, post-surgical etc. The goal of initial medical management hinges around stabilization of the existing thrombus, reduction of PE risk, reduction of possible recurrence and prevention of DVT related morbidity, namely PTS.

Choice of Anticoagulant

An understanding of the etiologic factors contributing to VTE are paramount to directing choice of anticoagulant. According to the 2016 guidelines from the ACCP suggest the following anticoagulation regimens based on the etiologic factors leading to VTE/PE. In patients with VTE not associated with malignancy (i.e., postsurgical), recommendations are for the use of novel oral anticoagulants (NOACs; rivaroxaban, apixaban, or edoxaban) in obligation over the use of vitamin K antagonists (VKAs), and, VKAs, over the use of LMWH. The basis of this recommendation is that there were fewer bleeding events observed when using NOAC versus VKA and patient convenience is favored when using NOAC.

In patients with VTE and cancer, the recommendations are different. Because the recurrence rate is lower in patients treated with LMWH versus VKA, and, the efficacy and risk of bleeding is similar between VKA and NOAC, the recommendation is for the use of LMWH over VKA and NOAC.

Duration of anticoagulation is generally based on etiologic factors and risk of recurrence. In general, duration of anticoagulation for most patients will be for 3 months. Included in this group would be unprovoked DVT, postsurgical DVT, and DVT provoked by other factors. In patients with recurrence of VTE or malignancy, suggestions would be for anticoagulation duration to exceed 3 months. In this determination, consideration should be given to the patient's risk of bleeding and periodic assessment of the patient's ongoing anticoagulation requirements should be made.

Role of Intervention

The role of venous thrombectomy has become markedly diminished in the era of endovascular venous techniques. However, in limb threatening phlegmasia situations, open venous thrombectomy remains an important tool for limb salvage. Aside from this rare condition, most venous interventions in the setting of VTE will be endovascular in nature.

In patients with acute iliofemoral DVT, approximately 20% will develop postthrombotic syndrome. PTS is characterized by pain, swelling, aching, and heaviness in a patient with a history of DVT in the ipsilateral limb. There are some small, randomized trials that have suggested that the dissolution of acute clot with endovascular means (thrombolysis, mechanical thrombectomy) can prevent the development of PTS. As a result, many patients with iliofemoral DVT have been treated with clot dissolution techniques (Figs. 4 and 5).

The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial randomized patients

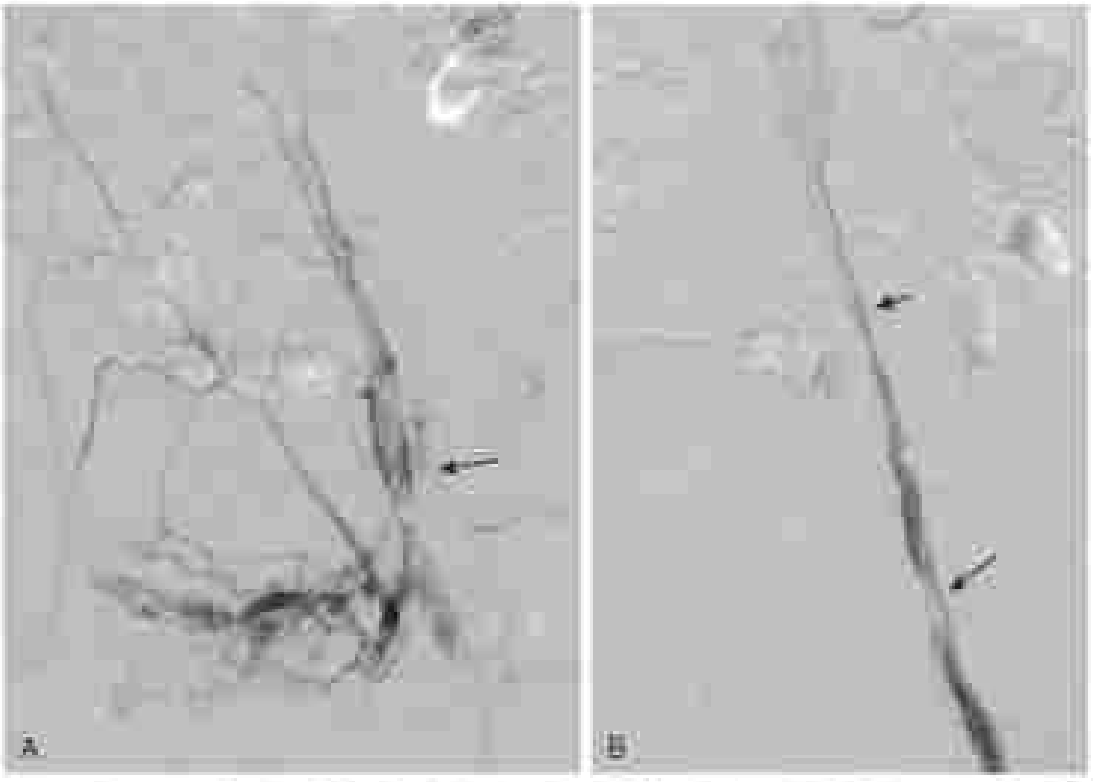

FIG. 4 (A) Lower extremity venogram of patient with ileofemoral deep vein thrombosis. Note the irregularity of the lumen as well as the filling defect in the ileofemoral segment (*arrow*). (B) The same patient after 24 hours of thrombolytic treatment as well as mechanical thrombolysis. Note the decrease in venous occlusion as well as improved luminal patency.

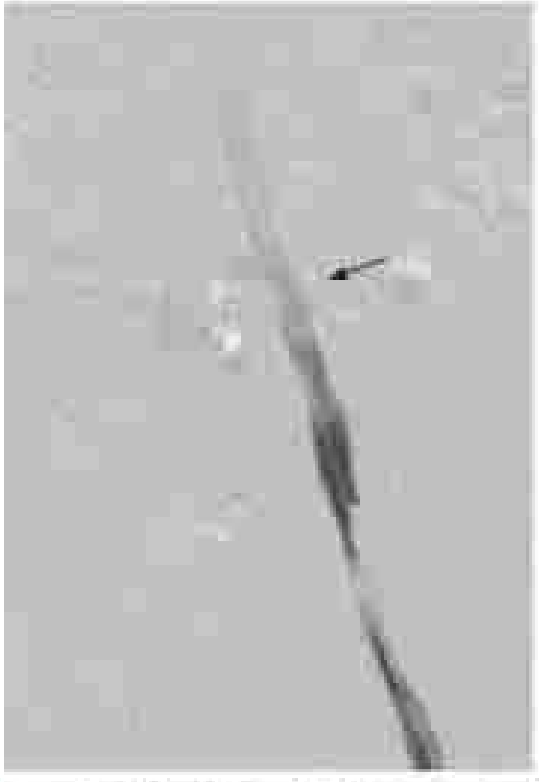

FIG. 5 Successful venous stenting (*arrow*) after pharmacomechanical lysis of deep vein thrombosis.

with DVT involving femoral, common femoral, and iliac veins to undergo pharmacomechanical thrombolysis and anticoagulation versus anticoagulation alone. The primary endpoint was development of PTS at any point in the 24 month follow up. The results showed no difference in the development of PTS (47% on mechanical vs 28% control). However, there was a significant increase in major bleeding events in the treatment arm versus the control arm (1.7% vs 0.3%). The authors concluded that the use of pharmacomechanical thrombolysis in patients with proximal DVT did not prevent the development of PTS but did put patients at risk of major bleeding.

These results differ from those of the Catheter directed Venous Thrombolysis (CaVenT) in which patients with isolated iliofemoral DVT treated with catheter directed therapy (CDT) and anticoagulation versus anticoagulation alone. In this study, in patients treated with CDT, there was a significant reduction in PTS (average relative risk, 14.8%) versus anticoagulation alone.

Possibilities for the disparate results from these two landmark trials may lay in the inclusion of femoral DVT in the Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter directed Thrombolysis trial versus iliofemoral DVT only in CaVenT. Furthermore, the methods of CDT were more uniform and there were less venous stents used for the in the CaVenT trial.

The decision to perform CDT in patients with DVT should be based on assessment of the individual bleeding risk and should only be used in DVT of the iliofemoral segment. Informed consent should include the risk of bleeding and the relatively high rate of PTS in patients with iliofemoral DVT following CDT treatment.

Pulmonary Embolism

Although PTS presents a significant morbidity for patients with DVT, the most feared and dangerous complication of DVT is PE. The

treatment strategy for PE is guided by the clinical assessment of cardiac and pulmonary status of the patient.

Specifically, patients with hypotension or systemic shock in the setting of an acute PE would be classified as high risk PE. For these patients, an assessment of bleeding risk should be made; in patients without significant bleeding risk and high-risk PE, systemic thrombolysis should be considered. For patients in whom the bleeding risk is high, systemic thrombolysis has failed, or are at risk of decompensation before thrombolysis can take effect should be considered for CDT to decrease clot burden.

Patients without cardiac compromise in the setting of PE would be considered low to moderate risk PE. These patients without contraindications to anticoagulation should begin an anticoagulation regimen (unfractionated heparin or LMWH) with transition to oral anticoagulation. Intravenous therapy can be avoided if NOACs are used. The sole exception would be in a patient with subsegmental PE and no DVT. These patients may be treated with clinical surveillance.

Inferior Vena Cava Filters

The role of inferior vena cava (IVC) filters in patients with DVT is that of salvage to prevent the migration of clot from the legs to the pulmonary circulation. They are to limited to those patients with a contraindication to anticoagulation or failure of anticoagulation with recurrent VTE.

Current ACCP guidelines do not recommend IVC filter therapy for patients who are eligible for or currently on anticoagulation. There are no guidelines that would support the routine use of IVC filters outside of contraindications to anticoagulation or failure of anticoagulation.

In fact, the Prevention and Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) trials have shown that IVC filters do prevent PE; however, there was no mortality benefit compared with the use of anticoagulation alone, and, the use of IVC filters came at the cost of more DVTs. Although PREPIC 1 used nonretrievable filters and PREPIC 2 used retrievable filters, the authors concluded that in patients with severe PE, a retrievable filter in addition to anticoagulation did not prevent recurrences.

The use of IVC filters is not without complication. Filter fracture, migration, and perforation of IVC into surrounding structures have all been reported. Most filters placed today are retrievable and despite the instructions for use as well as a US Food and Drug Administration guideline to remove the filters when not clinically useful, many IVC filters do not get removed. This has become a highly litigated area of vascular surgery practice. We recommend strict guidelines related to insertion and an electronic database to follow patients with filters in situ so there are not lost to follow up and assessment can be made as to the clinical utility of the filter with a view to removal if not clinically warranted.

SUMMARY AND CONCLUSIONS

VTE is a spectrum of disease that includes DVT, CVT, and PE and is common in both medical and surgical patients. VTE is often clinically silent but can result in significant morbidity and even mortality for patients. A high level of clinical suspicion as well as timely use of imaging modalities can help provide timely diagnosis and treatment. While there are a number of risk factors for VTE, postsurgical patients are all at least at intermediate risk of developing VTE and should therefore receive appropriate prophylaxis. Acute diagnosis should lead to a bleeding risk assessment followed by anticoagulation and potentially catheter directed therapy. Duration and agent of anticoagulation will depend on the etiologic factors leading to the thrombotic event. IVC filters, although having a role, do not improve mortality and should be used judiciously with a view to removal when their clinical utility has expired. Individual patient factors as well as VTE factors should be evaluated when planning therapy.

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Vena Cava Filters

Caroline Iyad Orfoua Chaar, MD, MS

Venous thromboembolism (VTE) remains a major health concern and a common cause of vascular morbidity and mortality. Anticoagulation is the cornerstone of therapy to prevent propagation, promote thrombus resolution, and prevent recurrence. Even though anticoagulation is administered to medical and surgical patients affected by VTE, several considerations come into play in the surgical patient population. Bleeding is a risk for every surgical procedure and anticoagulation can amplify that risk and is sometimes contraindicated. On the other hand, surgeries, especially with a long operating time, general anesthesia, and postoperative immobilization, are unique VTE risk factors in the surgical patients. Vena cava interruption is an important alternative therapy to prevent pulmonary embolism (PE). This chapter will provide an overview of the indications, techniques, and complications of vena cava filter placement and retrieval.

EVOLUTION AND CURRENT STATE

The concept of vena cava interruption was first introduced as an open surgical procedure consisting of ligation or plication of the inferior vena cava (IVC) to prevent embolization of thrombus from the lower extremities to the lungs. It evolved with the introduction of a variety of external clips that were applied surgically to the IVC via laparotomy. The Greenfield filter introduced in 1972 allowed, through its conical shape, trapping of significant thrombus volume without interfering with venous return and avoiding complete thrombosis of the vena cava. Its design represents the platform that most current IVC filters are based on. The Greenfield filter was initially inserted via surgical exposure of the jugular vein or femoral vein. Later, the development of percutaneous delivery systems increased the use of IVC filters in the United States by making the procedure minimally invasive and expanding its use to nonsurgical vascular specialists. Retrievable IVC filters fueled an exponential increase in placement of IVC filters in the past decade as these were perceived as "safe" alternatives to anticoagulation in patients who have contraindications for treatment or even prophylaxis as they can be retrieved when the risk of VTE resolved. Nationally low retrieval rates and increasing numbers of late complications from retrievable IVC filters led the US Food and Drug Administration (FDA) to issue a warning in 2010 mandating vascular specialists to follow the patients after IVC filter placement and retrieve them when the risk of PE resolves. In a recent study reviewing the Nationwide Inpatient database from 2003 to 2013, the incidence of VTE admissions had significantly increased but the associated mortality decreased. Although the use of catheter-directed thrombolysis has been steadily on the rise, the use of IVC filters increased from 2003 to 2009 significantly and then decreased in the latter part of the study period, suggesting that the medical community has become more aware of the potential dangers of IVC filters and therefore adopted more stringent criteria for placement (Fig. 1).

Indications

The decision to place an IVC filter should be individualized based on the patient's risk of VTE and taking into consideration the likelihood of bleeding and the potential duration of interruption of anticoagulation. There has been significant variation between different societies on the recommendations for IVC filter insertion. Although the American College of Chest Physicians strictly recommends placement of IVC filters in patients who have absolute indications, the Society of Interventional Radiology has traditionally endorsed a variety of indications that are clinically plausible but are not supported by high level of evidence. Indications for IVC filter placement can be divided into absolute, relative, and prophylactic (Table 1).

Absolute Indications

Patients who develop VTE and have contraindication for anticoagulation should be treated with an IVC filter based on consensus statements from multiple societies. These include patients with diagnosed VTE undergoing surgery with high risk of bleeding, neurosurgery, or patients with hemorrhagic stroke. On the other hand, up to 10% of patients who are started on anticoagulation for VTE develop a bleeding complication that warrants interruption of anticoagulation. Placement of a retrievable IVC filter provides protection from PE until anticoagulation is safe to be resumed. After the patient is stable on anticoagulation, the IVC filter should be removed. On the other hand, patients affected by recurrent VTE while on anticoagulation are considered therapy failures and traditionally treated with IVC filters. The availability of multiple direct oral anticoagulants (DOACs) on the market has shifted that practice slightly because some specialists may recommend trying a different anticoagulation agent before

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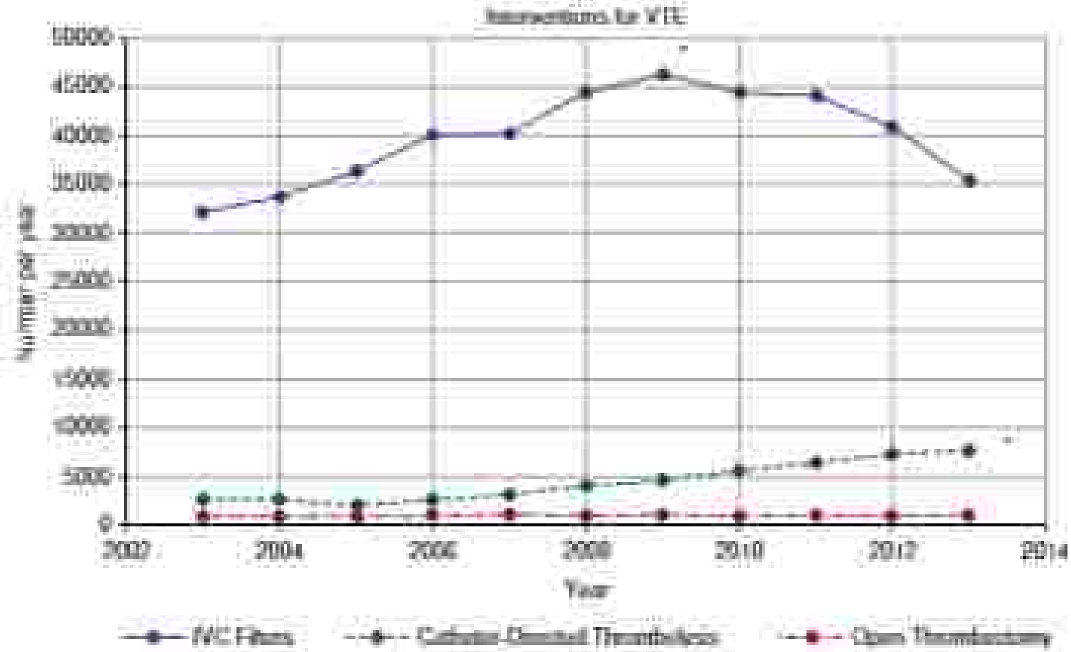

FIG. 1 Trends in inferior vena cava (IVC) filter placement. Trends of inpatient IVC filter placement, catheter-directed thrombolysis, and open thrombectomy for patients admitted with venous thromboembolism between 2003 and 2013. IVC filter placement significantly increased from 2003 to 2009 and subsequently significantly decreased from 2010 to 2013.

TABLE 1 Indications for IVC Filter Placement

Indications	Endorsed by	Patient Characteristics
Absolute	ACCP SIR AHA	Patient with VTE and one of the following: 1. Contraindication to anticoagulation 2. Failure of anticoagulation
Relative	SIR AHA (only characteristics 1 and 2)	Patient with VTE and one of the following: 1. Limited cardiopulmonary reserve 2. Massive PE treated with thrombolysis, thrombectomy 3. Chronic PE treated with thromboendarterectomy 4. Large free-floating iliocaval thrombus 5. Iliocaval DVT 6. Thrombolysis for iliocaval DVT 7. Recurrent PE with filter in place 8. Difficulty establishing therapeutic anticoagulation 9. Poor compliance with anticoagulant medications 10. High risk of complication of anticoagulation (i.e. ataxia, frequent falls)
Prophylactic	SIR	Patient at risk with no documented VTE: 1. Trauma patient with high risk of VTE 2. Surgical procedure in patient at high risk for VTE 3. Medical condition with high risk of VTE

ACCP, American College of Chest Physicians; AHA, American Heart Association; IVC, inferior vena cava; SIR, Society of Interventional Radiology; VTE, venous thromboembolism.

placement of an IVC filter. The current position of most societies on this situation is to place an IVC filter. A permanent device should be considered if the patient requires lifelong anticoagulation.

RELATIVE INDICATIONS

In certain circumstances, placement of IVC filters may provide additional protection from PE to patients with VTE tolerating anticoagulation. These patients can be divided into three categories. The first group suffer already from advanced cardiopulmonary disease, and a recurrent insult to the pulmonary circulation would be poorly tolerated or fatal. Patients already affected by massive PE, cor pulmonale, or undergoing pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension have very limited reserve. The second group includes those patients with increased odds of recurrent PE related to special characteristics of deep vein thrombosis (DVT) in the lower extremities. Patients with a heavy thrombus burden such as iliocaval DVT or free floating thrombi are thought to be at increased risk of PE and may benefit from an IVC filter. Sharifi et al. demonstrated that placement of an IVC filter during catheter directed

thrombolysis of lower extremity DVT reduce the risk of iatrogenic PE 8 times but there was no effect on mortality. The last group of patients have difficulty with the efficacy of anticoagulation or its safety. Patients on warfarin sometimes require a long time to reach a steady state therapeutic level or have difficulty with maintaining it. The introduction of DOACs has provided a reasonable alternative for these patients. Still, some have contraindications to DOACs and can be treated with IVC filters. Noncompliant patients and patients at high risk of falls (elderly, alcohol) can be effectively anticoagulated and monitored in the hospital but represent a high risk of failure of anticoagulation after discharge. Placement of retrievable IVC filters in these patients and reassessing compliance and safety of anticoagulation in the outpatient setting is a reasonable treatment option. Even though the benefit of placement of IVC filters in clinical scenarios that fall under "relative indications" is plausible, the level of evidence to support it is low and often lacking.

Prophylactic Indications

Patients at very high risk of VTE may benefit from IVC filter placement even if they have not developed a thrombotic event. The indication becomes more compelling if the patient has contraindication to pharmacologic VTE prophylaxis, is bedridden, and is expected to have a prolonged hospital stay or potentially have multiple trips to the operating room. The common scenario is a trauma patient with a combination of neurologic, blood and long bone fracture. Multiple studies have examined routine use of prophylactic IVC filters in specific groups of patients including trauma, bariatric surgery, high risk orthopedic spine surgery, surgical oncology, and high risk general surgery. The literature is very controversial and, despite multiple case series suggesting benefit, systematic reviews failed to show any advantage of routine use of IVC filters for prophylaxis in a predefined patient population. Thus, the decision of placement of prophylactic IVC filters should be individualized and discussed with the referring team of physicians. Also, it is important to acknowledge that IVC filters prevent PE and potentially a life threatening event, but do not protect against DVT. On the other hand, IVC filter placement can increase the risk of DVT.

TECHNIQUE

Planning

As with any surgery, planning for IVC filter placement involves a thorough review of the patient's chart and imaging focusing on the location and extent of the DVT if there is one documented. Access of a thrombosed vein should be avoided. Any cross-sectional imaging (computed tomography or magnetic resonance imaging) is helpful to assess the anatomy of the vena cava and its size. Anatomic variations can be detected before the procedure and will avoid trouble shooting in the operating room. An inferior filter are indicated for an IVC that ranges between 28 and 30 mm in diameter measurement, and documentation of the size of the cava is crucial. It is best to perform measurements on imaging obtained in an elective setting. Imaging obtained in dehydrated or bleeding patients can significantly underestimate the size of the IVC (Fig. 2).

Anticoagulation is held in the perioperative period. If the patient is on a heparin drip, it is held on call to the operating room. Patients on DOACs or low molecular weight heparin typically skip one dose before the procedure. Patients treated with warfarin as outpatients are asked to stop it 5 days before the procedure and are a low molecular weight heparin bridge. After IVC filter placement, anticoagulation is resumed in 24 hours.

Filter Type

IVC filters can be classified as permanent, retrievable (optional), convertible, and temporary. The first two are the most commonly used. A convertible filter is a device that is placed for interruption of the IVC and can be altered later to a no filtration state. The Veta Tech Convertible (R Stents) can be changed into a nonfiltration state by snaring the hook/apex of the filter, whereas Sentry (Novate Medical), recently approved by the FDA, spontaneously converts after dissolution of a biodegradable filament holding the arms of the filter together. Temporary IVC filters do not have wall fixation but are attached to a catheter or wire that traverses the venous system and is externalized. The Angel Catheter (Bard Medical) was approved by the FDA in 2011 to be placed at the bedside via femoral access and serve as an IVC filter as well as an infusion device for up to 30 days.

A permanent IVC filter should be used if the patient will require lifelong interruption of the vena cava. An analysis of the FDA Manufacturer and User Facility Device Experience database showed that the majority (86.8%) of reported long-term complications of IVC filter were due to retrievable filters, whereas permanent filters constituted only 13.2% of the cases. However, in a recent survey of vascular specialists, 42% of respondents chose to place a retrievable IVC filter and leave it in situ instead of using a permanent IVC filter. The most

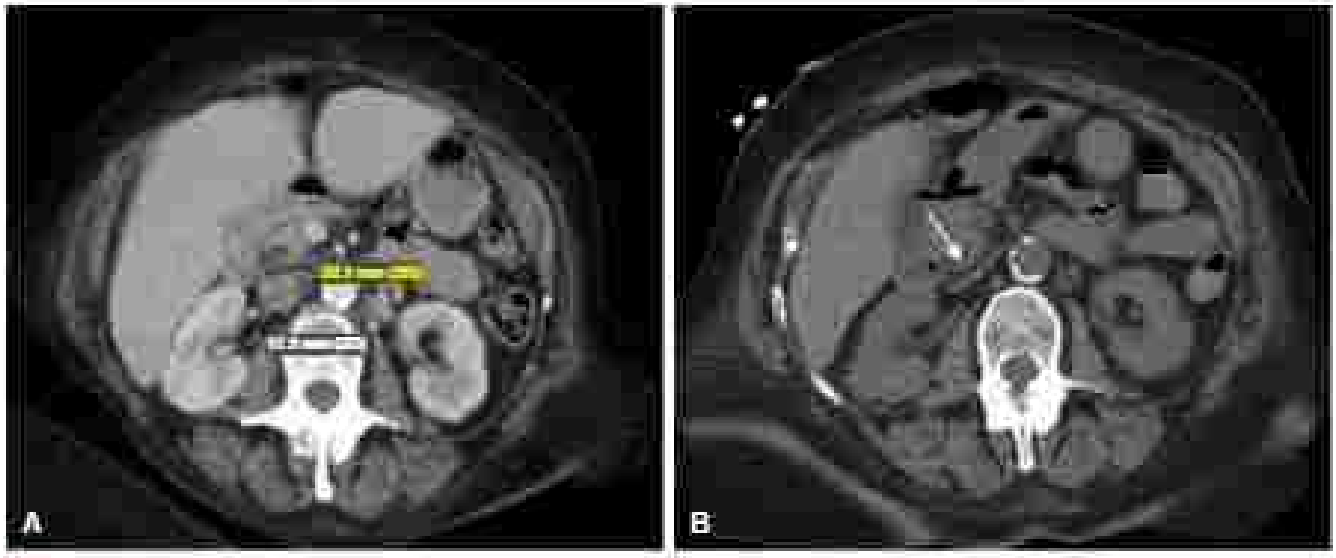

FIG. 2. Planning for inferior vena cava (IVC) filter placement. (A) Computed tomographic (CT) scan of a patient obtained for cancer surveillance on axial view demonstrates the vena cava with a diameter of 17 × 23 mm. (B) The same patient underwent CT scan emergently after an episode of bleeding and the IVC is totally collapsed.

common permanent filters used by operators were the Greenfield filter (29%) (Boston Scientific) and the Vena Tech LP (14%) (B. Braun). On the other hand, the Celect (27%) (Cook Medical Inc.) and Denali (20%) (Bard Peripheral Vascular) were the most popular retrievable filters. Both Celect and Denali have more advanced designs that incorporate a tilt centering mechanism to avoid tilting. Table 2 shows salient characteristics of commercially available IVC filters.

Access

Venous access is obtained under ultrasound guidance and using a micropuncture set to reduce iatrogenic injury. Ultrasound examination also confirms the patency of the vein and the absence of DVT. The vena cava is right sided in the vast majority of patients and access from the right femoral vein or right jugular vein is preferred as it provides optimal straight alignment and minimizes the risk of tilting with deployment. Left femoral vein access is a good alternative if the right sided veins are not accessible. IVC filter placement has been also described via brachial or popliteal vein access. A device with a long enough delivery system to deploy the filter in the desired anatomical location should be ensured in these special circumstances.

Venography

A 6Fr sheath is placed typically in the right common femoral vein. Angiogram can be performed through the sheath and can delineate the anatomy. A large volume of contrast, typically 20 mL (dilute contrast with saline 50:50), is needed to fully opacify the vena cava and visualize the confluence of the iliac veins and renal veins. Unlike arterial angiography, the branches in the venous system are tributaries and circulate blood into the IVC. This is analogous on angiography as rapid washing of contrast and mixing with blood (Fig. 3A). The renal veins commonly drain into the cava at the level of L1–L2 vertebral bodies while the confluence of the iliac veins is often at the level of L5. If there is uncertainty about the anatomy, a flush catheter can be placed at the confluence of the iliac veins and that typically improves visualization of the tributaries. (Fig. 3B) Alternatively, the iliac veins and renal veins in question can be selected and imaged individually.

This step is crucial to document the following:

1. Rule out IVC: In the presence of iliac vein thrombus, the operator should find alternative access to deliver the filter. Manipulation in the presence of thrombus should be avoided to prevent dislodgement and embolization.
2. Identify the optimal position for placement. The IVC filter should be placed in the infrarenal segment of the IVC with the tip/dome to or at the level of the lowest renal vein. As such, the filter does not interfere with the venous return of the kidneys. Having the tip at the level of the renal vein can prevent the formation of low flow state in the IVC above the filter if significant thrombus is trapped. The presence of thrombus in the infrarenal IVC is a contraindication for filter placement in that location. A suprarenal position is more appropriate if it is free from thrombus. Also, in pregnant women, IVC filters should be placed in the suprarenal position to avoid compression by the gravid uterus. A recent study of suprarenal IVC filters with up to 20 years of follow up found no incidence of renal vein compression. The authors suggested that suprarenal IVC filter placement is as safe as the infrarenal.
3. Measure the IVC diameter. As mentioned earlier, most IVC filters are indicated for placement in the vena cava with diameter between 28 and 30 mm, therefore, it is crucial to measure the IVC at the desired location of deployment to avoid embolization of the filter. This can be done with computerized software available in most angiography suites. Alternatively, a radiopaque marking ruler can be placed on the left side of the abdomen for calibration. Table 2 summarizes the diameter indicated for each IVC filter. The Bard's Recovery (Cook Medical Inc.) is a permanent filter and is the only device indicated for vena cava size between 28 and 40 mm.
4. Identify anatomic variation. Anatomic variations of the IVC that can affect filter placement are rare. Duplication of the vena cava resulting from persistence of the right and left supracardinal veins occurs in 0.2% to 3.0% depending on the series reported. The left-sided cava typically joins the left renal vein which then joins the right side IVC to form the suprarenal vena cava. This

TABLE 2 Characteristics of IVC Filters

Filter (Manufacturer)	Design	Maximum IVC Diameter (mm)	Delivery Sheath Size (Fr)	Mean Duration of Implantation Conversion (Range)
RETRIEVABLE				
Denali (Bard Peripheral Vascular)	Conical	28	6 F	149 days (5–34 days)
Günther Tulip (Cook Medical)	Conical	30	7	11 days (2–20 days)
Celect (Cook Medical)	Conical	30	7	55 days (7–869 days)
ALN (ALN)	Conical	28	7	85 days (78–108 days)
Option Elite (Argon Medical Devices)	Conical	30	6 F	Within 175 days
Option (Cordis Corporation)	Double basket	30	6	Up to 42 days
Convertible				
Vena Tech Convertible Filter (B. Braun)	Conical	28	10	130 days (15–391 days)
Permanent				
Stainless Steel Greenfield (Boston Scientific)	Conical	28	12	Life long
Titanium Greenfield (Boston Scientific)	Conical	28	12	Life long
Vena Tech LP (B. Braun)	Conical	28	7	Life long
Trapease (Cordis Corporation)	Double basket	30	6	Life long
Bard's Noir (Cook Medical)	Pre-shaped wires	40	12	Life long

IVC, inferior vena cava.

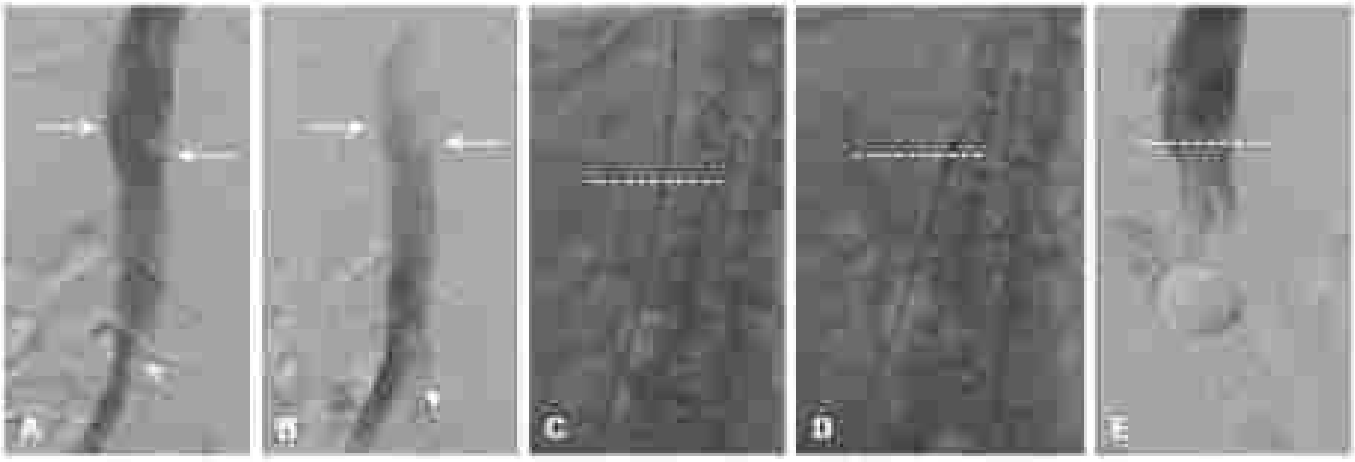

FIG. 1 (A) Placement of inferior vena cava filter (anteroposterior). Venography can be performed through a femoral sheath and normal anatomy is suggested by mixing of blood from the left. Blue vein (arrows). Pooling of blood at the level of L1–L2 demonstrates the location of the renal veins. (B) Alternatively a catheter can be placed at the confluence of the iliac veins and confirm the findings. A radiopaque graduated ruler helps with calibration and positioning and the lowest renal vein coincides with the 3-cm mark in this case. (C) The tip of the sheath is advanced to this mark (dotted line). (D) The inferior vena cava filter is unsheathed and the tip is maintained at the mark. (E) Completion angiogram demonstrating the alignment of the filter and tip location at the level of the lowest renal vein.

anomaly should be suspected when there is no opacification of blood at the iliac vein confluence and the IVC appears to be relatively small in caliber (Fig. 4A). Also, a relatively large left renal vein can be noted (Fig. 4B). The confirmation of this anomaly would require access of the left common femoral vein for angiography (Fig. 4C). The recommended treatment is placement of two separate IVC filters in each of the vena cava (Fig. 4D) or placement of a single suprarenal IVC filter. A single left sided IVC results from persistence of the left supracardinal vein and regression of the right one and occurs in 0.2% to 8.2% of them. The left sided IVC typically crosses to the right at the level of the renal veins. The presence of multiple renal veins on each side is common necessitating sometimes placement of a suprarenal IVC filter. Last, IVC atresia or the developmental absence of the IVC is a contraindication to placement and can be identified on preprocedure cross-sectional imaging or venography.

Deployment

IVC filters are deployed by unsheathing. All filters have delivery systems of variable calibers ranging from 6 Fr to 12 Fr (Table 1). The sheath and the catheter carrying the filter usually have markings to guide the operator in positioning. The sheath should be advanced over the wire under fluoroscopic guidance and the tip of the sheath (not the dilator) should be positioned at the desired location of the tip of the IVC filter (Fig. 3C). After, the filter is advanced all the way to the sheath. The filter is deployed by a pin and pull technique to unsheath the filter (Fig. 3D). Some filters have additional release mechanism that requires the operator to detach the filter from the delivery catheter when it is completely out of the sheath. After finishing deployment, the catheter carrying he filter should be retracted slowly under screen to make sure that the filter is completely detached, and the catheter is not trapped inadvertently between the legs of the filter.

Completion

A completion venogram is performed to ensure the position of the filter and the absence of tilting. Also, the relation of the filter to the renal veins is documented (Fig. 3E). The sheath is removed, and pressure is held on the access site for 15 minutes. Patients remain supine with bed rest for 3 hours after femoral puncture.

This is a comprehensive description for IVC filter placement under fluoroscopic guidance. Table 1 provides a summary for most frequently encountered anomalies encountered during the procedure. IVC filter placement can also be performed under guidance of intravascular ultrasound or transabdominal ultrasound at the bedside. These alternative techniques are particularly useful for unstable patients in the intensive care unit who cannot be transported safely to an operating suite. The learning curve is steep and there is higher incidence of filter malposition. Patients with advanced renal insufficiency may also benefit from ultrasound guidance. On the other hand, the use of carbon dioxide angiography can eliminate the need of nephrotoxic contrast dye.

OUTCOMES

IVC filter placement is a brief procedure with high technical success (94%–100%) and low complication rate (1%–3%). The Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption (PREPIC) trial randomized 400 patients with proximal DVT to anticoagulation alone compared with insertion of a Greenfield permanent IVC filter and anticoagulation. The results showed lower incidence of PE in the group of patients receiving IVC filters at 12 days (1.1% vs 4.8%, $P = .03$), 2 years (3.4% vs 6.3%, $P = .16$ not statistically significant), and 8 years (6.2% vs 15.1%, $P = .08$) of follow up. However, patients with IVC filters had significantly higher incidence of DVT at 2 years (20.8% vs 11.6%, $P = .02$) and 8 years (35.7% vs 27.5%, $P = .04$) compared with patients treated with anticoagulation alone. There was no difference in mortality or incidence of postthrombotic syndrome between the two groups. The PREPIC trial concluded that IVC filters offer protection from PE but increase the risk of DVT with no overall impact on mortality. Similarly, PREPIC2 randomized 399 patients with diagnosed DVT and PE to anticoagulation compared with insertion of an ALN retrievable IVC filter and anticoagulation. All the patients had at least one additional criterion of severity: age older than 75, active cancer, chronic cardiac or respiratory insufficiency, ischemic stroke with leg paralysis in the last 6 months, thoracal or bilateral DVT, or intermediate- or high-risk PE. Most filters were retrieved after evaluation at 3 months of insertion. There was no difference between the two groups in terms of recurrence of PE, recurrence of DVT, or mortality at 3 months and 6 months. PREPIC2 showed no benefit for the use of IVC filters in addition to anticoagulation in high risk patients and calls into question the relative indications for placement. In one study looking at patients with PE in the Nationwide Inpatient Sample, Stein et al. found that hemodynamically unstable patients with PE had lower mortality when IVC filters were placed compared to similar patients

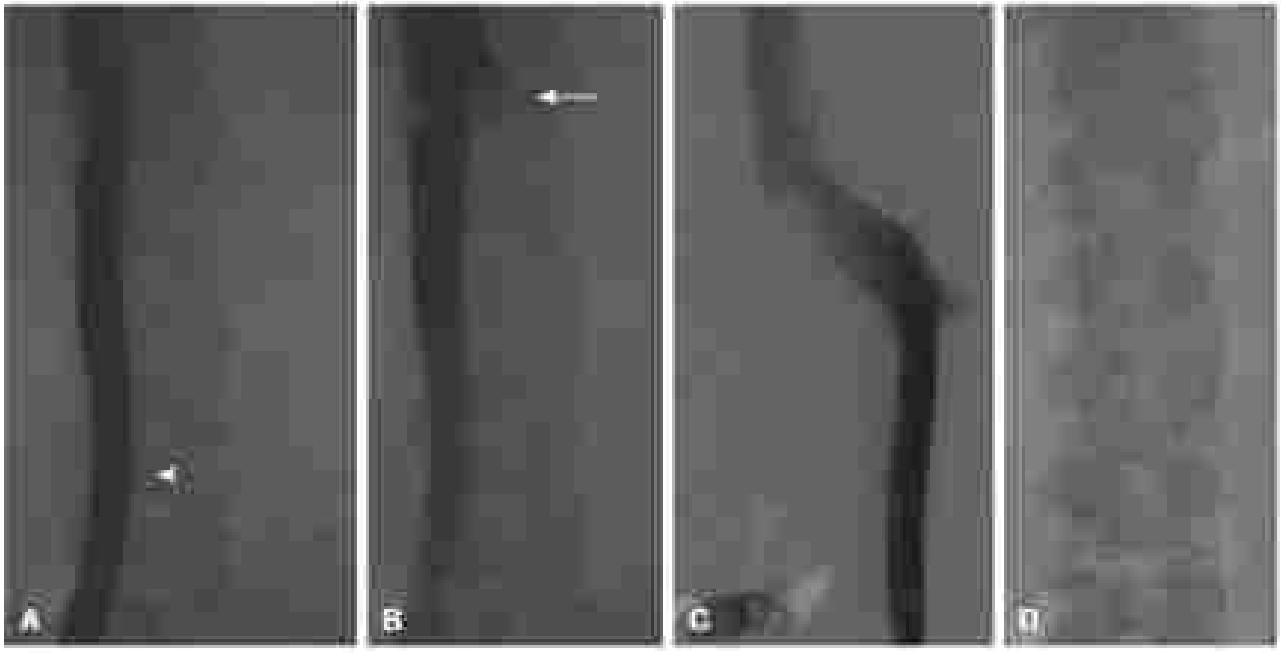

FIG. 4 (A) Duplication of the vena cava (preferred). The venogram of a patient with duplication of the inferior vena cava (IVC) demonstrates the relatively smaller right-sided IVC with lack of mixing of contrast at the expected location of the confluence (B, arrow) and a relatively large left renal vein. (C) Acquisition of the left femoral vein and duplicated venography demonstrates typical course of a left-sided IVC. (D) Patient treated with two separate IVC filters.

TABLE 3 Troubleshooting Unanticipated Findings on Venography During IVC Filter Placement

Unanticipated Finding	Suggested Action
Thrombus in ipsilateral iliac vein	Place IVC filter through alternative access
Thrombus in infrarenal IVC	Consider placement of suprarenal IVC filter via jugular access
IVC diameter >30 mm	Consider placement of Bird's Nest filter for IVC diameter 30–40 mm Consider placement of 2 separate iliac vein IVC filters
Duplication of the IVC	Consider placement of 2 separate IVC filters in each infrarenal cava Consider placement of suprarenal IVC filter
IVC stenosis	IVC filter contraindicated
Left-sided IVC	Consider suprarenal IVC filter placement depending on renal vein anatomy

IVC, inferior vena cava.

without IVC filters. The study suggested that IVC filters are associated with decreased mortality but has several limitations of large database analysis including lack of granularity and limited follow up.

COMPLICATIONS

Short-Term

The most common complications are related to access and include thrombosis, arteriovenous fistula, hematoma, and pneumothorax. These complications have likely decreased with the use of new lower profile devices and the use of ultrasound guided access. Filter tilt, malposition or incomplete opening also occur in some patients. Mortality is rarely reported (<1%) and is usually from patient comorbidities.

Long-Term

Breakthrough PE despite the presence of an IVC filter has been reported between 1% and 4% with different devices. Retrievable filters tend to have higher long-term complications including fracture, migration, and complete thrombosis of the IVC. Penetration of the struts through the wall of the cava is common and most patients remain asymptomatic. However, symptomatic penetration into adjacent structures have been reported to affect the aorta, ureter, bowel, pancreas, and ureter leading to significant morbidity and mortality. The incidence of these complications remains unknown and is the focus of the ongoing PRECISE (Predicting the Safety and Effectiveness of Inferior Vena Cava Filters) trial.

FILTER RETRIEVAL

Operators placing retrievable IVC filters should have a mechanism for follow-up for patients and educate them about the long term risks of filters and the importance of their removal. Every filter has a mean duration of implantation which is the window for safe retrieval (Table 2). Morales et al. used mathematical modeling incorporating the risks and benefits of IVC filter removal and suggested that the ideal time is between 29 and 54 days after implantation. Removing a filter in that time frame is usually a relatively simple and safe procedure performed via jugular access. A snare is used to capture the hook at the apex of the filter and a coaxial sheath is advanced to collapse it and free it from the wall of the vena cava. Prolonged dwell time, filter tilt, apposition of the hook to the wall of the cava, and penetration of the struts into adjacent structures make the procedure more challenging and can increase complications. Still, most IVC filters can be removed via endovascular means but require advanced techniques and skills. Brown and Haskal have a good review of the different advanced endovascular techniques described for IVC filter removal. These techniques require frequently multiple access sites and commonly involve the off-label use of devices such as bronchoscopy forceps, endoscopy

proper, and knee sheath. The retrieval rate of filters is 90% to 100% in experienced centers and filters have been removed up to 16 years after implantation. In rare cases, filter removal is impossible or deemed unsafe via endovascular means. If the patient has a complication from the IVC filter, then open surgical removal is a safe option via laparotomy. Alternatively, robot-assisted minimally invasive removal of IVC filter has also been described but requires transfer to a dedicated center where the appropriate expertise is available.

Suggested Readings

Indes JE, Abougergi MS, Sykes Chair CC. National trends in hospitalizations for venous thromboembolism. J Vasc Surg Venous Lymphat Disord. 2015;3(3):321–329.

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Shen WS, Malik F, Kwon DC, Millward CA. Impact of vena cava filters on in-hospital case fatality rate from pulmonary embolism. Am J Med. 2014;127(5):474–481.

Treatment of Varicose Veins

Misaki Kiguchi, MD, and Ellen Dillavou, MD, FACS

Varicose veins are a sign of increased venous pressure and are present in 10% to 30% of the general population, with increasing prevalence in older subgroups. Elevated venous pressure often occurs with valvular incompetency, inadequate calf pump function, and/or venous obstruction, and often cause achiness, fatigue, swelling, heaviness, and throbbing. These symptoms are exacerbated by standing, resulting from increased venous pressure and improved with leg elevation or compression. The chronicity and degree of venous hypertension contribute to its sequelae, ranging from mild vein dilation to longstanding venous ulcers. These clinical signs are classified by the CEAP categorization, describing the clinical manifestation (C), etiology (E), anatomic disease distribution (A), and pathophysiology (P). Consistent and appropriate use of the CEAP classification, as well as use of current anatomic terminology, is important for interprovider communication as well as communication to payers.

Increased venous pressure, for the most part, is of low mortality and morbidity, but the resultant symptoms undoubtedly affect quality of life (QoL). For venous disease, validated QoL assessments particularly for venous symptoms (e.g., Aberdeen Varicose Vein Score; Chronic Venous Insufficiency Questionnaire; Temple IWT, Venous Insufficiency Epidemiological & Economic Study, Charing Cross Venous Ulcer Questionnaire) play a vital role in not only distinguishing which patients would benefit the most from intervention, but also help manage expectations relating to therapeutic choices.

DIAGNOSIS

A detailed history and physical is the cornerstone to the assessment of the venous patient because this will elucidate whether the patient's complaints are related to venous causes and could thus be improved with treatment. It is imperative that the patient has a chance to express their symptoms and has a physical examination, which can assess the likely anatomic culprits leading to venous insufficiency. A venous ultrasound examination, performed standing or while in deep reverse Trendelenburg, is then necessary to delineate anatomy (deep, superficial, and perforators), assess reflux in all these beds, measure reflux time/vein diameter, and evaluate for acute or chronic thrombus and scarring. These data are then evaluated in the context of the patient's history to determine if there is a correlation between the patient's complaints and the anatomic or functional pathology that is evident. Because much of venous disease is symptomatic, responsible practitioners need to have a high degree of certainty that a chosen therapy will improve symptoms, and thus, also meet patient expectations.

Thresholds for Reflux

Pathologic reflux is defined by reversal of flow greater than 500 ms in duration in the superficial system and perforators. Pathologic reflux in the deep system (femoral and popliteal veins) is defined as longer than 1 second in duration. Saphenous veins larger than 5.0 mm and perforating veins larger than 3.5 mm in diameter should be noted and considered significant during the ultrasound evaluation for chronic venous insufficiency.

The evaluation of reflux is important, as all reflux is not the same. A diminutive great saphenous vein (GSV) (2–3 mm) with very prolonged reflux (4–5 seconds) likely has a low volume of reflux and is unlikely to cause symptoms (Fig. 1). A large GSV (>8 mm) with high flow is more likely to be clinically significant. Isolated segments of reflux between competent valves are unlikely to be problematic, unless they feed a large perforator that causes distal incompetence. Varicosities and telangiectasias over the lateral malleolus are unlikely to improve with GSV ablation even if the vessel meets criteria for reflux, unless there are incompetent branches that lead to the symptomatic area. Predominant varicosities in this distribution are typically due to small saphenous vein (SSV) or local perforator reflux (Fig. 2). These types of anatomic and symptomatic variants are the challenging part of venous assessment and treatment because appropriate care with optimal results requires a pairing of the patient history, physical exam, and ultrasound findings.

Management of Deep Reflux

Although valve transplantation, valvuloplasty, and other surgical therapies have been attempted, there are no current recommendations for surgical correction of deep venous reflux. Compression, weight management, exercise, and leg elevation are all useful behavioral strategies.

MANAGEMENT OF SUPERFICIAL REFLUX

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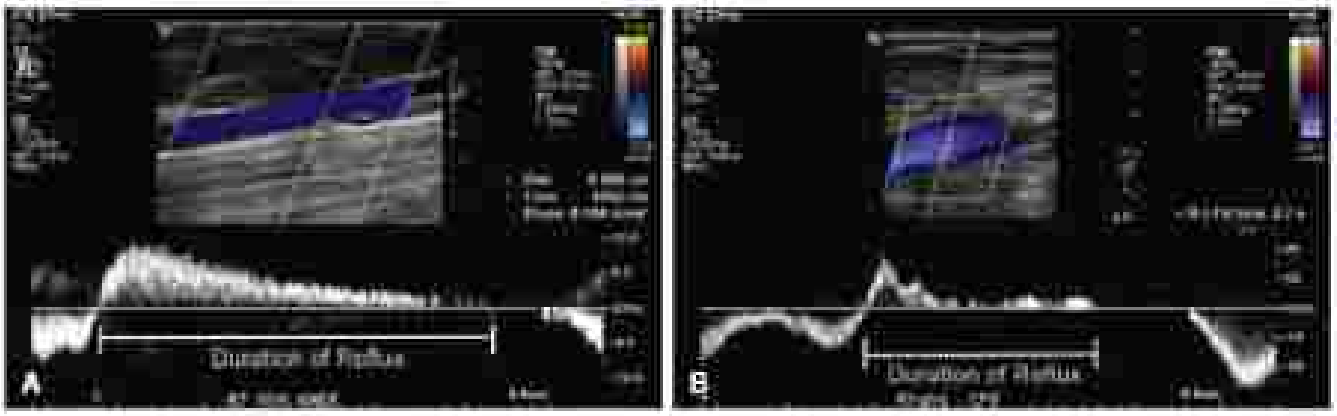

FIG. 1. (A) Augmentation and reflux measurements of the right great saphenous vein at the knee. Reflux time of 4563 ms, above the >0.5 sec threshold for significant reflux. Mildly dilated vein diameter at 3.7 mm. (B) Augmentation and reflux measurements in the right common femoral vein. Reflux time of 2300 ms, above the >1 sec threshold for significant reflux.

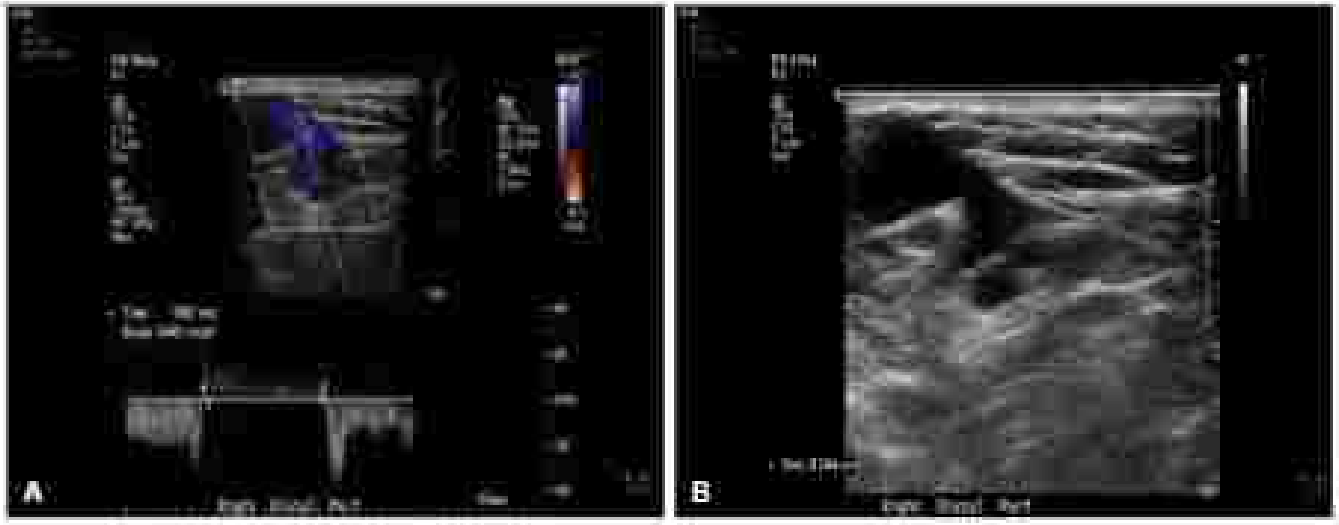

FIG. 2. (A) Augmentation and reflux measurements of a distal right calf perforator. Reflux time of 1907 ms, above the >0.5-sec threshold for significant reflux. (B) 2.54-mm midthigh vein diameter demonstrates dilation.

referral to a source of minimally invasive, low morbidity, and highly effective treatment. Currently, a wide variety of minimally invasive therapies is available to treat patients safely and comfortably (Table II).

Radiofrequency Ablation

The ClosureFAST catheter (Medtronic) has a bipolar electrode to provide radiofrequency heat energy directly to the vein, causing endothelial destruction, contraction of the vein wall, and thrombus formation. The vein will contract and scar over the 6 months following treatment.

Steps for radiofrequency ablation (RFA) of saphenous veins:

1. Prep the appropriate leg in the standard, circumferential sterile fashion.
2. Ultrasound scan is performed as the first step of the sterile procedure as before prep; map out the saphenous and assess the vein for occlusion, aneurysm, exceptionally superficial venous locations, webbing, or other anatomic details that may make the procedure difficult or less successful.
3. Access the vein percutaneously using ultrasound guidance after anesthetizing the superficial skin with lidocaine. Access is most easily initiated just below the popliteal area on the medial calf for GSV. Accessing more distally on the great saphenous may be indicated for treatment of reflux along the length of the vein in CEAP 3 to 6 patients, but it increases incidence of saphenous nerve injury. Similarly, small saphenous access is typically in the mid to lower one third of the calf as more distal access can result in sural nerve injury.
4. Thread microwire through the needle and confirm under ultrasound guidance.
5. Remove the needle while keeping the microwire in place.
6. Flush the 7Fr introducer sheath with saline and place over the microwire into the vein.
7. Remove the inner dilator and wire. Flush sheath.
8. Attach catheter to the generator.
9. Flush the catheter with sterile saline and cap the Luer port.
10. Insert the catheter through the sheath and advance.
11. Optional: If the catheter does not advance easily, a 0.025-inch Glidewire (Terumo Corporation) may be backloaded into the catheter to guide catheter insertion. Alternatively, distal traction on the skin of the leg and stabilization of the vein with the contralateral hand frequently allows for the catheter to be passed through moderately tortuous veins.
12. Confirm tip position with ultrasound guidance to be at least 2 cm inferior to the epigastric vein immediately distal to the saphenofemoral junction. For the small saphenous, catheter tip should

TABLE 1 Advantages and Disadvantages of Endovenous Techniques

Technique	Advantages	Disadvantages
RFA	• Good for large veins >1 cm • Used for entrapment	• Nerve injury • Use of tumescence • Difficult in partially occluded or tortuous veins • Compression use postprocedurally
EVLA	• Good for large veins >1 cm • Used for entrapment	• Nerve injury • Use of tumescence • Not used in very superficial veins • Difficult in partially occluded or tortuous veins • Compression use postprocedurally
MOCA	• No tumescence • Good for veins <12 mm • Good for superficial veins • Coil distributes into varicosities and perforators	• Poor for entrapment • Difficult in partially occluded or tortuous veins • Compression use postprocedurally
Pfahlstand endovenous microfoam	• No tumescence • Good for tortuous veins • Good for veins <10 mm • Good for superficial veins • Coil distributes into varicosities and perforators • Used for entrapment • Easy to use in partially occluded or tortuous veins	• Compression use post procedurally • Treated veins are often tender and thrombosed for months • Risk of >1 / 1 from extravasation through perforators • Closure of vein on ultrasound is lower than seen with other forms of ablation, although this may not predict a failure of clinical result
Glue	• No tumescence • Good for veins <10 mm • Good for superficial veins • Glue distributes into varicosities and perforators • Used for entrapment • No postprocedural compression needed	• Difficult in partially occluded or tortuous veins • Foreign body left in vein • Hypersensitivity reaction to adhesive occurs in 5% to 10% of patients

DVT, deep vein thrombosis; EVLA, endovenous laser ablation; MOCA, mechanochemical ablation; RFA, radiofrequency ablation.

be positioned in the superficial portion of the small saphenous and not advanced past the point where the vein dives deep to form the saphenopopliteal junction (SPJ). This point is typically at least 3 cm from the SPJ. The catheter and vein can be imaged in the longitudinal access distance measured and recorded to ensure adequate distance.

15. Move the grommet to the end of the sheath to mark the position.
16. Administer tumescent to the perivenous tissue under ultrasound guidance, striving to create a halo of tumescence around the vein within the saphenous fascia. Tumescence should extend at least 2 cm proximal to the tip of the catheter to ensure adequate anesthesia and to form a barrier between the heat of the catheter and the deep veins.
17. Position the heel in a Trendelenburg position to facilitate vein collapse.
18. Apply compression over the length of the heating element to facilitate contact between the vein wall and heating element.
19. Press the white device button on the catheter handle to initiate treatment. Watts used during treatment cycle should fall to below 10 at some point during the cycle. Increasing compression can decrease the watts needed to treat the segment of vein.
20. When the treatment cycle is complete, index the catheter to the next shaft mark position. Apply compression over the entire heating element and start next treatment. Treat the segment close to the junction twice. Consider a third cycle near the junction or a second cycle more distally if vein is greater than 10 mm, if there are large branches or perforators exiting from the segment, or if the wattage does not fall below 10. Do not treat any segment more than three times.
21. Repeat withdrawal in sequential shaft marks, compression, and treatment.
22. Remove the sheath over the catheter once the vein is treated over the hashmarks on the catheter.
23. Withdrawal until the last index mark is seen. Apply compression over the entire heating element and start last treatment. Take care not to withdraw the catheter beyond the three hash mark area as a more superficial catheter location could possibly get the heating element too close to the puncture site and burn the skin.
24. Remove catheter and sheath, and apply compression over the access site for hemostasis.
25. Apply compression from the foot up to the thigh.
26. Review postprocedure instructions.

RDA treatment of perforating veins (Fig. 3) should be reserved for vein diameters greater than 3.5 mm at the fascial level, within ranges from 0.5 seconds (2 J) to 2 seconds, and under or in proximity to ulcers.

1. Position the perforator vein to long view.
2. Make a small nick in the skin.
3. Through the small nick, use the RF catheter to directly puncture, or use Seldinger technique to access the perforator vein under ultrasound guidance.
4. Position the tip of the RF catheter 2 to 3 mm from the deep vein or at the fascial level, depending on anatomy.
5. Remove stylet and confirm tip position again.
6. Infiltrate local anesthesia around the perforator tissue.
7. Treat four quadrants for 30 seconds each.
8. Withdraw catheter 3 to 5 mm and repeat treatment.

Endovenous Laser Ablation

The laser ablation catheter provides laser heat energy directly to the vein, causing endothelial destruction, contraction of the vein wall, and thrombus formation, similar to RFA. There are several commercially

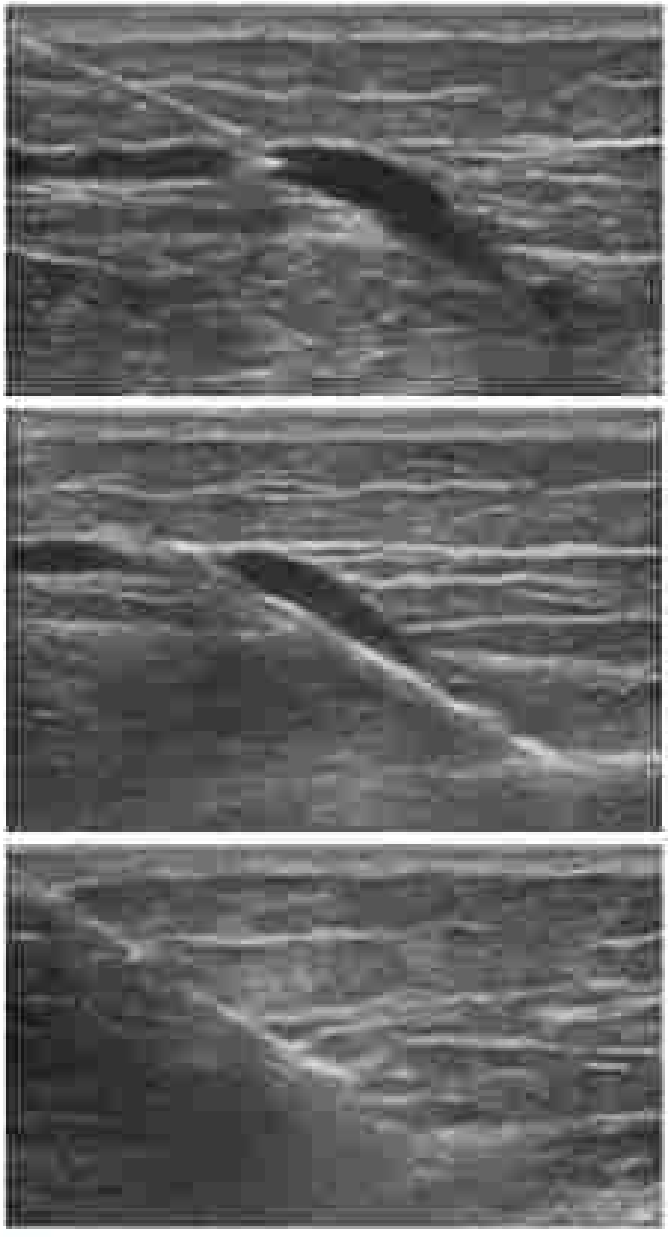

FIG. 3 Radiofrequency ablation of incompetent perforator with stylet in place.

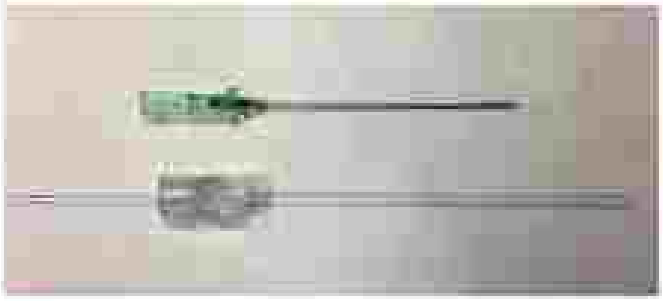

FIG. 4 Microsheath and introducer for perforator endovascular laser therapy.

available lasers in different wavelengths, from 980 to 1470 nm. The longer wavelengths are targeted to less dense matter (i.e., serum) and so are less likely to cause tissue destruction. Thus, 1470 nm is generally as effective as the shorter wavelengths but produces a more comfortable therapy.

Steps for endovenous laser ablation (EVLA) of saphenous veins are generally the same as for RFA. Differences related to use of the laser are described below:

1. Once a microsheath is in place as per the standard protocol, advance a 0.035-inch guide wire to the saphenofemoral junction under ultrasound guidance.
2. Remove the microsheath and select a long sheath based on the measured distance from the junction to the access site.
3. Remove the inner dilator and wire from the long sheath.
4. Advance fiber into the sheath.
5. Connect the fiber to the generator and aim the beam toward the skin.
6. While holding the fiber in place, the sheath is withdrawn to the locking mechanism and locked in place.
7. The tip of the fiber is exposed approximately 2 cm past the end of the sheath.
8. Confirm tip position with ultrasound guidance to be at least 2 cm inferior to the epigastric vein immediately distal to the saphenofemoral junction. For the small saphenous, the catheter tip should be positioned in the superficial portion of the small saphenous and not advanced past the point where the vein dives deep to form the SPJ. This point is typically at least 3 cm from the SPJ. The catheter and vein can be imaged in the longitudinal access, distance measured and recorded to ensure adequate distance.
9. Administer tumescence as described.
10. Position the bed in a Trendelenburg position to facilitate vein collapse.
11. Once the machine is turned and set to 5 to 7 watts from standby to ready mode, step on the foot pedal to deliver laser energy. Pull back the laser fiber and sheath together 1 cm every 5 to 6 seconds.
12. Treatment energy should be administered as per recommendations for each laser (ppm; 80 J/cm (1470 nm laser) and 80 J/cm (980 nm laser) are frequently used settings.
13. Stop treatment by releasing pedal when the laser fiber is 1 to 3 cm proximal to the entry site.
14. Remove fiber and sheath and apply compression over the access site for hemostasis.
15. Apply compression from the foot up to the thigh.
16. Review postprocedure instructions.

EVLA treatment of perforating veins (Figs. 4 and 5) should be reserved for vein diameters greater than 3.5 mm at the fascial level, reflux longer than 0.5 seconds, CEAP Rs 4 patients, and under or in proximity to ulcers.

1. Position the perforator vein in long view.
2. Make a small nick in the skin.
3. Through the small nick, direct puncture and Seldinger technique of the perforator vein under direct ultrasound guidance with the 21 g microneedle.
4. Thread a 1470 nm, 400 μm microfiber through the needle.
5. Position 2 to 3 mm from the deep vein or at the fascial level, depending on anatomy.
6. Infiltrate local anesthesia around the perforator tissue.
7. Set generator at 6 watts and treat with 50 to 100 J per 2 mm.

Mechanochemical Ablation

Thermal ablation requires tumescent anesthesia and has risks of thermal injury to the surrounding nerves and veins. Mechanochemical ablation uses a rotating wire to spasm the junction immediately before injecting sclerosant, which is then delivered with the mechanical agitation. The sclerosant creates chemical endothelial damage, causing fibrosis of the vein.

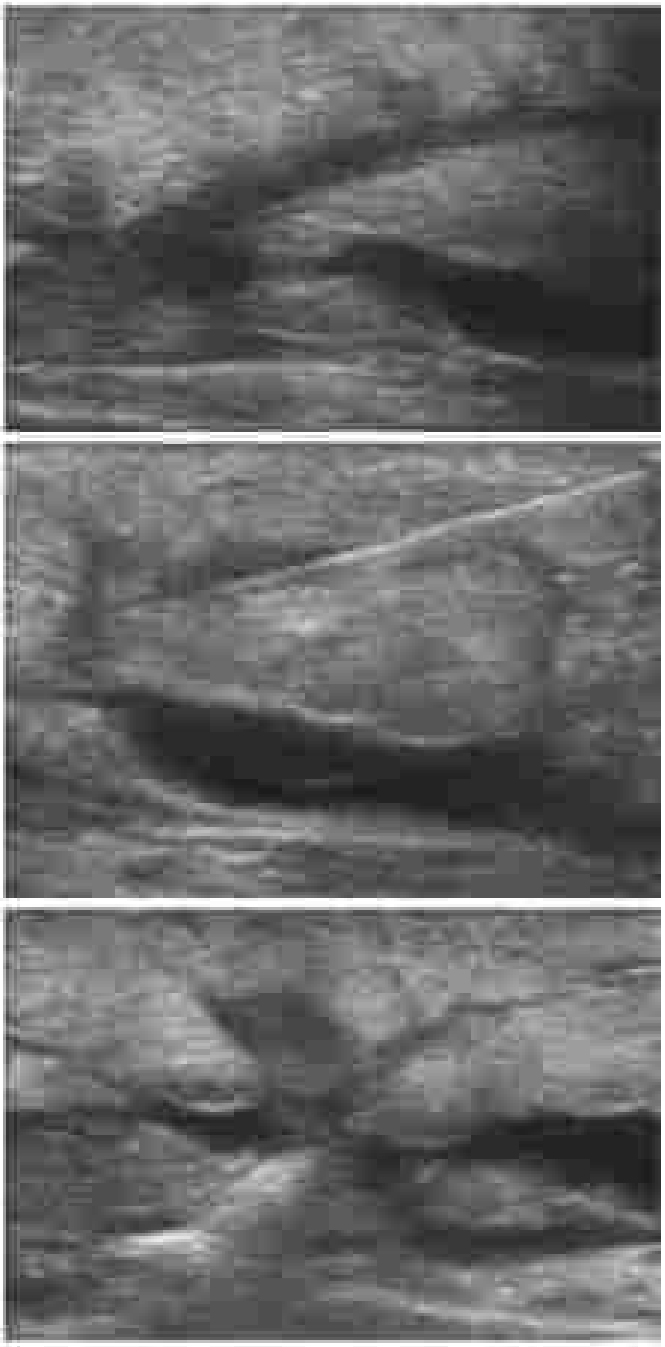

FIG. 8 Endovenous laser ablation treatment of incompetent perforator after local anesthesia infiltration.

Steps for mechanochemical ablation of saphenous veins:

1. The leg is prepped and the vein is accessed as per the RFA technique. Access can be much lower in the calf than for thermal ablation because there is no risk of thermal nerve injury.
2. Place 6F to 7F introducer at 45° angiocath into the vein.
3. A syringe is connected to the open end of the microsheath or angiocath while preparing the catheter.
4. Flush the ClariVein (Vascular Insights) catheter with saline. Place the stopcock in the closed position on the catheter luer lock. Have the sidearm face laterally when attached.
5. Attach the 5-mL sterile syringe containing sclerosant (typically 1% polidocanol or 1% to 3% sodium tetradecyl sulfate) to the stopcock. Ensure no air bubbles.
6. Place the catheter into the sheath or angiocath.

FIG. 9 Initial pull-back segment of ClariVein.

7. Under ultrasound guidance, place the wire tip at least 2 cm distal (inferior) to the SFJ. For SSV ablation, place the wire tip just distal to the fascial curve, within the straight segment of the SSV. If a gastrocnemius vein connects to the SSV, place the wire tip 2 cm inferior to the insertion.
8. Depress trigger briefly to test battery. An LED indicator should turn green.
9. Weld the catheter cartridge to the handle unit.
10. Pull back the cartridge wing further into the handle groove and turn slightly counterclockwise, clicking into the second stop position.
11. The tip of the fiber is exposed approximately 2 cm past the end of the sheath.
12. The index finger depresses the motor trigger while the thumb delivers sclerosant by pressing the syringe plunger after the stopcock is turned open.
13. Continue motor for 3 seconds to produce vasospasm with simultaneous pullback for 0.5 cm and initiate delivery of sclerosant after 0.5 cm pullback.
14. Continue treatment while pulling back 1.5 mm/s.
15. Treatment is stopped when 3 to 4 cm of catheter is left in the leg. A white mark on the catheter marks 4 cm distal to the catheter tip and alerts that only a short segment of catheter is remaining within the vein. Remember to pull the access device out of the vein and skin over the catheter before the catheter tip reaches the access site to ensure treatment of distal vein segments.
16. Once the vein segment is treated, ultrasound imaging of the vein is performed to assess for vein closure.
17. If the vein is patent, immediate retreatment is accomplished by passing the sheathed catheter tip proximally again for retreatment.
18. If the vein is occluded, the wire tip is redeployed by unclipping the syringe, twist the cartridge wing clockwise, and move the handle groove from the second lock position to the first.
19. Withdraw the catheter. Unbraid the wire and inspect.
20. Apply compression over the access site for hemostasis.

Endovenous Closure with Cyanoacrylate: Glue

Rather than using heat or sclerosant, VenaSeal (Medtronic) uses a medical adhesive to close the incompetent vein (Fig. 12). This mechanical technique also avoids nerve injury and then need for procedural anesthesia around the vein. The glue within the vein is technically a foreign body. There is a small population of patients who appear to have a sensitivity to the compound, and a local inflammation or phlebitis has been reported in up to 20% of treated veins or side branches. Steps for VenaSeal of the great/small saphenous veins include the following:

1. Prep the appropriate leg in the standard, circumferential sterile fashion.
2. Optional: a quick, sterile ultrasound scan is performed to mark the skin overlying the targeted treatment vein.

3. Access the vein percutaneously using ultrasound guidance after numbing the superficial skin with lidocaine. Access is routinely initiated at the most distal level of reflux. There is no risk of thermal nerve injury.
4. Insert the microwire and sheath, remove wire and dilator.
5. Advance the 0.035 J wire through the sheath into the vein and position just caudal to the junction. Confirm position under ultrasound.
6. Remove the introducer sheath over the wire and advance the 2Fr introducer/dilator from the system over the J wire to the junction.
7. Remove the wire and inner dilator.
8. Flush the sheath with sterile saline using a flushing syringe. Keep the syringe in place.
9. Position the tip of the sheath 5 cm inferior the junction under ultrasound guidance.
10. Extract the VenaSeal adhesive from its vial with a 3cc syringe. Purge air.
11. Connect the 3 mL syringe to the 5Fr catheter. Lock the 3 mL syringe attached to the catheter to the dispenser gun.
12. Prime the catheter by pulling the trigger to advance the adhesive to within 2 to 4 cm of the distal catheter tip.
13. Remove the saline filled flushing syringe from the introducer.
14. Insert the primed catheter/gun complex into the introducer and advance until the laser mark on the catheter is at the hub of the sheath.
15. Pull the sheath caudal another 3-4 cm. Advance the catheter cephalad and lock the sheath to the catheter/gun complex.
16. Verify tip is 5 cm away from the junction.
17. Position the ultrasound probe just cephalad to the catheter tip and apply pressure to compress the junction.
18. Deliver 0.10 mL of adhesive to the vein by pulling the trigger of the gun. Hold the trigger down for 3 seconds.
19. Immediately pull back 1 cm and deliver another 0.10 mL of adhesive and hold for 3 seconds.
20. Pull back the entire system 3 cm. Hold transverse compression at the junction for a minimum of 5 minutes.
21. Locate the catheter tip position with ultrasound. Apply probe compression caudal to the previous injection and cephalad to the catheter tip and deliver 0.15 mL of adhesive and hold the trigger down for 3 seconds.
22. Immediately pull back the entire system 3 cm and hold probe compression for 30 seconds.
23. Repeat steps of adhesive injection, pull back, and compression for 30 seconds, until 5 cm cephalad from access site.
24. Remove all catheters and apply manual pressure for hemostasis.

Polidocanol Endovenous Microfoam

Varithena (BTG Corp) is a commercially prepared 1% polidocanol microfoam that is uniform in density, size, and stability. This displaces blood within the incompetent saphenous vein, filling the vein, and damaging the endothelium with polidocanol subvenous. This nonthermal technology does not require tumescent anesthesia.

Steps for Varithena of the great saphenous veins are the following:

1. Prep the appropriate leg in the area of cannulation. Ultrasound as previously described, with special attention to marking perforators and large branches.
2. Access the vein percutaneously using ultrasound guidance after anesthetizing the superficial skin with lidocaine. Access is routinely initiated at the most distal level of reflux. There is no risk of thermal nerve injury.
3. Secure the intravenous or micropuncture catheter.
4. Elevate the leg 45 degrees.
5. Carefully the foam by connected the syringe to the canister and activating the canister to infuse foam into the syringe in 5 mL increments.
6. Inject the foam into the intravenous catheter while compressing the vein distally and compressing any perforators. Inject approximately 1 mL/s in the GSV and 0.5 mL/sec in accessory veins.
7. Monitor displacement of the foam into the saphenous vein during injection. Once the leading edge reaches 5 cm from the SFJ, occlude SFJ with an ultrasound probe for at least 5 minutes. At this point pressure to released from the distal aspect of the treated vein and over large branches. Pressure to continued over the perforators.
8. A maximum of 15 mL of foam is to be given in each treatment session. Patients can be brought back in as little as 24 hours to have repeat treatment as needed.
9. After 5 minutes, confirm with ultrasound that GSV spasm has occurred.
10. Remove IV. Hold external compression for hemostasis.
11. Additional local injections into untreated varicosities can be performed using a 23 gauge butterfly needle.
12. Keep leg elevated for 10 minutes while bandaged and compression is applied.

Postoperative Considerations for Endovenous Surgical Techniques

Most physicians use some type of compression for 7 to 10 days. The exception to this is cyanoacrylate closure, which does not require any postprocedure compression. Varithena instructions for use suggest compression for 14 days. Postprocedural duplex scanning is often performed within 48 to 72 hours of any vein ablation to assess for DVT and confirm closure of the treated vein. Patients are encouraged to ambulate immediately postprocedure and keep up normal activities as tolerated, including exercise.

Potential complications of all endovenous surgical techniques include postprocedural pain, ecchymosis, hematoma, infection, superficial vein phlebitis, deep vein thrombosis, and pulmonary embolism. Specific to thermal ablation, skin burn complications and nerve injury can occur if tumescence is not adequate or treatment involves the lower calf. Endovenous heat induced thrombosis (EHIT) is a specific complication to thermal ablations and is the formation of thrombus in the GSV, extending into the common femoral vein. Although often avoided by initiating treatment 2.5 cm away from the junction, the treatment of EHIT depends on the degree of clot extension into the deep system. Sclerosant use in endovenous surgical techniques, uniquely can cause neurologic complications such as strokes and transient ischemic attacks. Although rare and often self limiting, these symptoms can be quite jarring for both the physician and patient.

Open Surgical Techniques

Most varicose vein surgery is amenable to minimally invasive endovenous techniques. However, open techniques still have a role in treating varicose veins.

- If the target saphenous vein is less than 1 cm from the skin and the distance cannot be increased by tumescent anesthesia, thermal ablation is contraindicated because of the increased risk of thermal injury to the skin. Nonthermal or open techniques are thus preferred.
- Dilated, aneurysmal saphenous veins greater than 2.5 cm are preferentially treated by open techniques due to the risk of superficial thrombophlebitis and EHIT after endovenous treatment.
- The tortuosity of the saphenous vein may limit the passage of catheters. If the patient is not suitable for polidocanol endovenous microfoam, open surgery is then preferred.

Great Saphenous Vein High Ligation and Stripping

- After the standard sterile prep of the affected limb in the supine position, an oblique 2 to 4 cm incision is made over the SFJ as identified preprocedurally by duplex.
- The subcutaneous tissue and saphenous fascia are divided with electrocautery.
- Placement of a self retainer retractor will reveal the GSV underneath.
- The GSV close to the junction to the common femoral vein (CFV) should be dissected.

- Completely visualize the GSV proximally and distally to ensure the anatomy is appreciated and that the GSV is not injured.
- Place two vascular clamps on the GSV: 0.5 cm from the SPJ and the second one distally. Divide vein with Metzenbaum scissors.
- Double ligate the saphenous vein stump with 2.0 silk suture. Information may also come from the surgical site.
- The stripper is inserted into the distal aspect of the divided GSV and advanced to the upper part of the calf. This can be guided and detected manually or with ultrasound as dictated by body habitus.
- Stab the skin just above the end of the stripped with an 11 blade.
- Push the tip of the stripper outside the skin. Dissect the vein and ligate the distal end and divide the vein after the proximal GSV is tied to the stripper.

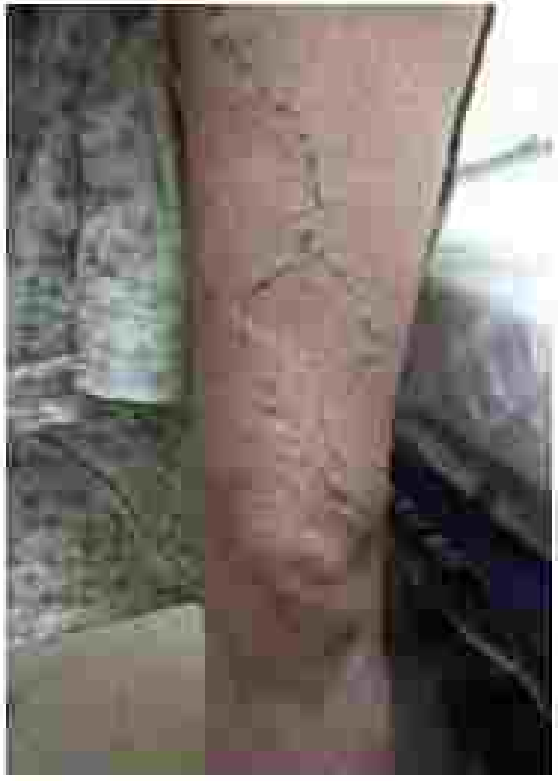

FIG. 7 Patient's veins are marked preprocedurally while patient is standing.

- The stripper and GSV are pulled out by an eversion technique.
- Place pressure on the GSV canal and place a pressure wrap on the leg for hemostasis.
- Close groin incisions in two layers: 2.0 Vicryl sutures for the fascia and 4.0 Monocryl for the subcutaneous skin.

Small Saphenous Vein Ligation and Stripping

- After the standard sterile preparation of the affected limb in the prone position, a transverse incision is made 2 cm below the SPJ, identified by duplex.
- After dissection of the superficial fascia, the SSV is identified and dissected out, avoiding the sural nerve.
- Placement of a self-retainer retractor will reveal the SSV underneath.
- All branches of the SSV at the SPJ should be double ligated and divided.
- Completely visualize the popliteal vein proximally and distally to ensure no missed SSV tributaries near the SPJ.
- Place two vascular clamps on the SSV: 0.5 cm from the SPJ and the second one distally. Divide vein with Metzenbaum scissors.
- Double ligate the saphenous vein stump with 2.0 silk suture.
- The stripper is inserted into the divided SSV and advanced to the upper part of the calf.
- Stab the skin just above the end of the stripped with an 11 blade.
- Push the tip of the stripper outside the skin. Dissect the vein and ligate the distal end and divide the vein after the proximal SSV is tied to the stripper.
- The stripper and SSV are pulled out by an eversion technique.
- Place pressure on the SSV canal and a wrap on the leg for hemostasis.
- Close larger incisions in two layers: 2.0 Vicryl sutures for the fascia and 4.0 Monocryl for the subcutaneous skin.

Phlebectomy

- All targeted veins should be marked preprocedurally, while the patient is standing (Fig. 7).
- After the standard sterile prep of the affected limb, using an 11 blade, small incisions are made along the previously marked vari cosities, following the direction of the Langer's lines, with the distal incisions being made first.
- Through the incision, the vein is hooked and pulled out of the skin and grasped with a pair of forceps or mosquitos as much as possible before being torn (Fig. 8).

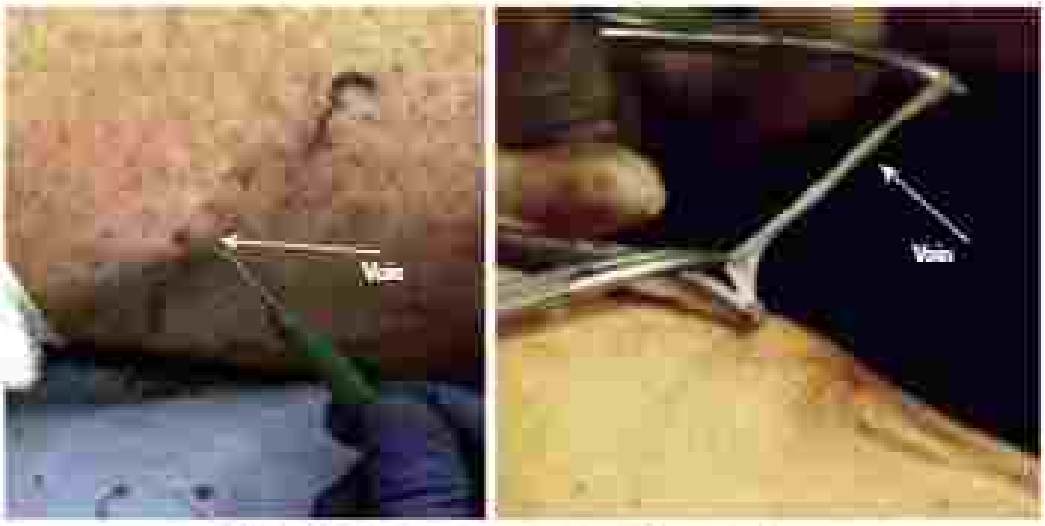

FIG. 8 Vein is hooked and grasped with a pair of mosquito clamps.

- A wrap is started at the distal most incision and the leg is wrapped as the procedure moves cephalad. This minimizes blood loss and ensures distal hemostasis by the end of the procedure.
- Either close the incisions with 4.0 Monocryl or place Steri Strips.

Transilluminated Powered Phlebectomy

Although traditional stab phlebectomy can be performed often in the ambulatory setting, with a scalpel and vein hook, commercial transillumination devices exist to assist in locating the vein. Advantages of transilluminated powered phlebectomy include a limited number of incisions, removal of veins under direct visualization, and a faster removal of varicose veins, especially in clusters (Fig. 9). The power phlebectomy system is made of a central tower with two handpieces. One handpiece is introduced through a small incision to provide proper transillumination (Fig. 10) while another handpiece is introduced to hydrodissect the vein. Small punch incisions (Fig. 11) are made to allow for drainage of the blood and tumescence that may collect in the vein tract to limit postprocedural hematoma and bruising. This procedure is typically performed under general anesthesia.

Postprocedural Considerations for Open Surgical Techniques

- Patients should have compression to the treated leg immediately postprocedurally
- Check for bleeding at the incision sites
- Check for paresthesias of the treated leg
- Mobilize as soon as possible

Cosmetic Treatment of Spider Veins

A thorough history and physical examination should always be performed with any patient evaluation, but with a cosmetic vein evaluation in particular, specific attention should be paid to the patient's goals and expectations. Pretreatment consultation should include discussion of previous treatments and their response. Unrealistic expectations should be avoided. Photo documentation of before and after treatment is recommended. Patients who are pregnant or breastfeeding should not undergo sclerotherapy. Patients who take ethinylestradiol have a higher risk of permanent hyperpigmentation (staining). Patients with a patent foramen ovale should also proceed with sclerotherapy with caution.

Sclerotherapy

Sclerotherapy destroys the vein by direct injection of solution to induce endothelial injury and collapse. Although many agents have been used, the most commonly used sclerosing agents are hypertonic saline, sodium tetradecyl sulfate (STS), and polidocanol (POL).

Hypertonic saline is inexpensive and has minimal allergy potential but is historically painful and caustic to soft tissue outside the vein. STS is less painful and can be used from spider to larger veins (up to 1 cm). It is contraindicated in patients with severe asthma. POL is nearly painless, minimally allergenic, and ulceration with extravasation is rare. It can be used with all sizes of veins up to 1 cm. All sclerosants can cause hyperpigmentation but can be mitigated to some extent with the amount of volume and concentration used.

For telangiectasias and smaller veins, direct injection of a liquid sclerosant with a 30- or 32-gauge needle is recommended. Doses of

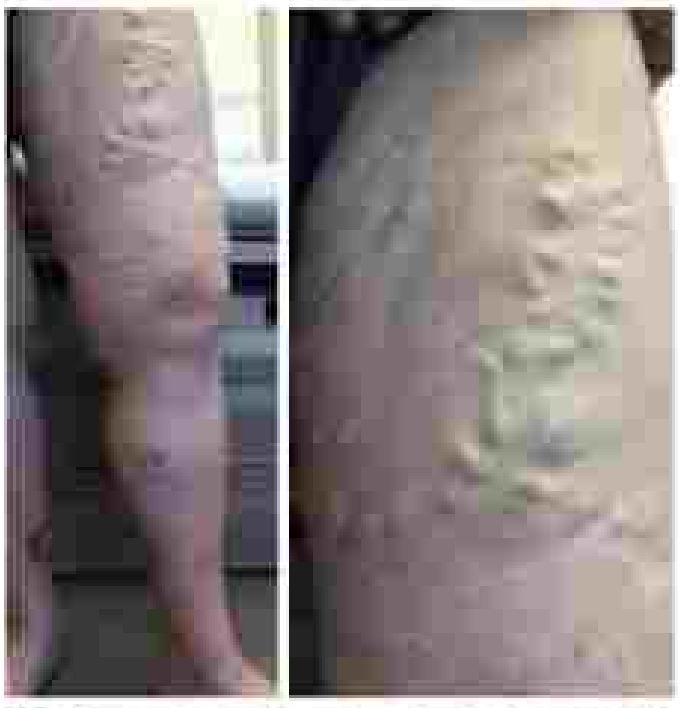

FIG. 9 Symptomatic varicosity appropriate for open phlebectomy or transilluminated powered phlebectomy.

FIG. 10 Transillumination of the vein.

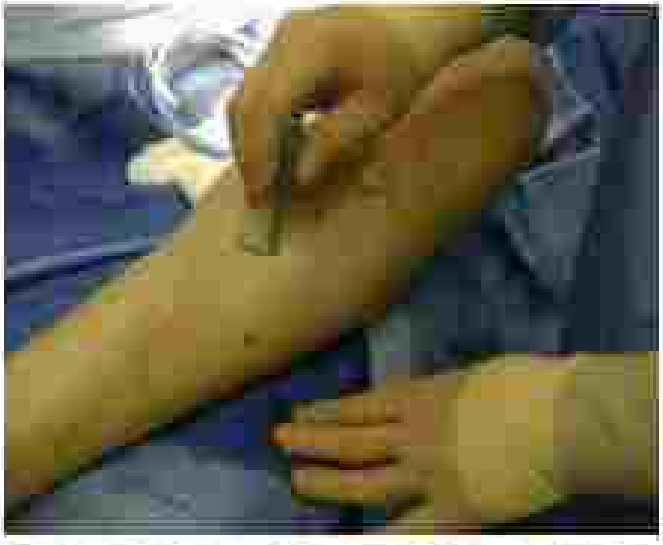

FIG. 11 Small punch incisions are made along the treated vein to allow for drainage of the blood and tumescence.

FIG. 12 Tessari method of physician-compounded foam.

0.25% to 0.5% POL and 0.5% to 1.0% STS are typically used for small veins. The needle angle should be very shallow with the bevel up. The sclerosant is gently injected, so as to avoid extravasation.

Physician-compounded foam is created by mixing a gas (typically room air, or carbon dioxide) with the POL or STS to a 1:4 sclerosant to gas ratio, using agitation of the Tessari method (Fig. 12). Of note, creating foam from POL or STS is an off-label use of these FDA-approved sclerosants.

Physician-compounded foam is inexpensive and well tolerated but causes more neurologic side effects. Varithena is an available proprietary foam that delivers a commercially prepared microfoam with a POL/oxygen base. No studies directly compare the safety and efficacy of physician-compounded foam to Varithena, although to extensive trials and aftermarket analysis there have been no published neurologic side effects of Varithena, whereas neurologic side effects, usually transient, are quite common with physician-compounded foam.

Foam sclerotherapy through a 22G butterfly needle allows for a longer period of contact with the vessel wall due to blood displacement rather than sclerosant dilution and a longer period of sclerosant/endothelial contact. The foam is also echogenic under ultrasound (Fig. 13), allowing more precise delivery to targeted veins such as incompetent perforators.

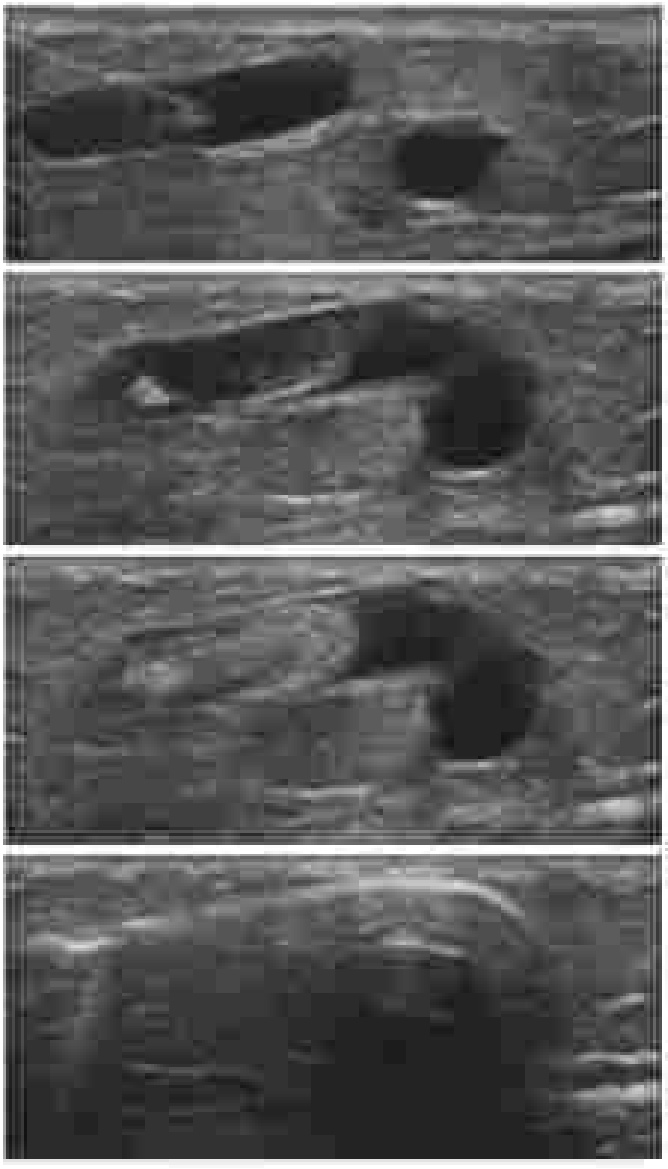

FIG. 13 Ultrasound-guided injection of physician-compounded foam. The foam can be seen to gradually fill and opacify the treated vein.

Comparative Studies

Rasmussen et al. performed 500 consecutive patients in a randomized clinical trial comparing EVLA, RFA, physician-compounded foam sclerotherapy, and surgical stripping of incompetent saphenous veins. Patients were examined by duplex imaging before procedure, after 3 days, at 1 month, and at 1 year. All examined treatments were initially efficacious, but recanalization was highest after foam sclerotherapy. Both RFA and foam sclerotherapy were associated with faster recovery and less postprocedural pain than EVLA and stripping, by QoL measures. A follow-up study at 3 years compared outcomes of recurrence, Venous Clinical Severity Score, and QoL. The treatment modalities were comparably efficacious and resulted in similar improvements in Venous Clinical Severity Score and QoL, but recanalization and reintervention were significantly more often in foam sclerotherapy. The newer nonthermal technologies all have performed very well in initial testing, with very high closure rates and patient satisfaction.

CONCLUSIONS

Endovenous treatments have revolutionized venous therapy, with current methodologies able to treat complex superficial venous pathology in the office with minimal side effects and recovery time. Thermal ablation is the most established of these techniques and delivers high efficacy venous closure with few complications. Radiofrequency may have the most durable results. Newer nonthermal technologies enable even more comfortable treatments that in short- and mid-term follow-up appear safe and effective. Sclerotherapy is a versatile technique to eliminate everything from small cosmetic veins to refluxing perforators causing ulceration. Choice of techniques depends on patient presentation, operator skill, and treatment setting. A thorough discussion of treatment options, expectations, recurrence, and possible morbidities is a mandatory part of any venous evaluation.

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Lymphedema

George Kokosis, MD, Hallay Darrach, BS, and Jamie M. Sacks, MD, MBA, FACS

Lymphedema is a chronic, debilitating disease of the lymphatic system that results from failure of the lymphatic transport capacity to overcome the lymphatic load. Impairment of lymphatic transport leads to interstitial accumulation of a protein-rich fluid that includes excess water, plasma proteins, extravascular blood cells, and cell products that are normally transported by the lymphatic system from the interstitium into the circulation. In addition, the peripheral lymphatic vessels play a significant role in the immune system and serve to transport leukocytes and regulate the immune response.

Progressively, lymphatic impairment leads to dilation of the remaining functional lymphatic vessels, failure of valves to maintain unidirectional flow, and eventually stasis. Accumulation of these macromolecules increases the osmotic pressure and influx of excess water into the interstitium. Persistent stasis and abnormal fluid accumulation lead to an inflammatory process mediated mainly by CD4+ cells that over time results in progressive fibrosis of the lymphatic vessels obliterating the lumen, as well as eliminating the lymphatic pumping potential. Lymphedema ensues when the capacity current overcomes the load of lymphatic fluid. Additionally, fibroadipose tissue deposition is promoted in the subcutaneous and subdermal tissues. This progressive underlying pathophysiologic process is reflected by initially soft, pitting edema, followed by induration, hypertrophy, acanthosis, hyperkeratosis, and skin breakdown. Infectious complications follow, with recurrent episodes of cellulitis and lymphangitis. In its rarest form, this process can lead to malignancy, with highly aggressive lymphangiosarcoma (Stewart–Treves syndrome) being a known clinical entity associated with chronic lymphedema. The International Society of Lymphology updated the staging guidelines in 2016 (Box 1).

ETIOLOGY

Lymphedema can be primary or secondary. Primary lymphedema results from a developmental abnormality, lack of an offending injury, and frequently a positive family history. This form of lymphedema may present at birth, during adolescence, or later in life. Primary lymphedema can further be subdivided into congenital lymphedema, lymphedema praecox, and lymphedema tarda. *Congenital lymphedema or Milroy disease* (10% to 25% of primary lymphedema) is seen within the first 2 years of life. It usually affects females (2:1 ratio to males), is bilateral, and involves the lower extremities. It often is not progressive and may improve spontaneously with time. The associated gene is *FLT4* and inheritance is autosomal dominant. *Lymphedema praecox or Meige disease* (65% to 80% of primary lymphedema) is seen before the age of 35, typically at puberty. It predominantly affects females (4:1 ratio to males), is unilateral, and involves the lower extremities. The associated gene is *FOXC2*, and inheritance is autosomal dominant. *Lymphedema tarda* occurs spontaneously after the age of 35 and is the rarest of all primary forms.

Secondary lymphedema is an acquired failure of the lymphatic system. Inciting events can be either a disease, trauma, radiation, or iatrogenic causes. Worldwide, the most common cause is infection by the nematoda *Wuchereria bancrofti*, transmitted by various mosquito vectors, an entity that affects almost 300 million people in developing countries. Adult filarial worms reside in and obstruct lymphatic channels, causing irreversible scarring and fibrosis and often massive edema. In developed countries the vast majority of the cases are due to secondary lymphedema, and of these, nearly all are related to cancer therapy. In the United States the most common cause is secondary to treatment of breast cancer. In 20% to 30% of patients undergoing axillary lymph node dissection, they will go on to have secondary lymphedema develop. The advent of sentinel lymph node biopsy dropped the prevalence of this disease to 7% to 8%. Adjuvant radiation therapy used for the local treatment of nodal disease can lead to upper or lower extremity lymphedema. Other factors such as trauma, infection, and obesity contribute to secondary lymphedema.

DIAGNOSIS

The workup for lymphedema starts with a thorough history and physical examination (Box 2). The patient complains of swelling, heaviness, tightness, and decreased quality of life. Other causes of extremity edema must be ruled out first, mainly venous insufficiency, deep vein thrombosis, and cardiac, renal, and hepatic failure.

Physical examination maneuvers that can aid with the diagnosis of lymphedema are limb circumference and volume measurement. Limb circumference can be measured at defined anatomic locations—for example, 5 cm above and below the olecranon. Differences of 2 cm when compared with the contralateral limb can be diagnostic; however, their utility is limited by interrater variability and in patients with high body mass index. Volume measurements can be performed with water displacement, with volume differences of 200 ml, or 10% considered diagnostic.

Imaging studies are as important and in diagnosis but also planning of surgical procedures. Lymphoscintigraphy uses radionuclide technetium (^{99m}Tc) to assess drainage of the lymphatic basin. Additionally the transport index can be calculated through this study to measure the severity of the disease. Indocyanine green (ICG) near-infrared lymphangiography has been proven useful in diagnosis and planning of lymphedema treatment. In an off-label use of the ICG, injection in the web space of the extremity digits can help visualize the lymphatic system and diagnose disruption of lymphatic flow, tortuous abnormal lymphatics, and dermal backflow (diffuse leakage of dye into the interstitium). Magnetic resonance lymphangiography has gained popularity in assessment of the lymphatic system, as well as the surrounding soft tissue changes. Intravenous injection of low-enriched is used to isolate the contrast enhancement of the venous system to aid with direct visualization of the lymphatic system. These above-mentioned imaging modalities can help with operative

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Lymphedema

George Kokosis, MD, Hallay Darrach, BS, and Jamie M. Sacks, MD, MBA, FACS

Lymphedema is a chronic, debilitating disease of the lymphatic system that results from failure of the lymphatic transport capacity to overcome the lymphatic load. Impairment of lymphatic transport leads to interstitial accumulation of a protein-rich fluid that includes excess water, plasma proteins, extravascular blood cells, and cell products that are normally transported by the lymphatic system from the interstitium into the circulation. In addition, the peripheral lymphatic vessels play a significant role in the immune system and serve to transport leukocytes and regulate the immune response.

Progressively, lymphatic impairment leads to dilation of the remaining functional lymphatic vessels, failure of valves to maintain unidirectional flow, and eventually stasis. Accumulation of these macromolecules increases the osmotic pressure and influx of excess water into the interstitium. Persistent stasis and abnormal fluid accumulation lead to an inflammatory process mediated mainly by CD4+ cells that over time results in progressive fibrosis of the lymphatic vessels obliterating the lumen, as well as eliminating the lymphatic pumping potential. Lymphedema ensues when the capacity current overcomes the load of lymphatic fluid. Additionally, fibroadipose tissue deposition is promoted in the subcutaneous and subdermal tissues. This progressive underlying pathophysiologic process is reflected by initially soft, pitting edema, followed by induration, hypertrophy, acanthosis, hyperkeratosis, and skin breakdown. Infectious complications follow, with recurrent episodes of cellulitis and lymphangitis. In its rarest form, this process can lead to malignancy, with highly aggressive lymphangiosarcoma (Stewart–Treves syndrome) being a known clinical entity associated with chronic lymphedema. The International Society of Lymphology updated the staging guidelines in 2016 (Box 1).

ETIOLOGY

Lymphedema can be primary or secondary. Primary lymphedema results from a developmental abnormality, lack of an offending injury, and frequently a positive family history. This form of lymphedema may present at birth, during adolescence, or later in life. Primary lymphedema can further be subdivided into congenital lymphedema, lymphedema praecox, and lymphedema tarda. *Congenital lymphedema or Milroy disease* (10% to 25% of primary lymphedema) is seen within the first 2 years of life. It usually affects females (2:1 ratio to males), is bilateral, and involves the lower extremities. It often is not progressive and may improve spontaneously with time. The associated gene is *FLT4* and inheritance is autosomal dominant. *Lymphedema praecox or Meige disease* (65% to 80% of primary lymphedema) is seen before the age of 35, typically at puberty. It predominantly affects females (4:1 ratio to males), is unilateral, and involves the lower extremities. The associated gene is *FOXC2*, and inheritance is autosomal dominant. *Lymphedema tarda* occurs spontaneously after the age of 35 and is the rarest of all primary forms.

Secondary lymphedema is an acquired failure of the lymphatic system. Inciting events can be either a disease, trauma, radiation, or iatrogenic causes. Worldwide, the most common cause is infection by the nematoda *Wuchereria bancrofti*, transmitted by various mosquito vectors, an entity that affects almost 300 million people in developing countries. Adult filarial worms reside in and obstruct lymphatic channels, causing irreversible scarring and fibrosis and often massive edema. In developed countries the vast majority of the cases are due to secondary lymphedema, and of these, nearly all are related to cancer therapy. In the United States the most common cause is secondary to treatment of breast cancer. In 20% to 30% of patients undergoing axillary lymph node dissection, they will go on to have secondary lymphedema develop. The advent of sentinel lymph node biopsy dropped the prevalence of this disease to 7% to 8%. Adjuvant radiation therapy used for the local treatment of nodal disease can lead to upper or lower extremity lymphedema. Other factors such as trauma, infection, and obesity contribute to secondary lymphedema.

DIAGNOSIS

The workup for lymphedema starts with a thorough history and physical examination (Box 2). The patient complains of swelling, heaviness, tightness, and decreased quality of life. Other causes of extremity edema must be ruled out first, mainly venous insufficiency, deep vein thrombosis, and cardiac, renal, and hepatic failure.

Physical examination maneuvers that can aid with the diagnosis of lymphedema are limb circumference and volume measurement. Limb circumference can be measured at defined anatomic locations—for example, 5 cm above and below the olecranon. Differences of 2 cm when compared with the contralateral limb can be diagnostic; however, their utility is limited by interrater variability and in patients with high body mass index. Volume measurements can be performed with water displacement, with volume differences of 200 ml, or 10% considered diagnostic.

Imaging studies are as important and in diagnosis but also planning of surgical procedures. Lymphoscintigraphy uses radionuclide technetium (^{99m}Tc) to assess drainage of the lymphatic basin. Additionally the transport index can be calculated through this study to measure the severity of the disease. Indocyanine green (ICG) near-infrared lymphangiography has been proven useful in diagnosis and planning of lymphedema treatment. In an off-label use of the ICG, injection in the web space of the extremity digits can help visualize the lymphatic system and diagnose disruption of lymphatic flow, tortuous abnormal lymphatics, and dermal backflow (diffuse leakage of dye into the interstitium). Magnetic resonance lymphangiography has gained popularity in assessment of the lymphatic system, as well as the surrounding soft tissue changes. Intravenous injection of low-enhancing gadolinium is used to isolate the contrast enhancement of the venous system to aid with direct visualization of the lymphatic system. These above-mentioned imaging modalities can help with operative

BOX 1 Lymphedema Staging

Stage 0: Latent or Subclinical

- Impaired lymphatic transport
- No evident edema, subtle changes in tissue fluid composition
- Changes to subjective symptoms
- May last months or years before progression

Stage I: Spontaneously Reversible

- Early accumulation of protein-rich fluid
- Pitting edema
- Subsides with elevation

Stage II: Spontaneously Irreversible

- Accumulation of protein-rich fluid
- Pitting edema may progress to nonpitting as excess fat and fibrosis develop
- Does not resolve with elevation alone

Stage III: Lymphostatic Elephantiasis

- Nonpitting
- Significant fibrosis
- Trophic skin changes

Data from the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 2013;46(1):1.

BOX 2 Diagnostic Workup for Lymphedema

Thorough history and physical examination
Rule out causes of edema (basic laboratory tests for renal and liver function)
Infectious disease workup (in patients with travel history or exposure)
Lymphatic imaging (lymphoscintigraphy, magnetic resonance lymphatic mapping, indocyanine green imaging)

planning and lymphatic vessel anastomosis when the decision is made to use microsurgical techniques.

CONSERVATIVE MANAGEMENT

Conservative therapies are usually used in early stages of lymphedema when fluid accumulation is predominant to prevent development of the cascade of further edema, inflammation, and fibrosis. Conservative management can be burdensome, and the main reason for failure is the need of lifelong treatment and thus noncompliance. It is important to discuss compliance with patients upfront, stressing that individual investment and long-term compliance are central to managing this chronic, lifelong condition. Conservative management includes lifestyle changes, pharmacologic treatments, compressive and decongestive therapy, laser therapy, and, more recently, advancements such as stem cell and growth factor or gene therapy. Additionally, a multidisciplinary team including a physiotherapist, an occupational therapist, a social worker, and even psychosocial support can be key in success of conservative modalities.

Lifestyle changes include daily hygiene and skin care to reduce skin breakdown and infection. Weight loss and aerobic exercise have recently been proven to help decrease the severity of lymphedema in large clinical studies.

Pharmacologic treatments are an area of study in lymphedema. If infection occurs, antibiotics are valuable in immediate treatment. Beyond antibiotics, further pharmacologic treatment has not been proven beneficial. Diuretics have been used historically; however, they are useful only in the case of comorbidities requiring their use. Diuretics may actually lead to further fibrosis and increased interstitial protein accumulation. The use of nutritional supplements such as sodium selenite or vitamin E with pentoxifylline have not demonstrated any significant benefit in patients with lymphedema.

Compressive therapy with compression garments, multilayered inelastic bandaging, and controlled compression therapy are widely used. Compression garments are utilized as swelling decreases. These methods reduced volume of edema by 30% to 45% approximately. External sequential compressive devices also have been used with variable success. Basic range of motion exercises can be a useful strategy as a complement to limb compression and elevation. Contraindications to compression include arterial disease, deep vein thrombosis, and painful postphlebitic syndrome.

Decongestive therapy is a more time intensive strategy. This modality involves manual lymphatic drainage through massage and use of compressive garments and intermittent pneumatic pumps. The combination of the above has been shown to be more beneficial than each individual approach of decongestive therapy. Additional nonsurgical modalities have been explored in recent years. Low-level laser therapy stimulates tissue changes through mechanical mechanisms. Autologous bone marrow–derived stem cells injected in the lymphedematous extremities resulted in significant volume reductions reported in recent studies. Growth factors (vascular endothelial growth factor [VEGF]) and gene therapy with adenoviral vectors have been tested in animal models, with promising results in decreasing swelling and increasing lymphangiogenesis.

SURGICAL TREATMENT

Surgical approaches to lymphedema had historically been used as a last resort in refractory cases; however, advances in microsurgical techniques have made surgery useful even in early stages of the disease. There are two main categories of surgical approach to lymphedema: Physiologic procedures and debulking or reductive procedures. Physiologic procedures are usually indicated in early stages of lymphedema to restore lymphatic continuity and improve the anterograde flow of lymph. Debulking or reductive procedures are more useful in later stages to remove fibrotic fatty tissue. Conservative therapy should be continued immediately after any surgical procedure; however, the goal is that the intensity of treatment should be significantly decreased.

Physiologic Procedures

Advances in technology that led to developing microscopic with higher magnification and instruments to support these "super microsurgical" approaches was paramount in the evolution of physiologic procedures. Lymphovenous anastomoses (LVA) and vascularized lymph node transfer (VLNT) have been shown to be effective treatment options in early stages of lymphedema.

LVA

This procedure was introduced in 1963 by Sherman and colleagues. Subdermal lymphatic vessels are anastomosed to adjacent venules using ICG near infrared lymphangiography (Box 3). This creates an artificial shunt to drain lymphedematous fluid into the venous circulation and thus improve lymphatic flow and drainage. ICG near infrared lymphangiography can be performed before surgical planning to help determine patient eligibility for LVA.

Chang et al reported a series of 100 patients undergoing LVA, resulting in improvement of symptoms in 96% of patients while they were able to show improvement in volume differential in 74%. Volume differential was reduced by >15% at 12 months after surgery for patients with disease stage I and II and overall 42%. Whereas this previous study focused more on upper extremity lymphedema, Campisi et al have reported their experience with more than 3600 patients treated for both upper and lower extremity lymphedema for more

BOX 3 Lymphovenous Bypass

1. Begin with lymphatic lymphangiography.
2. Inject 0.01 to 0.02 mL of indocyanine green into the web spaces in the extremity.
3. Visualize fluorescent images and mark visible lymphatic pathways and injection sites.
4. Inject local anesthetic with epinephrine.
5. Inject 0.1 to 0.2 mL of lymphazurin into the web spaces in the extremity.
6. Take subdermal postinjection dissection down to stained and lymphatic channels.
7. Use microsurgical *connection* to reestablish lymph flow with end-to-end anastomoses. End-to-side anastomoses can be used when veins are larger than the lymphatic channel.
8. Confirm that shunts are patent by observing passage of lymphazurin into the vein.
9. Evaluate postoperative flow and imaging studies.

BOX 4 Vascularized Groin Lymph Node Transfer

Donor Site

1. Palpate femoral pulse and design elliptical skin paddle lateral to pulse, inferior and parallel to the inguinal ligament.
2. Incise skin superficially.
3. Dissect from distal to proximal; see fascia of sartorius muscle as deep plane.
4. Harvest the superficial circumflex iliac vessels, lymph nodes, and surrounding fatty tissue.

Recipient Site

1. Make a transverse incision on the recipient site (e.g., wrist).
2. Transfer flap onto the recipient site.
3. Perform microvascular anastomosis to the radial artery and cephalic vein.
4. Consider *mesh* for extra coverage of the flap with a split-thickness skin graft.
5. Use a skin paddle for monitoring.

than 40 years using LVA or interposition vein grafted shunts for LVA that resulted in reduction of excess volume of more than 80%, with an average follow up of 10 years or more. There are, however, articles in the literature reporting variable results in symptomatic and volume improvement, and part of this discrepancy has to do with the lack of validated questionnaires or standardized measurements respectively.

LVA has also been used prophylactically in patients undergoing lymph node dissection. Boccardo et al reported their experience with 4 year follow up in 74 patients treated with prophylactic LVA at the same time with axillary lymph node dissection (ALND) what they called LYMPHA (Lymphatic Microsurgical Preventive Healing Approach). Lymphedema developed in only 8%, which compares favorably to the reported prevalence of 10% to 65%. Feldman et al performed the same approach in 27 patients (ALND and LYMPHA) but also had a control group of 16 patients (ALND) no LYMPHA). In a short-term follow up 36 months) the treatment group had development of lymphedema in 12.5% versus 50% in the control group.

VLNT

VLNT was first demonstrated in rats by Shioud in 1979 and used for a human patient by Chaoliu in 1982. This procedure harvests healthy fat tissue and lymph nodes and transfers them into the affected site (Box 4). Two mechanisms have been proposed for the effectiveness of VLNT. The first is the lymphatic "seed," the bridge of proximal and distal lymphatic vessels in the recipient site and a process of lymphangiogenesis stimulated by growth factors produced by the lymph nodes (VEGF) and antifibrotic interleukin 10. The second mechanism is the lymphatic "pump," which stems from lymphovenous communication within the lymph nodes of the transferred flap. Common donor sites are the supraclavicular area, the groin and the omentum. Chang et al have thoroughly discussed the supraclavicular lymph nodes found inferiorly within the posterior triangle of the neck, in the hamilla of fat between omohyoid and anterior scalene muscles. The fat is supplied by the underlying transverse cervical vessels. The nodes are usually harvested from the contralateral side to avoid any further disruption of the lymphatic flow. On the left side the surgeon should avoid the thoracic duct during dissection. The groin lymph nodes are another common donor site. It offers the advantage of a concealed scar and the use of a large skin paddle when needed. The lymph nodes are located at the level of the muscular aponeurosis and subcutaneous fat medial to the femoral artery. Preoperative magnetic resonance angiography has been used to identify lymph nodes, and Doppler imaging can confirm the location of the superficial circumflex vessels. Care must be taken not to dissect further caudally from the inguinal ligament or deep from the muscular aponeurosis, which risks damaging the lymphatic drainage to the lower limb. The benefit of using the groin flap is the opportunity to simultaneously perform an abdominal based autologous breast reconstruction and treat upper extremity lymphedema. However, other authors suggest staging these two approaches and only perform the groin lymph node transplantation once the autologous breast reconstruction has been deemed successful, this way the thoracodorsal vessels—as recipient vessels for the groin flap—are no longer needed for any potential salvage procedure (e.g., latissimus dorsi flap).

Dayan et al have suggested performing routine mapping of the lymphatic system to harvest only the expendable lymph nodes and to preserve those that drain the extremities and reduce donor site morbidity. Mapping of the lymphatic drainage is done by using technetium injected into the web spaces of the hand or foot and identifying the nodes using a gamma probe. Lymph nodes that drain the areas targeted for the flap are mapped using ICG (near infrared lymphangiography). In their study of 36 patients treated with VLNT and reverse lymphatic mapping, there had no donor site complications.

Another donor site that has gained popularity the last few years is the free vascularized omental lymph node transplant (VOLT). This is based off the right gastroepiploic vessels and can be harvested either through an approximately 8 cm upper midline laparotomy or via a minimally invasive laparoscopic approach. The remainder of the omentum is left behind to minimize the chances of donor site lymphatic congestion. However, the intraabdominal component of this approach does have associated risks, such as hernia development, bowel perforation and pancreatitis. Nguyen et al reported their outcomes of 42 patients treated with VOLT and followed up for an average of 14 months, resulting in subjective improvement in 83% and excellent volumetric improvement in 22%. Dayan et al have recently suggested splitting the VLNT in two parts to transplant to the proximal and the distal/middle aspect of the affected extremity in the case of significant edema to maximize the lymphatic flow through the extremity.

Overall the use of VLNT has been associated with appropriate outcomes. A systematic review of 18 studies in 305 patients undergoing VLNT revealed improvements in swelling (whether measured as limb circumference or volumetric difference) in 86% to 90% of patients with volume difference on average of 22% and no need for postoperative compression garment in about 50%.

Debulking Procedures

More advanced stages of lymphedema with significant fluid accumulation or established fibrosis (stages III/IV) require debulking procedures. There are three different approaches, liposuction that has been used in the treatment of lymphedema in the recent years and more aggressive, older approaches such as the Charles procedure and the Sistrunk procedure.

BOX 5 Liposuction

1. Mark out the affected area and 2 cm beyond.
2. Choose port sites to effectively reach all areas, both proximally and distally.
3. Inject tumescent solution (1 L lactated Ringer's solution mixed with 1 mL ampule of epinephrine 1:1000 and 50 mL of 1% lidocaine) until blanching is achieved and a moderate amount of output is seen.
4. Wait 30 to 45 minutes.
5. Suction with a 4- to 6-mm cannula in a deep plane in all areas, followed by a 2- to 3-mm cannula in a more superficial plane for a smoother contour.
6. Close port sites with absorbable sutures.
7. Apply sterile dressings and a pressure garment.
8. Advise the patient not to shower or remove the pressure garment for 72 hours, and encourage the patient to walk at least three times a day.
9. After 3 days, the patient can shower daily and may begin massaging the affected areas.
10. The pressure garment should be worn for 6 to 10 weeks.

Liposuction was first used for brachial lymphedema in 1987. Since then, the technique was refined in 1993 (Box 5). It is useful in addressing large adipose tissue deposits. It is safe and quick and allows for immediate decrease in volume and pressure of the lymph fluid, decreasing the burden and thus promoting better lymphatic flow. It is usually indicated when the excess volume is greater than 400 mL. Contraindications include presence of more than pitting edema, metastatic disease, open wounds, coagulation disorders, and reluctance to wear compression garments after surgery. Risks include lidocaine toxicity, thrombosis, need for cutdown, hematoma, seroma, and contour irregularities. Cart et al, in a systematic review of all surgical approaches of lymphedema, analyzed the results of liposuction and found that liposuction achieved an average excess volume reduction (the percent decrease in additional volume of the lymphedematous extremity compared with the contralateral side) of 56.6%, with additional improved overall well-being.

The Charles procedure (described by Charles in 1912) is an aggressive approach including radical excision of skin and subcutaneous tissue down to muscle fascia or epimysium (Fig. 1 and Box 6). Excised skin is used for grafting on the fascia, or other donor sites can be used. The van der Walt modification allows for negative pressure dressing, with grafting to be done in a delayed fashion. This approach is indicated for severe cases and carries a high risk of complications, including destruction of the remaining lymphatic vessels, infection, ulceration, hyperpigmentation, dermatitis, unstable scars, and a severely altered aesthetic outcome (excessive resection of leg tissues and exacerbated foot lymphedema bottleneck deformity). The Sistrunk procedure (1940) is a planned, staged excision of the affected subcutaneous tissues. This technique has been modified over the last 80 years and involves burying dermal flaps within skin flaps (Box 7). Long-term results include a reduction of at least half of the affected tissue in 75% of patients. The Sistrunk procedure is safe, reliable, and predictable. Complications include nerve damage to the affected area, epidermolysis secondary to poor blood supply, wound dehiscence, and infection.

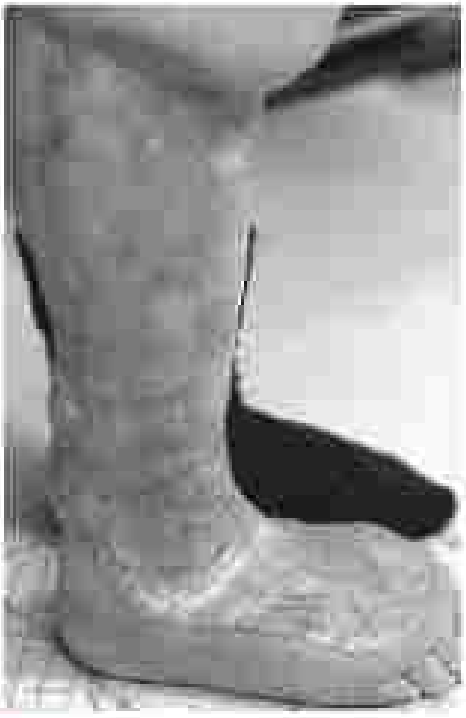

FIG. 1 Lower extremity after the Charles procedure.

BOX 6 Charles Procedure

1. Mark the lymphedematous area both proximally and distally.
2. Make an incision both medially and laterally down to the muscle fascia.
3. Excise all tissue superficial to this plane.
4. Remove the skin of the affected area with a dermatome for a split-thickness graft or with a knife for a full-thickness graft. If a full-thickness graft, make sure to remove all fat from the skin.
5. Use this graft to cover the exposed area.
6. Apply petroleum gauze or other nonadherent dressing over the graft.
7. Apply a pressure dressing via a vacuum-assisted device, bolster, or cotton.
8. Splint the extremity in the proper anatomic position.
9. Remove dressing after 3 to 5 days for a split-thickness graft or after 7 to 12 days for a full-thickness graft.

BOX 7 Sistrunk Procedure

1. Mark out the affected area.
2. Plan to excise and debulk sufficient tissue, leaving dermal flaps to bury beneath the skin to the closure. A variation of this is carried out in the Thompson procedure, in which dermal flaps are buried beneath the muscle.
3. Close the incision over drains.
4. Allow 12 weeks to heal before the next serial excision.

Combination of Procedures

Lymphedema, regardless of the stage, is a complex chronic process that requires multiple different modalities. Decongestive therapy is important and is almost always necessary, either alone or in combination with surgical procedures. More recently, combining different surgical approaches has become more common. Cart et al in their systematic review of the surgical treatment of lymphedema identified multiple different procedure combinations, including liposuction with VLNT, VLNT with Charles procedure, VLNT with LVA, and more in a total of eight studies involving 137 patients with variable results. Four of these studies used VLNT and identified the need for additional liposuction or radical reduction to 31.6% to adequately remove lymphedematous and fibrotic tissue. Likewise, in two LVA studies, an average of 16% of patients required liposuction after the LVA to achieve optimal reduction. The authors of this systematic review therefore suggest a thorough algorithm to approach lymphedema (Fig. 2).

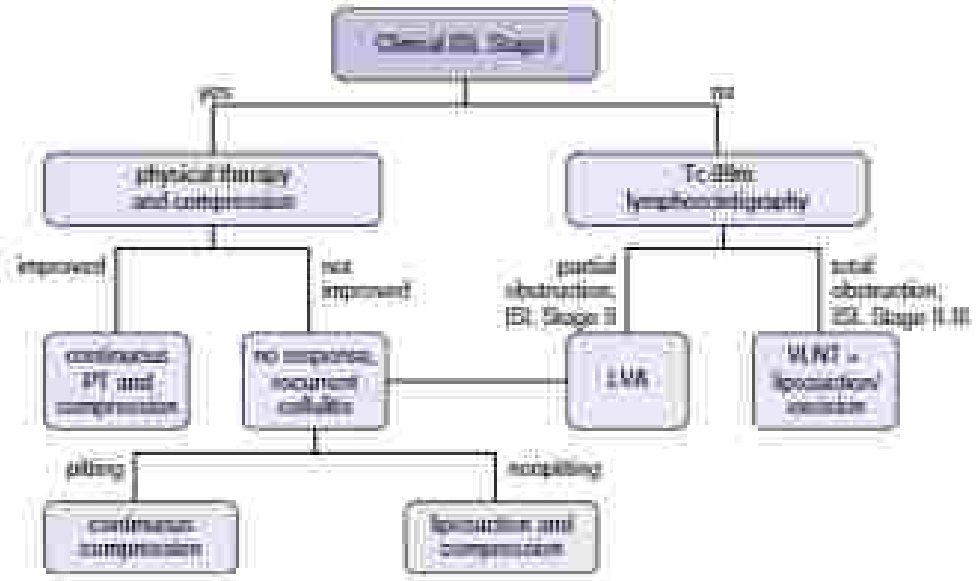

FIG. 2 Lymphedema treatment algorithm. ISL, International Society of Lymphology; LVA, lymphovenous anastomosis; PT, physical therapy; VLNT, vascularized lymph node transfer.

SUMMARY

Lymphedema is a challenging clinical problem that produces significant morbidity in a large population worldwide. All treatment modalities include long-term conservative measures along with support from a multidisciplinary team. Surgical procedures can be a useful adjunct to treatment according to the disease progression; physiologic procedures appear to be more successful in earlier stages of the disease, and debulking procedures are used only for later stages. Regardless of the treatment strategy chosen, patient commitment and lifestyle modifications are of paramount importance to achieving improvement in symptoms and quality of life.

SUGGESTED READINGS

Boccardo F, Casabona F, Deltetto F, et al. Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: over 4 years follow-up. *Microsurgery*. 2018;38(6):621–625.

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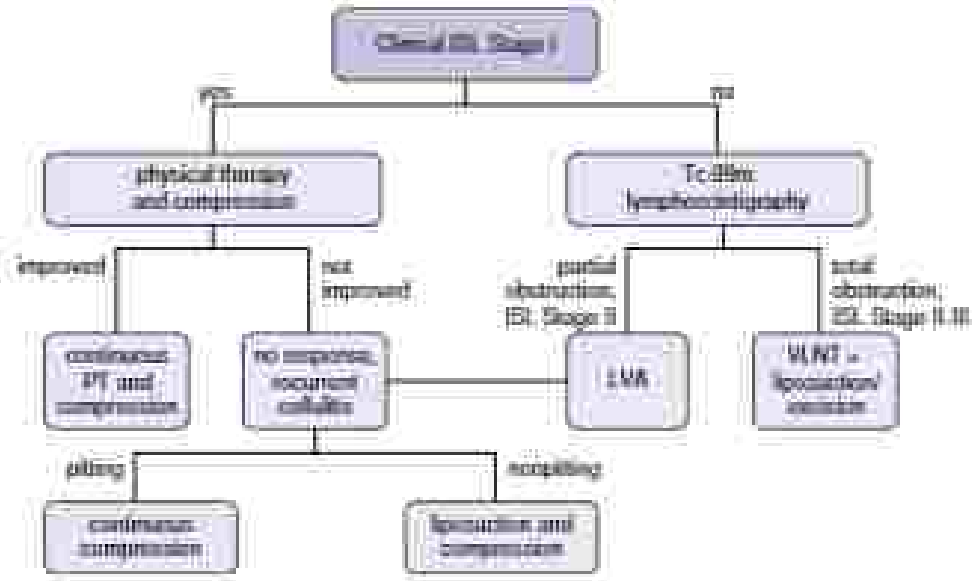
LOWER EXTREMITY AMPUTATION

Samuel I. Schwartz, MD, and Glenn M. aMuraglia, MD

A nonambulatory patient with a prior transfemoral femoropopliteal artery bypass comes to your clinic with forefoot dry gangrene and an ankle brachial index of 0.3. The patient has been nonambulatory resulting from a stroke for more than 5 years. She is present with her health care proxy and is here to discuss amputation.

This patient's case is a common scenario seen by many different subspecialists: orthopedic surgery, general surgery, podiatry) but within the context of a prior bypass is usually managed by a vascular surgeon. The patient's long-term prognosis is very poor, having suffered a major disabling stroke and developing severe ischemia to the point of requiring a major lower extremity amputation. Historically, patients with critical limb ischemia, manifested as either rest pain or tissue loss, have an annual mortality rate of approximately 25%. This statistic has not changed much over the past few decades despite advances in medical care. In contrast, amputation rates have improved substantially over the past 20 years in the endovascular era, with roughly 40% declines in above- and below-knee amputations.

Early on, peripheral arterial disease manifests as short- or long-distance claudication. Interestingly, claudicants now have a 5-year amputation rate of only 1% to 2% (in contrast to 5% several decades ago) in large part from advancement of medical management of risk factors. If their disease progresses, patients can develop deep, dull, aching rest pain. Eventually, their circulation will not be able to maintain daily tissue homeostasis and develop a nonhealing ulceration that can develop into gangrene.



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Samuel I. Schwartz, MD, and Glenn M. LaMuraglia, MD

A nonambulatory patient with a prior thromboembolectomy of the popliteal artery bypass comes to your clinic with forefoot dry gangrene and an ankle brachial index of 0.3. The patient has been nonambulatory resulting from a stroke for more than 5 years. She is present with her health care proxy and is here to discuss amputation.

This patient's case is a common scenario seen by many different subspecialists (orthopedic surgery, general surgery, podiatry) but within the context of a prior bypass is usually managed by a vascular surgeon. The patient's long-term prognosis is very poor, having suffered a major disabling stroke and developing severe ischemia to the point of requiring a major lower extremity amputation. Historically, patients with critical limb ischemia, manifested as either rest pain or tissue loss, have an annual mortality rate of approximately 25%. This statistic has not changed much over the past few decades despite advances in medical care. In contrast, amputation rates have improved substantially over the past 20 years in the endovascular era, with roughly 40% declines in above- and below-knee amputations.

Early on, peripheral arterial disease manifests as short- or long-distance claudication. Interestingly, claudicants now have a 5-year amputation rate of only 1% to 2% (in contrast to 5% several decades ago) in large part from advancement of medical management of atherosclerosis. If their disease progresses, patients can develop deep, dull, aching rest pain. Eventually, their circulation will not be able to maintain daily tissue homeostasis and develop a nonhealing ulceration that can develop into gangrene.

Annual mortality of 25% in patients with critical limb ischemia is paramount in decision making regarding amputation surgery. Many of these patients have end stage cardiac disease, and a less aggressive approach may be warranted. Goals of care should be discussed with the patient, ideally while the patient is symptom and in an elective setting. Often, patients are emotionally reluctant to undergo amputations because they do not meet the absolute indications for amputation: intractable pain or uncontrolled sepsis. Patients that refuse amputation commonly present later to the emergency room in sepsis or strongly request the procedure because of unrelenting pain.

AMPUTATION PRINCIPLES

The primary goal of an amputation is to resect necrotic or nonviable tissue and provide a stable, healed extremity. Function is also extremely important; patients that were previously ambulatory should have the lowest possible amputation level to provide the highest likelihood of prosthesis assisted ambulation. Permanently nonambulatory patients or patients with severe contractures at the knee joint are the best candidates for single stage, above knee amputations. A word of caution must be discussed with the patient and family: nonambulatory status confers additional late complications (e.g., pneumonia, pressure ulcers) that can lead to premature death.

Preoperative Assessment

As seen with most vascular patients, the preamputation patient needs to be evaluated systematically and regarding specific technical ramifications.

Patient Evaluation

The patient's vascular related medical problems need to be ascertained; these include, but are not limited to diabetes, smoking history or chronic obstructive pulmonary disease, hypertension, cardiac history, renal insufficiency, and prior surgical history. Particularly, the prior amputation and vascular surgical history needs to be part of the current operative plan. The history also should include medications that may impede wound healing, anticoagulants that may need to be temporarily withheld, and the patient's nutritional status.

Physical examination plays an important role; a standard peripheral pulse examination should be performed as well as consideration of the presence of soft tissue or bony infection. Infected tissue should be treated with antibiotics or amputated urgently to get source control. A second stage formalization can be done at any proximal level permitting adequate arterial inflow for healing. Joint mobility and range of motion are paramount regarding the likelihood of developing areas of pressure breakdown after amputation creation. Last, a motor and sensory examination will help guide the clinical decision. A globally insensate or paralyzed foot should not undergo limb salvage by any means (TMA or toe amputation) due to the high likelihood of recurrent ulceration.

Laboratory Evaluation

Many tests can be performed to help guide the practitioner regarding likelihood of healing a desired amputation level. These tests include segmental blood pressures (and pulse volume recordings) and transcutaneous partial pressure of oxygen measurements ($TcpO_2$). These two tests are commonly performed at our institution.

A minimal ankle pressure of 50 mm Hg (or 90 mm Hg in a diabetic or end stage renal disease patient) is the desired minimum threshold to heal an amputation of the foot. Plethysmography or pulse volume recordings are also very useful and at least 5 mm of pulsatile displacement at the planned amputation level is associated with a higher amputation success rate. Digital or transmetatarsal plethysmography can be used to predict success of healing were distal forefoot digital amputations.

When available, $TcpO_2$ measurements can be performed with an oxygen electrode at 45°C at the desired amputation level. A level of 40 mm Hg is associated with a higher amputation success rate, whereas a level below 20 mm Hg is associated with failure. Of note, $TcpO_2$ levels can be unreliable in the presence of infection or inflammation. A baseline chest wall measurement is helpful in validating the test result (a low chest wall measurement may indicate a falsely low extremity measurement). From our experience, $TcpO_2$ has higher positive predictive value than negative predictive value regarding amputation success.

Radiographic Evaluation

Despite the patient in our case having a thrombosed bypass graft, the patient's arterial anatomy is vital to determining an amputation level. If the patient in our case had a high grade proximal profunda artery stenosis, an endovascular treatment of this lesion (balloon angioplasty with possible stenting) should be considered before an above knee amputation to optimize healing. If our patient had an occluded external iliac artery with reconstitution at the common femoral artery by hypogastric artery collaterals (via the profunda artery), a high grade distal hypogastric artery lesion would also warrant treatment to optimize above knee amputation healing. In this patient population, undertaking open arterial reconstruction to heal an amputation is discouraged; however, arterial inflow to the groin is usually necessary for the healing of an above knee amputation.

Acute Versus Chronic Lower Extremity Ischemia

An acutely ischemic limb that is globally insensate and paralyzed may require an upfront amputation because of extensive tissue necrosis and systemic toxicity. Patients may also be in intractable pain and an amputation will lessen their pain medication requirement. In a more delayed presentation without systemic toxicity, the tissue necrosis can demarcate which will help determine the amputation level. Renal and cardiac function should be frequently assessed; unrelenting pain can cause a cardiac event and worsening myoglobinuria can lead to acute renal failure.

Infection and Amputation

Determining whether the patient has wet gangrene is crucial. Most vascular patients have minimal physiologic reserve and quickly progress to septic shock. A timely workup for infection, consisting of an arterial lactate, blood cultures, and initiation of broad spectrum antibiotics, is key. Sometimes the exudate from the tissue bed can be cultured directly. Antibiotic coverage should include *Staphylococcus*, *Streptococcus*, gram negative organisms, and anaerobic organisms (see the chapter on the diabetic foot for more details regarding antibiotic selection). Wide debridement or guillotine amputation should be done in an urgent fashion to prevent worsening sepsis. Once adequate source control has been obtained, formalization should be performed once the patient has a normalizing temperature curve and favorable profile.

Specific Sites of Amputation

Digital Amputation

Digital or ballet toe amputations involve intraphalangeal resection with lateral flap coverage. The blood supply to the toe is at the 2 and 8 o'clock positions; hence, skin flaps need to be fashioned accordingly. Septic arthritis and forefoot or web space infection are major contraindications for a digital amputation. Postoperatively, the patient should be placed on a pressure offloading shoe and only heel weight bearing for the first 2 to 3 weeks depending on their circulation status. The incision needs to be assessed before allowing the patient full weight bearing, and the sutures should be removed when the wound has healed, usually around 4 to 6 weeks postoperatively.

Transmetatarsal Amputation

Transmetatarsal amputation, which is resection of the toe and corresponding metatarsal phalangeal joint, is indicated when dry or wet gangrene is involving the forefoot or web space. An important consideration regarding this amputation is the patient's foot stability and ultimate vascular disease trajectory. Using more than a single toe ray amputation may result in poor forefoot stability and development of

adjacent digital ulceration. A very durable long-term result is a complete forefoot transmetatarsal amputation; this is the ideal procedure for patients with neuropathy as there is uniform pressure distribution over the entire forefoot. Patients do very well with this amputation level even after decades of follow-up when their circulation may actually deteriorate. Predictors of a successful amputation include the following clinical criteria: control of active infection, good healthy appearing skin to flap, and an forefoot dependent ulcer. Theoretically, laboratory criteria that have been used include an ankle brachial index of over 0.35 (or 0.40 in the diabetic or dialysis population), palpable pulse volume recording of the forefoot, and a transcutaneous pO_2 measurement over 40 mm Hg.

Ankle Amputation

A Syme or ankle amputation is no longer performed due to pressure ulcer formation and the superior quality of below knee amputation prostheses.

Below-Knee Amputation

The patient in our scenario is nonambulatory and a below knee amputation is not indicated. In patients with ambulatory potential, a below knee amputation is an excellent option. A palpable popliteal pulse is the strongest predictor of adequate arterial inflow to heal a below knee amputation. Typically, a posterior flap (Burgess technique) is performed with the tibia transected 10 to 12 cm distal to the tibial tuberosity. The fibula is transected 1 to 2 cm proximal to the tibia transection level. Postoperatively, patients need to be kept in knee extension to prevent contracture formation while they undergo rehabilitation (Fig. 1).

Above-Knee Amputation

The above knee amputation, typically created with a fish mouth myocutaneous, would be the ideal amputation for the nonambulatory patient described here. In the setting of an occluded superficial femoral artery, a patent profunda artery is key to heal an above knee amputation. To prevent unopposed abduction, an adductor myodesis to the transected femur is typically done as well.

Newer Treatment Modalities

Transfemoral amputees can have problems with socket fit, especially in the setting of a short residual limb. Osseointegration provides a percutaneous, bone-anchored prosthesis that helps avoid socket-related problems. Preliminary data are promising, but the main risk remains development of a deep hardware infection.

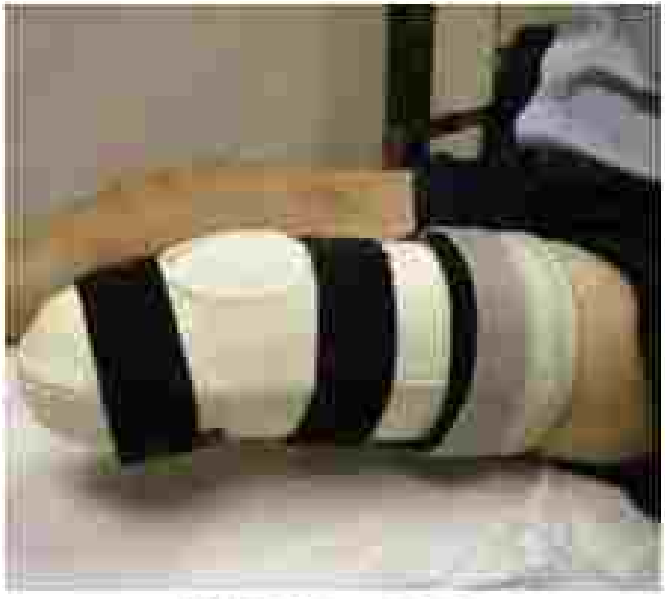

FIG. 1 Knee right removable dressing.

The most promising results have been recently achieved with targeted muscle reinnervation (TMR). TMR gained initial popularity for upper extremity myoelectric prostheses, and recently has gained utility for lower extremity amputees. Transected nerves are surgically transferred to the motor nerves of adjacent denervated target muscles. This results in more coordinated neural control signals to the missing limb and resultant prevention and/or treatment of neuropathic pain. Currently, TMR for lower extremity amputations is done by plastic surgery at our institution with good early results (Figs. 2 to 4).

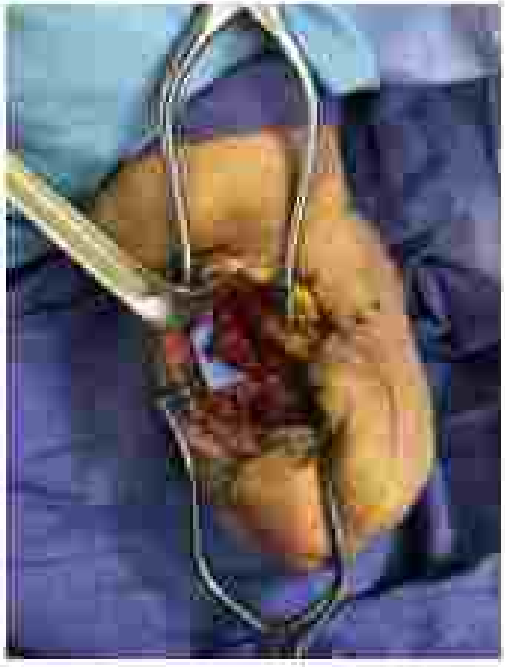

FIG. 2 Common peroneal neuroma after below knee amputation, presenting with immediate pain. (Courtesy Dr. Kyle Eberlin.)

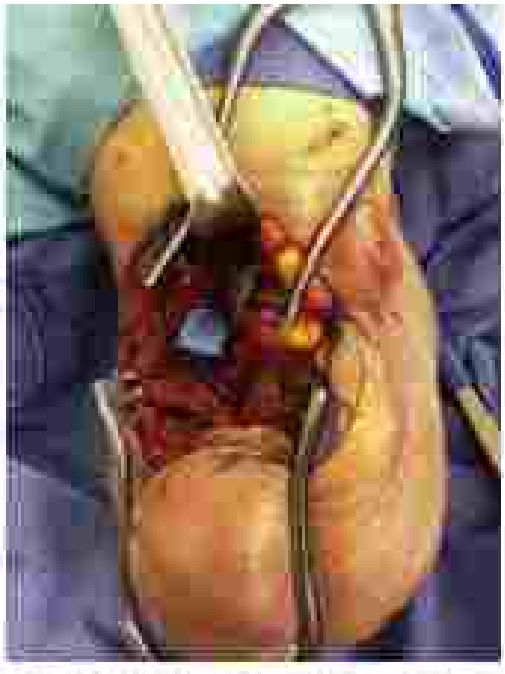

FIG. 3 After nerve transfer between common peroneal and tibial motor innervation and lateral distal nerve branches. (Courtesy Dr. Kyle Eberlin.)

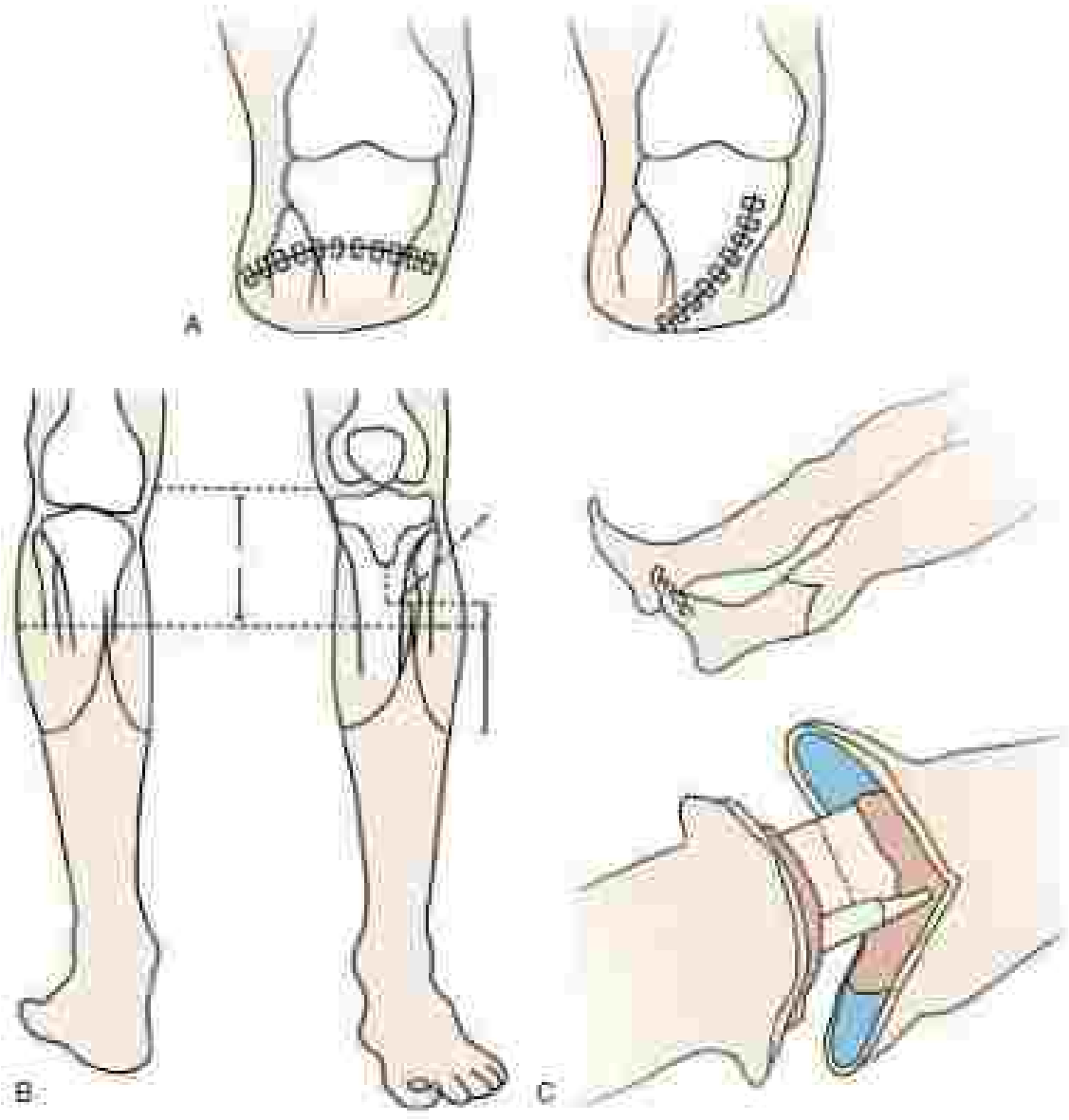

FIG. 4 Below-knee amputations. (Courtesy Ahmad R. Schwarz.)

Suggested Readings

Bobby KC, Jhingan CM. Contralateral limb and patient survival after leg amputation. Am J Surg. 1983;146:280–282.

Dumanian GA, Potter BE, Mioton LM, et al. Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: a randomized clinical trial. Ann Surg. 2018.

Goodney PP, Varkulis M, Lucitti AF, et al. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among Medicare patients. JAMA Surg. 2013;148(1):84–90.

Kaufmann A, Strecker DC, Mogerman J, et al. Transcutaneous oxygen tension to select site of amputation level. Am J Surg. 1984;147(4):505–513.

Trauma and Emergency Care

Initial Assessment and Resuscitation of the Trauma Patient

[illegible]

[illegible]

[illegible]

Primary Survey

[illegible]

[illegible]

Airway Management and Spine Protection

[illegible]

Breathing (Ventilatory Assessment)

[illegible]

TABLE 1 Major Life-Threatening Conditions in Trauma

Condition	Assessment (Signs/Symptoms)	Management
Airway obstruction (tongue, foreign body, maxillofacial disarticulations, swelling (face, pharynx, larynx)	• ...uarse or absent breath sounds • Stridor • Use of accessory muscles • Paradoxical movement of chest and abdomen • Intercostal retraction	• Jaw thrust/chin lift • Inspection of oral cavity • Suction • Endotracheal intubation • Needle surgical cricothyroidotomy
Severe traumatic brain injury	• Glasgow coma scale ≤... • ...local and/or global neurologic deficit • Rapidly deteriorating neurologic state • Abnormal/absent reflexes	• Airway management • Ventilatory support, avoid hypoxia, hypercarbia • Intracranial pressure management (mannitol, hypertonic saline) • Neurosurgery consultation (craniotomy)
Tension pneumothorax	• Tachypnea, air hunger, distress • Decreased/absent breath sounds • Tracheal deviation (away) • Distended neck veins (may not be present in the setting of severe hemorrhage) • Tympany on percussion • Hypotension/shock (lack of response to fluid challenge)	• Needle decompression, fourth intercostal space • Tube thoracostomy, fourth to fifth intercostal space
Massive hemothorax	• Tachypnea, air hunger, distress • Decreased/absent breath sounds • Flat neck veins • Dull sound on percussion • Hypotension/shock (lack of response to fluid challenge)	• Tube thoracostomy, fourth to ...fth intercostal space • ...L3 transfusion protocol • Emergency thoracotomy for >1500 mL initial blood return and/or ...200 mL/kg/ 2 - 4 hours
Cardiac tamponade	• Tachycardia • Hypotension/shock • Muffled heart sounds • Distended neck veins (may be absent due to hemorrhage) • Electrical alternans (electrocardiogram) • Focused assessment with sonography for trauma positive (88%, 95%)	• Volume resuscitation • Emergency thoracotomy or sternotomy by qualified surgeon (subxiphoid pericardiotomy with ultrasound guidance can temporize)
Flail chest/pulmonary contusion	• Tachypnea, air hunger • Asymmetric chest wall movement • Worsening oxygenation	• Diagnosis via clinical examination, chest radiograph, or CT • Supplemental oxygen • Pain control with I.v. narcotics, local/regional anesthesia • Restrict fluid administration in the absence of shock • Endotracheal intubation and ventilatory support (for partial pressure of oxygen <60 or arterial oxygen saturation <90 or fraction of inspired oxygen ...>50%)
Blunt cardiac injury (cardiac contusion)	• Tachycardia chest discomfort • Hypotension/shock (acute or worsening heart failure) • Arrhythmias	• Monitor patient in intensive care unit • Consider echocardiogram • Caution: intracardiac thrombus formation, myocardial infarction, valvular disruption, delayed cardiac rupture • Cardiac surgery consultation for unstable patients or complications
Traumatic aortic disruption	• Common cause of sudden death • Cause of massive (left) hemothorax or pericardial tamponade • Diagnosis on chest radiograph/CT (widened mediastinum, obliteration of aortic knob, deviation of trachea, depression of left mainstem bronchus, obliteration of aortopulmonary window, widened paraspinal interface, apical cap)	• β-Blockade if no contraindications; goal heart rate <80, mean arterial pressure 60–70 mm Hg • CT/vascular surgery consult (open or endovascular repair)

TABLE 1 Major Life-Threatening Conditions in Trauma—cont'd

Condition	Assessment (Signs/Symptoms)	Management
Blunt esophageal rupture	• Chest pain • Left pneumothorax or hemothorax (often without rib fracture) • Air in mediastinum on CXR or CT • Signs and symptoms of sepsis	• Fluid-directed sepsis therapy • Broad-spectrum antibiotics • Thoracic surgery consult: wide drainage with or without repair
Diaphragmatic rupture	• Often minimal symptoms initially • Tachycardia, chest discomfort • Signs of gastrointestinal obstruction or ischemia • Stomach, intestinal organs, spleen, or other in the chest on CXR or CT (small injuries often missed)	• Operative repair
Ongoing external or internal hemorrhage	• Identify the source: (1) Thoracic: see signs for massive hemothorax (2) Abdominal: distension, positive fluid on FAST (3) Pelvic: fracture on anteroposterior film, scrotal hematoma, abdominal distension	• 1:1:1 transfusion protocol for class II–IV shock • External/extremity: direct pressure, pressure dressing, tourniquet, operative or interventional definitive management • Thoracic: tube thoracostomy, emergent thoracotomy or sternotomy • Abdominal/pelvic: resuscitative balloon occlusion of the aorta (in a setting with appropriate training and certification), compartmental packing, interventional or operative management

CT, computed tomography; *FAST*, [illegible] ultrasonography.

FIG. 1 Trauma care [illegible]

All interventions for airway and breathing management should be followed up with an anteroposterior (AP) plain film chest radiograph to verify proper position of the endotracheal and/or chest tube and document the extent of the injuries.

Circulation Assessment and Management of Perfusion

The most important initial steps in the management of circulation/perfusion are to control any active source of bleeding, to establish two large-bore intravenous (or intraosseous) access, and to recognize and manage shock. Most injured patients have some degree of hypovolemia; in most cases, this is caused by blood loss (hemorrhagic shock), but hypovolemia can also be caused by systemic vasodilatation (neurogenic shock) and fluid losses resulting from burns and exposure to heat (Table 2). Assessment of peripheral (radial) and central (carotid, femoral) pulses, noninvasive blood pressure monitoring, and the evaluation for clinical signs of hypoperfusion (altered central nervous system status, decreased urine output, cool pale skin with decreased capillary refill) allow quick classification of blood loss to classes I to IV (mild to severe, <750 to >2000 mL) and take appropriate steps for initial resuscitation.

In addition to hypovolemic shock, injured patients may suffer from cardiogenic shock (cardiac contusion, myocardial infarction), obstructive shock (tamponade, tension pneumothorax), and/or neurogenic shock (relative hypovolemia and lack of afterload). The most sensitive method of restoring adequate cardiac output, perfusion, and tissue oxygenation is to restore normal venous return by (1) stopping ongoing blood loss and restoring lost volume (hypovolemic shock) and (2) relieving mechanical or pericardial pressure (tension pneumothorax, tamponade). Only after the patient has received volume resuscitation and ongoing blood loss and obstruction have been ruled out is the use of vasoconstricting agents appropriate in neurogenic shock.

The amount of fluid/blood required for resuscitation is often difficult to predict initially. An initial bolus of 20 mL/kg for pediatric patients (<40 kg) and up to 1 to 2 L of warmed balanced (Ringer's solution for adults is most appropriate. The patient's response to fluid resuscitation should be monitored: a lack of response, or only a transient response, may indicate greater than expected losses and/or ongoing bleeding, and the need for early administration of blood products and interventions aimed at hemostasis (Table 3). Balancing the goal of organ perfusion with that of avoidance of rebleeding has led to the concept of "controlled" or "[illegible]" resuscitation.

TABLE 2 Classification of Shock

	Class I	Class II	Class III	Class IV
Blood loss	<15% <750 mL	15%–30% >1000 mL	31%–40% <2000 mL	>40% >2000 mL
Heart rate	Normal to <100	Slightly elevated >120	Elevated 120–139	Elevated >140
Blood pressure (systolic)	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	Normal	Slightly elevated, <30	Elevated, 30–40	
Urine output (mL/h)	Normal <30	Normal to slightly decreased, >30	Decreased <30	Negligible
Central nervous system/mental state/ Glasgow Coma Scale	Normal	Anxious	Confused	Lethargic
Base deficit (mEq/L)	0–2	−2 to −6	−6 to −10	> −10
Need for blood products	Low likely; monitor	Possible	Yes	Massive transfusion protocol

Modified from American College of Surgeons Committee on Trauma: Advanced trauma life support (ATLS): 10th Edition, American College of Surgeons Committee on Trauma, Chicago, 2018. Other good data from Mutschler M, Nienaber A, Pfeifer R, et al. Could an early assessment of hemodynamic parameters predict the need for massive transfusion in severely injured trauma patients? Scand J Trauma Resusc Emerg Med. 2012;20:50. doi:10.1186/1757-7241-20-50.

TABLE 3 Response to Fluid Resuscitation

	Rapid/Complete	Transient	Minimal/No Response
Vital signs	Return to normal	Transient/incomplete improvement	Remain abnormal
Estimated blood loss	Minimal Class I, <15%	Moderate, ongoing Class II–III, 15%–40%	Severe, ongoing Class IV, >40%
Need for blood	Low Use type/cross-matched	Moderate to high Use type-specific	Immediate, massive transfusion protocol Use type O then type-specific or cross-matched
Presence of surgeon	Recommended	Required	Required

The recommended initial volume challenge is 20 mL/kg or colloid (~10 kg) and ~1000 mL of adult-dose crystalloid (largest amount of fluids, solutions). Lactated Ringer's solution may be repeated once or twice while "active consideration is" blood transfusion. Urinary output should be measured in all patients. With signs of hypovolemic shock, the goal is a urine output of ~1 mL/kg/h in children and ~30 mL/h in adults.

in which lower than normal blood pressure (>90 mm Hg systolic) is tolerated as bridge to definitive hemorrhage control.

Patients with class III or IV shock, ongoing losses, and minimal transient response to an initial volume bolus should be considered for early administration of blood products. If cross-matched blood is unavailable, type O red blood cells (Rh negative preferred) are indicated. To avoid hypothermia and associated coagulopathy, the use of blood warmers is critical. Each institution involved in the care of trauma patients should have a massive transfusion protocol. Severe coagulopathy is present on admission or develops in more than 30% of patients, and there is clear evidence that a ratio of blood plasma/platelets approaching 1:1:1 prevents excessive bleeding and related complications. Point of care testing (TEG, rotational thromboelastography), in addition to standard tests of coagulation can be helpful in the management of these patients.

External bleeding should be controlled first with direct manual pressure or a pressure dressing. If bleeding control cannot be achieved, a manual or pneumatic tourniquet (250–400 mm Hg) should be used and the patient transferred to the operating room in an expedited fashion. Active (hemodynamic internal bleeding (massive hemothorax, >1500 mL chest tube drainage initially or >200 mL/h for >3–4 hours) requires emergency thoracotomy in most cases, and management of the injury to the heart, great vessels, and/or lung. With internal abdominal bleeding, the use of the resuscitative endovascular balloon occlusion and with pelvic bleeding, the use of retroperitoneal pelvic packing may temporize patients on their way to the operating room or interventional angio suite. The trauma team leader must be committed to continuously reassess the patient's hemodynamic status (clinical examination, vital signs, urine output, laboratory values indicating perfusion) to prevent deterioration, and establishment of arterial lines and central lines serve as an adjunct but should not interfere with the adequate initial resuscitation.

Disability and Exposure

Every patient should have a focused baseline neurologic examination as part of the primary survey consisting of assessing the patient's general level of consciousness, pupillary size, and reaction, as well as the Glasgow coma score. A more comprehensive examination is completed during the secondary survey. Any patient with a Glasgow coma score less than 8, a deteriorating mental state, or a patient who is combative (a potential danger to himself or herself) should have an immediate placement of a secure endotracheal airway.

To allow for complete assessment, each patient must be completely undressed (undue movement of the patient/limbs should be avoided until injury has been ruled out); this may require cutting

all the patient's garments. Care must be taken to avoid hypothermia; the trauma room should be warmed, patients should be covered as soon as possible with warmed blankets, and intravenous fluid/blood warmers should be used whenever possible.

Monitoring and Adjunct Measures

While addressing the ABCDEs and identifying/managing injuries with potential threat to life and limb during the primary survey, each patient should receive: (1) adequate intravenous or intraosseous access; (2) supplemental oxygen and pulse oximetry; (3) cardiac and noninvasive blood pressure monitoring; and (4) basic blood work (complete blood count, prothrombin time/partial thromboplastin time, basic metabolic panel, and specialty studies as indicated (i.e., blood alcohol level, urine toxicology screen, arterial blood gas, lactate). Patients with significant injuries and/or the need for hemodynamic monitoring should also receive a urinary catheter. Gastric dilatation occurs frequently in trauma patients; it can cause bradycardia and hypotension (vagal response) and increases the risk of aspiration. Gastric decompression should be considered in all trauma patients, particularly patients with abdominal/chest trauma and those with altered mental state.

SECONDARY SURVEY

The secondary survey should not be done until the primary survey is completed and all potentially life-threatening conditions have been addressed. It answers the question "What injuries did the patient sustain?" and uses a systematic, comprehensive, head-to-toe evaluation as the main tool. The potential for missing an injury or failing to appreciate the significance of a subtle sign is significant, especially in unresponsive or unstable patients. Therefore, the secondary survey ideally is performed by one examiner, using inspection, auscultation, palpation, and the patient's responses to specific questions and commands. During the evaluation, distraction of the patient by other members of the team or interventions should be minimized and the examiner should verbalize his or her findings throughout the evaluation to allow the team and allow for concurrent documentation of all findings. Information about allergies, current medications, past illnesses, last meal, events/environment surrounding injury related to and the mechanism of the injury should be collected from the patient or family.

At the end of the secondary survey, the trauma team leader should be able to verbalize/initiate any needed diagnostic tests, specialist consultations, and be able to decide to what level of care the patient should be admitted. If the resources to provide optimal care are not available locally, this is also the time to initiate transfer to a higher level of care (trauma center), to avoid unnecessary delay.

TERTIARY SURVEY: REEVALUATION

Physiologic changes after injury are highly dynamic and injury severity is often underestimated in the initial phases of evaluation. Constant reevaluation of the trauma patient and timely review of test results are essential to prevent deterioration or secondary injury. This phase includes monitoring of vital signs, SaO_2, urine and mixed CO_2 monitoring, as well as urinary output; patients with altered mental state, (suspected) traumatic brain injury, or spinal cord injury should have serial neurologic evaluation. Patients with (suspected) abdominal/pelvic trauma should have serial abdominal examinations, and those with significant extremity trauma should have serial neurovascular examinations and compartment checks. The findings at reevaluations should be carefully documented and communicated to the members of the care team. Factors most commonly associated with worse outcomes in the posttrauma phase include (1) ongoing bleeding, (2) hypotension and hypoperfusion, (3) hypoxia and hypercarbia or hypocarbia and metabolic acidosis, (4) hypothermia, (5) coagulopathy, (6) compartment syndromes (abdomen, extremities, intracranial), and (7) evolving neurologic injury/deficit. These conditions must be actively sought and aggressively managed.

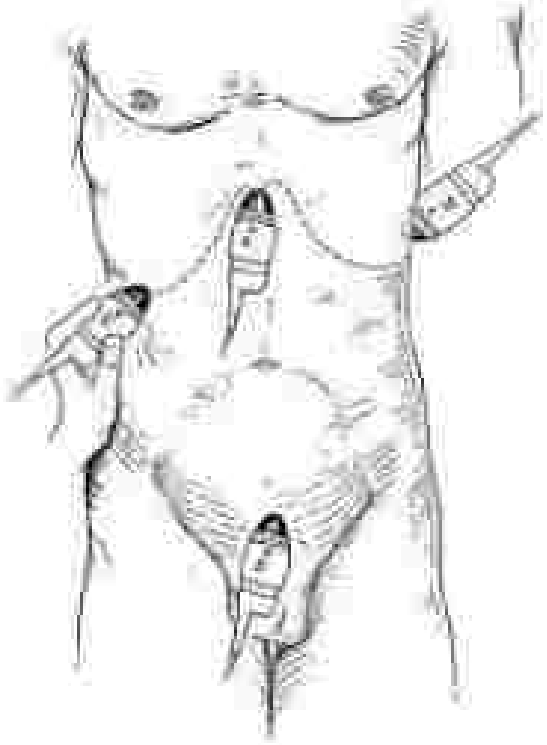

FIG. 2. Focused assessment with sonography for trauma windows for hemoperitoneum (right subcostal, left subcostal, and suprapubic areas). Demonstration of the urinary bladder before (top) and after (bottom) placement of an indwelling urinary catheter. Note the presence of fluid (arrows) in the bladder after catheterization. (From Tintinalli JE, Kelen GD, Stapczynski JS, et al. Emergency medicine: a comprehensive study guide. 6th ed. New York: McGraw-Hill; 2004.)

Diagnostic Imaging

Focused Assessment With Sonography for Trauma

Diagnostic peritoneal lavage has been supplanted by the adoption of focused assessment with sonography for trauma (FAST) and the improved quality and availability of high quality computed tomography. While its pitfalls include false positive results, injury to visceral structures and poor sensitivity to detect retroperitoneal injury, it remains useful (in lieu of diagnostic laparoscopy or formal exploration) to evaluate patients with equivocal FAST or CT findings (Fig. 2).

Bedside sonographic assessment of the trauma victim is considered standard of care and can be used as adjunct during both primary and secondary surveys. A low frequency transducer (3.5 MHz) is used to examine the hepatorenal and splenorenal recesses, subxiphoid area (pericardium) and the pelvic cul de sac. Identification of free fluid in these areas (blood, saccus, other) indicates a potential injury and necessitates further evaluation.

Approximately 200 mL of free fluid is required for detection; sensitivity ranges from 73% to 88%, and accuracy from 96% to 99%. In general, positive findings in a stable patient can be evaluated further with CT, whereas such findings in an unstable patient should prompt the surgeon to proceed with operative exploration. Performing the pelvic examination before insertion of a Foley catheter or after instilling 200 to 250 mL of saline can increase sensitivity and if patients are placed in the left or right lateral decubitus position, smaller amounts of fluid may be detected. Preexisting conditions such as ascites and peritoneal dialysis may render the assessment unusable, and since the FAST is somewhat dependent on operator experience, regular practice is recommended.

Plain Film Radiography

Even with the development of FAST and the ubiquitous availability of high resolution CT, (portable) plain film radiography continues to play an important role. Current trauma protocols advocate for obtaining an AP of the chest and AP pelvis radiograph because many potential life threatening injuries or complications can be rapidly identified and addressed. AP chest imaging may reveal a pneumothorax or hemothorax, rib fractures, location of foreign bodies, and endotracheal tube placement. An AP pelvis film can identify the type of pelvic fracture and guide further management, such as application of a binder or the need for external fixation/angiography.

Extremities with obvious deformities, joint swelling, or tenderness on physical examination should be investigated with additional plain film imaging. Obtaining images of the joint proximal and distal to the suspected injury may help identify additional injuries. AP and lateral views should be obtained routinely, and additional views after appropriate stabilization of the patient.

Although not routinely used, AP abdominal films may assist in the evaluation and surgical planning for penetrating injuries with unclear trajectory; when using a marker, the rough trajectory and location of the bullet/fragments can be identified. the same is true for gunshot trauma to the extremities. Plain film imaging of the spine (AP, lateral, odontoid, with or without oblique and/or swimmer's view) have been supplanted by the use of CT. Multidetector helical CT of the abdomen or chest offers more anatomical detail, routinely detects up to 40% more spine injuries, and does not require additional exposure. Adding dedicated CT imaging of the cervical spine requires minimal time and avoids inadequate imaging of the C1–2 and C7–T1 regions. According to the National Emergency X-Radiography Utilization study, patients with a normal level of alertness, no evidence of intoxication, no posterior midline C-spine tenderness, no focal neurologic deficits, AND no (painful) distracting injuries may be cleared clinically.

Computed Tomography

Helical multidetector computed tomography with and without contrast has become the most accurate diagnostic and screening method with patients with a wide spectrum of soft tissue, bony, vascular, and organ injuries. Its use has led to accepted classifications of organ injuries that affect the therapeutic approach. With current high resolution, high speed scanners, sensitivities, specificities, and accuracy approach 100%. The use of CT is particularly helpful in patients with altered mental state who cannot give a reliable examination. The routine use of oral contrast has fallen out of favor in trauma because of the risk of aspiration and time constraints, but intravenous contrast is recommended when evaluating for vascular, solid organ, and intestinal injuries. A high index of suspicion is required when looking for bowel injuries. Indicators are often indirect (free fluid, bowel wall thickening, mesenteric stranding) and can be missed. Active contrast extravasation, the detection of a vascular cutoff sign or pseudoaneurysm may provide the indication for angiography in solid organ injury.

Angiography

Angiography and CT angiography can be used for the assessment and treatment of trauma patients. Vascular injury, injury to solid organs, retroperitoneal and pelvic hemorrhage, as well as injury to named vascular structures of the head, neck, chest, and extremities may all be amenable to angiographic intervention (e.g., stenting, embolization, thrombectomy) in experienced hands. Hemodynamic stability and adequate volume resuscitation status should be established before transporting a trauma patient to a diagnostic procedure; the trauma surgeon must work together with the vascular surgeon, interventional radiologist, and/or orthopedic surgeon to properly prioritize and sequence the patient's care. If the patient is hemodynamically unstable or has clear loss of pulses, priority should be given to operative intervention. Angiography should be considered in any extremity trauma with a (left–right) difference in ankle brachial index, particularly if the injured side has an ankle brachial index less than 0.9. Patients with pelvic fractures and evidence of significant ongoing blood loss may benefit from angioembolization of the internal iliac arteries, regardless if the bleeding is arterial or venous. It is recommended that this be performed in a hybrid suite where conversion to an open exploration can be accomplished without delay, if necessary.

Special Populations

Children, pregnant patients, older adults, and medically obese patients warrant special consideration; these patients may exhibit a physiologic response to injury that does not follow expected patterns and/or may require special equipment or services (Table 6). Children have unique variations in anatomy, require weight based medication dosing, lose heat rapidly, and often compensate for prolonged periods with few signs of shock. When decompensation occurs, it is often sudden and deleterious. Pregnancy significantly alters the response to injury, circulating blood volumes, and coagulation, and adds the need for both fetal and maternal assessment and management. Older patients often have diminished physiologic reserve, preexisting conditions and medications may significantly interfere with the ability to respond to stress, and older patients commonly are overresuscitated or undertriaged. Despite these issues, older patients can do as well as younger patients, when optimally treated. Diagnostic and therapeutic procedures in morbidly obese patients are often more difficult or hazardous, and these patients may exhibit significantly reduced cardiopulmonary reserves. Familiarity with the special considerations in these patient groups and close monitoring is paramount for optimal outcomes.

CONCEPT OF DAMAGE CONTROL AND COORDINATED CARE

Many trauma patients present with a combination of injuries, requiring the coordinated approach of several specialists and functional areas within the acute care hospital. Physiologic changes after injury are highly dynamic and may require that one problem is addressed before another. The primary concerns center around the establishment of a secure airway and ventilatory support, as well as expeditious hemostasis and circulatory support. Secondary issues such as hypothermia, acidosis, and coagulopathy with their associated problems must be prevented or identified and corrected early and aggressively. Although progression to definitive care in the most expeditious fashion is the goal, attempting to provide or persisting with definitive treatment in the face of hemodynamic instability or physiologic deterioration may lead to poor outcomes. In such situations, a patient may do better with the initial goal of damage control under this paradigm, under continued resuscitation, the patient is moved between care areas (operating room, ICU, interventional radiology) for specific treatment goals, including temporary fixation of unstable fractures (i.e., external fixation), control of intestinal spillage (i.e., damage control laparotomy), restoration of blood flow (i.e., temporary shunt) or hemorrhage control (i.e., angiography), and the relief of intracranial hypertension (i.e., burr hole, craniotomy), interposed are periods of resuscitation to correct physiologic derangements and prepare the patient for further therapy. Once the patient has been stabilized, plans for (staged) definitive care of the patient's injuries is coordinated between the trauma team leader and all involved specialists.

Optimal care for injured patients is best delivered in well coordinated teams; these teams need to establish leadership, clear responsibilities, and communication patterns. To constantly improve and to allow team members to deal with the stress involved in trauma

TABLE 4 Patients Requiring Special Considerations

	Considerations
Pregnancy	• Rest initial treatment of the fetus is optimal treatment of the mother; when blood is needed, Rh-negative blood should be used; all pregnant Rh-negative mothers should receive Rh immunoglobulin within 72 hours unless injury to remote from the uterus • An obstetrician should be involved early; abdominal ultrasound should be done; fetal heart can be monitored with Doppler after 10 weeks; continuous fetal monitoring should be done after 20–24 weeks; all pregnant patients should be observed for at least 4 hours • Diagnostic imaging should be ordered with the same general indications as for nonpregnant patients; shield abdomen/pelvis with lead apron when possible • Uterus: intrapelvic until week 12, at umbilicus by week 20, to costal margin by weeks 36–40; uterus can cause vena cava compression and hypotension in supine position (third trimester), when possible, patients should be placed with the right side elevated at 15–30 degrees • Plasma volume increases throughout pregnancy and hematocrit decreases to 30%–35%; healthy pregnant patients can lose up to 1200 mL of blood before exhibiting signs of hypovolemia • Amniotic fluid can cause embolism and disseminated intravascular coagulation • Watch for signs of placental abruption (inelasticity can cause abruption in second and third trimester) and/or uterine rupture: uterine tenderness, frequent contractions or tetany, vaginal bleeding, abdominal rigidity, maternal shock, admission is mandatory for patients with these signs • Gastric emptying is delayed; consider decompression; consider antiemetics (metoclopramide, ondansetron) • To avoid fetal hypoxia, use supplemental oxygen
Pediatrics	• Because of increased body surface area, heat loss/hypothermia is more common • Skull, long bone, and rib fractures suggest high energy transfer; underlying organ injury must be sought • Need for weight-based dosing and resuscitation (use resuscitation tapes or calculators) • Airway smaller, shorter, and more anterior; use uncuffed endotracheal tube up to 3.5–4.0 kg/age 5–7 years; small children need 1 inch pad under body to avoid neck flexion; oral airways should only be used in unconscious children; preoxygenation is mandatory before intubation • Children often compensate for blood loss up to 30% without overt signs of hypovolemia/shock; normal systolic blood pressure for child is 80 to 90+ (2 × age in years), normal heart rate declines from <160 at birth to <100 at age 12–15 years; normal urine output is 2 mL/kg/h at birth and >0.5 mL/kg/h by age 12–15 years • Consider intraosseous access early if peripheral procedures; routine access in unsuccessful • When CT evaluation is necessary, radiation must be kept As Low As Reasonably Achievable; perform CT scans only when medically necessary when the results will change management, scan only the area of interest and use the lowest radiation dose possible • In serious trauma, brain injuries are more common; with TBI, increased intracranial pressure develops more frequently in children; neurosurgical consultation should be obtained early; children with bulging fontanelles or suture diastases should be assumed to have a more severe injury; persistent/recurrent vomiting and any seizure activity requires investigation by CT of the head • Spinal cord injury is uncommon in those <10 years old; the radiographic finding of pseudo-subluxation complicates 20%–40% of plain films in children <15 years • Child maltreatment should be suspected if suggested by suspicious findings on history or physical examination; these include discrepant history, delayed presentation, frequent prior injuries, injuries incompatible with developmental stage, and perineal injuries

care; trauma team leaders should actively debrief with the entire team, especially after resuscitation of severely ill multitrauma patients or trauma deaths.

SUGGESTED READINGS

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PREHOSPITAL MANAGEMENT OF THE TRAUMA PATIENT

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Optimal outcomes for severely injured patients are obtained in the context of an organized trauma system. Using a disease model for trauma, most trauma death and morbidity can be considered preventable. Prevention of death and morbidity from injury is the goal of the trauma system. However, most trauma deaths occur before the injured patient reaches definitive care. Optimal prehospital care provided by trained bystanders (immediate responders) and by emergency medical services (EMS) reduces preventable death and morbidity and is an essential component of the trauma system. Immediate responders initiate EMS by activating systems such as the 911 system. They can provide first aid and immediate bleeding control. EMS is more than the transport of injured patients; it has goals of prevention of further injury and death, appropriate resuscitation, and safe, timely transport. As part of a trauma system, the EMS system must include a robust performance improvement process, a series of evidence- and consensus-based care protocols, trauma triage criteria, appropriate paramedic or emergency medical technician (EMT) training, well-proven equipment, and destination policies. Triage protocols, communications, and high-quality medical direction and dispatch are also required for optimal EMS outcomes. EMS transports patients to facilities that are part of the trauma system and are able to care for injured patients, bypassing nontrauma facilities even if they are closer.

The principles of modern prehospital management were derived from lessons learned in past military conflicts, and new lessons continue to be learned in modern conflicts that are being applied today. Many of the recent innovations to civilian EMS such as helicopter EMS (HEMS), prehospital blood product administration, tourniquets, and others were pioneered in military conflict health systems. This chapter reviews the main tenets of prehospital trauma evaluation, discusses system processes of field triage and tiered response, and examines how military experience has shaped practice.

Mortality in trauma classically has been divided into three temporal categories. Fifty percent of deaths occur immediately and are attributable to exsanguination and head trauma. These patients can be targeted via prevention and public health measures but are not salvageable with the use of prehospital trauma life support (PHTLS) interventions. Thirty percent of deaths occur within 1 to 3 hours of injury and are potentially avoidable through proper resuscitation and hospital efforts. Prehospital management of the trauma patient intercedes during that critical golden hour, when life and health saving interventions are possible. The final peak in mortality occurs within 1 to 2 weeks after trauma and is usually secondary to infections or organ failure.

INITIAL PHASES OF PREHOSPITAL CARE

Scene Assessment

The first priority for everyone involved with a trauma incident response is assessment of the scene. This involves first ensuring that the scene is safe, considering carefully the nature of the situation. Some situations are changing rapidly and may present danger of causing further deaths and injuries to responders and casualties, such as structural collapse, vehicular traffic, spreading fire, active shooters, darkness, environmental conditions, hazardous materials, blood, and infectious diseases. There may be multiple casualties and casualties in need of rescue or extrication. Most hospital-based providers have not received training in scene assessment, and if encountering such a scene should take direction from professional first responders or risk death, injury, and impeding the EMS response.

First Aid/Buddy Aid

A lesson from military conflicts and described in military PHTLS and the Tactical Casualty Combat Care course is the concept of self-aid or "buddy" aid. This includes training all personnel how to provide immediate actions for life threatening conditions, even if under enemy fire. Selected personnel are given additional training to combat bleeding skills to supplement military medics. When safe, skills include maintaining the airway of an unconscious patient with a chin lift or jaw thrust and use of the recovery position. Tension pneumothorax may be managed by needle or finger thoracostomy. Open pneumothorax or sucking chest wounds are managed with three-sided occlusive dressings or pressure chest seal kits. Bleeding is managed with direct pressure, and wound packing with hemostatic dressings or tourniquets. Success in these interventions has led to the civilian program "Stop the Bleed."

"Stop the Bleed" Training for Civilians

Uncontrolled hemorrhage is the leading cause of preventable trauma deaths. The Hartford Consensus group, including the American College of Surgeons Committee on Trauma (ACS COT), the National Association of EMTs, and other professional and government agencies, has provided EMS guidelines for response to mass casualty events such as bombings and active shooters. Surveys have revealed that the majority of Americans are interested in learning bleeding control skills such as direct pressure, and wound packing with hemostatic dressings or tourniquets. The Hartford Consensus and the Department of Homeland Security launched the Stop the Bleed (STB) program in 2015, which teaches interested civilians steps for response to a bleeding trauma patient: (1) ensure the scene is safe, (2) call 911 or have someone else call, (3) identify life threatening bleeding, (4) apply direct pressure, (5) if it is extremity bleeding, use an available tourniquet, and (6) if a tourniquet cannot be used or is unavailable, pack the wound with clothing, gauze, or hemostatic dressing and apply pressure. The STB effort is supplemented by efforts to place accessible bleeding control kits in public locations such as schools, airports, malls, and stadiums.

Although tourniquets had fallen out of use secondary to a perceived concern for limb loss, proper placement of the tourniquet proximal to the injury for less than 2 hours reduces hemorrhage and saves lives. Several studies have demonstrated that tourniquet use on the battlefield does not lead to unintended amputation or long-term disability and does reduce mortality in patients with severe blast injuries. In a study of deaths that occurred during Operation Iraqi Freedom, prehospital tourniquet use was associated with improved hemorrhage control. Of the deaths that did occur, up to 57% may have been prevented by earlier tourniquet use. When direct pressure fails, tourniquet placement should be attempted. In a civilian trial in Texas, mortality was improved, although initial compliance with the tourniquet protocol by paramedics or EMTs was suboptimal, with some tourniquet application opportunities missed.

INITIAL FIELD CARE BY THE PARAMEDIC OR EMT

The key principles of prehospital evaluation for the EMT follow standard trauma resuscitation guidelines. After ensuring scene safety, airway is addressed first, followed by breathing, then circulation/shock, disability and exposure and environment (the ABCDEs).

Airway

In patients identified in the field with respiratory distress, supplemental oxygen and adjuvants such as nasal trumpets, oral airways, and bag-valve masks can be used. Advanced noninvasive airways include the

King airway, laryngeal mask airway, or I-gel airway. Although effective, these do not prevent aspiration as they do not place a cuffed tube in the trachea. In patients identified with severe respiratory distress or in those with an inability to protect their airway (emesis, oropharyngeal bleeding, altered mental status with a Glasgow Coma Scale [GCS] score <8), endotracheal intubation is considered if paramedic or EMT skills and local protocols allow. Controversy exists regarding intubating patients in the field. Although intubation may serve to protect the airway and oxygenate and ventilate the patient, time spent intubating is precious, aspiration risk during intubation may be increased, tubes can be dislodged in transport, and inadvertent esophageal or malposition intubations may lead to significant hypoxia. Several retrospective and prospective studies have demonstrated an increase in morbidity and mortality in patients with traumatic brain injury (TBI) who were intubated in the field. This increased mortality may be secondary to severe hyperventilation or hypoxia. If airway adjuncts and bag-valve masks are adequate, the "scoop and run" technique without scene intubation usually allows for the most rapid transport to the trauma center. Inability to ventilate, inability to maintain saturations in the prehospital environment are very challenging and usually lead to poor outcomes. Surgical airways such as cricothyrotomy are performed rarely and many paramedics or EMTs lack confidence, recent experience, or a local protocol allowing performance.

If the resources are available, a valuable aid in intubated patients is end tidal capnography, which is most useful in verifying endotracheal tube position avoiding hyperventilation and hypoventilation. End tidal capnography is being incorporated more frequently in the prehospital setting and is particularly advantageous in TBI. Several studies have demonstrated that noninvasive reduces the mortality rate in patients once they reach the emergency department (ED). As part of the San Diego Paramedic Rapid Sequence Intubation trial, patients had a reduced incidence of severe hyperventilation. These patients with significant hyperventilation had a 50% mortality rate compared with a 30% mortality rate in patients without hyperventilation.

Breathing

Paramedic and EMT care here through the timely identification of tension pneumothorax. This diagnosis can be made readily and addressed in the field with needle or finger pleural decompression. Clinical findings include respiratory distress, unilateral decreased breath sounds, crepitus, tracheal deviation, distended neck veins, hyperresonance to percussion, increased difficulty in bag masking, and hemodynamic instability. The affected side can be decompressed by perpendicular insertion of a finger or large bore 12- to 14-gauge intravenous (IV) catheter 4.5 inch catheter is used in smaller adults, and 8 cm in larger adults. In children, the catheter placed in the second or third intercostal space, passed over the superior surface of the rib in the midclavicular line. In adults, it is placed in the fourth or fifth interspace, anterior to the midaxillary line. Failure to decompress or kinking of the catheter is a common problem. In case of needle catheter failure or if no such catheter is available, finger thoracostomy is made through a 2- to 3-cm incision placed in the fourth or fifth interspace, and the pleural puncture and spread with a Kelly type clamp. Common pitfalls include late recognition of tension pneumothorax, improper needle or clamp placement causing lung laceration, or poor depth of needle placement such that the pleural space is not entered. Subsequently, a chest tube should be placed at the hospital for definitive decompression.

Circulation and Shock

Assessment of the patient for shock by the paramedic or EMT is first completed of looking for evidence of hemorrhage and assessing total body and regional perfusion. Quick recognition of actively bleeding sites with application of direct pressure, wound packing with a hemostatic agent or a tourniquet can prevent exsanguination. Frequently missed locations of wounds include scalp, back, perineum, and axilla. Although IV access is usually sought, administration of large volume crystalloid resuscitation, especially in penetrating torso trauma, is associated with increased mortality. Shock due to torso intracavitary hemorrhage cannot be controlled by the paramedic or EMT with current technology. This has led to the supposition that the best prehospital resuscitative fluid to use in such cases is "about" to avoid excess IV crystalloid administration and shorten scene and transport duration with a "scoop and run" approach.

Data indicate that in uncontrolled torso hemorrhage, controlled resuscitation with a goal systolic blood pressure (SBP) of 80 to 90 mm Hg may decrease mortality. In studies of penetrating torso trauma, patients who did not receive fluid resuscitation in the field had lower mortality compared with patients who were resuscitated with fluid. Liberal fluid resuscitation was associated with an increase in acute respiratory distress syndrome, pneumonia, and coagulopathy. Possible reasons for this difference include fluid administration leading to increased arterial pressure and venous dilation of bleeding sites, disruption of newly established clot, and possible dilution of clotting factors. However, in patients with suspected head injury, decreased mean arterial pressure could decrease cerebral perfusion pressure to harmful levels; therefore in patients with TBI an SBP of 100 mm Hg is the goal. Small trials of prehospital administration of a hypertonic saline solution (HTS) to reduce cerebral edema, improve blood pressure, and improve TBI outcomes showed promise, but use of HTS in a large multicenter randomized trial was unsuccessful.

If access is difficult to obtain but necessary secondary to clinical signs of hemorrhagic shock or to administer drugs, the intraosseous (IO) route is available and considered the next best choice. Possible locations depend on the device used and include the proximal anterior tibia (most common), sternum (used frequently in the military and may have faster flow rates), humerus, femur, distal tibia, and superior iliac crest. The IO route has equivalent plasma kinetics to IV (tracheal drugs, and both crystalloid and colloid infusions can be given at similar rates to IV access. Compared with central line placement, IO access has higher first attempt success rates and faster time to insertion.

Circulation and Shock: Prehospital Blood Products

During World War II and the Korean War, British Commonwealth and U.S. forces used lyophilized freeze-dried plasma (FDP), reconstituted and administered to combat casualties in the field by medics. This innovation was later lost owing to problems with viral disease transmission, but new detergent solvent extraction techniques are making this product available to military medics and civilian paramedics and EMTs. Experience in Iraq and Afghanistan by coalition forward surgical teams with improved surgical hemostasis in casualties receiving whole blood has reignited interest in bringing blood products administration to prehospital trauma care. Military guidelines emphasize earlier administration of plasma and platelet products in massive transfusion. Several military and civilian studies support using 1:1:1 replacement of fresh frozen plasma to platelets to packed red blood cells. In a combat hospital setting, 19% mortality was found when the plasma to red blood cell ratio was 1:1 , compared with 34% mortality when the ratio was 1:2.5 and 65% mortality when the ratio was 1:8. A similar retrospective review of 466 massive transfusion civilian trauma patients also noted improved survival, decreased intensive care unit stay, and improved ventilator- and hospital-free days among the high plasma and high platelet patients. Survival was most enhanced by a plasma to red blood cell ratio of greater than 1:2. A trial using thawed plasma administered to 144 hypotensive and tachycardic trauma patients in shock by ground based EMS did not show a benefit, but another trial of thawed plasma given to 901 hypotensive and tachycardic trauma patients transported by HEMS showed 30-day mortality was significantly lower in the plasma group (23.2% vs 33.0%). Prehospital trials using FDP are planned. Additional trials of low titer, whole O group blood (LTWOB) are being performed in some EMS systems for injured patients in hemorrhagic shock. LTWOB provides a 1:1 replacement of fresh frozen plasma to platelets to packed red blood cells in each unit.

Circulation and Shock: Prehospital Tranexamic Acid

The role of the antifibrinolytic drug tranexamic acid (TXA) has been studied as an adjunct to control bleeding. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study retrospectively evaluated nearly 900 casualties, demonstrating a significantly lower mortality among soldiers receiving TXA than among those receiving traditional therapy. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) study showed similar results in 20,000 civilian trauma patients in nearly eastern settings. Several trials have revealed a decrease in mortality, although some have only demonstrated a reduction in transfusion requirements and coagulopathy, particularly in patients requiring massive transfusion. CRASH-2 recommendations for trauma patients with clinical signs of hemorrhage include a TXA loading dose of 1 g given intravenously over 10 minutes in the first 3 hours after injury, followed by 1 g infused after 8 hours. The drug must be administered early to be effective in reverse traumatic coagulopathy. It has been linked to an increased risk of death from bleeding when given to survivors more than 3 hours after injury. Secondary to reports of thrombotic complications when TXA is used in conjunction with prothrombin complex concentrate (PCC), trauma centers generally are not administering these medications simultaneously. Many U.S. Level I trauma centers use thromboelastography to identify clotting deficits at admission preferentially to TXA, and many elderly patients with atrial fibrillation are taking direct acting oral anticoagulants requiring PCC or other agents for reversal. Therefore, EMS protocols for TXA use must be coordinated with the trauma system and trauma centers.

Circulation and Shock: Prehospital Traumatic Cardiac Arrest

As discussed earlier, following the standard algorithm of assessing trauma patients should identify reversible causes of cardiorespiratory collapse such as airway compromise, tension pneumothorax, open pneumothorax, massive hemothorax, cardiac tamponade, and hemorrhage. Prehospital arrest has a worse prognosis in the setting of blunt trauma when compared with penetrating trauma and has an overall bleak prognosis when it occurs during transit to the hospital by EMS. Cardiopulmonary resuscitation (CPR) is futile if the victim of blunt trauma is found already in arrest by healthcare personnel. In penetrating trauma, if pupillary reflexes, spontaneous movement, or organized electrocardiogram activity is present, CPR should be attempted, and the patient brought immediately to the trauma center. In general, CPR in blunt trauma for more than 10 minutes without restoration of vitals is ineffective. Many jurisdictions do not allow the paramedic or EMT to declare death except in the most obvious of cases, and so trauma patients with prolonged CPR and no significant chance of survival are still brought to hospitals with CPR in progress. In the event of hanging, drowning, hypothermia, electrocution, arrest from a medical condition, or in children, the paramedic or EMT or their medical director often may continue resuscitative efforts. However, in children with blunt cardiac arrest and CPR more than 10 minutes, outcomes are just as dismal as in adults.

Circulation and Shock: Advanced Techniques of Hemorrhage Control

The quest to prevent exsanguinating hemorrhage has led to prehospital trials of new devices such as REBOA (Retrograde Endovascular Balloon Occlusion of the Aorta) catheter and the Military Junctional Tourniquet (MTJ). In 2014, the London United Kingdom HEMS service performed a REBOA procedure in a roadside traffic accident patient in severe shock from pelvic fractures who survived. However, REBOA was limited to the London system in HEMS units. Because of the need to obtain femoral arterial access to perform REBOA, the MTJ was developed, which places heavy compression on the abdomen and aorta. Neither device has been proven effective in a Level I evidence trial. REBOA can have severe complications including ischemia reperfusion injury, vascular access injuries, and inability to control or actual worsening of expanding/stagnant bleeding. There are few survivors in trials of intraluminal aortic placement of REBOA for more than 30 minutes. MTJ has many of the REBOA adverse effects and potential compression injuries to bowel, bladder, and nerves. Results of prehospital trials are awaiting.

Disability: Head and Spinal Trauma

Traditionally, blunt trauma patients in the field, particularly those with a concerning mechanism of injury or high suspicion of spinal injury, were "immobilized" with a backboard and rigid cervical collar. Although current techniques limit or reduce unilateral motion of the spine, they do not provide true spinal immobilization. For this reason, the term spinal motion restriction (SMR) has gained favor over spinal immobilization, although both terms refer to the same concept. Debate exists about prehospital clearance of the cervical spine by properly trained EMS personnel. Several studies have demonstrated that trained EMS personnel are able to appropriately clear cervical spines in standardized patients. However, in the more chaotic and dynamic setting of the unstandardized field patient, EMS personnel immobilize fewer patients in practice than do their physician colleagues. No data exist as to whether this discrepancy leads to adverse outcomes. In trauma systems that incorporate cervical spine clearance in the field, the two common criteria used for clearance are the National Emergency X-Radiology Utilization Study (NEXUS) and the Canadian C-Spine Rule. According to the NEXUS guidelines, clearance is achievable if the patient has no posterior midline cervical tenderness, is not intoxicated, has no alterations in mental status or focal neurologic deficits, and has no distracting painful injuries. Under the Canadian C-Spine Rule, the patient can be cleared and does not require imaging if he or she is younger than 65 years, has a low impact mechanism, has no paresthesias in extremities, is either ambulatory or sitting upright in the ED, has no midline tenderness, and is able to rotate his or her neck 45 degrees to the left and right. Of note, this determination takes some time and may interfere with rapid transport of the patient to definitive care (Fig. 1, table 1). The ACS-COT, American College of Emergency Physicians, and the National Association of EMS Physicians provide these indications for SMR following blunt trauma: (1) acutely altered level of consciousness (e.g., GCS <15, evidence of intoxication), (2) midline neck or back pain and/or tenderness, (3) focal neurologic signs and/or symptoms (e.g., numbness or motor weakness), and (4) anatomic deformity of the spine. Because of the risk of deep tissue injury and skin ulcers from prolonged use of SMR, once the patient is safely positioned on the ambulance cot, immobilization or extrication SMR devices may be removed. This requires an adequate number of trained personnel are present to minimize unnecessary movement during the removal process. If transport time is expected to be short, it may be better to transport a patient on the device and remove it on arrival at the hospital. If the decision is made to remove the extrication device in the field, SMR should be maintained by ensuring that the patient remains securely positioned on the ambulance cot with a cervical collar in place.

Exposure and Environment: Hypothermia

Approximately 66% of trauma patients in the civilian setting arrive at the ED with hypothermia. Prevention of hypothermia (body temperature <34°C) is a practice championed by the military, with the idea that instituting rewarming methods early impedes the spiral into the trauma triad of death of hypothermia, coagulopathy, and acidosis. Layers of blankets and modified jacket body bags to provide warmth are used in current combat situations. Passive rewarming can be achieved by increasing ambient temperatures, whereas active rewarming uses blankets and air or fluid circulating covers. Core rewarming uses fluid warmers to heat infusing fluid to 42°C. The key is to initiate prevention early in the field, as adequate rewarming is much more difficult to achieve once hypothermia occurs.

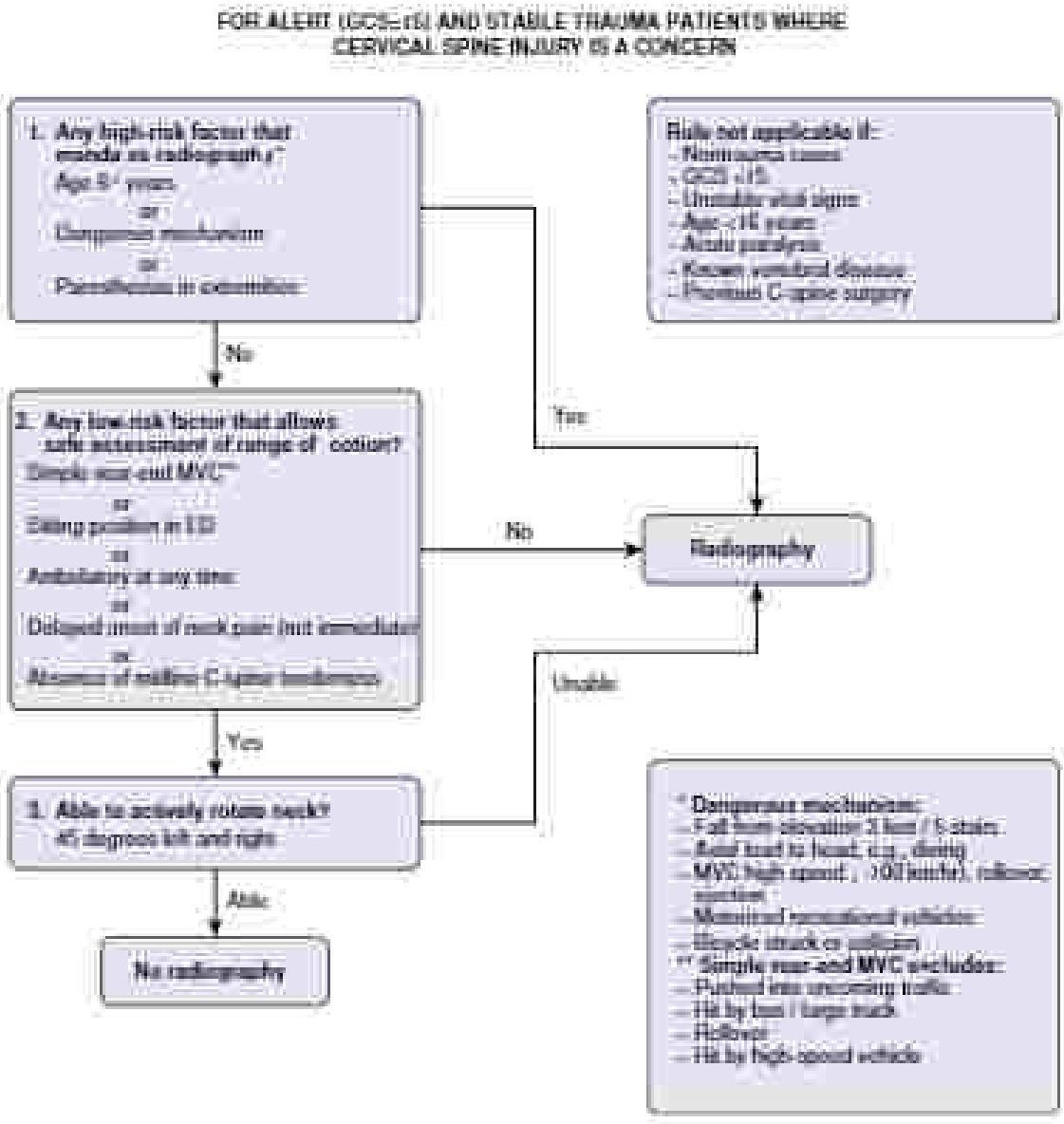

FIG. 1 Canadian C-spine rule (CCR). ED, emergency department; GCS, Glasgow Coma Scale; MVC, motor vehicle collision.

TABLE 1 NEXUS Criteria for Low Probability C-Spine Injury

1	No midline tenderness
2	No focal neurologic deficit
3	Normal alertness
4	No intoxication
5	No painful distracting injury

NEXUS, National Emergency X-Radiology Utilization Study.

Adjuncts: Splints

An adjunct frequently used in the prehospital setting is the splint; common materials include box, vacuum, and traction splints. In the case of obvious extremity fractures, splinting the injured extremity can stabilize the injury and potentially reduce pressure on skin and neurovascular structures, and decrease pain and bleeding. The splint must extend to the joints above and below the fracture to provide support.

CARE DURING TRANSPORT

Prehospital Field Triage

In the United States, in-hospital and 1-year mortality are significantly lower in trauma patients treated at trauma centers compared with those treated at nontrauma centers. Having a predetermined system in place to address injuries and triage patients saves lives. Trauma centers are divided into different tiers based on their capabilities. Level I trauma facilities have the resources for all-encompassing trauma care, including subspecialty providers, research capabilities, education, outreach, prevention, and rehabilitation. Level II trauma centers retain almost equivalent resources and can provide resuscitation and stabilization of patients, but do not provide similar education and research opportunities. Level III trauma centers have more limited resources and staff. They are able to treat minor traumas and possess the capability to stabilize and transfer more severely injured patients to a higher level of care. Allocation of trauma patients into these systems requires the use of thoughtful triage parameters in the field. Proper triage in the prehospital setting can lead to expedient transfer of the most ill patients to definitive care. The key is to maintain a balance between guaranteeing that the majority of

critically ill patients are transported to a higher level of care facility and ensuring that these systems are not overburdened with patients who have sustained minimal injuries. A 50% overtriage rate is tolerated to attain a 5% or lower undertriage rate per the ACS COT.

Prehospital triage situations can be divided into field triage and mass casualty. As per the Centers for Disease Control and Prevention (CDC) Guidelines for Field Triage of Injured Patients, a step-by-step algorithm is critical in filtering patients into appropriate avenues of treatment (Fig. 1). When measuring vitals and assessing GCS, patients with an SBP of less than 90 mm Hg, a respiratory rate of less than 10 or more than 29 breaths/min (<20 breaths/min in infants aged <1 year), the need for ventilator support, or a GCS score of less than 14 should be transported preferentially to the highest level of care available within the defined trauma system.

Similarly, EMT assessment and location of injury and mechanism and evidence of high impact. Specific injury patterns require evaluation in a Level I trauma center or at an institution with the most advanced care within that trauma system. The particular sequence of concern include penetrating trauma to the head, neck, torso, and extremities proximal to the elbows and knees (hall chest); two or more proximal long bone fractures; crushed, degloved, or mangled extremities; amputations proximal to the wrist or ankle; pelvic fractures; open or depressed skull fractures; and paralysis.

Depending on the particular trauma system, if the patient does not have the aforementioned clinical signs or anatomic indications, he or she does not necessarily need to be transported to the highest level of care. Indications for transfer to at least a lower level trauma center include high-impact mechanisms such as falls from higher than 20 feet (2 stories) in adults or more than 10 feet in children; intrusion of more than 12 inches in the occupant site or more than 18 inches in any site; ejection from a vehicle; death in a compartment; speed greater than 20 mph or patient thrown or run over in an automobile versus pedestrian or bicycle collision; and motorcycle collision at a speed greater than 20 mph. Decisions about transport to a trauma center or hospital capable of trauma management also should consider comorbidities, age, particularly older adults and children; burns; pregnancy greater than 20 weeks; premorbid conditions such as congestive heart failure and end-stage renal disease; or anticoagulation therapy are found on EMS judgment.

Type of transportation to definitive care (ground vs air) must take into consideration multiple factors, such as the patient's clinical condition, weather conditions, weight of patient and necessary equipment, location of helipads, distance to most appropriate level of care, and local emergency needs if there are limited EMS vehicles in the region and the patient must travel far.

Helicopter Emergency Medical Services

Approximately 400,000 patients are transported by HEMS in the United States annually. Uncertainty exists regarding the added benefits of HEMS versus ground EMS (GEMS). A 2015 Cochrane review of 38 HEMS studies did not show an overall benefit, because many studies had methodical problems. HEMS may have advantages in regions with difficult geography and can carry more specialized crew and equipment. From 1972 to 2014, there were 343 HEMS accidents, 123 of which had at least one fatality. In 1980, an HEMS crewmember had a 1 in 50 chance of being in a fatal accident, in 2014 the rate was 1:850, but being an HEMS crew member is still one of the most dangerous US occupations. In 2008, the US National Transportation Safety Board conducted an investigation into a spate of HEMS crashes and made recommendations to the Federal Aviation Administration that were largely accepted, since then the HEMS accident rate has reduced somewhat.

Given the risk benefit ratio of HEMS, triage criteria for safe HEMS use should be carefully created for the trauma system. Studies suggest that trauma patients most likely to benefit can be identified using validated scores such as the Air Medical Prehospital Triage (AMPT) Score. Factors in the AMPT include those patients with chest wall instability or deformity including flail chest or multiple rib fractures, tension pneumothorax, GCS score less than 14, respiratory rate less than 10 or greater than 29 breaths/min, multiple trauma (>1 anatomic body region injured), or any one physiologic criterion plus any one anatomic criterion present from the ACS COT national field triage guidelines (Fig. 2). Unfortunately, some HEMS operations are not full participants in regional or state trauma systems or in the planning for such systems, and HEMS is sometimes still used to cope with non-patient-related system issues such as inadequate local GEMS resources or lack of local verified trauma centers.

DISASTERS AND EMERGENCY PREPAREDNESS

In mass casualty situations, the paramedic or EMT must change focus on optimal care for a single or limited number of patients to providing a population-based standard of care. Resources are typically inadequate, communications are disrupted, and there may be severe environmental challenges including hazardous materials, weapons of mass destruction, and terrorist acts. Most EMS systems have a detailed plan for activation and execution to disasters, typically called the emergency operations plan (EOP). The EOP describes principles for preparation, planning, incident command, interoperability with other agencies, triage, dispatcher actions, regional plans, blast, radiation and chemical threats, special populations, recovery, and business continuity. Typically, an adjacent safe area is used for casualty collection and triage, and patients are sorted using a disaster triage protocol such as SALT (sort, assess, lifesaving interventions, treatment, and/or transport) or START (simple triage and rapid treatment) to the adjacent treatment area marked with red, yellow, and green tarpaulins. SALT uses the ABCDEs principles to assign a color code corresponding to triage tags that can be used to designate status. The walking wounded (green) have minor trauma and are ambulatory patients who can be removed from the scene, if they require care, it can be delayed for approximately 3 hours. Delayed (yellow) and immediate (red) victims are nonambulatory patients who require medical attention, with immediate patients having at least one derangement in respiration, perfusion, or mental status that requires emergent care. Therapy can be postponed for approximately 1 hour in delayed patients. Expectant (gray) victims are considered dead after one attempt to open or reposition the airway demonstrates no respirations. Comfortable, compassionate care also should be administered to these patients; the designation of expectant does not signify that no further interventions should be made, if the situation later improves the patient can be transported. It should be remembered that in some events, patients may leave the scene or be transported by bystanders before the EMS response can even be safely established, such as in the 2017 Las Vegas shooting.

HOSPITAL RESPONSE TO TRIAGED PATIENTS

Once the trauma center receives the field EMS call activation, the ED physician or mobile intensive care nurse determines whether the trauma team activation is warranted. To define the extent of the ED response and determine which resources should be apportioned, similar guidelines to those in CDC triage decision scheme are followed, with healthcare personnel weighing physiologic and anatomic parameters. Mechanism of injury is also considered but is less significant. Standard criteria for hospital activation response exist in few systems, and different institutions use distinct processes. Some trauma centers use an "all or none" approach, whereas others divide patients into two or three categories by number or color scheme to classify patients as critical, low severity (injured but with potential to decompensate), and minimally wounded. In patients with grave injuries, a full response from the hospital occurs with mobilization of the ED and trauma surgeons, residents, or fellows; nursing staff; respiratory therapy; the blood bank; radiology; and anesthesia made available. Partial responses require the ED attending physician, surgical residents,

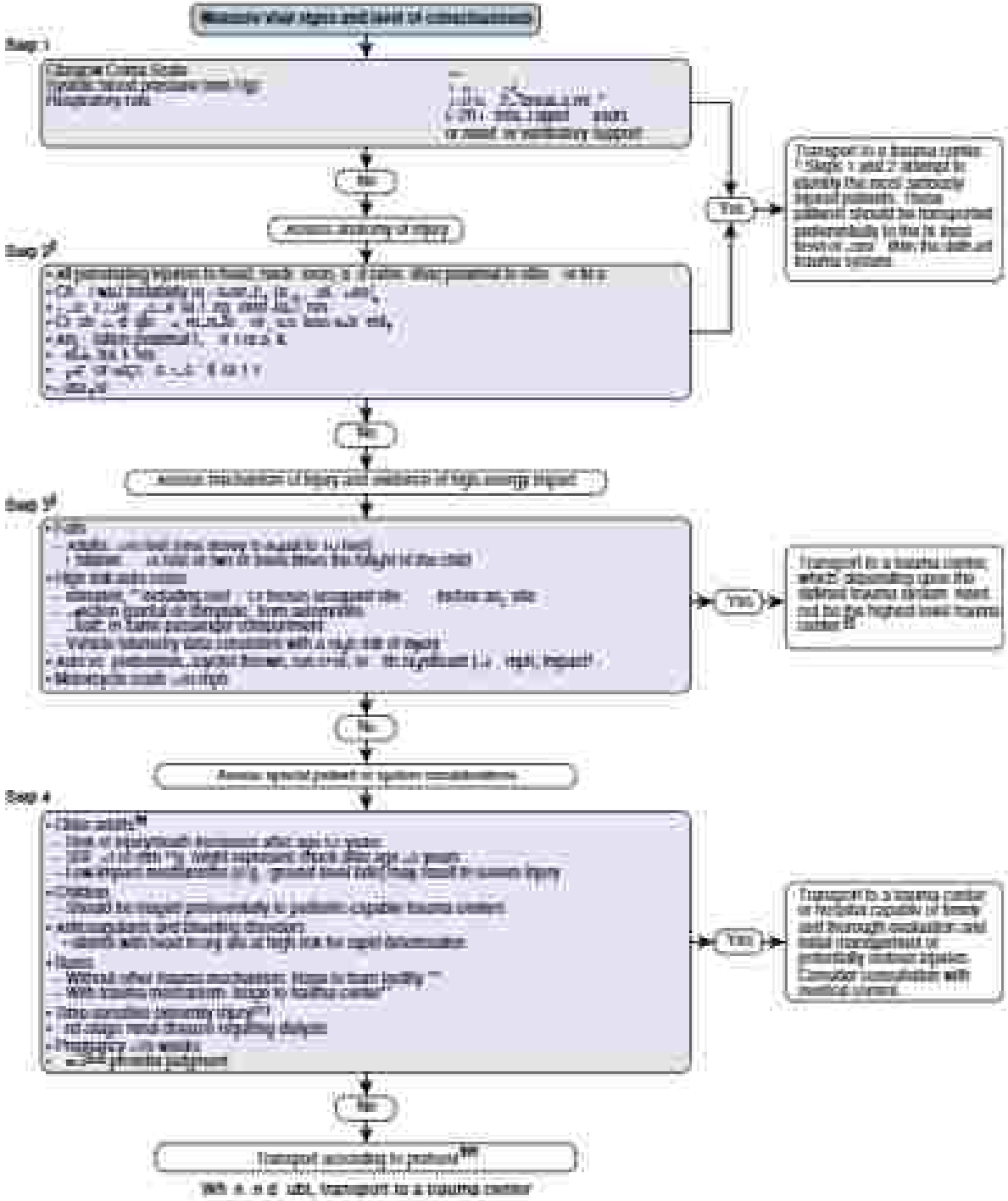

FIG. 2 Centers for Disease Control and Prevention Guidelines for Field Triage of Injured Patients. EMS, emergency medical services; GCS, Glasgow Coma Scale score; SBP, systolic blood pressure; RR, respiratory rate; AV, atrioventricular; ED, emergency department; IV, intravenous; MI, myocardial infarction; PE, pulmonary embolism; TBI, traumatic brain injury; VTE, venous thromboembolism. Adapted from Field Triage Decision Scheme. Available at: https://www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm. Accessed January 2, 2023.

*Upper limit of respiratory rate in infants is >29 breaths per minute to maximize the likelihood of identifying the infant with severe thoracic trauma who requires immediate intervention. Consider infants at risk for head injury (e.g., ground level fall) may result in severe injury.

†Consider advanced interventions (e.g., ventilatory support, blood transfusion, surgical intervention, intracranial pressure monitoring, tranexamic acid administration) in the trauma bay.

‡Consider transport to a burn center for patients with burns and concomitant trauma (e.g., fracture, polytrauma, blast injury, inhalation injury).

§Consider transport to a burn center for patients with partial-thickness burns ≥10% total body surface area (TBSA).

¶Consider transport to a burn center for patients with full-thickness burns ≥5% TBSA.

**Consider transport to a burn center for patients with burns to the face, hands, feet, genitalia, perineum, or major joints.

††Consider transport to a burn center for patients with burns and electrical injury, including lightning injury.

‡‡Consider transport to a burn center for patients with burns and chemical injury.

§§Consider transport to a burn center for patients with burns and preexisting medical disorders that could complicate management, prolong hospitalization, or increase mortality.

¶¶Consider transport to a burn center for patients with burns and inhalation injury.

***Consider transport to a burn center for patients with burns in children who will be cared for in facilities that are not capable of providing definitive care to children.

†††Consider transport to a burn center for patients with burns who require special social, emotional, or long-term rehabilitative intervention.

nursing staff, and radiology. Having a structured and controlled response system in place with predetermined trauma team activation has been shown to decrease mortality and time for resuscitation, for transport to computer tomography scan and operating room, and to ED discharge. The handoff from EMS providers to the trauma team should be a structured communication with acknowledgement and feedback to ensure all prehospital information is transferred. A typical paramedic or EMT handover format is MIVT (mechanism of injury, injuries seen or suspected, vital signs, and treatments given).

LESSONS LEARNED FROM THE MILITARY

As described earlier, many practices in prehospital civilian resuscitation and care have been extrapolated from or reinforced by military practice, including guidelines for use of tourniquets and needle chest decompression, and the practice of IO access. Incorporation of methods for providing the use of field ambulances traces back to the Ambulance volante du modèle Larrey (flying ambulance) used by Dominique-Jean Larrey (1766–1842), Napoleon Bonaparte's chief surgeon, and helicopter transport of patients was initiated during the Korean and Vietnam wars. Resuscitation guidelines have been influenced strongly by combat trauma data, including hypotensive resuscitation to SBP of 80 to 90 mm Hg and massive transfusion protocols. Currently North Atlantic Treaty Organization forces are supporting flying trauma teams on medium helicopters in Afghanistan and Africa and combining the EMS, HEMS, and forward surgical team roles aboard the same vehicle, down directly to the point of wounding. Further innovations in pre-hospital care from military providers can be expected.

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USE OF RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA IN RESUSCITATION OF THE TRAUMA PATIENT

James N. Stewart, MD, FACS, and Megan P. ...on, MD, MS, FACS

Hemorrhage remains the most common potentially treatable cause of death in the trauma patient. The American College of Surgeons' Advanced Trauma Life Support (ATLS) curriculum encourages rapid identification and control of hemorrhage as the central tenet in caring for the injured patient. Initial attempts at direct pressure and application of hemostatic dressings are warranted for most bleeding. However, if these are not available or not effective, proximal control of the bleeding is warranted. For the extremities, hemostasis may be accomplished with a tourniquet. For noncompressible truncal hemorrhage, hemostasis can be accomplished by occlusion of the aorta.

Resuscitative thoracotomy (RT) was described by Dr. Ledgerwood and others as a method to avoid cardiovascular collapse upon laparotomy and the resultant release of tamponade in the patient with abdominal hemorrhage. Through the left anterolateral thoracotomy incision, the thoracic aorta can be clamped and open cardiac massage performed, thus providing direct resuscitation and proximal control for subdiaphragmatic truncal hemorrhage. In cases of noncardiac injury, pericardial tamponade can be relieved and thoracic hemorrhage can be controlled.

Another option for proximal control of the aorta that does not require a thoracotomy incision is balloon occlusion using endovascular devices. Endovascular balloon occlusion of the aorta for trauma was first described by Dr. Hughes in the 1950s. Other attempts were described in the 1980s but the technique fell out of favor because of cumbersome equipment and poor results. In the early 2000s, with the development of better endovascular equipment, endovascular balloon occlusion became more commonplace for the treatment of those with ruptured abdominal aortic aneurysms. With translational studies demonstrating potential physiologic advantages of endovascular occlusion over RT, military and civilian collaboration led to adoption of the technique as resuscitative endovascular balloon occlusion of the aorta (REBOA).

INDICATIONS

REBOA can be conceptualized as a tourniquet for the trunk. Most patients for whom rapid proximal control of truncal hemorrhage would be lifesaving may benefit from REBOA. Patients with an indication for REBOA can be divided into those without a palpable pulse (cardiac arrest) and those with a palpable pulse who are hypotensive but not responding to blood product administration and other standard resuscitative measures.

In the coding trauma patient who we feel is be a candidate for RT, REBOA is strongly considered as a means to augment cerebral and coronary perfusion. Fig. 1 is an adaptation of the military Joint Trauma System's guideline for managing trauma patients in cardiac arrest. In blunt trauma patients with cardiopulmonary resuscitation (CPR) ongoing for less than 5 minutes and no cardiac tamponade

nursing staff, and radiology. Having a structured and controlled response system in place with predetermined trauma team activation has been shown to decrease mortality and time for resuscitation, for transport to computer tomography scan and operating room, and to ED discharge. The handoff from EMS providers to the trauma team should be a structured communication with acknowledgement and feedback to ensure all prehospital information is transferred. A typical paramedic or EMT handover format is MIVT (mechanism of injury, injuries seen or suspected, vital signs, and treatments given).

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James N. Bulger, MD, FACS, and Megan Brenner, MD, MS, FACS

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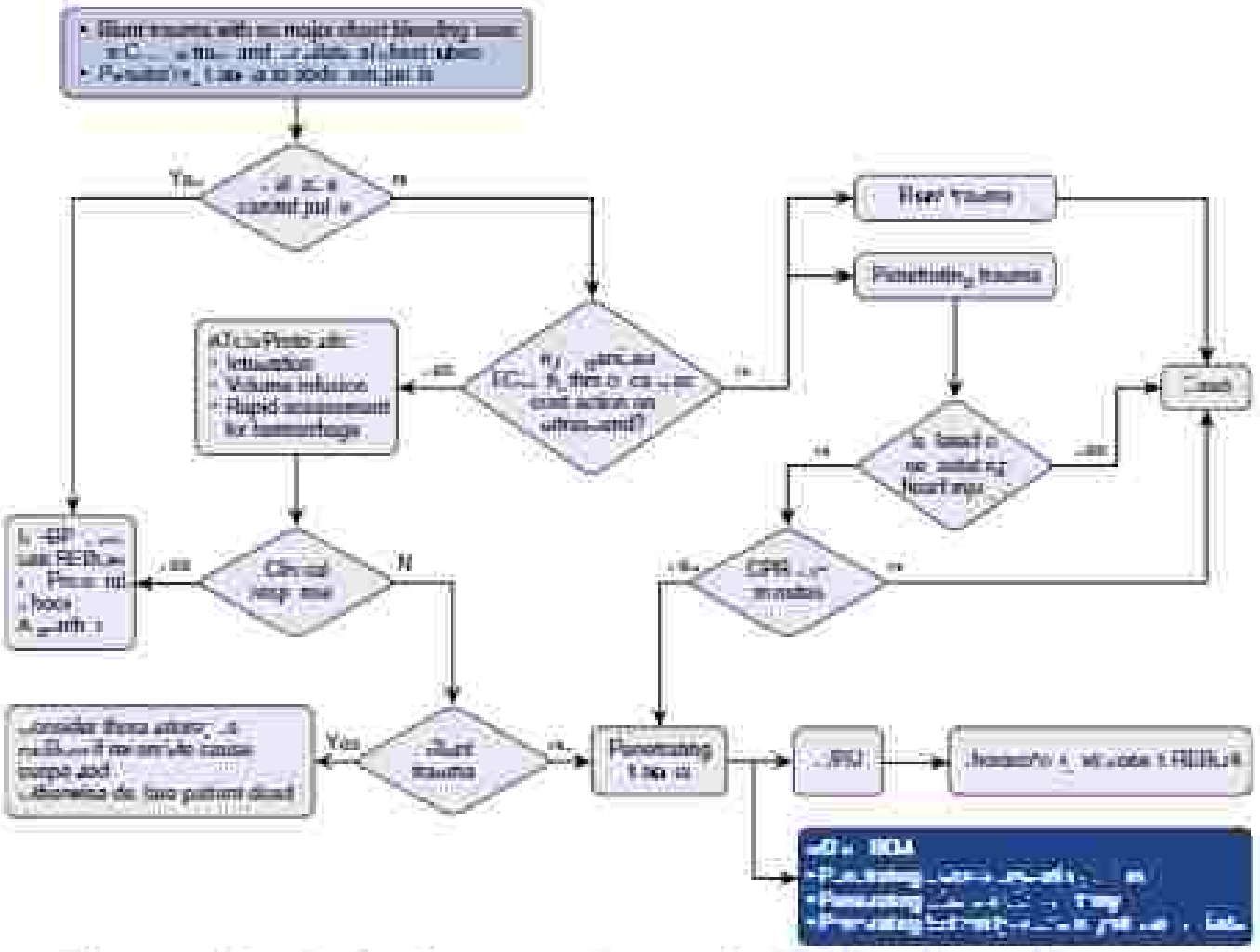

FIG. 1 US Department of Defense Joint Trauma System traumatic cardiac arrest algorithm. ABP, Abdominal pelvic/junctional hemorrhage; AT, extremity; AT, advanced trauma life support; CPC, cardiopulmonary resuscitation; CXR, chest x-ray; ECG, electrocardiogram; EDG, resuscitative endovascular balloon occlusion of the aorta; IBP, invasive blood pressure; [illegible] et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA) for hemorrhagic shock. PLOS One. 2017;12(12):e0189454.

or pneumothorax on ultrasound evaluation, REBOA is strongly considered. The advantage to REBOA in this situation is that it can be performed without the need to stop chest compressions required for RT, permitting cardiac compressions throughout the procedure. Preliminary data suggest markers such as end tidal CO_2 are higher in patients with REBOA compared with RT with aortic cross-clamp likely due to the overall higher total cardiac compression fraction in REBOA patients. However, REBOA does not offer therapy for other causes of cardiac arrest in the trauma patient such as cardiac tamponade or tension hemothorax or pneumothorax. Both entities should be ruled out before performing REBOA using physical examination, extended focused assessment with sonography for trauma (FAST), and/or radiography. Small hemothoraces or pneumothoraces, rib fractures, and so forth are not a contraindication to REBOA because it is unlikely these conditions have predominantly led to the patient's severe physiologic derangement. For patients with penetrating mechanisms of injury and severe hemorrhage below the diaphragm, we consider REBOA. RT demands a sternal incision, whereas REBOA is less invasive and may minimize exposure risks to providers. In patients with penetrating thoracic trauma, RT is both diagnostic and potentially therapeutic, although REBOA may be performed in this setting purely for aortic occlusion.

We consider any trauma patient with evidence of truncal hemorrhage and a systolic blood pressure less than 90 mm Hg who is either a nontransfusion or transient responder to blood product administration to be a REBOA candidate (Fig. 2). In patients with hypotension but a palpable pulse, ATLS primary and secondary surveys and blood product resuscitation should take priority. We advocate early common femoral artery (CFA) arterial line placement in these patients. Should resuscitative efforts fail to restore the patient's hypotension and REBOA is considered, CFA access is usually the rate limiting step. As with the cardiac arrest patient, a thoracic cause for the refractory hypotension (massive hemothorax or cardiac tamponade) must be ruled out before REBOA. This is most commonly accomplished with chest radiography and a FAST exam. In civilian trauma patients with refractory shock secondary to noncompressible hemorrhage, REBOA can restore central perfusion and slow hemorrhage while hospital resources such as angiography or the operating room are being mobilized. In patients with severe pelvic fractures and hypotension not responding to resuscitative measures (pelvic binder and blood products), REBOA placed at the aortic bifurcation is an option to restore central and visceral perfusion and decrease pelvic bleeding until angiography can be performed (see Fig. 2).

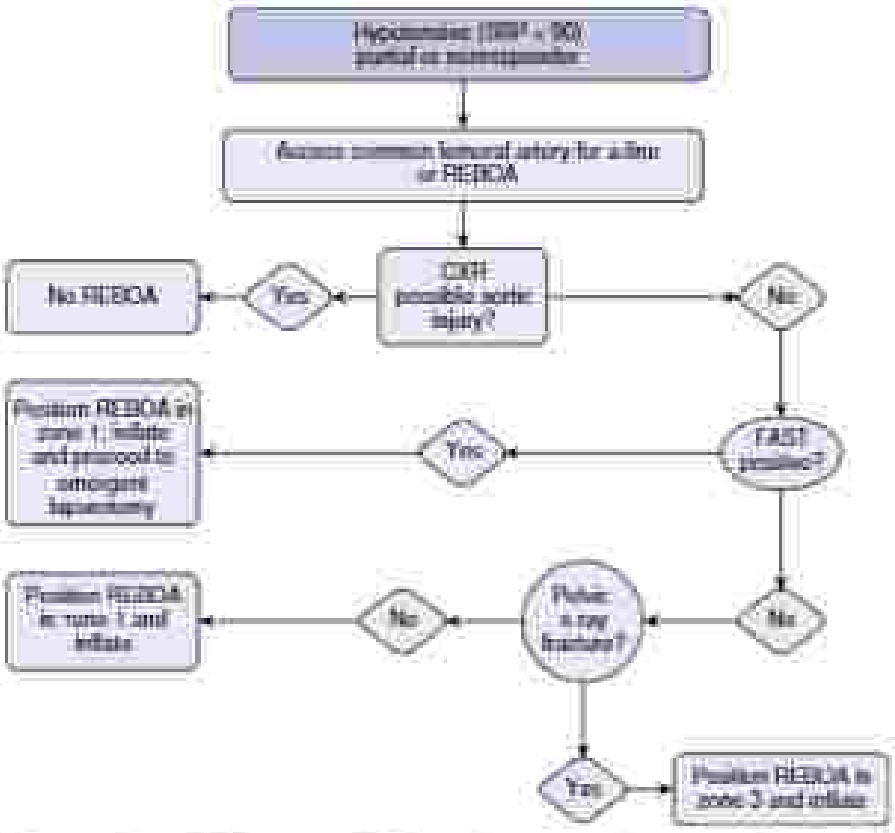

FIG. 2 Algorithm for REBOA zone selection. CXR, Chest x-ray; FAST, focused assessment with sonography for trauma; REBOA, resuscitative endovascular balloon occlusion of the aorta; SBP, systolic blood pressure. (from Moore LJ, Brenner M, Kozar RA, et al. Implementation of resuscitative endovascular balloon occlusion of the aorta as an alternative to resuscitative thoracotomy for noncompressible truncal hemorrhage. J Trauma Acute Care Surg. 2015;79(4):515.)

CONTRAINDICATIONS

Several contraindications to REBOA must be kept in mind. Patients who are not candidates for aggressive resuscitation (such as those with an pulse for more than 15 minutes or an obviously nonsurvivable injury) should not receive REBOA, although this decision is both physician and patient dependent. Patients with noncranial bleeding, such as from a proximal upper extremity or neck wound, should not receive REBOA unless direct control of bleeding is achieved before occlusion for resuscitation. For distal upper and lower extremity injuries, a tourniquet can be placed. Patients with widened mediastinum on chest radiography who have a mechanism consistent with a moderate to severe blunt thoracic aortic injury should not have REBOA placed because balloon inflation in an area distal to or at the level of thoracic aortic injury could result in worsening of injury and rupture. Using REBOA in patients with severe isolated traumatic brain injury (TBI) in the absence of hemorrhage below the diaphragm is generally not needed. However, in patients with TBI and truncal bleeding, REBOA should be considered if the patient's hypotension is thought to be caused by blood loss. Rapid definitive hemorrhage control in these patients can halt the worsening of primary and secondary TBI and, in cases of noncorrectable injury, can bridge patients to organ donation.

RISKS

One must be cognizant of significant potential risks REBOA poses to trauma patients. These risks must be weighed against the perceived benefit to the patient in deciding whether to proceed with REBOA. Furthermore, the practitioner placing REBOA must be aware of these risks, their mitigation, and their management for prompt identification and treatment to occur.

Any time the femoral artery is cannulated, the risk of thromboses and/or distal embolization leading to limb ischemia and possible amputation is present. This risk rises as the size of the catheter being used increases. This risk also increases as the size of the vessel being cannulated decreases. Because patients are often so hypotensive that pre-REBOA documentation of limb perfusion is not feasible, the importance of post-REBOA assessment of limb perfusion becomes paramount. Any question of limb ischemia after REBOA should elicit prompt diagnostic studies and/or vascular surgery consultation. Furthermore, with the larger sheaths required for REBOA, cannulation of the CFA rather than the superficial femoral artery (SFA) allows for collateral flow from the profunda femoris artery to serve the distal limb while the sheath is in place if the sheath is occlusive in the CFA. A strategy for consistent and accurate cannulation of the CFA is required of anyone performing REBOA. Data demonstrate that the rate limiting step in REBOA is time to CFA cannulation, thus it is a skill demanding proficiency with both open surgical and percutaneous methods with or without ultrasound.

REBOA is often placed in a highly dynamic and chaotic environment surrounding a severely hypotensive or coding trauma patient. Arterial blood may look very dark and may lack pulsatility. Inadvertent placement of the REBOA catheter in the venous system has been reported, and inflation of the balloon in the inferior vena cava not only does nothing to stop truncal bleeding, it may, in fact, worsen the patient's hemodynamic status by severely limiting cardiac preload. Furthermore, placing the REBOA catheter in the wrong location within the vascular tree may cause vessel injury or cardiac outflow

obstruction. The importance of imaging to ensure proper positioning of the REBOA catheter before inflation cannot be overemphasized. Imaging can greatly assist in avoiding complications such as balloon overinflation and malpositioning, which can lead to balloon rupture, aortic injury, thrombosis, and/or distal embolism and ischemia. Exceptions to device confirmation with imaging before balloon inflation include a patient in arrest, where CPR is not paused for x-ray, but rather is performed if and when return of spontaneous circulation occurs. Other exceptions to imaging confirmation include environments without this capability (austere), in which case the balloon can be palpated during exploration if required for definitive hemorrhage control or confirmed on fluoroscopy if angiography is the only mode of treatment required.

TECHNICAL POINTS

The first step of REBOA is to access the CFA. This is often the most technically challenging and rate limiting step of REBOA. For this reason, we often start CFA access before determining whether the patient is a REBOA candidate. Reliable access in the CFA is also paramount to avoiding limb ischemia–related complications. Knowledge of the CFA anatomy is the point is paramount (Fig. 2). The external iliac artery becomes the CFA as it traverses beneath the inguinal ligament and then bifurcates into the SFA and the profunda femoris artery 3 to 4 cm distal to the inguinal ligament. The inguinal ligament runs from the anterior superior iliac spine to the pubic tubercle. One should note that the groin crease is not useful for identifying the underlying vascular anatomy. To reliably cannulate the CFA, one of three methods may be used depending on the experience level of the surgeon, the clinical situation, and the availability of ultrasound: open cutdown, ultrasound guided percutaneous, and blind percutaneous. In the setting of ongoing CPR, percutaneous access can be exceptionally challenging, and data demonstrate that most of these patients are being cannulated via open surgical exposure. A vertical groin incision is used to identify the CFA as it appears from under the inguinal ligament. The CFA is cannulated under direct visualization. If percutaneous access is desired, ultrasound guidance is highly recommended to ensure the CFA, not the SFA, is cannulated. Lastly, for experienced providers, a blind percutaneous stick can be performed ensuring that the vessel is entered within 2 cm of the inguinal ligament. It is important to note that this requires a skin entry site more superior than is standard for a typical femoral arterial line placed in the resuscitation area. Experience with endovascular devices confirms that percutaneous CFA access is much easier to perform when a palpable femoral pulse is present.

Once the decision has been made to perform REBOA, the arterial line catheter or micropuncture catheter (whichever was used for initial access) must be upsized to a larger sheath. Depending on the device being used, this can range from 7Fr to 14Fr. External landmarks are utilized to estimate insertion lengths of devices within the aorta. While upsizing and inserting devices, the catheter should always move freely within the sheath and ilium. Advancing devices against resistance is unsafe because severe injury can occur. Utilizing tactile feedback, imaging, and experience can ensure a smooth procedure.

For the purposes of REBOA, the aorta has three zones (Fig. 4). Zone 1 starts at the left subclavian artery and ends at the celiac artery. Zone 2 runs from the celiac artery to the lowest renal artery, and zone 3 is the infrarenal aorta from the lowest renal artery to the aortic bifurcation. The goal is to inflate the REBOA catheter in zone 1 or zone 3. The balloon should not be inflated in zone 2 to avoid occlusion of visceral vessels impeding retrograde flow and promoting a thrombotic environment.

Choosing the location of balloon inflation involves determining the most likely site of bleeding and planning to inflate the balloon as distally as possible but proximal to the site of bleeding. Using chest

FIG. 3. Common femoral artery (CFA) demonstrated in a cadaver model. Wire is in the CFA. Top arrow indicates the bifurcation into the superficial femoral artery and profunda femoris. Bottom arrow indicates the inguinal ligament.

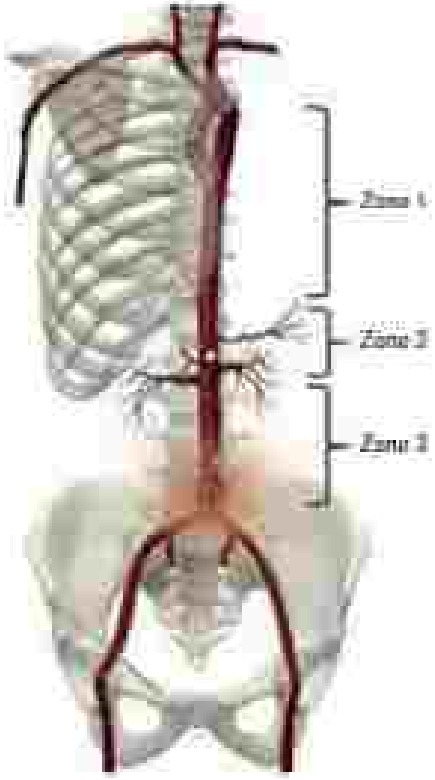

FIG. 4. Zones of the aorta with overlying surface landmarks. [From Inaba K, Lee WM, Karamanos E, Hall S, Teixeira PG, Matthews MR. Resuscitative endovascular balloon occlusion of the aorta with a low profile, axillary device: a game changer? Trauma Co e Rep. 2016;Suppl 1(1):7–9.]

radiographs, FAST, and pelvic radiographs, one can estimate the site of bleeding and plan for the proper aortic zone for inflation. A positive FAST exam denotes abdominal bleeding and requires zone 1 inflation to occlude occlusion proximal to the site of bleeding. An isolated pelvic fracture, on the other hand, requires only a zone 3 inflation to ensure occlusion of the aorta proximal to the bleeding site (see Fig. 2). For all patients in arrest, REBOA at zone 1 is indicated as both

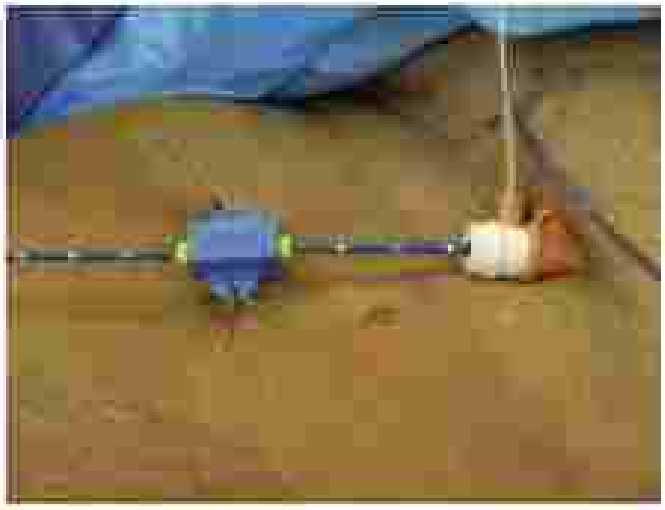

FIG. 3. ER-REBOA catheter (Prytime Medical) has centimeter markings for insertion length measurement. The catheter must be secured to the skin before, during, and after balloon inflation because the catheter will displace inferiorly with increasing proximal pressure.

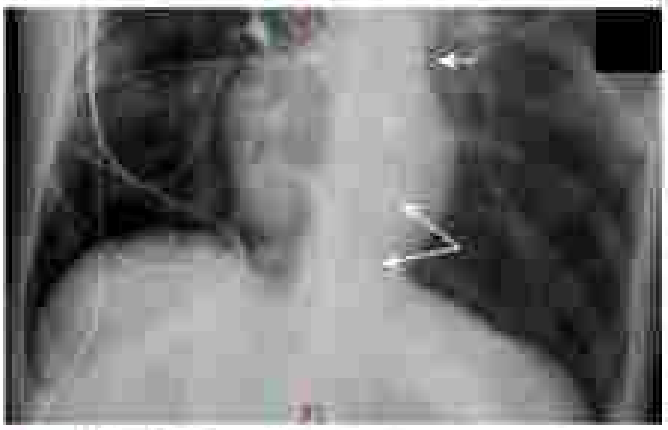

FIG. 4. ER-REBOA (Prytime Medical) can be seen in zone 1 for a patient with persistent hypotension, negative chest x-ray, and positive abdominal focused assessment with sonography for trauma exam. Chest radiography was used to confirm placement before inflation. Lung zones denote the proximal and distal extent of the balloon. Short arrow shows the end of the catheter.

a resuscitative tool for cerebral and coronary perfusion and secondarily as a measure to temporize distal hemorrhage.

Surface landmarks are used to estimate the required depth of catheter insertion to arrive at the desired aortic zone for balloon inflation. The xiphoid process corresponds to the inferior border of zone 1, and the umbilicus corresponds to the inferior border of zone 3. Depth of insertion of standard, over the wire balloon catheters is determined by placing the tolerable edge of the balloon just above the desired landmark (xiphoid process for zone 1 and umbilicus for zone 3) and measuring the distance to the end of the introducer sheath following the path of the iliac artery and aorta. Alternatively, when using the ER-REBOA catheter (Prytime Medical) (because the balloon is set back from the tip of the catheter), one can measure from the sternal notch to the end of the sheath for zone 1 and from the xiphoid process to the end of the sheath for zone 3.

Once the depth of balloon insertion has been determined, the catheter should be marked with tape, or, if the catheter has distance makers on it, the distance noted in the trauma flowsheet. The balloon is inserted over the guidewire and into the sheath if using a Coda type balloon (Cook Medical). If using an ER-REBOA catheter, no guidewire is required and the catheter is inserted directly into the sheath. The catheter is advanced to the previously determined depth and secured with suture, an occlusive dressing, or a catheter clip (Fig. 5). Before inflating the balloon, proper positioning of the catheter in the aorta should be confirmed with imaging. Most centers use x-ray (Fig. 4) or fluoroscopy, but ultrasound use to confirm that the balloon is in the aorta has also been described.

After confirmation of correct placement in the aorta, balloon inflation is begun until occlusion of the aorta is achieved. The balloon should be inflated with saline or dilute contrast material. Full-strength contrast is viscous and will clog the balloon lumen. The balloon is slowly inflated until the contralateral femoral pulse is lost. If arterial pulse waveform monitoring is available, this can be used as well to guide the volume of inflation. If the waveform is proximal to the balloon, as with the ER-REBOA catheter, inflation continues until a step-up is seen on the tracing. This is much like the changes one would see while floating a pulmonary artery catheter. If the arterial waveform is distal to the balloon, inflation would stop when the arterial waveform is lost. Lastly, in the absence of these signs, a subtle increase in resistance to further inflation can be detected by the surgeon. This should prompt cessation of further installation of saline or dilute contrast material. Alternatively, inflating the balloon with dilute contrast material under fluoroscopic visualization allows the surgeon to see in real time as the balloon makes contact with the wall of the aorta. The balloon will cease widening with further volume and will elongate the balloon. Inflation of the balloon should stop once this is visualized. Portable radiography can also demonstrate adequate aortic occlusion by the shape of the balloon. If overinflation has occurred, the balloon will appear as an oversized rectangle with "shouldering" at the proximal and distal portions (Fig. 7).

After aortic occlusion has been achieved, plans for definitive surgical or endovascular hemostasis should begin without delay. This requires immediate transport to the operating room or angiography suite. Safe duration of full aortic occlusion is unknown, but a goal of 30 minutes is reasonable and likely to avoid significant visceral ischemia. Zone 1 occlusion has been tolerated for most patients for up to 60 minutes. For zone 3, the maximum recommended duration of occlusion is less well defined, but ideally less than 60 to 90 minutes. With "normal" appearing vital signs during aortic occlusion and no open chest to remind the trauma team the severity of the situation, the teams sense of urgency may wane. It is the surgeon's responsibility to ensure the trauma team maintains focus on the urgent need to obtain definitive hemorrhage control and deflate the balloon.

When the aorta is occluded, one must bear in mind that the size of the vascular space has been drastically reduced, and the effects of such dramatic afterload increase in the heart and proximal organs are unknown in these patients. Adjustments in blood product resuscitation may be required and continuous monitoring of arterial pressure is mandatory.

On occasion, the clinical situation will not allow for definitive hemostasis within 30 minutes of balloon inflation. Intermittent balloon deflation to provide perfusion to visceral and distal vascular beds may help to prevent irreversible ischemia. This is an active area of investigation. Some have attempted to perform partial occlusion as a means of providing some blood flow to the distal organs without significant blood loss, potentially extending the time period to which the balloon may remain inflated. In practice, this is difficult to perform because very small changes in balloon volume result in large changes in blood flow distal to the balloon.

Balloon deflation can lead to highly labile vital signs due to washout of acidic blood from the bed of ischemia combined with the abrupt drop in afterload. Hypotension often results from a combination of relative hypovolemia and vasodilation. Close communication between the surgeon and anesthesiologist to ensure rapid availability of medications and volume expanders to combat these entities is paramount. The balloon should be deflated slowly over the course of 3 to 5 minutes initially, and sometimes this requires 15 minutes

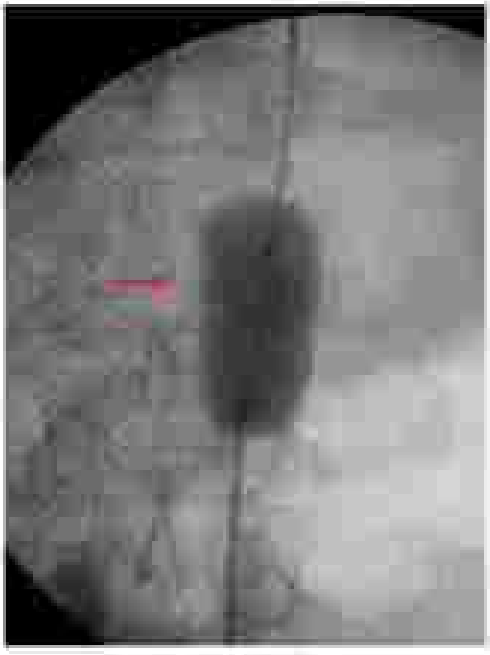

FIG. 7. Balloon overinflation demonstrated by extension of balloon far outside of balloon edge (arrow) in an oblong balloon.

or more. Less than 1 mL should be removed from the balloon at a time, pausing between each withdrawal to assess and treat any physiologic changes that may arise. As discussed earlier, very large changes in blood flow across the balloon occur over a small change to balloon volume. This inflection point is where the surgeon should be doubly cautious about removal of more than 1 mL from the balloon. Slow deflation in the setting of a completed exploratory laparotomy affords the opportunity to reexamine the abdomen for new onset bleeding not appreciated earlier with proximal occlusion.

With successful definitive hemostasis and balloon deflation, removal of the sheath is the next priority because of increasing ischemic complications to the limb with increasing sheath dwell time. In all patients, documentation of distal perfusion is required. This can be a formal angiogram documenting flow all the way to the foot or with Doppler signals symmetric to the contralateral leg. We recommend angiography, however, in situations where this is not readily available, an ankle to brachial index may be used before and after removal of the sheath. Any evidence of distal flow limitation should result in prompt angiographic imaging and involvement of a vascular surgeon in the therapeutic decision-making.

In patients who have had a cutdown approach to the CFA, surgical repair of the artery is required. Forgarty balloons should be used to clear the proximal and distal artery of any suspected thrombus to restore adequate inflow and outflow. Completion angiogram or documentation of symmetric Doppler signals is required. For patients with a percutaneously placed 7Fr sheath, the sheath may be pulled with pressure held for 30 minutes. Postremoval Doppler signal character and symmetry must be documented. Post REBOA lower extremity neurovascular checks should be done every hour for the first 12 hours after sheath removal. We suggest vascular ultrasound of the CFA puncture site at 72 hours for early identification of access site complications.

PITFALLS

The rate-limiting step for REBOA is accessing the CFA. Obtaining safe, accurate CFA access after the need for aortic occlusion has been recognized can be difficult and time consuming. With CFA access already established, REBOA becomes a more time efficient means of achieving aortic occlusion. Early CFA access in any patient with hypotension is highly recommended because this provides more accurate systolic blood pressure measurements than a standard cuff and secures access for REBOA if needed. With this strategy, CFA access is often in place by the time the patient is recognized as a non-responder to blood transfusions, and REBOA can proceed without delay. Wire free devices may further decrease procedural time from access to aortic occlusion.

Indiscriminate inflation of the balloon without careful attention to signs of aortic occlusion often leads to overinflation. Balloon overinflation can cause injury to the aorta in a patient who is already physiologically stressed, and in the worst case can turn a survivable injury into a unsurvivable combination of injuries. Other consequences include luminal injury to the aorta that can progress to dissection after balloon removal, and balloon rupture. To prevent this pitfall, the surgeon must remain aware of the endpoints of balloon inflation discussed previously. It is also important to know the relative size of the aorta to zone 1 and zone 3 in hypovolemic, vasoconstricted patients. The aortic diameter at zone 1 can vary between 15 mm and 38 mm in diameter, whereas at zone 3 the aortic diameter can vary between 6 mm and 28 mm. Most balloons will require only a fraction of their maximum volume to achieve occlusion.

Malposition of the balloon within the aorta can lead to ineffective hemostasis and ongoing bleeding, injury to visceral vessel origins, or injury to smaller than anterior. In addition, venous placement of the balloon leads to ongoing blood loss and possible venous injury when the balloon is inflated. In hypotensive patients, arterial blood often lacks pulsatility and may look dark like venous blood. The character of blood return is not adequate to determine arterial versus venous entry, nor is the strength of palpability. Despite guidewires and catheters designed to remain in the aortic lumen, inadvertent placement into branch vessels has been described. Using fluoroscopy or radiography to confirm proper location of the balloon before inflation is the most effective method for identifying and correcting malposition.

Failure to properly secure the sheath and balloon will lead to migration of the balloon distally. This can cause luminal injury, injury to the visceral vessels, or rebleeding as the balloon migrates distal to the site of hemorrhage. When using the IR REBOA device, the catheter must be secured within 5 cm of the sheath before balloon inflation (Fig. 5). When using a Cook type balloon, the guidewire must remain in place while the balloon is in place. The guidewire is the first thing in and the last thing out.

Occlusion of the aorta in trauma patients on the verge of exsanguination will cause a dramatic increase in measured blood pressure. Vital signs often appear normal despite the drastically altered physiology aortic occlusion creates. In the case of IFI, the trauma team has very apparent visual cues that the patient, despite normal appearing vital signs, remains critical and requires urgent progression to the next phase of care in the operating room. With REBOA, these visual cues (an open chest with a large protruding clamp) are not present. In trauma systems with little REBOA experience, there is a danger that the trauma team, as a group, will lose their sense of urgency to transport the patient to the next phase of care such as the operating room or angiography suite. It is the trauma surgeon's job as the team leader to ensure that the pace of care does not worsen once the vital signs improve with REBOA. Educating all members of the team on REBOA and the physiology it produces will help to avoid this phenomenon.

COMPLICATIONS

REBOA is an exciting minimally invasive technique to occlude the aorta in trauma patients. However, the procedure brings with it a new set of potential complications that must be anticipated, diagnosed early, and promptly treated to prevent serious injury, limb loss, or death.

Inadvertent SFA cannulation when attempting to gain CFA access can occur. When an 18-gauge arterial line is placed in the SFA, there is rarely an adverse outcome. However, when a 7Fr or larger sheath is placed into the SFA, the chance of adverse events rises dramatically. These events include ischemia due to thrombo-embolism, poor collateral flow, or dissection, which can lead to amputation. Reliable CFA access has been discussed earlier in this chapter and its role in preventing complications related to REBOA is paramount.

Dissection can occur at the groin access site or as a result of balloon trauma. Careful groin access and judicious inflation of the balloon after cross-once occlusion has occurred are the best strategies to avoid this complication. Angiography after the REBOA procedure is the most reliable way to diagnose a dissection early. Once diagnosed, prompt vascular surgery consultation is required to prevent progression and further complications.

All intravascular devices are a risk for thrombus formation. In most elective endovascular cases, this morbidity is managed with heparin administration. In actively bleeding trauma patients, however, heparin is contraindicated. Thrombus formation can occur at any location from the access site to the tip of the balloon or the guidewire. After balloon inflation, it is imperative to check distal pulses or Doppler signals. Before removing the introducer sheath, angiography is highly recommended to ensure no distal thromboembolism has occurred. Should these entities be detected, prompt vascular surgery consultation is warranted.

When the balloon is overinflated, aortic injury, balloon rupture, or both may occur. Deliberate and careful titration of balloon inflation is required to prevent these complications. We suggest using dilute contrast material under fluoroscopy to inflate the balloon whenever possible. In the case of balloon rupture, the patient will not have the expected improvement in blood pressure with inflation. There may be a temporary improvement of vital signs as the balloon achieves occlusion that suddenly reverses when the balloon ruptures. Aspiration of the balloon may reveal blood, imaging of the balloon will reveal an uninflated balloon. If balloon rupture occurs and the patient remains a candidate for aortic occlusion, the occlusion catheter may be removed and a new one placed or conversion to an REBOA may be used to achieve aortic occlusion.

CONCLUSION

REBOA is a minimally invasive method to achieve proximal control of bleeding in trauma patients with noncompressible torso hemorrhage. It can be performed on patients in the emergency department before they reach the point of cardiac arrest, and saves the patient the morbidity of RT. To safely deploy a REBOA balloon, the surgeon must understand the involved anatomy, physiology, and potential complications. Employed with careful technique, REBOA is a useful strategy for aortic control when caring for the trauma patient in refractory shock.

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AIRWAY MANAGEMENT IN THE TRAUMA PATIENT

Samuel M. Galvagno Jr, DO, PhD, FCCM, and Thomas M. Scalea, MD, FACS, FCCM

Early, aggressive, definitive management of the airway is emphasized as a crucial initial priority for trauma patients because hypoxia and airway obstruction are closely linked to preventable morbidity and mortality. Airway management in trauma patients is frequently complicated by cervical spine instability, brain injury, hemodynamic instability, lack of patient cooperation, risk of aspiration, time pressure, and facial injuries. For these reasons, airway management is an essential skill given the well-defined adverse clinical outcomes that occur when trauma patients develop acute respiratory insufficiency and hypoxia due to delays in securing the airway. This chapter describes techniques that can be used to rapidly establish and maintain a patent airway, with an emphasis on the importance of providing adequate oxygenation and ventilation throughout all phases of airway management.

RAPID CLINICAL AIRWAY ASSESSMENT: INDICATIONS FOR MANAGEMENT

A patient who is alert, oriented, and speaking normally to the absence of any abnormal injuries to the head or neck has an adequate airway. Any change in voice, complaint of a sore throat, dysphagia, tachypnea, use of accessory muscles, noisy breathing (snoring or stridor), or unexplained agitation may be ominous signs of imminent airway compromise.

For patients who are not able to safely maintain a patent airway, a focused examination should be performed while preparing the necessary equipment. The majority of the anesthesiology literature suggests that a combination of airway parameters found during an airway examination will provide the best chance for predicting a potentially difficult airway. A systematic approach to airway assessment should be employed, following the line of sight of the anesthesia provider from the upper incisors to the vocal cords, with a focus on the inside

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BOX 1 Airway Parameters That May Predict Poor Visualization of the Vocal Cords During Direct Laryngoscopy

- Prominent incisors or abnormal dentition
- Mandibular protrusion (Fig. 1)
- Mouth opening (>3 fingerbreadths or 5 cm, is normal)
- Mallampati classification (Fig. 2)
- Thyromental distance (>3 fingerbreadths, or 6 cm, is normal)
- Cervical range of motion (should not be tested in any patient with a suspected C-spine injury)
- Anatomic abnormalities (masses, swelling)
- Thickness of neck
- Length of neck (shorter neck associated with difficult intubation)

of the mouth and pharynx, concluding with examination of the mandibular space, neck, and chest. Box 1 and Figs 1 and 2 describe clinical traits that can be used to determine if visualization of the vocal cords is likely to be poor during direct laryngoscopy.

Of utmost importance during airway management is the ability to ventilate a patient with a mask. Independent risk factors for impossible mask ventilation include male sex, a history of sleep apnea, Mallampati 3 or 4 status, and the presence of a beard. Ultimately, few will argue that having an armamentarium of skills to manage the difficult airway is the most important aspect of management, especially considering the myriad factors that may preclude a thorough airway assessment in the trauma patient.

OXYGEN THERAPY AND AIRWAY ADJUNCTS

Initial interventions for airway management include provision of supplemental oxygen and a variety of noninvasive airway maintenance techniques. Complicating this process is the fact that the spinal cord must be protected until the possibility of a spinal cord injury has been excluded. Oxygen therapy should be provided to maintain the SpO_2 above 92%. A logical first step is to apply a nonrebreathing mask, which provides a FIO_2 greater than 60%. Oxygen therapy can then be deescalated accordingly after the patient has been assessed and stabilized, to a simple face mask (FIO_2 35%–55%), a Venturi mask (FIO_2 24%–60%), or a nasal cannula (FIO_2 24%–44%).

If the airway is compromised and the patient is not ventilating and oxygenating adequately, rapid noninvasive interventions are indicated during the interval preceding preparation for establishing a definitive airway. Bag-valve-mask (BVM) ventilation with 15 L/min of oxygen should be initiated (FIO_2 90%–100%). Addition of a nasal cannula beneath the mask is advised, when available to provide additional high-flow (>10 mL) oxygen throughout the intubation procedure. This technique may help prevent desaturation during intubation by improving preoxygenation while also providing apneic oxygenation during the intubation attempt. Oropharyngeal or nasopharyngeal airways can be inserted to alleviate airway obstruction by the tongue. Oral airway size can be gauged by measuring the airway from the corner of the patient's mouth to the external auditory canal. Nasopharyngeal airways should not be used if the patient has a suspected craniofacial injury for fear of inserting the device intracranially. The chin lift maneuver, which is performed by gently lifting the mandible without hyperextending the neck, may help open the airway. Alternatively, the jaw thrust maneuver can be performed by displacing the mandible forward while applying pressure to both angles of the mandible. Either technique is preferable for trauma patients since both techniques can be performed during in-line cervical stabilization.

RAPID SEQUENCE INDUCTION AND INTUBATION

A definitive airway in a trauma patient is defined by the placement of a cuffed tube in the trachea attached to a source of oxygen, and

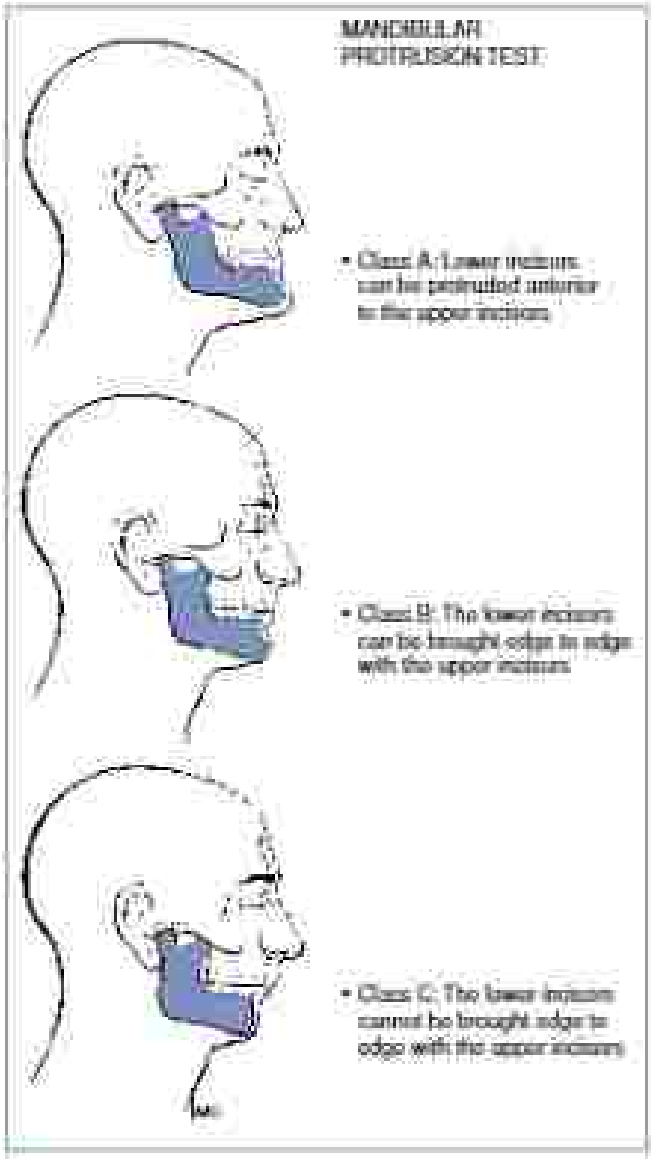

FIG. 1 *Mandibular protrusion test of jaw mobility. Class A portends better vocal cord visualization during direct laryngoscopy than class B or C. (Modified from Munoz LJ, de Bordalba A, Sanchez MS. Airway problems in pregnancy. Crit Care Med. 2005;33:S259–S260.)*

properly secured. Endotracheal intubation, nasotracheal intubation, cricothyrotomy, or tracheotomy can be performed to establish a definitive airway. In the majority of trauma patients, rapid sequence induction and endotracheal intubation (RSII) is used to establish a definitive airway.

RSII is predicated on the fact that the trauma patient has a full stomach, and excessive BVM ventilation will cause gastric insufflation with aspiration of gastric contents. RSII involves a highly organized sequence of events starting with preoxygenation for at least 3 minutes. The *6 Ps* of RSII describe the recommended sequence (Table 1). During the preparatory stage, a suction catheter is prepared and tested, an adequate source of oxygen is established and readied for connection, a pulse oximeter is attached to the patient, pharmacologic agents are prepared, and airway equipment organized. It should be noted that proper performance of RSII ideally requires at least four providers: one to apply cricoid pressure, one to maintain in-line cervical stabilization, one to ventilate with a BVM and intubate, and one to administer drugs and assist with airway devices (Fig. 3).

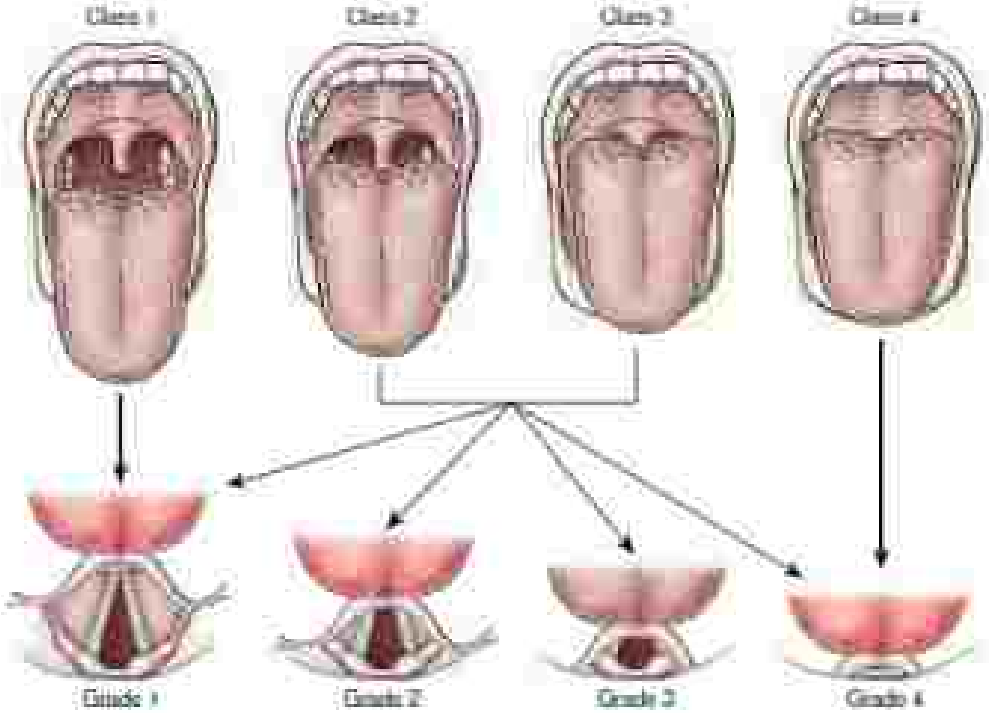

FIG. 3 Mallampati classification. The higher the class, the worse the Cormack-Lehane view of the vocal cords during direct laryngoscopy. (From Lippincott AE, ed. Cases in Diagnosis and Treatment in Otology. Head and Neck Surgery. 2nd ed. New York: McGraw Hill; 2004.)

TABLE 1 6 P's of Rapid Sequence Induction and Intubation

Step	Time Interval	Pharmacologic Agents
Preoxygenation	0–3 min	Oxygen, including addition of nasal cannula
Premedication	3 min	Induction agent + fentanyl, lidocaine, atropine, defasciculating agent (rocuronium, vecuronium, usually one-tenth the induction dose)
Paralysis	3.5–4.5 min	Midazolam, ketamine, etomidate, propofol or other induction agents followed by succinylcholine or rocuronium
Placement	6–6.5 min	Oxygen
Performance	7–7.5 min	Oxygen
Postintubation management	7.5 + min	Oxygen, sedatives, analgesics, etc.

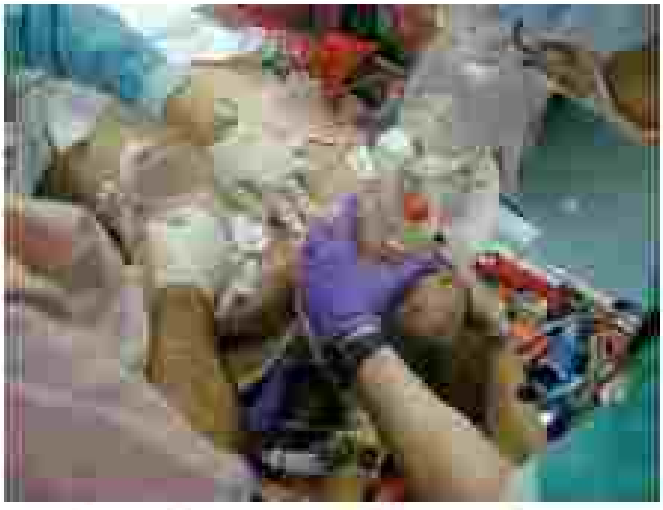

FIG. 4 Four providers are recommended for securing the airway. Providers are assigned to (1) ventilate with the bag-valve-mask and intubate, (2) maintain in-line cervical stabilization, (3) administer cricoid pressure, and (4) push drugs and assist with airway devices.

Although avoidance of BVM ventilation has been the traditional recommendation in RSI, many practitioners find that gentle mask ventilation (inspiratory pressure <20 cm H_2O) is acceptable during the induction sequence. Gentle mask ventilation may help prevent hypoxemia in obese, pregnant, pediatric, and critically ill patients, and also allows testing for the adequacy of mask ventilation in the event that intubation attempts fail. Additionally, to help prevent desaturation, a nasal cannula can be applied before intubation at a high flow rate (10–15 L/min) to both help with preoxygenation and to provide some degree of apneic oxygenation during intubation attempts. If a high-flow humidified nasal cannula device is available, higher rates (up to 60 L/min) can be used at higher FiO_2 (100%).

Before paralytics are given, an induction agent is administered. A review of induction agents is provided in Table 2. Paralytics are recommended as part of RSI because attainment of neuromuscular blockade has been shown to result in suboptimal intubating conditions. Either succinylcholine (1–1.5 mg/kg) or vecuronium (0.8–1.2 mg/kg) is administered for paralysis. Succinylcholine can be administered intramuscularly if an intravenous line is not established, but an increased dose of 3 to 4 mg/kg is recommended for this route.

TABLE 2. Induction Agents Commonly Used for Rapid Sequence Induction and Intubation

Induction Agent	Dose	Onset	Duration of Action	Comment
Propofol	0.5–3 mg/kg	10–30 sec	5–10 min	Dose usually reduced, sometimes by as much as one-tenth of the recommended induction dose, causes decreased systemic vascular resistance and hypotension
Ketamine	1–2 mg/kg IV 2–4 mg/kg IM	30–60 sec	5–20 min	Acceptable for use in patients with increased ICP; direct myocardial depressant but has indirect stimulatory effects (best avoided in patients with coronary artery disease)
Etomidate	0.2–0.3 mg/kg	30–45 sec	10–20 min	Single dose causes adrenocortical suppression; recent evidence supports safety in septic shock
Remifentanil	1 μg/kg	30–60 sec	<10 min	250 times more potent than morphine; may cause hypotension; not a reliable amnestic; does not accumulate; broken down by nonspecific esterases
Midazolam	0.3–0.6 mg/kg	2–3 min	20–30 min	When combined with opioids, can cause marked hypotension and respiratory depression

ICP, intracranial pressure; IM, intramuscular; IV, intravenous.

In the majority of patients, both succinylcholine and rocuronium provide optimal intubating conditions by all accounts when dosed appropriately. Priming doses of nondepolarizing agents are usually not considered for trauma patients once these agents must be administered at least 3 minutes before the loading dose of muscle relaxant is administered, and in elderly or debilitated patients, pretreatment with a small dose of muscle relaxant may predispose to aspiration. Succinylcholine is contraindicated in patients with burns, open globe injuries, neuromuscular disorders, hyperkalemia, pseudocholinesterase deficiency, severe crush injuries, or chronic paralysis. Rocuronium, a nondepolarizing agent, is an alternative when succinylcholine is contraindicated, but this agent cannot be administered intramuscularly and the duration of action is much longer (typically up to 45 minutes) than succinylcholine (6–10 minutes).

Pharmacologic adjuvants such as opioids may be considered during RSII, but owing to time pressure, these agents are frequently omitted. If administered, fentanyl (2 μg/kg), alfentanil (20–30 μg/kg) or remifentanil (1 μg/kg) may help attenuate hemodynamic responses to intubation, but opioids alone do not provide adequate amnesia and are usually not recommended as sole induction agents for RSII due to a higher incidence of patient recall. Midazolam is a short acting benzodiazepine with excellent amnestic properties that may also be given intramuscularly, but this agent may take 2 to 3 minutes to work. Following preoxygenation, lidocaine may be given to attenuate increases in intracranial pressure, although strong evidence is lacking to support this purported benefit.

ENDOTRACHEAL INTUBATION

In many trauma centers, cricoid pressure is used throughout the RSII process to prevent regurgitation, although application of this technique remains controversial. Cricoid pressure involves backward and upward application of pressure to the cricoid cartilage to occlude the esophagus. 3 to 4 kg of pressure is recommended to occlude the esophagus. The use of cricoid pressure remains controversial since the technique is often incorrectly applied, may worsen laryngoscopic views, can cause airway trauma, and could impair BVM ventilation. Nevertheless, it is a reasonable initial measure recommended for use during RSII, but if the laryngoscopic view worsens with the technique, pressure can simply be released or adjusted as required to facilitate intubation.

Approximately 1.5% to 8% of all trauma patients may have an undiagnosed cervical spinal cord injury, hence, cervical immobilization is obligatory. Manual in-line stabilization has been shown to be superior for preventing inadvertent movement of the cervical spine during intubation as compared to a cervical collar alone. During intubation, one provider is dedicated to maintaining manual in-line stabilization.

Fig. 4 demonstrates the correct placement of a Macintosh or MacGill laryngoscopic blade. The laryngoscope should be held in the left hand and inserted into the right side of the patient's mouth, displacing the tongue to the left. The airway structures are blind into view, avoiding using the blade as a fulcrum on the teeth, and the epiglottis and vocal cords are visualized. The endotracheal tube should be gently inserted with the cuff past the vocal cords and inflated with enough air to provide a good seal (~20 cm H_2O). In general, intubation attempts should not take more than 30 seconds. Verification of tube placement is accomplished by auscultation of bilateral lung sounds, observation of chest rise, absence of epigastric/gastric gurgling or distension, and presence of end tidal carbon dioxide (CO_2) with either a colorimetric device or continuous capnography. If a colorimetric device is used, the color indicator should change from purple to yellow, and at least six ventilations with an appropriate color change should be observed to avoid potential false positives. A chest radiograph should be obtained to confirm the position of the tube.

In patients with suspected cervical spine injuries, the laryngoscopic view may be impeded by the requirement of in-line cervical stabilization. For patients with a Cormack–Lehane grade 3 or 4 view, the gum elastic bougie may be used to intubate the endotracheal tube. The bougie is a flexible, 60-cm, 15-French introducer with a Coude tip angled at 45 degrees, 3.5 cm from the distal end (Fig. 5).

The bougie is lubricated and inserted with the Coude tip directed anteriorly, advancing until at the level of the tracheal rings. The endotracheal tube is then advanced over the bougie into the trachea.

Video laryngoscopy (VL) has evolved as a technology that allows direct visualization of the airway by all airway team members. Studies have been mixed regarding advantages for use in patients with difficult airways, but some research has shown that VL results in a higher success rate at first attempt as compared to direct laryngoscopy, especially for less experienced airway providers. VL can be used at all stages of intubation, including initial laryngoscopy, awake intubation, and for helping to confirm proper endotracheal tube position.

SUPRAGLOTTIC AIRWAY DEVICES

A variety of supraglottic devices exist for use when attempts at endotracheal intubation or BVM ventilation fail. The laryngeal mask airway (LMA), multilumen esophageal airway (Combitube), and the laryngeal tube airway are three devices that can be placed without direct visualization of the glottis. Although these devices enable

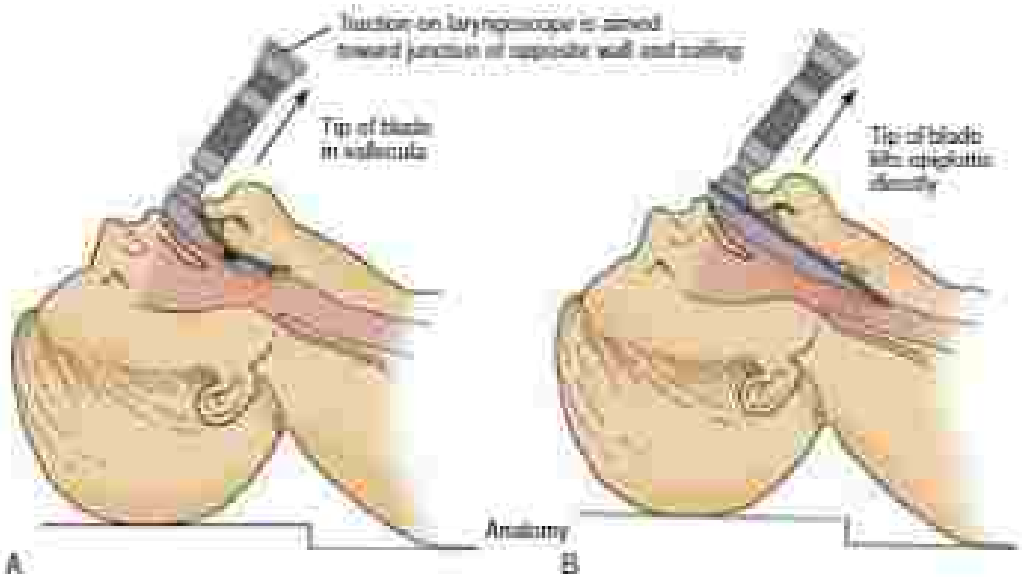

FIG. 4 (A) Macintosh blade. (B) McGill blade. Note that the patient in this figure does not have cervical spine precautions; in the majority of patients, manual in-line stabilization must be performed during intubation attempts to prevent exacerbation of neurologic damage.

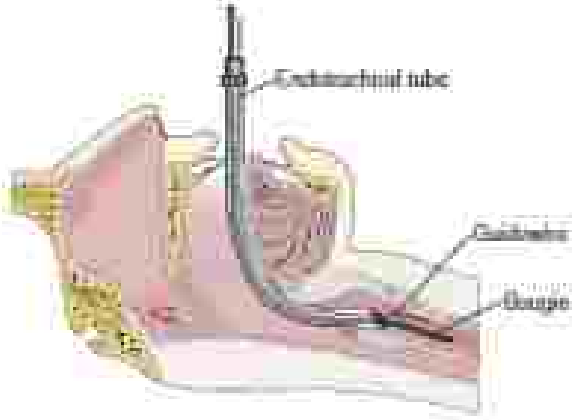

FIG. 5 Gum elastic bougie insertion. (From Hagberg MD, et al. [In: MGH Handbook of Anesthesia] Lippincott Philadelphia Boston 2016.)

ventilation, whether by providing a seal around the laryngeal inlet or occluding the esophagus, some of these devices represent a definitive airway. Each of these devices requires additional training, and all must eventually be replaced with a definitive airway in the trauma patient. In cases of traumatic arrest during prehospital management, immediate endotracheal intubation may not be feasible or safe. In these instances, placement of a supraglottic airway may be considered to prevent unacceptable pauses in chest compressions and to decrease the time to ventilation.

AWAKE FIBEROPTIC INTUBATION

When patients are suspected of having cervical spinal cord injuries, but do not require emergent intubation, awake fiberoptic intubation (AFOI) is one method that can be used to secure the airway. The term awake is a misnomer; the patient will maintain spontaneous ventilation throughout the procedure under sedation with amnestic agents. This method may be advantageous in patients with injuries to the cervical spine because cervical spine movement can be minimized, thus preventing neurologic impairment. Careful titration of sedation is mandatory for AFOI since abolition of spontaneous ventilation obviates any advantage when using this technique. Monitors are applied and oxygen is delivered via a nasal cannula. Patients are premedicated with glycopyrrolate (0.2–0.4 mg) to attenuate secretions (barring any known cardiac conditions where tachycardia might be avoided). Sedation is achieved by careful administration of midazolam (0.5 mg, titrated to effect). Opioids are avoided due to the synergistic respiratory depression that occurs when these agents are coadministered with benzodiazepines; however, opioids may be used instead of benzodiazepines, keeping in mind that these opioids do not provide reliable amnesia. Alternatively, a dexmedetomidine infusion (0.2–1.5 μg/kg/hr) may be considered, but for trauma patients, this agent is seldom used due to the preparatory time required and onset of action (>10 minutes). For topicalization, 2 to 3 mL of 5% lidocaine ointment is applied to the posterior tongue via a tongue depressor to anesthetize the glossopharyngeal nerve. Next, 1 to 2 vials of 4% lidocaine are emptied into a specimen cup and cotton balls (with strings attached to ensure easy retrieval from the airway) are soaked in this solution. Using either a Magill forceps or right-angle nasal hitcher, the cotton balls are gently introduced deep into the posterior nares and held in place for 60 to 90 seconds. The process is repeated for each side, effectively anesthetizing both branches of the superior laryngeal nerve. Finally, an oral airway is inserted (to prevent biting of the fiberoptic scope), and the fiberoptic scope is introduced. Once the vocal cords are visualized, 1 to 2 mL of 1% or 2% lidocaine is sprayed through the injection port on the fiberoptic scope directly on the vocal cords. This anesthetizes the recurrent laryngeal nerve. Once all three nerves are anesthetized, the endotracheal tube can safely be inserted with either a video laryngoscope (i.e., "awake" video laryngoscopy) or over a fiberoptic bronchoscope. Careful attention must be paid to the amounts of lidocaine used since a dose greater than 5 mg/kg may result in anesthetic toxicity. The technique can be modified accordingly for nasotracheal intubation with use of topical vasoconstrictors as well as anesthetics to anesthetize and mitigate bleeding in the nasal passages. It should be noted that this technique is not recommended for patients who are deemed to be at increased risk for aspiration.

AIRWAY MANAGEMENT DECISION MAKING

For patients in need of an immediate airway, Fig. 6 provides a decision algorithm. Initial priorities always include adequate preoxygenation

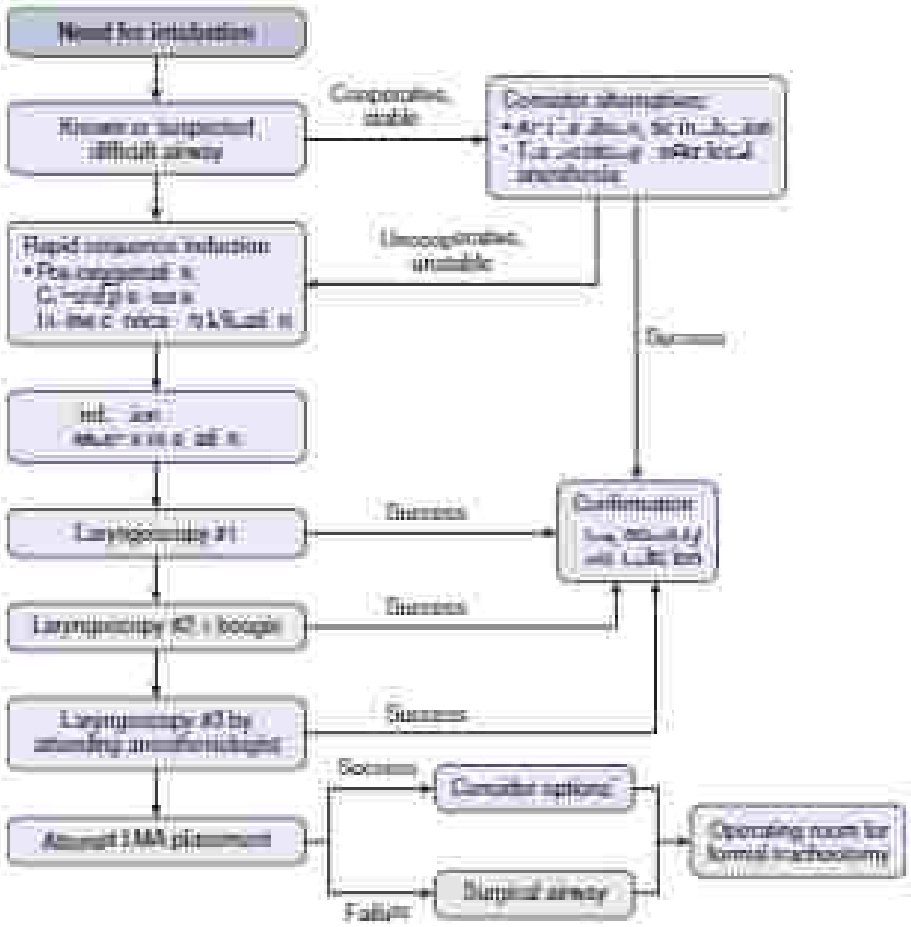

FIG. 1. Airway management algorithm at the R Adams Cowley Shock Trauma Center. Laryngoscopy may include the use of a video laryngoscope such as the GlideScope or Ranger (storz bett) as multiple steps. LMA, laryngeal mask airway. *Options after LMA placement include further intubation attempts, intubation through the LMA, and surgical airway. (From Stephens CJ, et al. The success of emergency endotracheal intubation in trauma patients: A 10-year experience at a large adult trauma center. Accid Anal Prev. 2009;41:837–842.)

and in-line cervical immobilization. In trauma patients, the option to wake up the patient, as one would do for an elective surgical procedure, is not feasible. After a third failed attempt at intubation by an attending anesthesiologist, an LMA can be inserted to facilitate the transition to a definitive airway via fiberoptic intubation or intubation through the LMA. However, if the airway cannot be expeditiously secured after the third laryngoscopy attempt, a surgical airway is necessary. It should be noted that in the hands of experienced trauma airway experts, the rate of conversion to a surgical airway has been reported to range from 0.2% to 2%.

SURGICAL AIRWAY

A patient committed to RSI (i.e., paralyzed), who subsequently cannot be ventilated or intubated, requires a surgical airway. Options include a surgical cricothyrotomy or tracheostomy; cricothyrotomy is preferred as the surgical technique of choice (Fig. 7). The patient is placed in the supine position with the neck in a neutral position. After the neck is prepped and draped, the thyroid notch, thyroid cartilage, cricothyroid membrane, cricoid cartilage, and trachea are identified by palpation. Stabilizing the thyroid cartilage with one hand, a 2.0- to 2.5-cm vertical incision is made over the cricothyroid membrane with a No. 10 or 11 surgical blade. A hemostat or tracheal spreader is introduced into the incision and rotated 90 degrees to open the airway. Either a cuffed endotracheal tube (6.0 or 6.5 mm) or tracheostomy tube is inserted through the cricothyroid membrane incision. The cuff is inflated, and placement of the tube is confirmed by lung auscultation, chest rise, and end tidal CO_2 detection.

In the event that there is insufficient time to complete the dissection for a full cricothyrotomy, a needle cricothyrotomy can be performed. After the neck is prepped and draped, the anatomic landmarks are identified, and a 12- or 14-gauge needle attached to a 5- to 10-mL syringe is used to puncture the skin in the midline directly over the cricothyroid membrane. A small incision with a #11 blade may enable passage of the needle through the skin. Once the needle has passed through the skin, the needle is angled 45 degrees caudally for insertion through the lower half of the cricothyroid membrane. Aspiration of air should be noted once the needle is in the airway, and the syringe is removed. The needle is then connected to a jet ventilation device. Alternatively, a 3-mL syringe can be connected to the needle and attached to a plastic endotracheal tube connector. This will allow for connection to a BVM device. Ventilation via a needle cricothyrotomy only maintains oxygenation for approximately 30 to 45 minutes; hypercarbia may quickly develop. For both needle and surgical cricothyrotomies, the airway is typically converted to a formal tracheostomy by 24 to 48 hours.

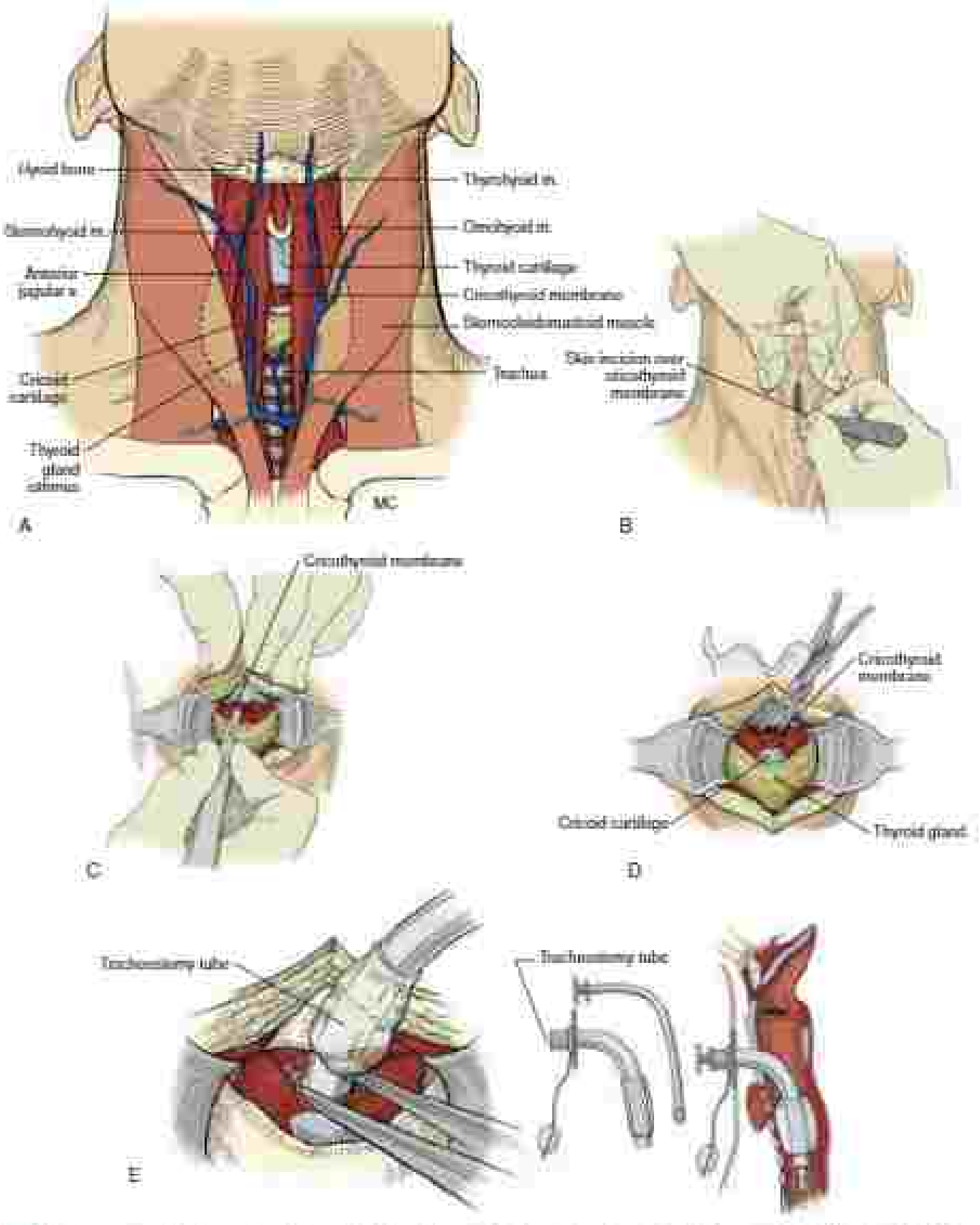

FIG. 7 Cricothyrotomy. (A) The cricothyroid membrane is located between the thyroid cartilage above and the cricoid ring below. (B) The operator's nondominant hand holds the thyroid cartilage, while the other hand performs the procedure. A vertical skin incision avoids the anterior jugular veins to minimize bleeding. (C) The cricothyroid membrane is incised transversely. (D) The opening is widened with a small hemostat. (E) The tracheostomy tube is placed into the airway and the cuff is inflated. [Citation: "and ; (E) a midsagittal and axial cross-section of the anterior portion of the neck." Advanced Trauma Life Support for Doctors, 8th ed. Chicago, IL: American College of Surgeons; 2008:215–217.]

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Surgical Use of Ultrasound in the Trauma and Critical Care Settings

Alina Cross, MD, and Grace S. Rozycki, MD, MBA, RDMS

For more than 25 years, surgeons in US trauma centers have successfully performed, interpreted, and taught ultrasound examinations of patients who are injured or critically ill. According to the Rogers Diffusion of Innovations Theory, surgeons are considered to be early adopters of the technology and their presence in so many areas of the hospital helped to promote ultrasound as a useful tool for evaluating patients in the elective and emergent settings. Real-time imaging allows the surgeon to receive instantaneous information about the clinical condition of the patient and, therefore, helps to expedite the patient's management. In most trauma centers, ultrasound machines are standard equipment in the trauma resuscitation rooms. Although diagnostic peritoneal lavage and computed tomography (CT) scanning are still valuable diagnostic tools for detecting intraabdominal injury, ultrasound is faster, noninvasive, painless, and well tolerated by adults and children. Moreover, the portability of the ultrasound machine allows for an evaluation of the patient in multiple settings, including the trauma bay and intensive care unit (ICU).

As an extension of the physical examination, surgeons routinely use ultrasound in the acute setting to determine the presence or absence of fluid in the peritoneal cavity, the pericardium, and the pleural cavities. Additional uses of this modality include detecting pneumothoraces and sternal fractures. What follows is a discussion of the use of ultrasound in blunt and penetrating thoracoabdominal trauma with an additional discussion of the use of ultrasound in the ICU.

USE OF ULTRASOUND IN TRAUMA

Focused Assessment for the Sonographic Evaluation of the Trauma Patient

Developed for the evaluation of injured patients, the Focused Assessment for the Sonographic Evaluation of the Trauma Patient (FAST) is a rapid diagnostic examination to assess patients with potential injuries to the thorax or abdomen. The test sequentially surveys for the presence or absence of fluid in the pericardial sac and in the dependent abdominal regions, including the Morison's pouch of the right upper quadrant (RUQ), the left upper quadrant (LUQ) behind the spleen and between the spleen and kidney, and the pelvis posterior to the bladder.

The FAST is performed in a specific sequence: the pericardial area is visualized first so that blood within the heart can be used as a standard to set the gain. Most modern ultrasound machines have presets so that the gain does not need to be reset each time the machine is turned on. Occasionally, if multiple types of examinations are performed with different transducers, the gain should be checked to ensure that intracardiac blood appears anechoic. This maneuver ensures that hemopericardium will also appear anechoic and will be readily detected on the ultrasound image. The abdominal part of the FAST should begin with a survey of the RUQ, which is the location within the peritoneal cavity where blood most often accumulates and is most readily detected with the FAST. In a multicenter trial of 275 blunt and penetrating trauma patients, montgomery found that regardless of the injured organ (with the exception of patients who had an isolated perforated viscus), blood was most often identified on the RUQ image of the FAST. This can be a time saving measure because when hemoperitoneum in the RUQ view is identified on the FAST examination of a hemodynamically unstable patient, then that image alone, in combination with the patient's clinical picture, is sufficient to justify an immediate abdominal operation. In a hemodynamically stable patient, after examination of the RUQ, the LUQ and pelvis are visualized as discussed next.

Technique

Ultrasound transmission gel is applied on four areas of the abdomen/thorax, and the examination is conducted in the following sequence: pericardial area, RUQ, LUQ, and pelvis (Fig. 1). Abdominal structures are best imaged with a lower frequency transducer, which allows for deeper penetration into tissues (sacrificing some resolution). Most ultrasound transducers are now capable of imaging in multiple frequencies, allowing the sonographer to achieve the best balance of resolution (higher frequency) and tissue penetration (lower frequency) based on a patient's individual body habitus.

To begin the examination, a 3.5-MHz curvilinear transducer is oriented for sagittal or longitudinal views and positioned in the subxiphoid region to identify the heart and to examine for blood in the pericardial sac. The normal and abnormal views of the pericardial area are shown in Fig. 2. The subxiphoid image is usually not difficult to obtain, but a severe injury to the chest wall, a narrow subcostal area, subcutaneous emphysema, or morbid obesity can prevent a satisfactory examination. The two latter conditions are associated with poor imaging because air and fat reflect the wave too strongly and prevent penetration into the target organ. If the subcostal pericardial image cannot be obtained or is suboptimal, a parasternal ultrasound view of the heart should be performed.

Next, the transducer is placed in the right anterior or midaxillary line between the 11th and 12th ribs to identify a sagittal section of the liver, kidney, and diaphragm (Fig. 3). The presence or absence of blood is sought in Morison's pouch and in the right subphrenic space. Next, attention is turned to the LUQ and with the transducer positioned in the left posterior axillary line between the 10th and 11th ribs, the spleen and kidney are visualized and blood is sought in between the two organs and in the left subphrenic space (Fig. 4). The splenic window is often the most difficult to obtain because the presence of gas in the stomach may interfere with the imaging. To ensure the best imaging, the stomach may need decompression with a nasogastric tube. Further, the transducer should be placed significantly more posterior (posterior axillary line) and superior (one to two rib spaces higher) than with the RUQ window.

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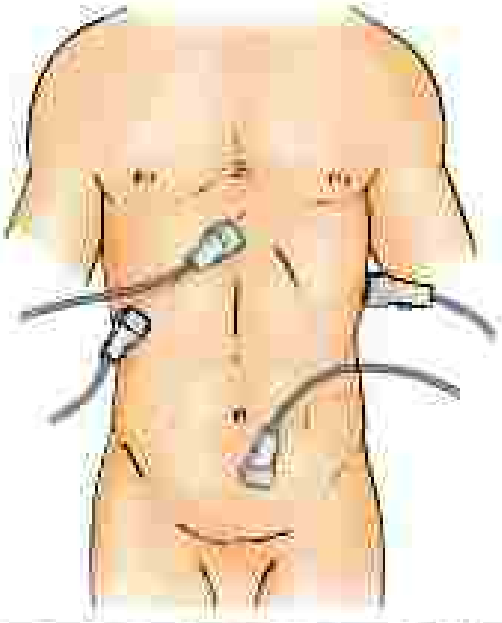

FIG. 1 Transducer positions for focused assessment for the sonographic evaluation of the trauma patient: pericardial, right upper quadrant, left upper quadrant, and pelvis.

Finally, the transducer is directed for a transverse view and placed about 4 cm superior to the symphysis pubis. It is swept inferiorly to obtain a coronal view of the full bladder and the pelvis examining for the presence or absence of blood (Fig. 5).

Accuracy

Improper technique; incompetence of the examiner; and inappropriate use of ultrasound have long been known to adversely impact ultrasound imaging, and, more recently, the etiology of injury, the presence of hypotension on admission, and select associated injuries have also been shown to influence the accuracy of this modality. Failure to consider these factors has led to inaccurate assessments of the accuracy of the FAST by inappropriately comparing it with a CT scan and not recognizing its role in the evaluation of patients with penetrating torso trauma. Both false-positive and negative pericardial ultrasound examinations have been reported to occur in the presence of a massive hemothorax or mediastinal blood. Repeating the FAST after inserting a tube thoracostomy improves the visualization of the pericardial area and decreases the number of false-positive and negative studies. Notwithstanding these circumstances in which false studies may occur, a rapid focused ultrasound survey of the subcostal pericardial area is an accurate method to detect hemopericardium in most patients with penetrating wounds to the "cardiac box." In a large multicenter study of patients who sustained either blunt or penetrating injuries, the FAST was 100% sensitive and 99.3% specific for detecting hemopericardium in patients with precordial or transthoracic wounds. Furthermore, the use of pericardial ultrasound has been shown to

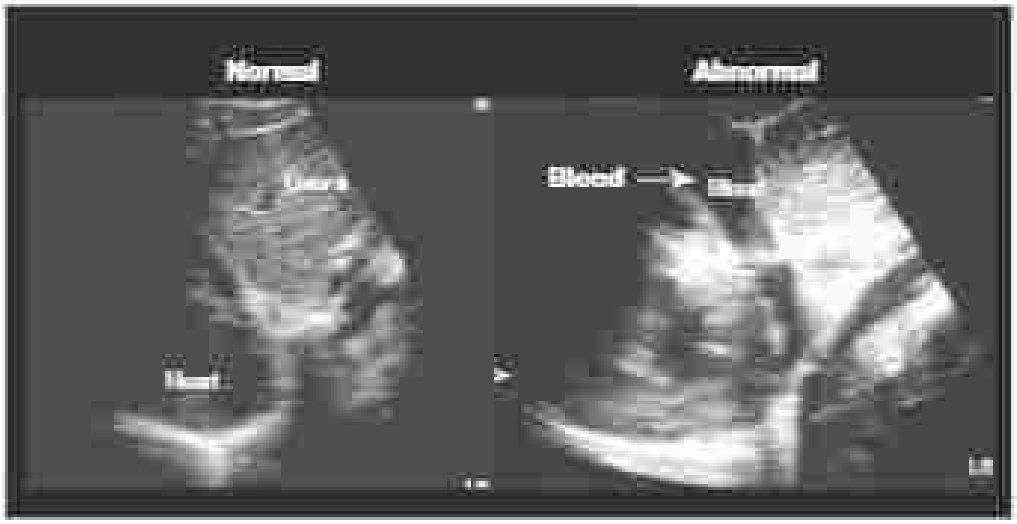

FIG. 2 Left, Normal sagittal view of pericardial area showing pericardium as single echogenic line. Right, Abnormal sagittal view of pericardial area showing separation of visceral and parietal areas of pericardium with blood (arrow) that appears anechoic.

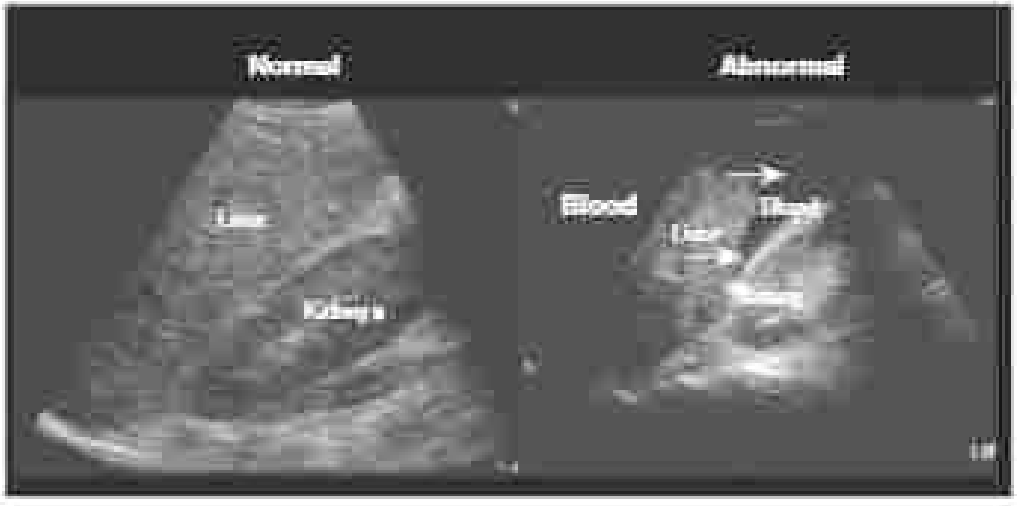

FIG. 3 Left, Normal sagittal view of liver, kidney, and diaphragm. Note: Gerota's fascia is hyperechoic. Right, Abnormal sagittal view of liver, kidney, and diaphragm. Note fluid (blood) in between liver and kidney (arrow).

be especially helpful in the evaluation of patients who have no overt signs of pericardial tamponade. This was highlighted in a study in which 10 of 22 patients with precordial wounds and hemopericardium on the ultrasound examination had admission systolic blood pressures greater than 110 mm Hg and were relatively asymptomatic. Based on these signs and the lack of symptoms, it is unlikely that the presence of cardiac wounds would have been strongly suspected in these patients and, therefore, this rapid examination provided an early diagnosis of hemopericardium before the patients underwent physiologic deterioration.

The FAST is a focused examination for the detection of fluid in dependent areas of the abdomen and designed to answer the simple question of "fluid or no fluid?" Therefore, its results should not be compared with those of a CT scan because the FAST does not readily identify intraparenchymal or retroperitoneal injuries. Therefore, select patients considered to be at high risk for occult intraabdominal injury should undergo a CT scan of the abdomen regardless of the FAST examination results. These patients include those with fractures of the pelvis or thoracolumbar spine, major thoracic trauma (pulmonary contusion, lower rib fractures), and hematuria.

Traumatic Hemothorax

A focused thoracic ultrasound examination was developed by surgeons to rapidly detect the presence or absence of a traumatic hemothorax in injured patients. This examination is worthwhile because it dramatically shortens the interval from the diagnosis of a hemothorax to the insertion of a thoracostomy tube.

Technique

The technique for this examination is similar to that used to interrogate the upper quadrants of the abdomen in the FAST and also uses the same type and frequency transducer. With the patient in the supine position, it is performed one to two rib spaces higher than the RUQ and LUQ FAST views. Ultrasound transmission gel is applied to the right and left lower thoracic areas in the mid- to posterior axillary lines between the ninth and fifth intercostal spaces (Fig. 4). The transducer is slowly advanced cephalad to identify the hyperechoic diaphragm and to interrogate the supradiaphragmatic space for the presence or absence of fluid (Fig. 5 and 6), which appears anechoic. In the positive thoracic ultrasound examination, the hyperechoic lung can be seen "floating" amid the fluid. The same technique can be used to evaluate a critically ill patient for a pleural effusion.

Accuracy

A study that compared the time and accuracy of ultrasound with that of the supine portable chest x-ray found both to have similar high sensitivities and specificities for the detection of hemothorax but the performance times for the thoracic ultrasound examinations were statistically much faster ($P < .0001$) than those for the portable chest

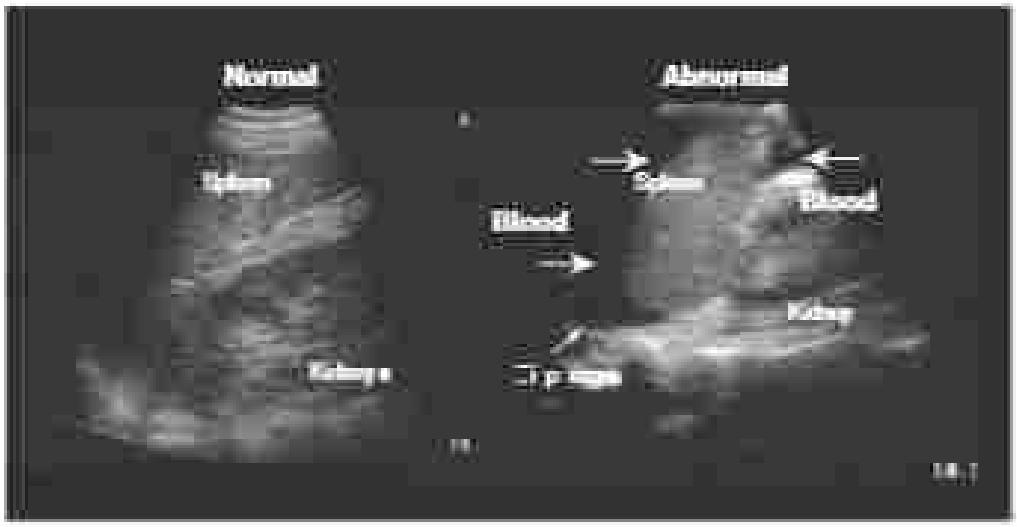

FIG. 4 Left, Normal sagittal view of spleen, kidney and diaphragm. Right, Abnormal sagittal view of spleen, kidney, and diaphragm with fluid (blood) in between spleen and kidney and above the spleen in the subphrenic space (arrows).

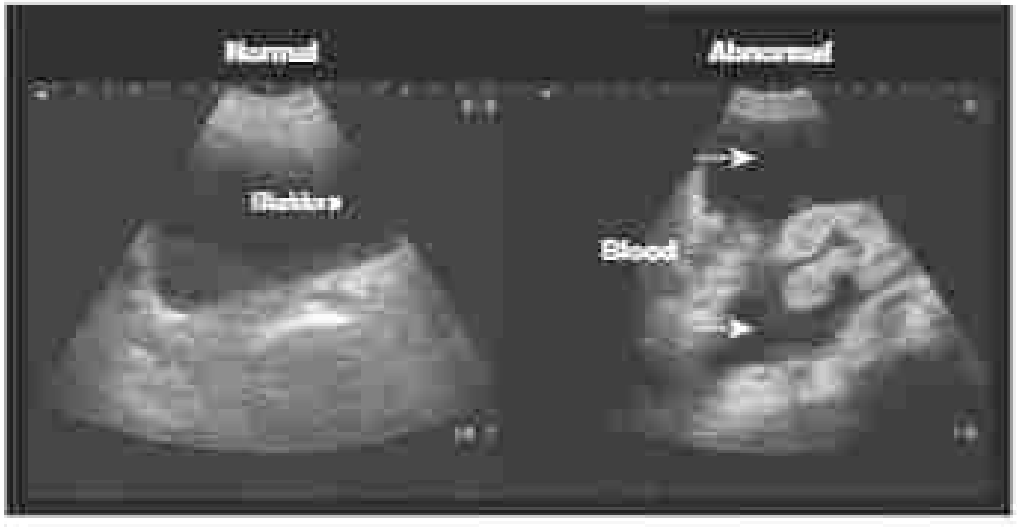

FIG. 5 Left, Normal coronal view of full urinary bladder. Right, Abnormal coronal view of full bladder with fluid in pelvis. (Note the bowel floating in fluid [arrows].)

x ray. Although it is not recommended that the thoracic ultrasound examination replace the chest x ray, its use can expedite treatment to many patients and decrease the number of chest radiographs obtained.

Pneumothorax

Ultrasound examination for the detection of a pneumothorax is unique in that there is an absence of two findings. The first is a reflection artifact called a comet tail that occurs because of the interaction of air with the lung tissue (Fig. 6). The second finding is pleural sliding indicating the visceral and parietal layers of the pleura are in normal apposition. Hence a pneumothorax is not visualized on ultrasound but rather diagnosed by the absence of these two normal findings.

Technique

A 5.0- to 7.5-MHz linear array transducer is used to evaluate a patient for the presence of a pneumothorax. The examination may be performed while the patient is in the erect or the supine position. Ultrasound transmission gel is applied in the right and left upper thoracic areas at about the third to fourth intercostal space in the midclavicular line, and the presumed unaffected thoracic cavity is examined first. The transducer is oriented for longitudinal imaging, is placed perpendicular to the ribs, and is slowly advanced medially toward the sternum and then laterally toward the anterior axillary line. When a pneumothorax is present, air becomes trapped between the visceral and parietal pleura and does not allow for the transmission of the ultrasound waves. Therefore, the visceral pleura is not imaged and pleural sliding and the comet tail artifact are not observed. If desired, the examination may be repeated with the transducer oriented for transverse views, with images obtained with the probe parallel to the ribs.

Accuracy

Several studies have documented the sensitivity and specificity of ultrasound for the detection of a pneumothorax. Dulchavsky and colleagues showed that ultrasound can be successfully used by surgeons to detect a pneumothorax in injured patients. Of the 360 patients (262 trauma, 98 spontaneous) evaluated with ultrasound, 39 had pneumothoraces and ultrasound successfully detected 37 of them, yielding 95% sensitivity. Pneumothoraces in two patients could not be detected because of the presence of significant subcutaneous emphysema. The authors recommended that when a portable chest x ray cannot be readily obtained, the use of this bedside ultrasound examination for the identification of a pneumothorax could expedite the patient's management.

Sternal Fracture

Fractures of the sternum are visualized on a lateral x ray view of the chest but this film may be difficult to obtain in a patient with multisystem injuries. Therefore, an ultrasound examination of the sternum can rapidly detect a fracture while the patient is still in the supine position, thus avoiding the need to obtain a lateral x ray of the chest wall.

Technique

With the patient in the supine position, the ultrasound examination of the sternum is performed using a high-frequency linear array transducer that is oriented for sagittal or longitudinal views. Beginning at the suprasternal notch, the transducer is slowly advanced in a caudal direction to interrogate the sternum for a fracture and then the examination is repeated with the transducer oriented for transverse views. The examination of the lateral sternum is shown in Fig. 9. A sternal fracture is identified on the ultrasound examination as a disruption of the cortical reflex (Fig. 10). Investigators have found that the use of ultrasound for this diagnosis is as accurate as (and much more rapid than) a lateral x ray view of the chest.

Special Situations

Ultrasound would seem to be an ideal method for evaluating an injured pregnant patient but because of the anatomic changes of pregnancy, the data do not support it to be a very sensitive test for the detection of intraabdominal fluid.

Ultrasound for diagnosis of injuries after penetrating trauma has been studied much less extensively than its use in blunt trauma. Ultrasound has a high sensitivity and specificity for the diagnosis of hemopericardium in patients with penetrating injury to the cardiac box, but when compared with local wound exploration of a stab wound in the abdomen the sensitivity is poor. A report by Murphy

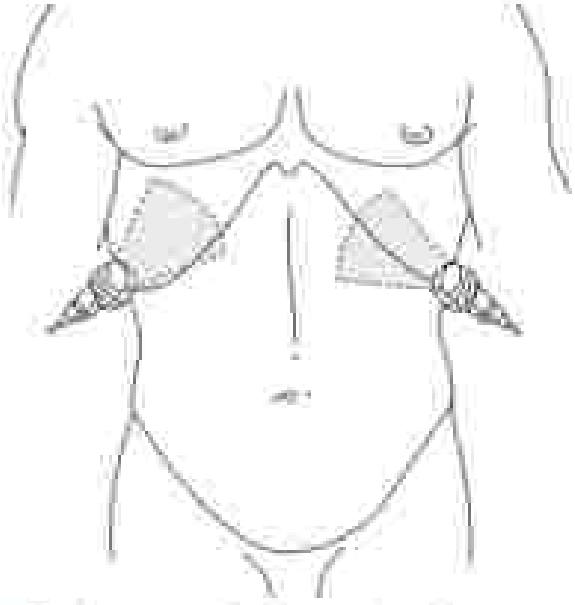

FIG. 6 Transducer positions for thoracic ultrasound examination (detecting hemothorax).

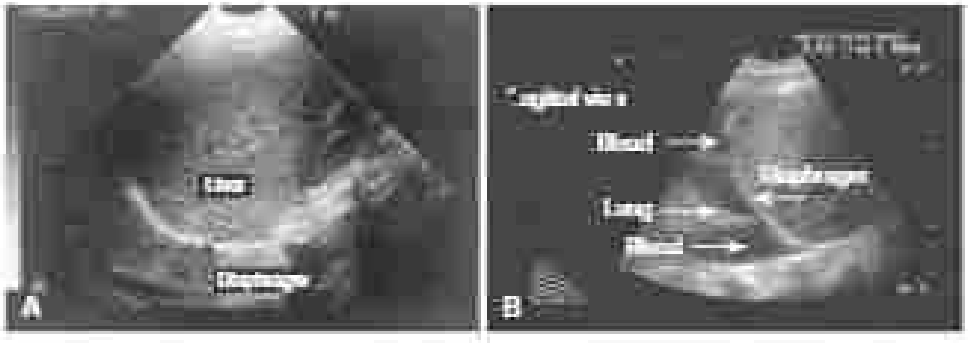

FIG. 7 (A) Sagittal view of liver, kidney, and diaphragm. Note supradiaphragmatic (lung) area but absence of pleural effusion. (B) Sagittal view of right supradiaphragmatic space. The right hemithorax contains fluid (blood), which appears anechoic.

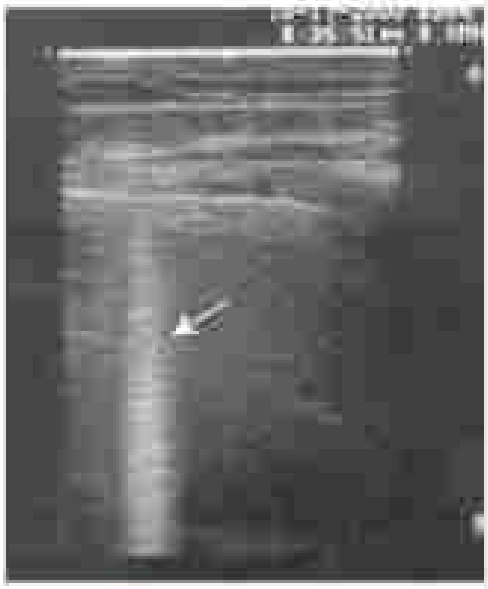

FIG. 8 Comet-tail artifact (arrow).

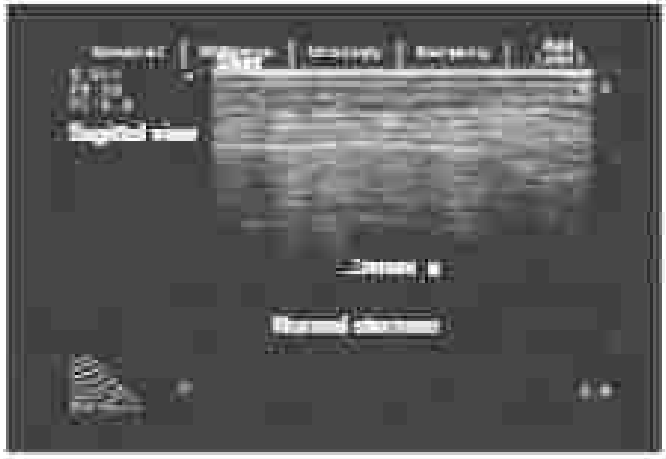

FIG. 9 Sagittal view of diaphragm. Normal finding.

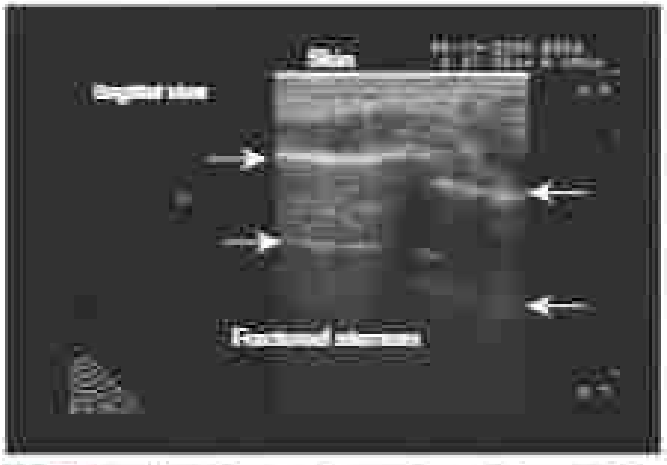

FIG. 10 Sagittal view of sternum illustrating fracture (interruption of hyperechoic line).

et al. examined the utility of ultrasound to diagnose fascial penetration after anterior abdominal stab wounds. In this study, 35 patients underwent ultrasonic evaluation of their anterior abdominal fascia with an 8.6 MHz linear array transducer followed by a local wound exploration. Although ultrasound had only a 69% sensitivity (13 of 32 patients), it did have 100% specificity with no false positive studies. Thus, if fascial penetration is noted on ultrasound, a more invasive wound exploration is probably not needed. But under these circumstances, a negative ultrasound evaluation is clearly less helpful and does not preclude peritoneal penetration.

USE OF ULTRASOUND IN SURGICAL CRITICAL CARE

Given technologic advancements in the technique, ultrasound has been shown to be a valuable tool for the evaluation of critically ill patients. Performed by the intensivist at the bedside, these focused examinations are useful for a number of diagnostic dilemmas and procedures, including detection and drainage of a pleural effusion, rapid evaluation of hypotension of unknown origin, diagnosis of deep vein thrombosis, and rapid diagnosis of critical venous line complications immediately after placement. In several studies, ultrasound findings have contributed to a change in the patient's management and, consequently, to a decrease in morbidity and length of stay.

Pleural Effusion

The superiority of ultrasound over plain radiography for detecting pleural fluid is well documented. On ultrasound, pleural effusion is identified as an anechoic area surrounded by the chest wall, lung, and diaphragm. Diaphragmatic motion with respiration and the movement of the lung in the surrounding pleural fluid effusion aid in the diagnosis. Once diagnosed, ultrasound-guided drainage optimizes the location, ensures complete drainage, and minimizes the complication of a pneumothorax.

Technique

The patient is placed in the supine position, and the head of the bed is elevated 45 to 60 degrees. A 3.5- or 5-MHz curvilinear transducer, oriented for sagittal sections is placed at the ninth or 10th intercostal space in the mid- to posterior axillary line. The transducer is advanced cephalad until the hyperechoic diaphragm, the subdiaphragmatic organs (liver or spleen), chest wall, lung, and effusion are seen. A felt-tipped pen is used to mark the spot where the needle will enter the chest. The image is frozen and the distance is measured from the mark to the midportion of the effusion so as to choose the correct needle length. The needle is attached to a syringe and advanced superior to the rib (to avoid the neurovascular bundle) while aspirating until pleural fluid return is returned. Using the same principles, the pleural effusion can be easily drained via a thoracostomy tube using Seldinger technique via a wide variety of commercially available drainage kits.

Venous Interrogation for Deep Vein Thrombosis

Venous thromboembolic disease is a common cause of morbidity and mortality in the critical care population and has a reported incidence of 5% to 40% in high-risk injured patients. The use of a focused ultrasound examination performed at the bedside by critical care physicians can provide valuable information to potentially support or exclude the diagnosis of deep vein thrombosis (DVT). In 2010, Parra and colleagues reported their results of a multicenter retrospective study of critically ill patients suspected of having a DVT. They compared a focused, intensivist-performed ultrasound evaluation with the standard duplex study and found that their focused examination compared favorably with the duplex study, showing a sensitivity and specificity of 88% and 98%, versus 81% and 100%, respectively. In addition, the intensivist-performed focused examination confirmed the diagnosis of DVT 18 hours sooner than the duplex study.

Technique

The patient is placed in the supine position with the leg externally rotated and the knee flexed. A high-frequency, 7- to 12-MHz linear transducer is placed in a transverse position just inferior to the inguinal ligament where the common femoral vein is identified. Compression is applied while sliding the transducer distally along the common femoral vasculature until the deep femoral vein and superficial femoral vein are visualized. The examination is repeated with the transducer oriented in the sagittal position (Fig. 11). If the vein is well visualized, it is followed distally to the popliteal area. Although this focused examination does not include flow dynamics, it covers the most common areas where DVT is found (i.e., common, deep, and superficial femoral and popliteal veins). The findings consistent with a DVT are inability to fully compress the vein and the presence of hyperechoic intraluminal material, i.e., clot (Fig. 12).

Placement and Confirmation of Central Venous Lines

In 2001, the Agency for Healthcare Research and Quality recommended the use of ultrasound guidance for the placement of central venous lines and these recommendations were subsequently endorsed by the American College of Surgeons. The benefits of using ultrasound for central line placement are ease of vessel cannulation and fewer complications, especially arterial punctures and pneumothorax. This description is limited to internal jugular venous access because the visualization of the subclavian vein is more difficult due to bone artifact.

Technique

Before preparing the patient's neck, anatomic landmarks (sternal notch, trachea, carotid) should be marked and the internal jugular vein scanned to ensure ease of compressibility and absence of clot. The patient's head should be elevated about 30 degrees and slightly extended and rotated to the contralateral side. A high-frequency linear transducer is held in the nondominant hand, placed in the transverse position (i.e., perpendicular to the long axis of the neck), and oriented so that the left side of the transducer correlates with the left side of the ultrasound screen. The ipsilateral carotid artery and pulsating internal jugular vein are identified. The insertion site is determined and the depth to the internal jugular vein is measured. The needle (attached to a syringe) is inserted at a 45- to 60-degree angle near the center of the transducer. The needle is advanced while aspirating the syringe and visual confirmation of the needle tip within the vein is confirmed along with venous blood return. The transducer is then rotated to the longitudinal position so that the guidewire is visualized within the lumen of the vein. The remainder of the procedure follows the guidelines of the Seldinger technique. Although a chest x-ray is still recommended for the confirmation of central line position, ultrasound offers an alternative method. The 2.5- to 5-MHz curvilinear transducer is selected for the sagittal view and placed in either the apical or subcostal parasternal areas to obtain the four cardiac chambers view. The distal port of the central venous line is flushed rapidly with 10 mL of sterile saline. A rapid atrial swirl is visualized on the ultrasound real-time image as a turbulence entering the right atrium from the superior vena cava immediately after the flush and then migrating into the right ventricle. The rapid atrial swirl indicates that the central venous line is in the correct position. Turbulence initially identified in the right ventricle is consistent with a central venous line that should be withdrawn into the atriocaval position and lack of turbulence indicates intracardiac placement and should be removed.

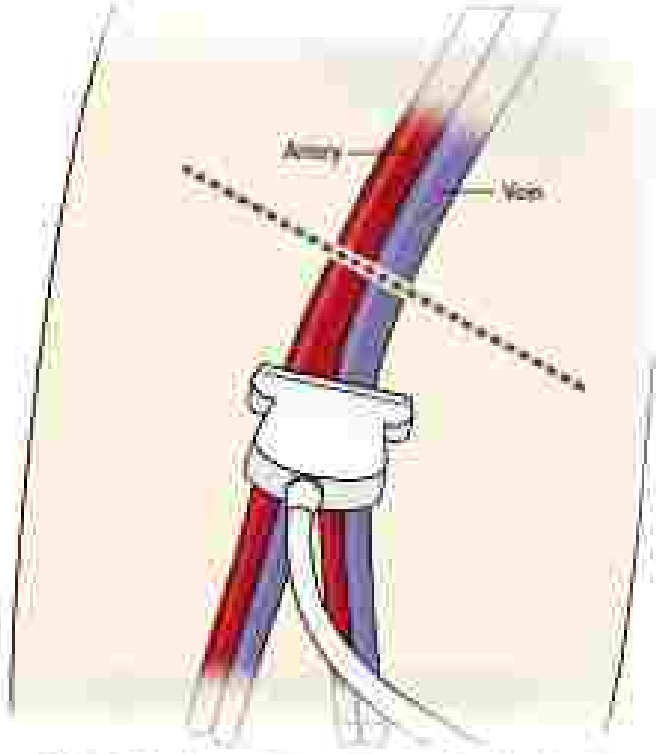

FIG. 11 Transducer position to interrogate the femoral vein.

USE OF ULTRASOUND TO ASSESSING INTRAVASCULAR VOLUME AND CARDIAC FUNCTION

For several years, ultrasound has been used by specialists to assess a patient's intravascular volume status. An inferior vena cava that is easily compressible indicates that the patient is hypovolemic, whereas an inferior vena cava that is noncompressible or has a diameter greater than 2 cm indicates that the patient is euvolemic or hypervolemic (Fig. 13).

Technique for Assessing Intravascular Volume Status

This focused examination is performed with the same transducer as that used for the FAST examination. With the patient in the supine position, the transducer is oriented for sagittal sections and placed in the subxiphoid area. The inferior vena cava is identified and then the transducer is rotated to obtain a long axis view. The width of the inferior vena cava is measured and then the vessel compressed. The transducer is once again rotated to obtain a transverse view of the vessel and the diameter measured and the vessel compressed.

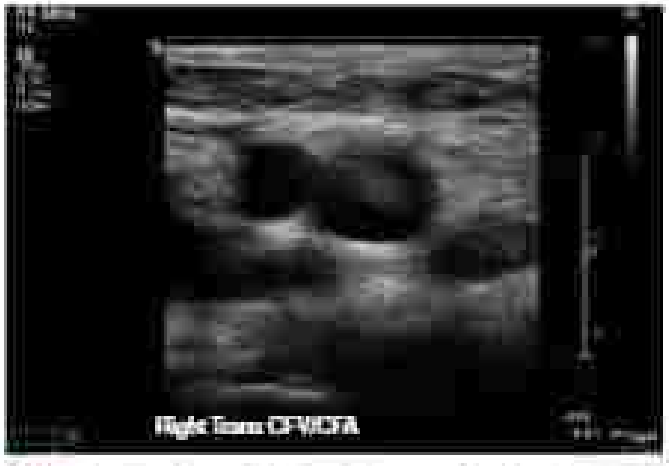

FIG. 12 Transverse image of hyperechoic material consistent with clot within the femoral vein. *CFA* Common femoral artery, *CFV* common femoral vein.

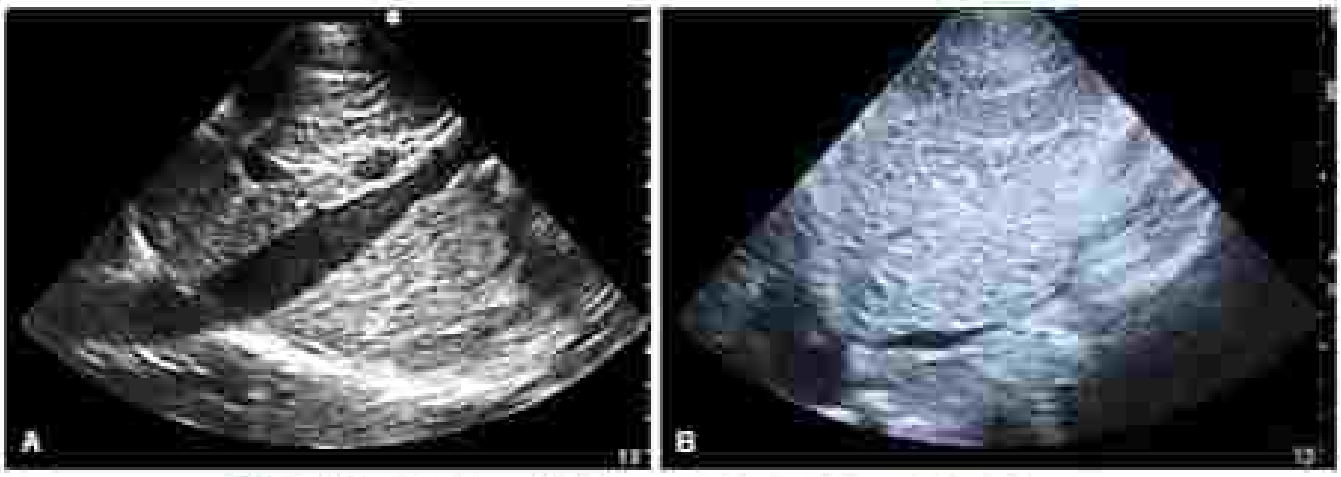

FIG. 13 (A) Longitudinal image of full vena cava. (B) Longitudinal image of collapsed vena cava.

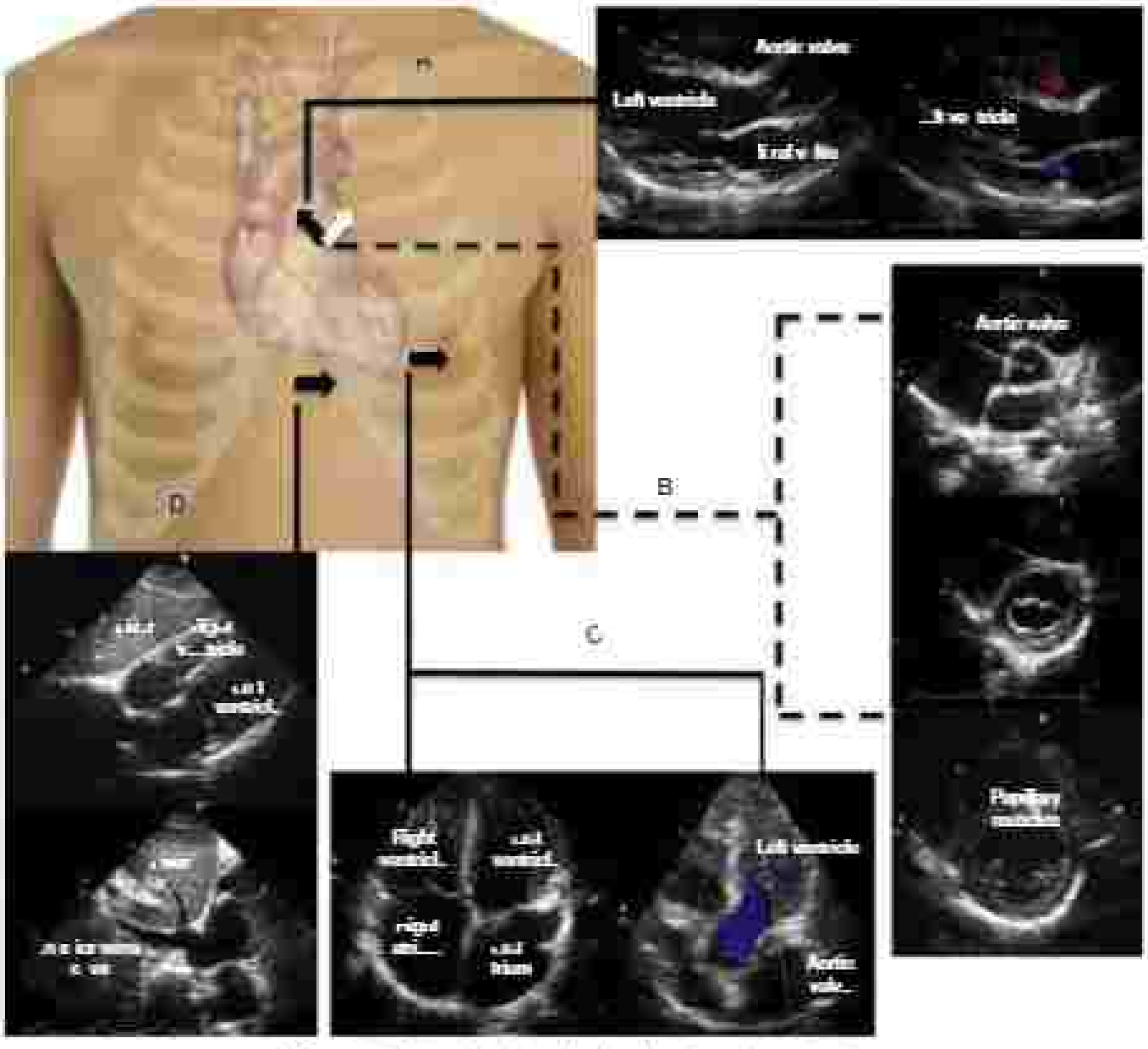

FIG. [illegible] clinical views of the focused rapid echocardiographic evaluation.

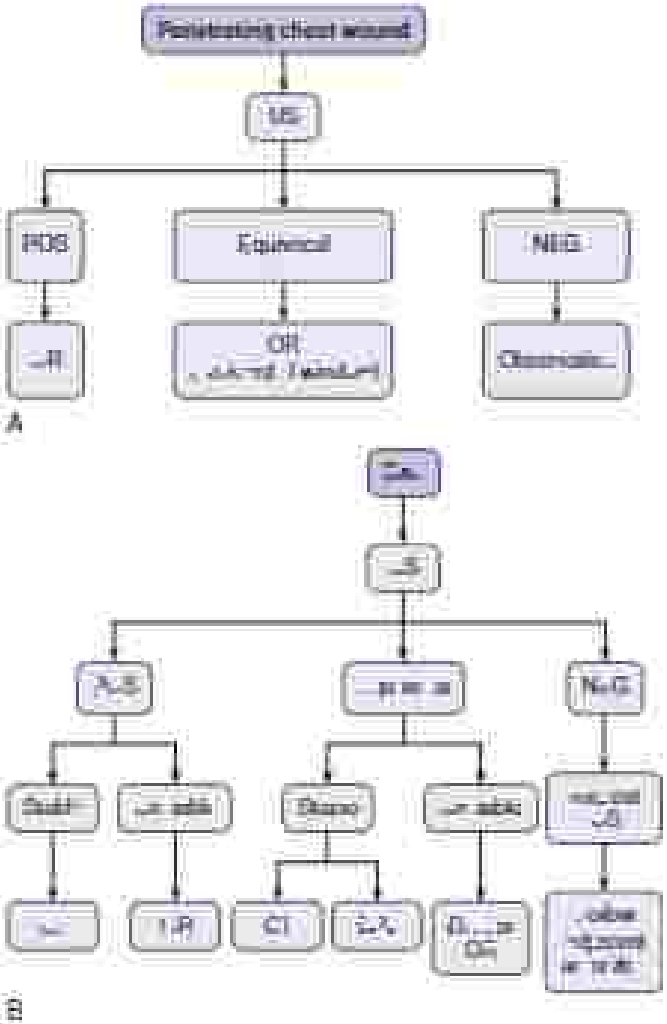

FIG 1 (A) Algorithm for ultrasound (US) use in patients with penetrating chest wounds. (B) Algorithm for ultrasound use in patients with blunt abdominal trauma (BAT). CT, Computed tomography; DPL, diagnostic peritoneal lavage; FAST, focused assessment with sonography for trauma; –, negative; +R, operating room (OR) positive.

depicts it graphically. Fig. 1 indicates the transducer positions and the resultant images.

SUMMARY

As the role of the general surgeon continues to evolve, the surgeons use of ultrasound will surely influence practice patterns, particularly for evaluating patients in the acute setting. With the use of real time imaging, the surgeon receives instantaneous information to augment the physical examination, narrow the differential diagnosis, or initiate an intervention. Algorithms for the suggested use of ultrasound in penetrating trauma and blunt abdominal trauma are shown in Fig. 1.

The advantages of ultrasound are easily seen in each of the following clinical scenarios. As a noninvasive, minimally radiation modality, ultrasound can be used to evaluate the injured pregnant patient and simultaneously identify the fetal heart so that its rate can be recorded. For the patient with multiple fractures who is in traction, the portable machine is wheeled to the patient's bedside and the FAST is performed without having to move the patient. If hypotension or an unexpected decrease in hematocrit occurs, an ultrasound examination can be easily repeated to exclude hemoperitoneum as the source of hypotension. When several patients with penetrating thoracoabdominal injuries present simultaneously to the emergency department, a rapid FAST examination with thoracic views can assess for pericardial effusion, massive hemothorax, or hemoperitoneum within seconds. This information helps the surgeon prioritize resources and triage patients. Finally, this painless noninvasive modality is well accepted, even by children, because it is performed at the bedside and is not intimidating.

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Emergency Department Resuscitative Thoracotomy

Ryan R. Frankman, MD, and David T. [illegible], FACS

Noncompressible thoracic trauma (hemorrhage) is the number one cause of death in urgent/ed trauma centers. The emergency department (ED) resuscitative thoracotomy originally described during the late [illegible] is still arguably one of the most controversial procedures performed in the trauma field to date. It is a heroic last effort that has the potential to be lifesaving, if performed by an appropriate provider in the rapid elegant fashion it is intended. Using minimal instrumentation, access to the pleura, pericardium, and aorta can be achieved within minutes of patient arrival to the trauma bay.

The attraction of this procedure is the satisfaction of attempting drastic measures to save a life. The morbidity of the procedure is significant and identifying the appropriate patient is of utmost importance. Although the intention when accessing the chest of these patients is to save a life, even if successful, iatrogenesis can result in avoidable harm. This invasive intervention, if performed by an untrained hand is a futile effort at best, can be fatal (to an otherwise potentially salvageable patient), and places unnecessary personnel at risk for direct injury as well as exposure to copious amounts of bodily fluids. Iatrogenic injury to thoracic structures will lead to added injury including potential further blood loss, lung parenchymal compromise, nerve transection, and direct cardiac injury.

Over the years, multiple recommendations and guidelines have been provided and revised in an attempt to specify when it is appropriate to attempt this maximally invasive procedure. (Table 1) Although the supporting data are all retrospective in nature, the short number performed and reviewed by expert panels has allowed the creation of some recommendations for elective intervention. It should be remembered that the thoracotomy is performed for two distinct reasons: (1) access the chest for a direct surgical intervention (relief of tamponade, hemorrhage control) and/or (2) optimize resuscitation (open pericardial massage, aortic cross-clamping). Often, both needs are present; however, outcomes are very different depending on the patient's mechanism of injury, physiologic state, and presenting characteristics (age and comorbidities).

All current guidelines rely on a few key factors to best advise the practitioner on which candidates would likely benefit as opposed to those in which intervention would be futile. Mechanism and location of injury are two common starting points on various intervention models along with supporting downstream intervention clues' points such as time of last perfusing vital signs, electrical cardiac activity, pupillary response, and cardiac activity on bedside echocardiogram.

The patient in extremis with a single penetrating stab injury to the cardiac box (often loosely defined as the anatomic area of the anterior chest where a stab may penetrate to the pericardium) with evidence of pericardial tamponade on bedside echocardiogram and witnessed loss of vital signs in the [illegible] is the most likely to benefit from this intervention, with the highest proven survival rates approaching close to 70%. Access to the heart is gained via the left hemithorax with evacuation of pericardial clot and direct repair of the cardiac injury. In contrast, a patient who is in traumatic cardiac arrest after blunt trauma, with unwitnessed loss of vital signs in the prehospital setting, have close to, if not zero survival. Based on retrospective data, ED thoracotomy intervention for thoracic trauma secondary to stab injuries have an improved outcome versus gunshot wounds. Traumatic cardiac injuries have increased survivability compared with noncardiac traumatic injuries, in particular, single chamber pathology and penetrating injuries are favorable compared with blunt injuries.

With the amount of controversy surrounding this topic, there are relative indications allowing some form of discretion to remain at the hands of the provider. Penetrating abdominal, pelvic, or extremity trauma with witnessed loss of vitals in the [illegible] and blunt abdominal trauma with loss of signs of life in the trauma bay are deemed appropriate candidates, with survivability reaching up to 10%. ED thoracotomy performed for abdominal trauma associated cardiac arrest is undertaken with the goals of cross-clamping the descending aorta, prioritizing perfusion to the brain and heart, ruling out intrathoracic pathology, stopping active arterial hemorrhage into the abdomen, and simultaneously allowing access to the heart for open massage and defibrillation in the event of cardiac arrest.

Although absolute indications (and contraindications) are clear, there remains a wide swath of patients with relative indications. They are conditionally recommended for ED thoracotomy because there remains an extremely low likelihood of survival and for those that live, there is a high incidence of some form of neurologic disability and, in more unfortunate cases, complete vegetative states (and ascending cost). However, this is balanced against the chance for some to enjoy a meaningful survival. Operating in the smallest of "what if" and not "what if" gives this small percentage of potential survivors a chance.

It needs to be remembered that the resuscitative thoracotomy is just a beginning maneuver and rapidly proceeding to definitive management of the downstream injuries is vital to the patient's survival. Additionally, the open chest introduces another large wound to these severely injured patients. Another very important concept is that the ED thoracotomy, unlike other invasive procedures, is truly an operation. Pathology findings need to be definitively addressed whether for cardiac repair or lung resection. At the very least, in a patient who survives with a resuscitative thoracotomy, the chest needs to be closed with precision.

Anterolateral Thoracotomy

Adhering to the Advanced Trauma Life Support algorithm approach to the trauma patient, a resuscitative thoracotomy would systematically fall into the circulatory bucket, succeeding airway intubation, chest decompression, blood pressure assessment with infusion protocols, and pulse check. In reality, a patient in arrest calls on all hands-on deck efforts (that is, where resources permit, intubation occurring simultaneous to the performance of the thoracotomy). Although an anterolateral thoracotomy may be performed rapidly, it does take some time and requires familiarity with anatomic physiology and an understanding of the subsequent repair to injuries that the patient will receive.

When the decision is made to undertake the procedure, the site is identified at the anterolateral chest wall, the left arm is raised above the patient's head while the patient is in the supine position, and the chest cage rapidly painted with an antiseptic, usually with betadine. If possible, placement of an orogastric tube down the esophagus may assist in differentiating it from the aorta. The anterior chest should be cleared of all equipment in case of the need for clamshell extension for further exposure.

A left anterolateral thoracotomy incision is made from the left sternosternal margin approximately at the fourth/fifth intercostal space; the left inferior mammary fold (in a female) or just below the nipple (in a male) is an excellent external landmark, with the intention to target the inferior border of the pectoralis major muscle group on the chest wall; this minimizes the amount of tissue to go through as well as subsequent problematic bleeding of the thoracotomy is successful. When performing this procedure to a female with large breasts, the mammary tissue should be retracted toward the ipsilateral shoulder and maintained in place to optimize exposure. The incision

TABLE 1 Summary of Eastern Association for the Surgery of Trauma Practice Management Guidelines for Emergency Department Thoracotomy

Signs of Life on Arrival to Emergency Department	Injury Mechanism	Location of Injury	Recommendation for Emergency Department Thoracotomy
Yes	Penetrating	Thoracic	Strongly yes
Yes	Penetrating	Thoracic	Conditional yes
Yes	Penetrating	Extrathoracic	Conditional yes
Yes	Penetrating	Extrathoracic	Conditional yes
Yes	Blunt		Conditional yes
Yes	Blunt		Conditional no

Does not pertain to isolated cranial injuries.
Poor data and largely based on speculation of patient preference.

FIG. 1 Line of the left anterolateral thoracotomy note that it follows the curve of the rib. The inframammary fold (in a woman) or the lower border of the nipple are key landmarks for righting the incision.

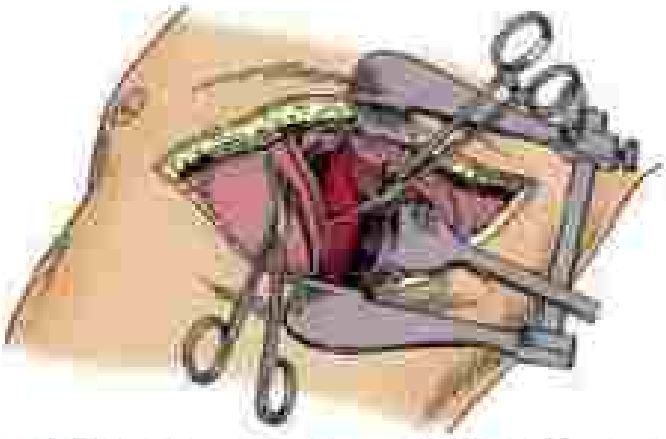

FIG. 2 The pericardiotomy is made anterior and parallel to the phrenic nerve.

follows the natural curvature of the rib vertically down toward the stretcher (Fig. 1). The intervention is carried out in a rapid fashion, moving through the skin and subcutaneous tissue, exposing serratus anterior musculature for transection and finally allowing access to the intercostal muscle group for access into the chest cavity. At this level, entrance into the thoracic cavity through the intercostal muscle can be done bluntly with the Mayo scissors. Using a finger to protect the underlying lung, the incision can be rapidly made again with the Mayo scissors. special attention should be placed on maintaining the incision on the superior aspect of the inferior rib to avoid damage to the intercostal neurovascular bundle. With anatomical awareness, the internal mammary artery may be avoided when approaching the lateral sternum. Posterolaterally, the chest wall is opened all beyond the midline border of the latissimus dorsi. There is no need to divide the latissimus dorsi muscle, which again, if done, results in problematic bleeding if the thoracotomy is successful. A patient who has arrested and requires a thoracotomy will have no bleeding as the procedure is started but will definitely bleed a lot once effective cardiac activity has been restored. Occasionally, patients will have pleural adhesions, so attention should be paid to the lung parenchyma when entering the chest as to not cause parenchymal damage.

A Finochietto retractor (rib spreader) is placed and the ribs are spread. There is debate over the optimal orientation of the retractor. If a dumbbell extension is possibly required, then the handle is placed closer to the stretcher (i.e., away from the sternum to allow extension to the contralateral side). In the event of thoracotomy extension, the incision is taken across the sternum down to the bone and extended in the same fashion down the right hemithorax. A heavy set shears or if one has access to a Lebsche knife this can be used to transverse the distal sternum. Unfortunately, anatomically, when extending the initial thoracotomy across the sternum, both internal mammary arteries will be transected and will require ligation once blood flow has been restored.

PERICARDIOTOMY AND CARDIORRAPHY

Upon entering the chest, immediate inspection allows for assessment of pathology. The pericardium should be opened routinely to rule out cardiac injury and tamponade and facilitate open cardiac massage. An incision on the pericardium should be made anterior to the phrenic nerve (usually will note with an accompanying fat stripe) and extended parallel to the phrenic nerve as superiorly as possible and inferiorly to the cardiac apex (Fig. 2). The pericardium is tough and fibrous and is often difficult to grasp with forceps, especially if bulging with blood. A nick with a scalpel blade is often required. Inspection alone can give a great deal of information, which helps drive therapeutic intervention. Is there cardiac injury or pericardial blood? Is the heart empty and still moving (in which case, more effective intravascular repletion may be warranted)? Does the heart have effective electromechanical activity (does it need cardioversion)?

In the event of tamponade, cardiac delivery should precede the evacuation and methodical examination of the myocardium. If cardiac injury with active extravasation is identified, prompt control with light digital pressure should be swiftly undertaken. A number of options have been well described for temporary control of full thickness cardiac injuries and include Foley catheter placement (through the injury into the chamber) with balloon inflation and minimal traction, staples (know the size of the staples to be used), vascular

clamps may be effective on atrial injuries), or suture control until definitive cardiorrhaphy can be achieved in the operating room. Remember that gunshot wounds to the heart most frequently have both entrance and exit wounds, so thorough inspection of the heart is vital to management.

NON-CARDIAC-RELATED THORACIC HEMORRHAGE

Access to the posterior thorax allows for ligation of the inferior pulmonary ligament. This is well identified by grasping the inferior lobe from below with one's left hand and slipping a finger posteromedially to the left lobe. It will fall into the groove between the lung and the medial thoracic border. Gentle lateral retraction demonstrates the thin ligamentous tissue for sharp division. Care must be taken to stay short of the hilar vessels. This releases the left lower lobe for easy superior traction and provides access to the inferior descending thoracic aorta. Intentional collapse of the left lung further aids visualization. With the assistance of the airway management team, the endotracheal tube can be advanced into the right main stem bronchus to collapse the left lung, allowing optimum exposure of the left hemithorax.

In the event of entering the chest and encountering a significant hemothorax without evidence of cardiac or descending aortic injury, blood should be evacuated and immediate exploration should begin for identification of the source. When identified, temporizing measures with direct pressure should be attempted if control cannot be achieved in the ED until the patient gets to the operating room because most of the aortic branch mediastinal vascular injuries are nearly impossible to achieve adequate exposure for repair in the ED. Pulmonary parenchymal injury as the source of hemorrhage is another likely source of major blood loss, and these injuries, when encountered, should be controlled with direct finger occlusion or clamp placement until the patient is transported to the operating room for formal dissection and repair. Many trauma texts also describe the ability for pulmonary hilar clamping or complete twisting of the lung about the pulmonary hilum once the inferior pulmonary ligament has been divided. This maneuver is effective in the way of completely occluding vascular inflow for hemorrhage control yet will also cause atrition in the lung and has a high morbidity and mortality rate with the physiologic stress it places on the already shocked myocardium with its increased pulmonary vascular resistance increase and resultant right heart stress and resultant right heart failure. It should therefore be a last ditch effort at life preserving intervention.

Aortic Cross-Clamping for Nontho ac Hemorrhage Control

Control of the aorta during an emergency thoracotomy is achieved by pressure at the distal descending thoracic aorta. The aorta runs anterior to the vertebral bodies and directly near and to the left of the esophagus in this location. It is separated from the left hemithorax proper by the mediastinal pleural tissue and posteriorly the prevertebral fascia is quite firm. The aorta is easily palpable where there is a pulse that may be difficult to feel as distinct from the esophagus in the arresting patient. As mentioned previously, a nasogastric versus orogastric tube helps to distinguish the aorta from the esophagus.

The inferior pulmonary ligament will need to be released and lung collapse should be facilitated with main stem endotracheal tube placement. Initial aortic control may be achieved with manual pressure of the aorta against the vertebral bodies. This has the disadvantage of blocking effective manual cardiac massage should that be required as well.

To expose the aorta for placement of a cross-clamp the overlying mediastinal pleural needs to be opened over the aorta. This is often difficult to get started. One trick is to use a clamp with the tips pushed against the vertebral column just posterior to the aorta and spread parallel to both structures. This should cause a rent in the fascia and

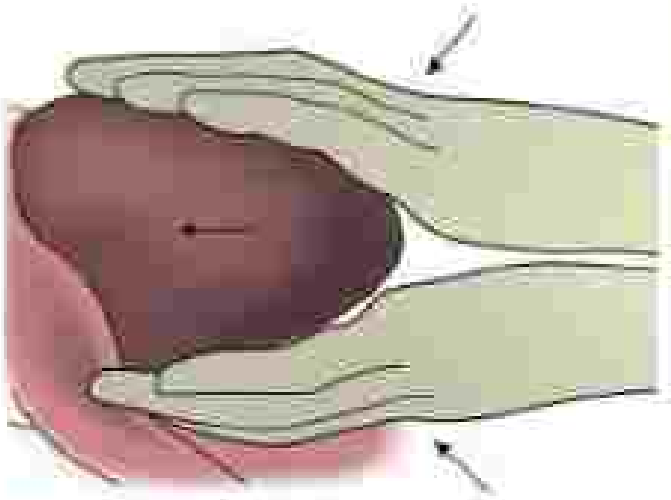

FIG. 3 Open cardiac massage is best achieved with a bimanual open, fist-basket approach.

facilitate the dissection. Finger fracturing will allow exposure of the aorta and esophagus off their respective pleural covering anteriorly and prevertebral fascial tissue posteriorly and will also allow separation of the two structures from one another. Once this has been achieved, the aorta should be accessible and mobile enough to allow enough elevation for aortic clamp placement and successful cross-clamping. When placed for proximal distal hemorrhage control, once cardiac activity is attained, the patient must proceed expeditiously to the operating room for other definitive management.

Although this maneuver allows for preferential blood shunting to the brain and the myocardium, all distal structures will in turn be exposed to prolonged ischemia with simultaneous massive physiologic changes proximally. As with all arterial clamping, an effort needs to be made to minimize clamp time. Restoration of global perfusion can be challenging given the punishing physiologic stress of reperfusion and reperfusion injury. Acidosis, hyperkalemia, and shock all should be anticipated but with prolonged continual aortic clamp times (>40 minutes), this is frequently fatal.

Approach to Open Cardiac Massage

Effective internal cardiac massage should be undertaken as soon as cardiac arrest is identified and appropriate ED surgical intervention has been completed. The bimanual approach is the preferred approach to effective cardiac massage is a "finger clapping" motion using the entirety of the palms of the hands and fingers commencing the compression at the apex of the heart and completing the compression at the base. This maneuver can be further described by firmly adducting the fingers and cupping the anterior hand with the posterior base hand in a rigid, flat, supinated position, allowing a flat surface for the heart to be compressed against. Appose both palmar aspects of the hands to firmly compress the myocardium (Fig. 3). This provides effective circulation and avoids direct cardiac injury.

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

There is a growing enthusiasm for the use of endovascular aortic occlusion in the management of a selected group of severely injured patients. Tried first in the early 1950s with the idea of an intraluminal rapid occlusion of the descending thoracic aorta/abdominal aorta without the morbidity of thoracotomy, there has been a resurgence of its use and promulgation in the past several years, primarily because of practical and specifically designed catheters. Femoral dependent, the technique is commenced percutaneously or via vascular cutdown of

the femoral vessel, an arterial puncture needle with Seldinger's technique, and introducer catheter followed by the balloon occlusion device are inserted into the chest via the aorta over the guidance wire. Alternatively, the device is positioned without guidewire assistance, using catheters with pressurized markings.

Position the balloon occlusion catheter in the thoracic aorta above the renal arteries (zone 1) for intraabdominal hemorrhage control or just above the aortic bifurcation (zone 3) for control of pelvic hemorrhage. Once again, depending on the brand, positioning can later be confirmed with fluoroscopy or computed tomography imaging if the balloon is filled with dye mixed saline in the place of air. It is vital to understand that the ED resuscitative thoracotomy and the resuscitative endovascular balloon occlusion of the aorta (REBOA) are not interchangeable procedures. It is obvious that REBOA would have no use in a patient that arrives with penetrating thoracic trauma, neck trauma, and blunt thoracic trauma related hemopericardium and/or hemothorax with arrest and in fact would be contraindicated. However, for patients who require subthoracic hemorrhage control with aortic occlusion, REBOA is a very attractive alternative to the traumatically invasive traditional full thoracotomy.

Multiple algorithms are being used to ascertain the optimum scenario for ED REBOA placement. The one most fitting with the best success data is in those patients arriving in extremis (i.e., having vital signs, yet unstable), with minimal or no response to volume resuscitation and no evidence of aortic trauma on simple chest films (e.g., severe pelvic fractures). As for the ideal positioning of the device, the Focused Assessment with Sonography for Trauma examination is undertaken with a positive result requiring positioning of the balloon occlusion in zone 1 (above the celiac artery) and a negative result requiring a pelvic plain film. Should the pelvis show any signs of instability, the balloon is deployed in zone 3 (below the renal arteries and above the aortic bifurcation) and if the film proves to be unremarkable the balloon is deployed in zone 1.

There is a growing body of evidence supporting the effectiveness of the ED REBOA; however, definitive data remain lacking. As with any intervention, it too is associated with adverse outcomes, high mortality rates, and the potential for significant morbidity, yet it certainly has a place and role in the acute care trauma setting being an effective intervention and tool to buy the trauma surgeon time for definitive operative intervention in a controlled setting.

Suggested Readings

Galvagno SC, Moore EE. Emergency department thoracotomy for the critically injured patient: objectives, indications, and outcomes. *Wkly Clin Emerg Surg*. 2006;16:1–8.

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Management of Traumatic Brain Injury

Christina Ramirez, MD, and Debora ... ez, MD, M. H

Traumatic brain injury (TBI) is a leading cause of death after injury. There is nothing that can be done to reverse the primary insult to the brain that occurs at time of injury. However, secondary injuries to the brain are the indirect result of injury that can occur immediately after the primary insult. It is the result of factors including cerebral hypoxia, hypotension, edema, and intracranial hypertension. Therefore, treatment strategies in severe TBI are targeted at preventing and treating these factors.

INITIAL TRAUMA EVALUATION AND TREATMENT

All trauma patients should undergo evaluation per Advanced Trauma Life Support guidelines. Initial interventions should be focused on treating any life-threatening injuries identified in the primary assessment. Ensure the patient has an intact airway, is receiving adequate oxygen delivery (with optimal oxygen saturations [SpO_2] of at least 94%) and maintaining a systolic blood pressure (SBP) of greater than 100 mm Hg. Concurrent life-threatening injuries should be identified, and any hemorrhage should be rapidly controlled to prevent and/or minimize hypotension. This should be done as expeditiously as possible.

The patient's medical history should be promptly obtained from family or emergency medical services, including any use of antiplatelet or anticoagulant medications before presentation. A focused neurologic examination should be performed, including brainstem reflexes, motor function in all extremities, and the Glasgow Coma Scale (GCS) score. The GCS is a quick and reliable method to assess the level of consciousness and quickly classify the severity of TBI: mild (13–15), moderate (9–12), and severe (3–8). The GCS score was last updated in 2014 to address variations in examination techniques (Table 1). The most important steps in the initial trauma evaluation in suspected TBI involve (1) maintaining normal oxygenation, ventilation, and blood pressure; (2) antiplatelet and anticoagulation reversal; and (3) identifying herniation.

Oxygenation, Ventilation, and Blood Pressure Management

Providing adequate oxygenation, ventilation, and blood flow is critical to maintaining adequate oxygen delivery to the brain. Derangements in blood pressure, oxygenation, and ventilation are independently associated with increased morbidity and mortality in TBI. Hypotension is historically defined as an episode of SBP less than 90 mm Hg and is one of the most significant predictors of poor outcomes. However, the *Guidelines for Management of Severe T...*, 4th edition, by the Brain Trauma Foundation (BTF) currently recommend maintaining SBP of 100 mm ...g or higher for patients 50 to 69 years old and SBP 110 mm Hg or higher for other ages because these thresholds are associated with decreased mortality and improved outcomes. Fluid resuscitation and rapid definitive treatment of hemorrhagic injuries is essential to limit the secondary brain injury that can result from hypotension. Normal saline is the preferred resuscitative fluid because it is hyperosmotic, thereby avoiding cerebral edema. Arterial line monitoring and vasopressor support may be indicated in those with labile pressures.

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Suggested Readings

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Christina Ramirez, MD, and Deborah Stein, MD, MPH

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TABLE 1 2014 Glasgow Coma Scale

Subcategory	1974 Classification	2014 Classification	Point
Eye opening	Spontaneous	Spontaneous	4
	To speech (command)	To sound	3
	To pain	To pressure	2
	—one	None	1
Verbal response	Orientation	Oriented	5
	Confused conversation	Confused	4
	Inappropriate speech	Words	3
	Incomprehensible speech	Sounds	2
	—one	None	1
Motor response	Follows commands	Obeys commands	6
	Localizes painful stimuli	Localizing	5
	Withdraws from pain (nonlocalizing)	Normal flexion	4
	Abnormal flexion (decorticate)	Abnormal flexion	3
	Abnormal extension (decerebrate)	Extension	2
	Does not make response	None	1

TABLE 2 Reversing Anticoagulant and Antiplatelet Agents

Anticoagulant	Mechanism	Reversal Strategy
Vitamin K antagonist (e.g., warfarin)	Inhibits vitamin K–dependent clotting factors	PCC, fresh frozen plasma, TXA, vitamin K
Direct thrombin inhibitor (e.g., dabigatran)	Competitive, reversible direct inhibition of thrombin	Idarucizumab (Praxbind), PCC (including FEIBA, rFVIIa), TXA
Direct factor Xa inhibitor (apixaban, rivaroxaban)	Competitive, reversible direct inhibition of factor Xa	PCC, TXA, andexanet
LMWH (e.g., enoxaparin)	Potentiation of antithrombin III	Protamine sulfate, rFVIIa
COX inhibitor (aspirin)	Irreversible cyclo-oxygenase inhibition	Platelet transfusion, desmopressin
Antiplatelet agents (clopidogrel, ticagrelor)	Irreversibly reduce platelet aggregation	Platelets, desmopressin

COX, cyclo-oxygenase; FEIBA, factor VIII inhibitor bypassing activity; LMWH, low molecular weight heparin; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VIIa; TXA, tranexamic acid.

Similarly, hypoxia (defined as SpO_2 <90%) is associated with significant detrimental outcomes in TBI. Irreversible brain damage can occur after only 4 to 6 minutes of cerebral anoxia. Therefore, all patients should have continuous SpO_2 monitoring. Those with evidence of severe TBI or persistent hypoxia should be intubated both for airway protection and to ensure adequate oxygenation. Oxygen supplementation or ventilator support should be adjusted to maintain a goal SpO_2 higher than 94% or a partial pressure of oxygen in arterial blood (PaO_2) level greater than 70 mm Hg. However, be aware that prolonged hyperoxia has also been associated with worse outcomes secondary to free radical toxicity and cerebral vasoconstriction. The few studies evaluating the effects of high levels of fraction of inspired oxygen and high PaO_2 levels have demonstrated poor functional outcomes including higher mortality rates, lower discharge GCS scores, and longer hospital length of stay compared with patients with normal oxygen levels.

Patients with severe TBI should also have continuous end-tidal carbon dioxide ($EtCO_2$) monitoring to ensure eucapnia because both hypocapnia and hypercapnia can worsen TBI. Significant hypercapnia results in cerebral vasodilation, which can further increase intracranial pressure (ICP). However, hypocapnia results in cerebral vasoconstriction, which compromises cerebral blood flow and decreases oxygen delivery to the brain. Routine prophylactic hyperventilation has been associated with increased mortality and is no longer supported. Instead, controlling the ventilator rate to important to maintain eucapnia (partial pressure of carbon dioxide in arterial blood [$PaCO_2$] to a normal range of 35–40 mm Hg). Hyperventilation is utilized only as a temporizing measure to reduce elevated ICP in dire situations, such as ongoing signs of herniation.

Antiplatelet and Anticoagulation Reversal

Anticoagulant or antiplatelet agents should be reversed in the setting of intracranial hemorrhage (ICH). A list of antidotes for common anticoagulants is listed in Table 2. Laboratory assays should be obtained in all patients, including prothrombin time, activated partial thromboplastin time, and platelet count. If available, thromboelastography can be helpful in determining the coagulopathic dysfunction present in patients. This is especially useful with patients on direct oral anticoagulants (such as factor Xa inhibitors) or with patients whose prehospital medication status is unknown. Any coagulopathic dysfunction should be rapidly corrected. Platelets are typically transfused for platelet counts of less than 100 × 10⁹ cells/L in patients with ICH. However, the exact threshold for transfusion is still debatable.

Identifying Herniation

Signs of impending herniation should be identified as quickly and efficiently as possible. Pupils should be examined for symmetry and reactivity. A dilated or "blown" pupil is concerning for uncal herniation on the ipsilateral side of the dilated pupil. Loss of motor function and/or the presence of a Babinski reflex is concerning for

contralateral brain injury. Decerebrate or decerebrate posturing is especially concerning for brainstem injury. Similarly, certain breathing, such as Cheyne-Stokes ventilations (repeating cycle of slow, shallow breaths followed by deeper and rapid breaths) are also concerning for brainstem injury and/or compression. Significant systolic hypertension (with or without bradycardia) can be secondary to a Cushing's reflex in severe intracranial hypertension and should not be rapidly reversed.

If the patient has any lateralizing signs or evidence of impending herniation, urgent neurosurgical consultation should occur to evaluate for immediate surgical intervention. Measures to decrease ICP should also be initiated, which is later discussed. Otherwise, a computed tomography (CT) head scan without intravenous contrast should be obtained to evaluate for the extent of TBI. Specific findings should be identified on imaging, including the presence of intracranial blood, midline shift, mass effect, herniation, and/or skull fractures. Neurosurgical consultation should shortly follow. If neurosurgery is not available, the patient should be transferred as expeditiously as possible to the nearest neurosurgery-capable facility.

MEDICAL MANAGEMENT

Fortunately, most patients with TBI can be medically managed. Maintaining normal oxygenation, ventilation, and blood pressure is still paramount. Patients with severe TBI are typically admitted to the intensive care unit because they require close monitoring, specifically blood pressure, oxygen saturation, and neurologic status. As previously mentioned, these patients require continuous SpO_2 and $EtCO_2$ monitoring, as well as an arterial or central venous line (if indicated). They require hourly neurologic examinations, because the pathophysiology of TBI is a dynamic process. Examination findings may fluctuate significantly within a short time and change management. Any acute change in neurologic examination should trigger an additional head CT scan to evaluate for bleeding or herniation, which could require surgical intervention.

Monitoring Intracranial Pressure

Another significant predictor of poor outcome in TBI (besides hypotension) is prolonged ICP elevation. Thus monitoring and treating ICP is often the mainstay of treatment. Previously, the 3rd edition of the BTF guidelines recommended ICP monitoring in all salvageable patients with a severe TBI and an abnormal CT scan findings. They also recommended monitoring in patients with severe TBI and an unremarkable CT scan if two or more features were present on admission: age greater than 40 years, unilateral or bilateral posturing, or SBP less than 90 mm Hg. However, the updated 4th edition did not carry forward these guidelines given the lack of supportive evidence. Instead, the guidelines only recommend "management of severe TBI patients using information from ICP monitoring...to reduce in-hospital and 2-week post-injury mortality." Thus, the decision to place a monitor should be made in consultation with neurosurgery.

There are three main methods of invasive neurologic monitoring: external ventricular drain (EVD), intraparenchymal pressure monitor (IPM, also known as bolt), and continuous brain tissue oxygen tension (PbO_2) monitor. EVDs are useful because they are both diagnostic and therapeutic. EVDs are placed in one of the lateral ventricles and can be used to both measure ICP and drain cerebral spinal fluid (CSF). However, they can be difficult to place and are more subject to blockage by hemorrhage or debris. Conversely, IPMs are easier to place because their placement is less precise and not influenced by midline shift or brain swelling. The risk of hemorrhage and infection is also less with IPMs compared with EVDs. A PbO_2 monitor is performed by placing a probe in the penumbra of injured parenchyma and enables quantification of tissue oxygenation in areas that are at the highest risk for secondary brain injury. PbO_2 levels less than 15 mm Hg should be treated by increasing systemic oxygenation. Alternative noninvasive methods include optic sheath diameter measurements or transcranial Doppler ultrasound, both of which are promising but not regularly used in the clinical setting.

Once an ICP monitor is in place, it can be used to track ICP and calculate cerebral perfusion pressure (CPP, where CPP = mean arterial blood pressure − ICP). Treatment of ICP higher than 22 mm Hg is recommended because values higher than this level are associated with increased mortality. Similarly, the recommended target CPP for survival and favorable outcomes is between 60 and 70 mm Hg. A CPP level less than 50 mm Hg is associated with brain ischemia, whereas a CPP level persistently elevated higher than 70 mm Hg is associated with increased rates of acute respiratory distress syndrome with no improvement in outcomes.

Managing Intracranial Pressure

The Monro-Kellie doctrine states that the relationship between intracranial contents, mainly consisting of brain tissue, blood, and CSF, remain constant to maintain ICP. Therefore, if the volume of one component increases (such as ICH), then the other components must be compensated to maintain ICP within normal ranges (<15 mm Hg). If the volume of one component continues to increase past a critical threshold, brain herniation and death will ultimately occur. Medically decreasing ICP is therefore targeted at these main components: brain, blood, and CSF.

Decreasing CSF is typically performed with CSF drainage using an EVD. Brain cell volume is decreased by reducing cerebral parenchymal cell water through osmolar therapy. Cerebral blood flow (CBF) and volume are most affected by cerebral metabolic requirements. As previously mentioned, $PaCO_2$ values are strongly and directly related to CBF; a lower $PaCO_2$ results in low CBF and vice versa. However, both hyper- and hypocapnia are associated with detrimental outcomes, so ventilators should be adjusted to maintain $PaCO_2$ levels between 35 and 40 mm Hg. The head and neck should be maintained in a neutral position to prevent cerebral venous outflow obstruction. Poor head position (such as flexion) and tight-fitting cervical collars have been demonstrated to cause significant increases in ICP, especially in children, who typically have larger occiputs and floppier necks. Other factors that affect CBF and volume include hyperventilation therapy, medications, and core temperature.

Hyperosmolar Therapy

Hyperosmolar therapy can decrease ICP by decreasing blood viscosity and cerebral parenchymal cell water, thereby decreasing the volume of cerebral blood and brain tissue. Hypertonic saline is becoming increasingly utilized to maintain serum sodium levels above 140 in severe TBI (or a minor GCS <8). Mannitol can also be utilized but its diuretic effect is detrimental in hypotensive patients or patients being actively resuscitated. The fourth edition of the BTF guidelines makes no formal recommendation on the ideal hyperosmolar therapy, given the lack of sufficient evidence. However, the previous edition recommended restricting mannitol in patients with signs of transtentorial herniation or progressive neurologic deterioration that is not attributed to extracranial causes.

Sedation, Analgesics, and Seizures

Anesthetics, sedatives, and anesthetics help prevent unnecessary movement, coughing, and agitation, which is important in intubated patients. However, they are also used for neuroprotection and to control ICP. They help suppress cerebral metabolism, oxygen consumption, and oxygen radical mediated lipid peroxidation. Decreasing metabolic demands also decreases the CBF requirement, which subsequently decreases cerebral blood volume and ICP. Short-acting agents such as fentanyl for pain control and propofol for sedation are ideal because they can be held for frequent neurologic examinations. Generally, continuous infusions should be used instead of boluses to decrease hypotension and mitigate rebound ICP elevation. Other agents, such as dexmedetomidine or midazolam, can also be used, especially when ICP elevation is associated with agitation.

Barbiturates are used as a last line to control elevated ICP refractory to maximum standard treatment because they have been shown to reduce both ICP and cerebral metabolism but can cause hypotension and fail to improve overall outcomes.

Normothermia

Temperature management is important in severe TBI because hyperthermia is associated with increased cerebral metabolic demands, resulting in increased CBF and elevated ICP. Normothermia should be maintained using a combination of acetaminophen, ice packs, and external and/or central cooling. Conversely, previous research has shown hypothermia to have neuroprotective and ICP reducing effects. However, the risks of hypothermia, including coagulopathy, immunosuppression, cardiac dysrhythmias, and death, outweigh the benefits. Recent trials have also failed to show any benefits to outcome. Therefore, routine prophylactic hypothermia is not recommended to improve outcomes in patients with severe TBI.

Preventing Hemiation

The dosage of analgesics, sedatives, and hyperosmolar therapy can be increased as needed to maximum doses or given in boluses. However, despite optimal and maximum medical management, ICP can continue to increase, resulting in herniation. Short-term ventilation can be utilized ($PaCO_2$ <35 mm Hg). The neurosurgery department should be notified of any elevated ICP that persists despite medical management. If intracranial hypertension remains refractory, barbiturate therapy, and/or therapeutic hypothermia can be considered, but the outcomes are generally poor.

General Considerations

In addition to ensuring adequate oxygenation, ventilation, blood pressure, and normal ICP and CPP, other systemic considerations need to be addressed, including managing seizure prophylaxis, nutrition, glucose levels, infections, and venous thromboembolism (VTE).

Seizure Prophylaxis

Patients with acute TBI are at risk for seizures because ischemic or damaged brain tissue can be lost to produce seizures. Generalized seizure activity can also be induced by hypoxia, hypoglycemia, or electrolyte abnormalities. When generalized seizures occur, the excessive neuronal activity rapidly decreases oxygen and glucose levels and can further worsen cerebral ischemia. Post-traumatic seizures (PTSs) are early if they occur within 7 days of injury. Risk factors for early PTS include GCS score of 10 or less, immediate seizures, post-traumatic amnesia >30 minutes, linear or depressed skull fracture, penetrating head injury, age 65 years or younger, chronic alcoholism, and either subdural, epidural, or intracerebral hemorrhage. Phenytoin is recommended by the BTF to decrease the incidence of early PTS. Levetiracetam is also often used but the available studies are inconsistent for BTF guideline recommendations. Early PTS has not been associated with worse outcomes, although it can result in prolonged hospital stay. Prophylactic use of antiepileptics is not recommended to prevent late (>7 days) PTS.

Nutrition and Glucose Management

Glucose is a primary fuel source to the brain. However, glucose metabolism is depressed in severe TBI, and the duration of glucose depression increases with age. In the absence of glucose, ischemic neurons can be permanently damaged. The location of depressed metabolism is important because as higher metabolic rates in the thalamus, brainstem, and cerebellum correlate positively with levels of consciousness. Hyperglycemia can also jeopardize ischemic brain tissue; prolonged serum glucose level greater than 150 mg/dL has been associated with a poorer neurologic outcome. Therefore, maintaining normoglycemia (serum glucose <180 mg/dL) is critical in the management of severe TBI. This is one of several reasons why ensuring adequate nutrition is critical in all patients with TBI. The American Society for Parenteral and Enteral Nutrition recommends initiation of enteral feeding within the first 24 to 48 hours of admission, meeting nutritional goals over 48 to 72 hours. BTF guidelines also emphasize the need for feeding by at least the end of the first week, indicating that early feeding improves outcomes.

Infection Prophylaxis

Patients with severe TBI are often at risk for infection due to a variety of reasons including mechanical ventilation and invasive monitoring (such as central lines and EVDs). Ventilator-associated pneumonia in TBI patients may be as high as 40% and is associated with longer mechanical ventilation days. Thus, early tracheostomy is recommended to reduce mechanical ventilation days, even though there is no evidence that doing so reduces mortality or pneumonia rates. Antimicrobial-impregnated catheters should be utilized whenever possible because they are associated with lower rates of infection and catheter bacterial colonization. Prophylactic antibiotics are not currently recommended because there is no difference in mortality and they are associated with an increased risk of developing antibiotic resistance.

Venous Thromboembolism Prophylaxis

TBI is an independent predictor of VTE in trauma patients, with a three- to fourfold increase in VTE despite the use of mechanical and chemical prophylaxis. The risk is increased as the severity of TBI increases, usually due to hypercoagulability from brain injury, focal motor deficits, and prolonged immobilization. However, there is also an increased risk of worsening ICH with chemical prophylaxis. Therefore, the VTE prophylaxis should always be considered if the brain injury is stable and the benefits outweigh the risks. Because there is insufficient evidence, there are currently no BTF recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis.

Steroid Use

Steroid use is not recommended to reduce ICP or improve outcomes. The 2004 Corticosteroid Randomization After Significant Head Injury (CRASH) trial demonstrated high-dose methylprednisolone to be associated with increased mortality and severe disability. Another 2004 study demonstrated an increased risk of late seizures with use of glucocorticoids less than 1 week in the post-traumatic period.

SURGICAL THERAPY

As described by the Monro-Kellie doctrine, elevated ICP can cause brain tissue displacement, leading to cerebral herniation. This is often caused by mass effect from ICH or cerebral edema that occurs as a result of primary and secondary brain injury. Decompressive craniotomy (DC), or surgical removal of a portion of the skull, is performed to relieve elevated ICP by removing ICH and providing room for the brain to expand.

According to the Surgical Management of TBI Author Group, acute subdural hematomas should typically be evacuated if the hematoma is more than 10 mm thick or if there is midline shift greater than 5 mm. An epidural hematoma greater than 30 cm^3 should be evacuated regardless of GCS. DC is also indicated with severe TBI and frontal or temporal contusions greater than 20 cm^3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, or patients with lesions greater than 50 cm^3. Urgent indications for operative intervention include any signs of transtentorial herniation and deterioration of neurologic function secondary to parenchymal lesions. The role of DC in diffuse injury and elevated ICP refractory to medical management is debatable because of insufficient and controversial evidence. The Decompressive Craniectomy (DECRA) trial was a 2006 randomized control trial that compared early bifrontal unilateral DC with medical management for refractory raised ICP (>20 mm Hg). DC was demonstrated to reduce ICP and intensive days in the intensive care unit, but it was also associated with poorer outcome scores at 6 months compared with medical care. The most recently published RESCUEicp trial is another randomized

control trial comparing DC with medical care in patients with refractory elevated (ICP >25 mm Hg). They found DC to be associated with lower mortality but higher rates of vegetative state and severe disability compared with medical therapy. Based on these studies, the BTF guidelines do not recommend DC to improve outcomes in patients with severe TBI who have diffuse injury (without mass lesions) or ICP elevations >20 mm Hg for more than 15 minutes within a 1 hour period that are refractory to first tier medical therapies. Those with open cranial fractures should undergo operative intervention to prevent infection if there is clinical or radiologic evidence of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, gross wound contamination, or pneumocephalus. Closed (simple) depressed fractures can typically be treated nonoperatively.

Complications of DC include infection, CSF absorption disorders (subdural hygroma, hydrocephalus, and CSF leak), postoperative hematoma expansion, and surgical site infection. Contralateral hematoma after DC occurs in up to 7.4% of patients. Subdural hygromas can occur due to an imbalance between production and reabsorption of CSF. Post DC hydrocephalus is seen in 2%–30% of cases, can complicate prognosis, and occasionally require placement of a ventriculoperitoneal shunt. A CSF leak can also lead to infections, wound complications, and prolonged recovery. Subsequent cranioplasty, or interval replacement of the bone, is also associated with an increase of infection, cerebral edema, and decreased bone flap reabsorption.

BRAIN DEATH

Brain herniation ultimately results in brain death, or the complete, irreversible cessation of brain function. Determination of brain death consists of prerequisite criteria, neurologic assessment(s), and ancillary confirmatory tests (if indicated). The American Academy of Neurology guidelines state that the patient must be normothermic (>36°C) and normotensive (SBP >100 mm Hg) with an irreversible and proximate known cause of the coma. The presence of central nervous system depressants, neuromuscular blocking agents, or severe electrolyte, acid base, or endocrine disturbances should be excluded. The patient must lack all evidence of responsiveness to noxious stimuli. Brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, grimace, gag, and cough) and be apneic. An apnea test is performed by disconnecting the patient from the ventilator but preserving oxygenation (after ensuring normotension, normothermia, euvolemia, eucapnia, and no prior evidence of CO_2 retention). The test is positive if respiratory movements are absent and $PaCO_2$ of 60 mm Hg or greater (or a 20 mm Hg increase over baseline). The test can be repeated if it is inconclusive. Other ancillary tests, including electroencephalogram, CT angiography, or nuclear scan, can also be performed to confirm brain death. Hospital guidelines and state law may dictate additional requirements/criteria for pronouncing brain death.

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CHEST WALL, PNEUMOTHORAX, AND HEMOTHORAX

Gregory Sutton, DO, FACS, FACOS, and Mary McCarthy, MD, FACS

Chest wall injury describes of fractures of the thoracic cage, including the ribs, sternum, and costal cartilage. Associated injuries to the thoracic cavity carry significant morbidity and mortality and are described elsewhere. Chest wall injury is one of the most common injuries encountered by the acute care surgeon, with over 140,000 patients in the United States presenting yearly and carries a mortality rate as high as 20%. Chest wall injury results not only in significant pain, but decreased pulmonary function, inability to cough and clear secretions, atelectasis, pneumonia, and respiratory failure. These injuries can place a significant burden on the healthcare system by increasing length of hospitalization, overall healthcare expenditures, and long-term disability. The chronic disabling pain is not often appreciated by surgeons who provide the majority of their care during the acute phase of injury in the hospital. In one study, patients with two or more rib fractures were more disabled at 30 days than a reference population of chronic illness. In the same study, the total mean days lost from work and usual activity was 70 ± 41 days and the number of rib fractures correlated with pain levels, days lost from work, and self-reported energy levels. Of patients who were followed 5 years after their rib fractures, less than one third had returned to full time employment. Greater than 50% of patients complained of thoracic cage pain and mild dyspnea, and 25% reported subjective chest tightness and a decline in overall activity. Incentive spirometry readings were abnormal in over half of these patients. These findings underscore the need for a comprehensive and evidence-based approach when caring for patients with these complex injuries.

INITIAL EVALUATION

Patients with suspected trauma to the chest wall should initially undergo emergency stabilization protocols, such as those outlined in Advanced Trauma Life Support. Initial priorities include performing lifesaving interventions to the airway, breathing, and circulation as needed. Special attention should be paid to the chest wall with inspection for external signs of injury, observation for equal chest rise, and auscultation for bilateral breath sounds. The absence of unilateral breath sounds in combination with jugular venous distention and tracheal deviation should raise suspicion of tension pneumothorax. This should be promptly treated with needle decompression of the chest followed by placement of a thoracostomy tube. Absent unilateral breath sounds without findings of tension pneumothorax

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can be suggestive of pneumothorax or hemothorax. The presence of paradoxical chest wall motion is suggestive of, but not necessarily diagnostic for, flail chest. These findings are concerning for significant chest injury and should promptly be evaluated radiographically. The patient's blood pressure should be rapidly assessed and peripheral large bore intravenous line should be placed. Tachycardia and hypotension should be assumed to be a result of hemorrhage and fluid, and/or blood administration should be initiated promptly. Tension pneumothorax, cardiac tamponade, and cardiogenic shock due to blunt cardiac injury should also be considered in the patient with blunt chest trauma. Following the primary survey, resuscitation moves into a secondary survey that should include a focused history and a head to toe examination of the patient. Adjuncts to the secondary survey should include laboratory tests and radiographic imaging including a chest x ray and pelvic x ray. Attention should be paid to the chest x ray for the presence of pneumothorax, hemothorax, rib fractures, and widening of the mediastinum. The focused abdominal sonogram for trauma (FAST) is increasingly being used in both trauma and nontrauma centers. With regards to the thorax, ultrasound can quickly be utilized to detect the presence of cardiac tamponade. This so-called extended FAST or eFAST also evaluates the pleural cavity for the presence of pneumothorax or hemothorax with relatively good sensitivity.

Computed tomography (CT) has become the workhorse of rapid diagnosis of injuries in trauma patients. While routine CT scans of the chest are costly and could expose the patient to unnecessary radiation, thoracic injuries can carry major morbidity and mortality. The National Emergency X-ray Utilization Study (NEXUS) chest criteria have been developed to help identify patients at risk for thoracic trauma and guide clinical decision regarding necessity of CT scans. The rate of occult pneumothorax, that is those that are seen on CT but not seen on chest x ray, is as high as 22% in some series. Three-dimensional (3D) reconstructions of the ribs and sternum can be extremely useful in evaluating chest wall injuries. The anatomic nature of the ribs, which extend through three planes, makes it difficult to evaluate with plain films or even axial computed tomography. Three-dimensional imaging can improve visualization of displacement and flail segments and is especially useful in planning for surgical intervention.

SPECIFIC INJURIES

Rib Fractures

In 10% of patients with multisystem trauma and 59% of patients with blunt chest trauma, two or more rib fractures will be identified. As previously noted, these injuries carry a high morbidity that can lead to a need for mechanical ventilation, pneumonia, increased length of stay, and chronic pain and disability. Many rib fractures can be identified on plain chest x rays, but CT scans carry increased sensitivity and specificity and allow for more precise identification of fracture morphology. Multiple studies have shown that with increasing number of rib fractures, the risk of complications and mortality are increased. Ribs four to nine are the most commonly injured ribs, which is important because these are the ribs most involved in respiration. Injuries of lower ribs (9–12) may portend injury to upper abdominal viscera such as the spleen or liver, while high rib fractures (1, 2) can be associated with blunt cerebrovascular injury. Extremely posterior rib fractures (within 3 cm of the transverse process), are usually well tolerated as these fractures are stabilized by the erector spinae musculature. Similarly, very anterior fractures are cartilaginous in nature and do not carry significant pulmonary morbidity.

Flail chest is poorly defined in the literature, but most experts have come to agree that there exists both clinical and anatomic flail chest. Clinical flail chest is the more classical description of a patient with paradoxical chest wall motion in which the chest wall moves inward during inspiration. Anatomic flail chest, on the other hand, describes a single rib that is fractured in two or more places (flail segment), thus being free floating and disconnected from the thoracic cage. Clinical flail chest can be caused by a flail segment but may also be seen with severely displaced contiguous rib fractures, or with bilateral rib fractures near the sternum. It is therefore possible to have clinical flail chest without anatomic flail chest, and vice versa. In any case, flail chest carries significant morbidity and mortality, with up to three-fourths of patients exhibiting pulmonary contusion, hemothorax, or pneumothorax.

Pain control is essential in patients with rib fractures (Box 1). The ideal strategy would provide complete and prolonged analgesia, permit deep breathing and secretion clearance, allow patient cooperation, minimize central nervous system and systemic side effects, allow for early mobilization, be safe, and be cost effective. Unfortunately there is no agent that can provide all these benefits while providing adequate pain relief. A multimodal pain control strategy, such as those outlined in the table, should be used in an attempt to minimize narcotic use. Opioids, such as morphine or fentanyl, cause sedation, respiratory depression, cough suppression, hypotension, immune suppression, constipation, and are highly addictive. When these drugs must be used in higher doses, a patient-controlled analgesia device should be employed to minimize some of these side effects. Acetaminophen can be used around the clock fashion as a baseline pain control. Nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen or ketorolac, have been shown to be extremely effective in patients with rib fracture. In one study, a treatment group of patients with multiple rib fractures that received ibuprofen was shown to have decreased daily morphine use and lower overall pain scores and length of stay versus a control group. NSAIDs, however, must be used with caution in patients with renal impairment, cardiovascular disease, gastrointestinal ulcers, and orthopedic injuries. Other nonnarcotics including gabapentin and muscle relaxers are advocated by many clinicians who care for patients with rib fractures, but currently there is little evidence supporting their use. Another interesting option is intravenous ketamine, which blocks N-methyl-d-aspartate receptors, thus reducing the risk for opioid hyperalgesia. The low doses of ketamine used for its analgesic effect (typically 1–3 μg/kg per minute) are not associated with the side effects of delirium, hallucinations, respiratory depression, and sedation seen at higher doses.

BOX 1 Standardized Pain Regimen for Patients with Multiple Rib Fractures

Acetaminophen 650 mg qid
Ibuprofen 600 mg qid*
Gabapentin 300 mg tid*
Oxycodone 5 mg q4h prn

For Refractory Pain (Pain Score >6 Despite Above):
Intercostal block or paravertebral infusion catheter
Ketamine drip, 1–3 μ kg/min
Consider intravenous narcotics (patient controlled analgesia)
Consider epidural catheter
Consider surgical stabilization of rib fractures

*Use with caution in elderly and renal failure patients

Local regional anesthesia is an excellent option for pain control. Intercostal nerve blocks were one of the earliest attempts at local pain relief for rib fractures and continue to be used in some centers. Local anesthetic in the form of bupivacaine or ropivacaine is injected just below the rib proximal to the fracture site. Due to the overlapping innervation of the intercostal nerves, it is important to block at least one rib above and one rib below the injured segment. Unfortunately, the effects of local anesthetics begin to wane after only 6 hours. The need for multiple injections and the risk of pneumothorax make this an unattractive option. Liposomal bupivacaine, whose effects linger for up to 72 hours, offers a theoretical advantage if the block is performed properly. Topical lidocaine patches, which were developed to treat postherpetic neuralgia, have been attempted in some centers. A randomized controlled study of 58 patients, however, showed no improvement in pain scores or narcotic usage versus a placebo.

Epidural anesthesia has been extensively studied in this patient population. These catheters can easily be placed in the high thoracic spine at the bedside and using continuous infusion of local anesthetic, opioids, or both. This provides excellent pain relief to the rib cage while avoiding the sedation and respiratory depression associated with narcotics. This allows the patient to continue to participate in the pulmonary toilet and cough adequately. Multiple studies have shown that epidural anesthesia decreases mortality and pulmonary complications in patients with rib fractures, while increasing functional residual capacity, lung compliance, and oxygenation. Furthermore, this translates into a decreased intensive care unit (ICU) and hospital length of stay, especially in the older patient population. Unfortunately, the use of epidural catheters can be limited in the trauma population. Possible risks of placement include hypotension, epidural hematoma, infection, and spinal cord injury. They should not be used in patients with elevated intracranial pressure, or those with suspected abdominal trauma as injuries can be masked. Other relative contraindications include spinal fractures, history of spinal surgery, valvular heart disease, and coagulopathy. The placement of an epidural catheter should not preclude use of chemoprophylaxis for deep venous thrombosis.

Paracostal infusion combines the benefits of an epidural catheter with the safety and relative ease of placement of an intercostal block. An entry site is chosen inferior to the lowest fractured rib two fingerbreadths lateral to the spinous process. After making a small skin incision, a tunneler is used to create a longitudinal subcutaneous tract that is just superficial to the rib cage. The infusion catheter is then inserted and the peel away sheath removed. The catheter is then secured using tape and the catheter is connected to a reservoir containing bupivacaine. In a study of 102 patients with greater than 3 rib fractures, placement of the paracostal infusion catheter was shown to improve pain scores, lung volumes, and respiratory rates compared to historical controls.

Surgical Stabilization of Rib Fractures

Reduction and fixation of acute fractures is one of the central tenets of orthopedic surgery. Although there have been historical attempts at external fixation of the ribs using traction or sand bags, the very nature of the ribs' movement with each breath makes this impractical, and may worsen respiratory complications. Surgical stabilization of rib fractures (SSRF) has gained popularity in the early twenty-first century due to development of low profile, anatomically contoured plates that allow for extrathoracic internal fixation. Multiple retrospective studies have now shown that SSRF decreases length of mechanical ventilation, need for tracheostomy, incidence of pneumonia, ICU length of stay, hospital length of stay, and overall cost of care. In perhaps the first prospective study, Pieracci et al. evaluated 30 patients over a 2-year period. For the first year of the study, patients with flail chest, three or more displaced rib fractures, 30% or greater hemithorax loss, and severe pain or respiratory failure were managed medically and followed. In the second year, patients with the same criteria underwent SSRF. The operative group was found to have a 76% lower incidence of respiratory failure and an 82% lower need for tracheostomy. With regards to the timing of surgery, a retrospective review of 551 patients over a 10 year period at four high-volume SSRF centers showed improved outcomes in the first 24 hours of hospitalization.

Indications for SSRF are influenced by the results of these studies as well as expert opinion (Box 3). SSRF of flail segments is nearly universally agreed upon, and a multicenter prospective randomized trial of patients with three or more rib fractures, sponsored by the Chest Wall Injury Society (CWIS; NCT01928498; ELAIN), is ongoing.

The decision to proceed with operative intervention for rib fractures should take into account the above guidelines, as well as the patient's overall clinical picture. The goal of the operation should be for a muscle-sparing exposure, open reduction, and internal fixation of all clinically significant rib fractures, irrigation and evacuation of any hemothorax, and local regional pain control. A thorough understanding of chest wall anatomy is critical when planning the operative approach. The most commonly encountered muscles include the latissimus dorsi, which arises from the transverse processes of lower thoracic and lumbar vertebrae and courses superiorly and anteriorly just inferior to the scapula before inserting on the humerus. The trapezius is found superior and medial to the latissimus dorsi and forms the so-called *triangle of auscultation* with the inferior border of the scapula. The serratus anterior is found deep to these muscles and the scapula. The positioning on the operating room table will depend on the location of the fractures. The majority of fractures are posterolateral, which are best approached through a standard posterolateral thoracotomy type incision with the patient in the lateral recumbent position. Hinging or "breaking" the bed, while typically used when performing a thoracotomy, is not recommended when performing SSRF. The chest wall may be accessed in a muscle sparing fashion by elevating muscle flaps through the triangle of auscultation. More inferior fractures can also be exposed by splitting the latissimus dorsi in the direction of its fibers. We find that this technique with the assistance of a circular wound protector provides excellent exposure (Fig. 1). Anterior fractures are approached with the patient supine and via a submammary incision, with elevation of a pectoral flap. Posterior fractures often require prone positioning of the patient, with a vertical incision made halfway between the spinous processes of the upper thoracic vertebra and the scapula. When repairing a large flail segment, a second vertical incision can be made anteriorly.

The past decade has seen an explosion in the availability of commercial rib fixation hardware systems. U plates were one of the early innovations and are placed over the superior margin of the rib and secured in place with bicortical screws after drilling holes on either side of the fracture. Precontoured plates, applied to the exterior surface of the rib and designed to match the specific contours, are similarly fixated with bicortical screws. Fixation plates with self-tapping monocortical screws are also available. No matter which fixation system is used, attention should be made to adequately reduce all fractures into anatomic alignment. Dissection of the rib periosteum is minimized to ensure adequate blood supply. The chosen plate should be anatomically contoured to the rib to be repaired. The plate should be affixed to the middle or slightly superiorly on the rib to avoid damage to the intercostal bundle. A variety of instrumentation is available to secure the plate as holes are drilled and screws inserted. Right angled instrumentation is essential when working in low clearance areas, such as under the scapula. All current systems require three to four screws to be placed on either side of the fracture. Most experts recommend repair of all accessible fractures from ribs 3 to 10. We find that repairing the most easily accessible fracture first affords repair of subsequent ribs that may be in more challenging locations. Following adequate reduction and internal fixation of all fracture ribs, pleural irrigation and drainage of any hemothorax should be undertaken. This can be thoroughly performed through a chest tube without the

BOX 3 Indications for Surgical Stabilization of Rib Fractures*

- Flail chest (anatomic or clinical)
- ≥3 displaced rib fractures
- Failure of medical management
  - Pain score > 6 despite maximal therapy
  - Respiratory insufficiency requiring ICU transfer or intubation
- During thoracotomy performed for another indication
- Chronic nonunion or malunion

*Modified from Chest Wall Injury Society consensus.

FIG. 1 *Posterolateral approach to exposure of the chest wall for surgical stabilization of rib fractures. A wound protector can be useful for soft tissue retraction.*

need for entering the pleural cavity. The necessity of leaving a chest tube is debatable, but we generally advocate for leaving a small-bore pleural drainage catheter postoperatively. Finally, local regional pain control should be provided at the time of surgery. This can be performed with either an intercostal block or the placement of a paravertebral infusion catheter placed under direct visualization.

Sternal Fractures

Historically called a *steering wheel injury*, motor vehicle crashes remain the most common cause of sternal fractures despite the widespread use of shoulder restraints. One fourth of sternal fractures are isolated, with the remainder being most commonly associated with extremity fractures, head and neck injuries, rib fractures, spine injuries, and pulmonary contusions. Many clinicians fear complications such as blunt cardiac injury or great vessel injury, but these have been shown to be present less than 2% of the time. Because they carry significant morbidity, these injuries should promptly be evaluated for with liberal use of CT angiography of the chest. Blunt cardiac injury (BCI, formerly known as a cardiac contusion) is poorly defined in the literature but generally describes blunt force trauma to the myocardium, which may be clinically silent, produce arrhythmias, or result in deadly myocardial rupture. Patients with suspected BCI should be observed for electrical abnormalities, such as unexplained sinus tachycardia (most common), premature ventricular contractions, new bundle branch block, or ST segment changes. Echocardiography should also be considered to evaluate for valvular or wall motion abnormalities.

Operative considerations for repair of sternal fractures is similar to that for rib fractures, that is, patients with displaced sternal fractures that are refractory to medical management. Chest CT with 3D reconstruction of the sternum is useful in surgical planning. A median sternotomy provides adequate exposure and a variety of plating systems are available. Newer sternal plating systems can extend on to the ribs, providing repair of the parasternal cartilage and allowing for stabilization of the entire anterior chest wall.[1]

Pneumothorax

A pneumothorax occurs when air enters the pleural space and the visceral and parietal pleura are separated. The pneumothorax may be occult and contain a small, stable amount of air, or extend to a complete, tension pneumothorax, where the lung is completely collapsed and additional air enters the pleural space, creating an increase in pleural pressure and a shift of the mediastinum to the opposite side, with resulting impaired venous return, hypotension, shift of the trachea, and distended neck veins. The diagnosis of pneumothorax is suggested on physical exam, noting decreased or absent breath sounds on the side of the lesion. This may be accompanied by subcutaneous emphysema palpable in the chest wall or pain due to rib fractures. An anteroposterior chest radiograph performed in the trauma bay on arrival may initially appear normal as it is done in the supine position and air rises to the front of the chest. Look closely for the presence of a deep sulcus sign, which provides a clue to the presence of air in the hemithorax. An eFAST includes an assessment at the second intercostal space—failing to demonstrate lung sliding and comet tails in the presence of a pneumothorax. A CT scan performed as part of the trauma evaluation is highly sensitive and specific for the presence of pneumothorax.

If the pneumothorax is occult and stable, it may be observed. Initial treatment for a simple pneumothorax is placement of a small-bore chest tube (e.g., 20 Fr) under sterile conditions. In the trauma bay, the potential for elevation of the diaphragm or presence of a diaphragmatic hernia should be considered; the tube may be placed at the upper margin of the fourth or fifth intercostal space in the midaxillary line. A short skin tract will ensure a seal when the tube is removed. After sweeping the chest to ensure the absence of adhesions, the tube should be directed posteriorly and toward the apex. Appropriate placement is confirmed by the presence of condensate in the chest tube and bubbling in the drainage chamber as air is evacuated. The tube should be secured with a large silk suture to prevent slippage, connected to an underwater suction collection device, and a sterile occlusive dressing applied. The connections should not be covered with tape, but secured with nylon cable tie ties to ensure visible security of connections. A mesentery should be placed around the drainage tube so that traction on the tube will not directly pull on the site of chest entry. Blunt trocars may shorten introduction time; however, limited data are available on their risks, benefits, and complications compared to more traditional methods. Sharp trocars should never be used to place chest tubes in trauma, as they are associated with a higher incidence of malposition and significant complications. Tube placement and lung expansion should be confirmed by chest radiograph prior to breakdown of the sterile field. If this is done, repositioning is available as an option, whereas if the field is broken down, a new site should be chosen for chest tube reintroduction.

A tension pneumothorax is a clinical, not a radiologic, diagnosis. Decompression should be performed with a 14-gauge angiocatheter introduced in the second intercostal space in the midclavicular line (MCL), a site that may be identified by carrying the line from the sternomanubrial junction to the MCL and inserting the needle perpendicular to the chest wall. If the diagnosis is correct, when the chest is entered a rush of air will be heard, and the patient's hemodynamic status will improve. In obese patients or patients with developed pectoral muscles, the angiocath may not be of sufficient length to enter the pleural space. Therefore, alternative sites have been described on the lateral chest wall to the fourth or fifth intercostal space (ICS). After needle decompression, a definitive chest tube should be placed. Even if there is no visible pneumothorax on the chest radiograph, a pneumothorax may develop abruptly later in an unmonitored setting, and cause harm to the patient.

Hemothorax

Hemothorax may be the result of chest wall, pulmonary parenchymal, cardiac or mediastinal bleeding. Blood accumulates in the pleural space; the symptomatic presentation will depend on the amount of

blood and the rate of ongoing bleeding. Breath sounds will be diminished or absent and hemodynamic instability may occur. Opacification of the entire chest may be seen when the radiographic film is done in the supine position in the trauma bay. An *e*FAST is useful in the identification of the hemithorax. A tube thoracostomy should be placed in the fifth ICS, with the same concerns for potential abdominal visceral injury as seen in the placement of a tube for pneumothorax. The tube should be at least 28 to 32 Fr in a trauma population requiring open chest tube drainage. Larger tubes are not required and pain may be reduced. An initial blood loss of 1200 cc or ongoing blood loss of 200 to 250 cc/hour should prompt consideration for thoracotomy.

Continuing air leak should be addressed early, within 72 hours, using video assisted thoracoscopy (VATS) with closure of lung lacerations. Residual hemothorax may result in empyema or fibrothorax if not addressed early in the patient's course within 48 to 72 hours. Irrigation of the tube thoracostomy immediately after placement with 1 liter of warmed sterile saline will reduce the need for secondary intervention. Ongoing bleeding or delayed clot formation may require VATS. Concurrent evacuation of the hemithorax when rib fixation is performed is essential.

Suggested Readings

Dominguez KM, Clark AP, Schurr KM, et al. Is routine tube thoracostomy necessary after prehospital needle decompression for tension pneumothorax? *Am J Surg*. 2013;205(3):329–332.

Inaba K, Lustenberger T, Recinos G, et al. Does size matter? A prospective analysis of 28-32 versus 36-40 French chest tube size in trauma. *J Trauma*. 2011;72:422–427.

John M, Barr S, Sabanthan A, Harropdaley C. Is the trocar technique for tube thoracostomy safe in the current era? *Interact Cardiovasc Thorac Surg*. 2014;19(1):125–128.

Kiefer NW, Garner DW, Mills D, et al. Thoracic irrigation prevents retained hemothorax: a prospective propensity scored analysis. *J Trauma Acute Care Surg*. 2017;83(6):1136–1141.

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Blunt Abdominal Trauma

L.D. Britt, MD, MPH, FACS, and Michael Mareyak, MD

The abdomen remains one of the most critical and vulnerable anatomic regions in blunt trauma. Prior to focusing on any specific management strategy for a patient who has sustained blunt abdominal trauma, an initial assessment of the entire patient is imperative. The concept of initial assessment includes four essential components: rapid primary survey, resuscitation, a detailed secondary survey (evaluation), and re-evaluation. Integrated into primary and secondary surveys are often necessary adjunct interventions, such as electrocardiographic monitoring, arterial blood gas determination, pulse oximetry, insertion of urinary and/or gastric catheters, and obtaining necessary radiographs and other diagnostic studies, when applicable. The management of blunt abdominal trauma continues to evolve more in the nonoperative arena, as opposed to surgical intervention. The workup has shifted largely from the use of a physical examination, plain radiographs, laboratory findings, and diagnostic peritoneal lavage to physical exam and liberal use of computed tomography (CT) and ultrasonography. Treatment for visceral injury has traditionally been surgical. However, many forms of solid organ injury can now be successfully managed nonoperatively or with minimally invasive and interventional radiology techniques. Nonoperative management of the multiple injured trauma patient at level I trauma centers, with state of the art techniques, has conclusively shown significantly improved patient outcomes and survival.

DIAGNOSTIC AND IMAGING ADJUNCTS

Diagnostic peritoneal lavage has now been essentially supplanted by the adoption and now popularity of abdominal sonography—focused abdominal sonography for trauma (FAST). The utilization of diagnostic peritoneal lavage has diminished substantially. Originally described by Root in 1965, diagnostic peritoneal lavage (DPL) was once a mainstay in the management of blunt abdominal trauma for over four decades. Before the era of routine CT scanning, it was used as a screening tool to evaluate patients having blunt or penetrating abdominal trauma, with an accuracy rate reported between 92% and 98%. CT scans and FAST are now the diagnostic modalities of choice in the assessment of the injured patient. However, DPL remains an excellent tool for further workup of occult bowel injury or in unstable patients when FAST is not available or has questionable findings. In the workup for occult bowel injury, traditional parameters (Table 1) should be used to guide therapy. In unstable patients and when FAST is not an option, a diagnostic tap is usually all that is necessary and exploration is indicated when there is aspiration of greater than 10 mL of gross blood.

The pitfalls of DPL are a relatively high false-positive rate, risk of creating visceral injury and poor sensitivity for detecting injury to retroperitoneal structures such as the pancreas and duodenum. Iatrogenic errors are minimized if a Foley catheter and nasogastric tube are placed prior to the procedure. Patients with pelvic fractures and suspected retroperitoneal hematoma or pregnant females should undergo a supraumbilical approach.

Focused Abdominal Sonography for Trauma

In the diagnostic assessment of the acutely injured patient, the bedside ultrasonographic for detection of cardiac and intraabdominal injury is considered the standard of care. Because focused abdominal sonography for trauma is of a noninvasive nature, this diagnostic modality allows the operator to perform an exam simultaneously during the initial resuscitation and stabilization of a multiple injured trauma patient. Due to the relative insensitivity of abdominal examination in the severely injured patient, this technique may provide evidence of significant hemorrhage early in the course of an evaluation. An ultrasound probe is used to examine four key windows for fluid: the subxiphoid area permits visualization of the pericardium, the left subcostal area visualization of the splenorenal recess, right subcostal area visualization of Morison's pouch, and the suprapubic area visualization of the pelvic cul de sac (Fig. 1). The presence of fluid may indicate presence of cardiac tamponade fluid in the pericardial space, intraabdominal hemorrhage, hollow viscus perforation,

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TABLE 1 Diagnostic Criteria for a Positive Diagnostic Peritoneal Lavage

Any Viscus	Bowel
10 mL gross blood	Bacteria
>100,000 red blood cells/mm³	Bile
>500 white blood cells/mm³	Food particles
>7% EAAT amylase	

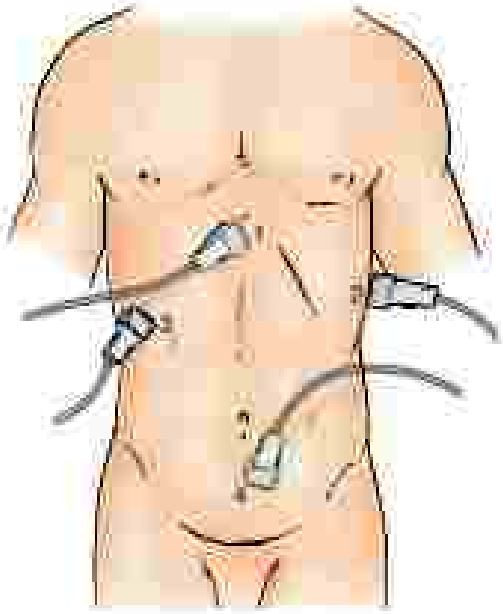

FIG. 1 Schematic showing sonographic windows for (1) Morison pouch, (2) left subcostal, (3) right subcostal, and (4) suprapubic areas. Distension of the urinary bladder either prior to Foley catheter placement or by installation of 150 to 200 mL normal saline will enhance sensitivity. [illegible]

hemoperitoneum, or ascites. False positive results secondary to pre-existing ascites or false negatives due to operator error and/or body habitus are the main limitations. Scanning the suprapubic area with distension of the urinary bladder will enhance the sensitivity of the exam for the detection of pelvic fluid.

A threshold of at least 200 mL of fluid in the abdominal cavity is necessary for detection and intraabdominal injuries must be associated with the presence of this much free fluid for a positive finding. Reported sensitivities range between 73% and 88% and specificity between 98% and 100%. Accuracy rates range from 96% to 98%. FAST is an inexpensive, rapid, portable, noninvasive technique that can be performed in serial fashion, if there is a change in patient stability. Additionally, it obviates the risk of exposing pregnant females to radiation. Positive findings in stable patients can be further evaluated with CT, while unstable patients with a positive finding should prompt the surgeon to take the patient to the operating room for emergent exploration.

Computed Tomography

Steady advances in the technology and speed of CT have continued to be an integral part of the diagnostic management of trauma patients. Multidetector scanners have dramatically improved resolution and accuracy of these imaging studies. Negative predictive values as high as 99.5% have been reported for patients sustaining significant mechanisms of blunt trauma allowing the use of CT as a reliable and noninvasive screening tool for screening patients with blunt abdominal trauma. In light of modern day CT capabilities, prospective data have demonstrated that patients with a significant mechanism and a benign abdomen can be released from the emergency department if a CT scan of the abdomen shows no evidence of visceral injury provided that there are no other reasons for hospitalization.

CT reliably identifies injuries to solid organs such as the spleen, liver, and kidney because of the associated vascular nature demonstrating disruption of normal architecture, associated free fluid, and the so called vascular blush. Established grading scales continue to be used for accurate classification and determination of management plans (Tables 2 to 4).

Detection of bowel injury via CT scan in patients, who are intoxicated, intubated, or have associated closed head injury or other distracting injuries, can present a diagnostic challenge in absence of a reliable abdominal exam. The incidence of blunt bowel injury varies from series to series but is generally reported in the 1% to 5% range in all blunt trauma patients admitted to level I trauma centers. A high index of suspicion is predicated on mechanism of injury and physical exam findings, such as abdominal wall ecchymosis, tattooing, and/or seat belt sign. CT findings may be overt, such as extravasation of oral contrast or pneumoperitoneum, or more commonly, subtle findings such as bowel wall thickening, stranding of the mesentery, or free fluid in the absence of solid organ injury. Indirect findings may be fairly nonspecific and secondary to bowel edema from resuscitation or pre-existing ascites. In reproductive age females may have a small amount of normal or physiologic pelvic fluid present, sometimes adding to the complexity of the evaluation. Patients on positive pressure ventilation or with significant barotrauma may develop mediastinal or subcutaneous emphysema that can track through the peritoneum or retroperitoneum and give the appearance of free air. Great care in the radiologic interpretation and clinical correlation are necessary in such cases. The liberal use of diagnostic modalities (e.g., abdominal CT scan) in the hemodynamically normal injured patient may prevent nontherapeutic laparotomies. Obviously, when significant doubt remains, abdominal exploration may be required to confirm an injury.

The role of oral contrast in the evaluation of the acutely injured patient has recently come under question. Little time is usually available in the emergency setting to permit adequate opacification of the small bowel. Patients are further at risk for aspiration of the contrast media and administration often requires placement of a nasogastric tube. There have been several reports that have shown that elimination of oral contrast media does not lead to an increased incidence of missed bowel injury. Many centers have now safely eliminated the use of oral contrast media from their routine trauma protocols expediting management and ease of patient care. Resuscitation edema may cause a hazy appearance around the head of the pancreas and duodenal C loop causing the question of a pancreas or duodenal injury. Further clarification in this situation can be obtained when it occasionally occurs via repeat CT scan with the administration of oral contrast and/or injection of 300 to 500 mL bolus of air down the nasogastric tube in order to make pneumoperitoneum obvious.

Computed tomography may also be of great importance in identifying patients with arterial hemorrhage related to pelvic fracture. CT imaging may demonstrate an arterial blush or large hematoma in the vicinity of a pelvic fracture indicating the need for pelvic arteriography or pelvic external fixation. A CT cystogram may also be helpful and eliminate redundancy of radiographic evaluation. The Foley catheter is clamped after placement in the trauma bay. Real-time interpretation of the CT scan is performed by the evaluating physician, which may dictate further delayed images or a formal three view (anterior/posterior, lateral, and post void) stress cystogram.

TABLE 2 Spleen Injury Scale of the American Association for the Surgery of Trauma

Grade[a]	Injury	Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area; intraparenchymal, <5 cm in diameter
	Laceration	1–3 cm parenchymal depth that does not involve a trabecular vessel
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma Intraparenchymal hematoma >5 cm or expanding >3 cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascular ization (>25% of spleen)
V	Laceration Vascular	Completely shattered spleen Hilar vascular injury that devascularizes spleen

[a]Advance one grade for multiple injuries, up to grade III.

TABLE 3 Liver Injury Scale of the American Association for the Surgery of Trauma

Grade[a]	Injury	Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area; intraparenchymal, <10 cm in diameter
	Laceration	1–3 cm parenchymal depth, <10 cm in length
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma Intraparenchymal hematoma >10 cm or expanding >3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% of hepatic lobe or 1–3 Couinaud's segments within a single lobe
V	Laceration Vascular	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a single lobe Juxtahepatic venous injuries (retrohepatic vena cava/central major hepatic veins)
VI	Vascular	Hepatic avulsion

[a]Advance one grade for multiple injuries, up to grade III.

TABLE 4 Kidney Injury Scale of the American Association for the Surgery of Trauma

Grade[a]	Injury	Description
I	Contusion	Microscopic or gross hematuria, urologic studies normal
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding perirenal hematoma confined to renal retroperitoneum
	Laceration	Parenchymal depth of renal cortex (<1.0 cm) without urinary extravasation
III	Laceration	Parenchymal depth of renal cortex (>1.0 cm) without collecting system rupture or urinary extravasation
IV	Laceration Vascular	Parenchymal laceration extending through the renal cortex, medulla, and collecting system Main renal artery or vein injury with contained hemorrhage
V	Laceration Vascular	Completely shattered kidney Avulsion of renal hilum that devascularizes kidney

[a]Advance one grade for bilateral injuries up to grade III.
Modified from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma*. 1989;29:1664.

While computed tomography can be an important diagnostic modality in the assessment of the trauma patient, it is contraindicated in the hemodynamically unstable patient who is in shock.

SPECIFIC CONSIDERATIONS FOR BLUNT TRAUMA

Bowel

There is no place for nonoperative management of hollow viscus injury, and the success of nonoperative management of blunt abdominal trauma is, therefore, the missed bowel injury and all its catastrophic consequences. Otherwise, most management is straightforward; debridement and primary repair for nondestructive injuries and resection with primary repair versus ileostomy formation for destructive injuries.

Radiographic Findings of Blunt Bowel Injury

There are two basic types of findings of bowel injury on CT scan, direct and indirect. Direct findings are usually straightforward if present and consist of extravasation of oral contrast (if administered) and free air, which have been reported to occur in 8% and 28% of the time, respectively. Indirect findings include mesenteric hematoma or contrast blush, bowel wall edema, unexplained free fluid, fat stranding, and bowel loops, which do not opacify with intravenous contrast.

Mesenteric hematoma is nonspecific and can occur from associated injuries, such as pelvic fractures or renal injuries with hematomas from these structures expanding into the bowel mesentery. However, a vascular blush in the lumen of the mesentery is indicative of active hemorrhage until proven otherwise and, generally, a determinant for immediate operative exploration. Bowel wall edema and ascites are common in blunt trauma patients, can occur from resuscitation of other injuries, and do not necessarily connote bowel injury. Free fluid in the absence of solid organ injury can be further evaluated with

19%, if the abdominal cavity is unviable. Fat stranding can occur with mesenteric contusion and does not necessarily portend an operative indication. Unopacified bowel loops can indicate vascular disruption of the mesentery or simply be due to poor contrast timing to an under-resuscitated patient. Evidence of these findings increases the likelihood of finding an injury at exploration and increased when there was an increasing number of these findings.

Operative Management

Appreciation of the American Association for the Surgery of Trauma (AAST) organ injury grading scale is helpful in describing wounds of the bowel. Grade I injuries are contusions and partial thickness lacerations of the bowel wall without perforation. Grade II injuries are full thickness wounds involving less than 50% of the bowel wall circumference. Grade III are lacerations comprising greater than 50% of the bowel wall circumference without complete transection. Grades IV and V injuries represent complete transection of the bowel wall and transection with segmental tissue loss and/or devascularization of the mesentery, respectively. The terms destructive and nondestructive simplify the terminology; nondestructive wounds are those injuries that can be managed with debridement and primary suture enterorrhaphy and are comprised of grades I through III. Destructive wounds require resection of an entire segment of the bowel due to loss of bowel integrity or devascularization of the mesentery and encompass grades IV and V (tables 5 and 6).

The distinction between destructive and nondestructive wounds is important in terms of the prescribed management. Nondestructive wounds of the large or small bowel can generally be repaired without further consideration. Most small bowel destructive injuries should be resected and reconstituted unless damage control conditions prevail. In contrast to the small bowel, the management of colon injuries has received great scrutiny. Ushering in the dawn of modern-day trauma surgery, the World War II military experience dictated that all colon wounds, destructive or not, be managed by colostomy. This philosophy remained surgical dogma until the 1980s. In a comprehensive review of the literature since 1979, primary repair of the colon for nondestructive wounds was shown to have a leak rate of 1.6%. Compared to patients receiving colostomy for similar types of wounds, the incidence of intraabdominal abscess was 0% for primary repair and 12% for colostomy, and overall complication rate was 14% for primary repair and 30% for colostomy. Mortality rates were similar at 0.11% for primary repair and 0.14% for colostomy. These findings clearly show the superiority of primary repair for nondestructive wounds of the colon.

Several risk factors for anastomotic failure pertaining to destructive colon injury have been addressed in the literature: hypotension, shock, interval from injury to operation, amount of fecal contamination, associated organ injury, transfusion requirement, and comorbid disease. No data have conclusively shown that any of these risk factors increase the likelihood of anastomotic failure. Patients with massive blood loss or shock may be better served by undergoing a damage control procedure, with delay of definitive repair. Interval from injury to repair greater than 12 hours can be a relative contraindication to definitive repair; if there is widespread (more than one quadrant) fecal contamination. Greater than one or two organ system injury has been a concern, but this may just be a marker for degree of shock and overall physiologic derangement. Comorbidities, such as AIDS and cirrhosis, deserve special consideration, and these patients may be better off with the establishment of an ostomy diversion. Patients with any of these risk factors have a higher incidence of intraabdominal abscess and overall complication rates.

Notwithstanding the caveats of the previously mentioned comorbidities, colonic resection and primary anastomosis for destructive wounds would be permissible in most trauma settings. In a collective review of 207 patients reported in the literature, management of destructive bowel injury with resection and primary anastomosis had a reported leak rate of 7.2%, with a mortality of 1.7% attributable to

TABLE 5 American Association for the Surgery of Trauma Small Bowel Injury Scale

Grade*	Injury	Description
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration >50% of circumference without transection
IV	Laceration	Transection of the small bowel
V	Laceration Vascular	Transection of the small bowel with segmental tissue loss Devascularized segment

*Advance one grade for multiple injuries, up to grade III.

TABLE 6 American Association for the Surgery of Trauma Colon Injury Scale

Grade*	Injury	Description
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration >50% of circumference
IV	Laceration	Transection of the colon
V	Laceration	Transection of the colon with segmental tissue loss

*Advance one grade for multiple injuries, up to grade III.

the colon wound. In the largest single institution experience, Murray showed a leak rate of 11% in 112 patients undergoing resection and primary anastomosis for destructive colon wounds, with two deaths related to leaks. However, the ultimate decision for the choice of operation should be up to the discretion of the surgeon, at the time of operation, and on a case-by-case basis.

At laparotomy, the bowel should be examined in its entirety after all other sources of major bleeding are controlled. Small injuries should be noted and tagged with an identifiable suture for easy reference. Larger wounds contributing to ongoing soiling can be temporarily controlled with a whip stitch (quick running suture) or Babcock clamps. Mesenteric injuries are identified and active bleeding controlled appropriately. Attention should be directed to the location of the superior mesenteric artery for injuries approaching or in the root of the mesentery. Mesenteric hematomas should be explored with ligation of injured vessels and mesenteric defects closed by careful approximation of the peritoneal edges so as not to compromise any associated vasculature. Bowel viability should be noted in relation to any mesenteric injury. Clusters of grade I through III injuries may be resected or multifocally repaired depending on the particular injury pattern. In blunt trauma, there is usually only one or two grade II or III wounds that can be repaired primarily or one or more devitalized segments that require resection.

Small, superficial grade I injuries can be left alone, while deeper, longer grade I injuries can be closed with a simple running suture or interrupted Lembert sutures. Grade II and III wounds should be

debrided back to healthy, viable bowel and closed transversely preventing narrowing of the lumen of the bowel. Single layer running or interrupted closure is generally sufficient for repair of small bowel. When there is significant bowel wall edema, peritonitis or soiling, a two layer closure with a running inner layer and interrupted Lembert outer layer may be preferential. Grade I and II colon wounds may be managed with single layer closure. However, grade III colon wounds should be closed in two layers for added protection.

The leak rate associated with stapled versus handsewn anastomosis for destructive wounds of the bowel has been an area of ongoing controversy. In two retrospective studies totaling 284 patients undergoing stapled versus handsewn anastomosis, Brundage showed that handsewn procedures had lower leak rates. Two other retrospective studies totaling 484 patients showed no difference in the leak rate of stapled versus handsewn procedures. Brundage's two studies included 78 colon wounds, while the other studies were confined only to the small bowel. Stapled procedures may be a little quicker, particularly if there is more than one anastomosis. In general, the technique chosen according to the literature can be a matter of surgeon's preference. However, with edematous bowel, the handsewn technique is a more prudent approach.

Spleen

The spleen is the most commonly injured intraabdominal organ, followed by the liver and small bowel in blunt trauma patients. The spleen's location in the left upper quadrant lends susceptibility to injury from broken ribs, deceleration, and blunt percussion forces. Clinically, patients with splenic injury may present with hypotension, left upper quadrant pain or tenderness to palpation or diffuse peritonitis from extravasated blood. Referred pain to the left shoulder on deep inspiration, in face of splenic hematoma, is known as Kehr's sign.

Nonoperative Management

Most series indicate that approximately 60% to 80% of patients presenting with blunt splenic injury can be managed nonoperatively at level I or II trauma centers. Facilities without the resources and experience of a busy life trauma team may not easily meet the demands of nonoperative management and should consider patient transfer. Patients selected for nonoperative management must have normal vital signs, be free of peritoneal signs or other concern for hollow viscus injury and have no evidence of free extravasation of intravenous contrast from the splenic parenchyma (Fig. 2).

Considerable debate remains regarding risk factors for failure of nonoperative management. Higher AAST splenic injury grade, age greater than 55 years, evidence of large hemoperitoneum, subcapsular hematoma, and portal hypertension have all been suggested to increase the risk of failure. Early reports on the evolution of nonoperative management regarding AAST grade did not demonstrate higher failure rates for higher grade injury. More recent reports using high resolution multidetector CT scanners allow better assessment of injury grade. The data from these studies show that patients with injury grades III to V to be at increased risk for nonoperative failure. Age continues to be controversial subject matter in the literature, with numerous reports claiming that age greater than 55 years is or is not a risk factor for failure. Documentation of a moderate or large hemoperitoneum is suggestive of a major injury and should be considered a significant factor in individual patient assessment.

Patients with splenic subcapsular hematoma or history of portal hypertension are specific subgroups of patients that deserve special consideration. These patients are at increased risk for delayed rupture 4 to 8 days following injury and may already be discharged from the hospital if they have isolated injury. Furthermore, splenic embolization is not a very effective treatment of this condition because it usually necessitates coiling of the main splenic artery, which can lead to significant pain and abscess formation. History of portal hypertension or cirrhosis, while not an absolute contraindication to nonoperative management, certainly should serve as a caveat. The general risks of laparotomy in a Child Pugh B or C cirrhotic need to be carefully weighed against the risk of ensuing and worsening coagulopathy. This scenario may indeed dictate the need for splenic artery embolization. None of these risk factors alone should dictate the decision to proceed immediately to operative intervention. Non operative management does reduce hospital length of stay and transfusion requirement, however, the morbidity of splenectomy should remain low in any surgeon's hands. Overall, the patient's condition, including comorbidities, coagulopathy, and other problems (such as traumatic brain injury, aortic injury and suspicion for concomitant hollow viscus injury) factor into the decision making process. No one should ever succumb to splenic hemorrhage that was undergoing nonoperative management.

Approximately 20% of patients initially undergoing nonoperative management of blunt splenic injury require further intervention. Failure has been associated with the presence of a contrast blush in up to two thirds of these patients. The presence of a contained contrast blush within the parenchyma of the spleen represents pseudoaneurysm formation of a branch of the splenic artery. Angioembolization is now commonly used to selectively occlude the arterial branches containing these injuries. Implementation of this salvage technique at centers that routinely screen for the presence of pseudoaneurysm has increased the success of nonoperative management to 95% or greater. Pseudoaneurysm formation has been observed in even grade I and II injuries and may not be present on the initial imaging. Therefore, a follow up CT scan is recommended on all patients with splenic trauma within 24 to 48 hours after injury. If these images show stable injuries, without pseudoaneurysm formation, expectant management can continue.

Long term data are unavailable concerning the risk of outpatient or delayed rupture, but the incidence is low and has been reported to be about 1.4%. The average date to readmission for delayed splenectomy after discharge was 8 days in this study. Lower grade (I, II) injuries tend to heal quicker, and most all injuries are healed by 5 to 6 weeks. However, approximately 20% of blunt splenic injuries will not show complete healing and may be at risk for pseudocyst formation. A CT scan should be repeated in 4 weeks for grade I and II injuries and 10 to 12 weeks in grades III to V before allowing patients to return to normal activity.

Splenectomy

Patients requiring urgent or emergent intervention for splenic hemorrhage may develop hypothermia, coagulopathy, and visceral edema. The most expeditious and safest course of action under these conditions is removal of the spleen. The general assumption of abdominal exploration for trauma is that there are known and, possibly, unknown injuries. The operative approach to via a midline vertical incision that allows the best exposure and facilitates temporary abdominal closure should visceral edema or damage control measures be necessary.

With respect to performing a splenectomy, an UMBNF retractor can be used to expose the left upper quadrant. The spleen is retracted medially, with some downward compression, while taking down the posterior attachments with the cautery. Once these attachments are freed, the spleen can be mobilized medially for optimal exposure. The assistant stands on the left side of the table and supports the spleen while the surgeon ligates short gastric and hilar vessels. Being careful to avoid the tail of the pancreas, a large clip placed on the specimen side of the splenic hilum, will reduce backbleeding and expedite the procedure. Once the spleen has been removed, the splenic fossa is meticulously inspected for further bleeding with a rolled laparotomy pad.

Splenorrhaphy

Hemodynamically stable patients found to have small to moderate amounts of parenchymal hemorrhage, or lacerations, may be

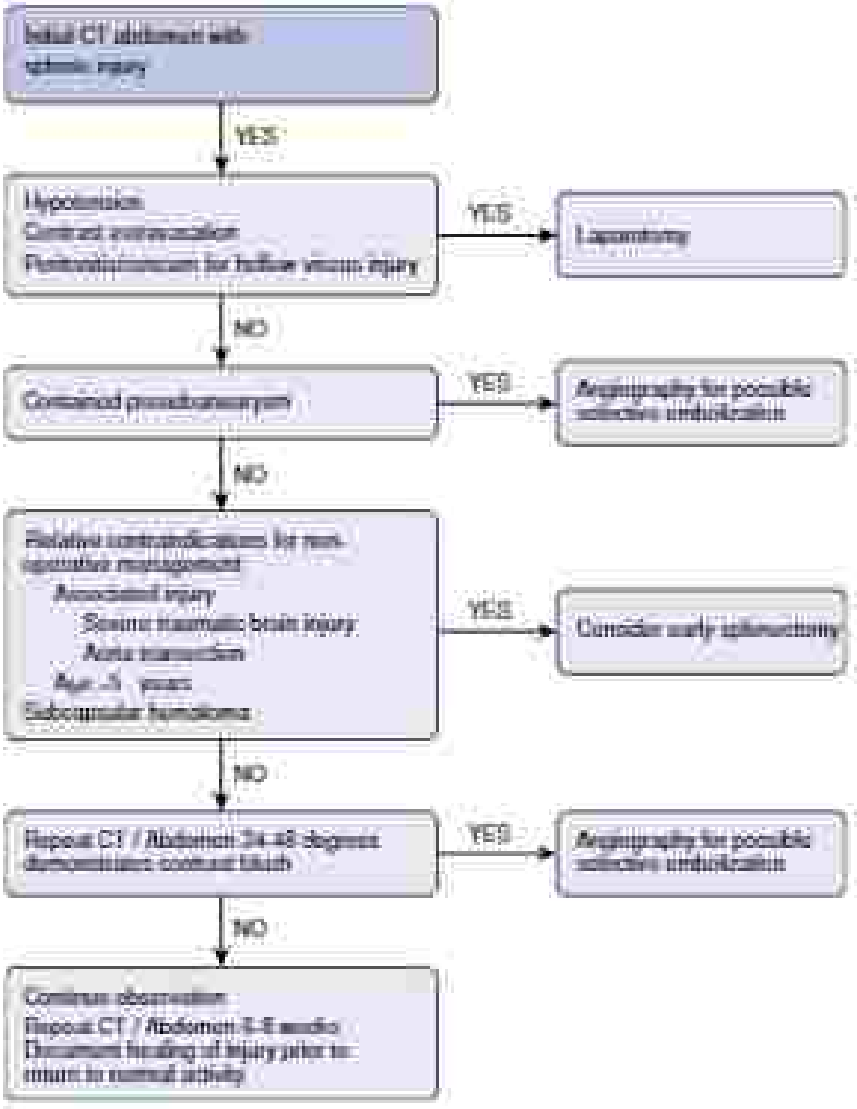

FIG. 2. Management of blunt splenic injury CT, Computed tomography.

candidates for splenic preservation. The spleen is mobilized into the wound using the same technique as for splenectomy. The injury to the spleen is assessed and a decision is made whether to resect a portion if the parenchymal injury extends into the hilum or if arterial bleeding is coming from within the splenic laceration itself. If the decision is made to resect the upper or lower pole, the pancreatic tail is divided with the cautery and the associated hilar vessels are taken with clamps and ties. Any arterial bleeding from the parenchyma is controlled with suture ligature and the cautery is used to control oozing from the parenchyma. A tongue of omentum is then sutured into the laceration or to the raw surface of the remaining spleen in the case of a partial splenic resection. Approximately 50% of the spleen is required to preserve adequate phagocytic and immunologic function. If this cannot be achieved, a splenectomy is probably the best option.

Overwhelming Postsplenectomy Infection

The incidence of overwhelming postsplenectomy infection (OPSI) following trauma is not well understood because it may not be appreciated when it occurs, along with the fact that it is not routinely reported. However, the reported incidence of OPSI in adult patients undergoing splenectomy for all causes is 0.9% with a mortality of 0.8%. The risk of OPSI in adults following trauma is felt to be lower than the incidence seen after splenectomy for hematologic disorders such as idiopathic thrombocytopenic purpura, lymphoma, and thalassemia. Children are at greater risk for OPSI and should receive prophylactic penicillin V 125 mg twice daily until age three and then 250 mg twice daily until age five. Currently, anyone greater than 2 years of age should receive the 23 valent pneumococcal vaccine and a one time dose of the *Haemophilus influenzae* and meningococcal vaccine. A one time booster dose of the pneumococcal vaccine is recommended 5 years after the original vaccine.

Hepatobiliary System

Blunt trauma contributes over 75% of mechanisms of injuries for most of the trauma centers in the United States. The liver, the largest solid organ in the body, is one of the most frequently injured abdominal organs by either blunt or penetrating mechanisms. Fortunately, the majority of hepatic injuries are low grade injuries and require no surgical repair (Table 7). Suspicion of liver injury is predicated on several factors including clinical suspicion derived from the mechanics of the crash, hemodynamic state of the patient, and findings obtained during abdominal examination (Fig. 3). High energy

TABLE 7 American Association for the Surgery of Trauma Liver Injury Scale (1994 Revision)

Grade	Injury	Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area Intraparenchymal <10 cm in diameter
	Laceration	Capsular tear, 1–3 parenchymal depth, <10 cm in length
III	Hematoma	Subcapsular, >50% surface area or ruptured subcapsular or parenchymal hematoma Intraparenchymal hematoma >10 cm or expanding
	Laceration	>3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% hepatic lobe or 1–3 Couinaud segments
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe
	Vascular	Juxtahepatic venous injuries, i.e., retrohepatic vena cava/central major hepatic veins
VI	Vascular	Hepatic avulsion

crashes involving application of force to the upper abdomen or to the right thoracoabdominal area should arouse immediate suspicion of a possible hepatic injury. Hemodynamic lability, although not an exclusive feature of liver injury, mandates evaluation to exclude it as the source of the hemorrhage. Tenderness to the right upper quadrant, in the absence of other signs, can be supportive of subcapsular hematoma requiring attention and further evaluation. Unfortunately, the physical examination is not perfect and has a false-positive rate of approximately 50% and a false-negative rate of 40%.

The additional methods available to evaluate the abdomen include FAST, CT, and DPL. FAST has become a highly reliable test used when seeking to determine whether there is blood in the abdomen in a patient who is hemodynamically labile. In the stable patient in whom liver injury is suspected, the use of CT has become widespread. Several classification schemes have been described for liver injuries, but the grading scheme proposed by the AAST is now in wide use (see Table 7).

Approach to the Injured Liver

With hepatic injuries, the paramount decision is to determine if and what intervention is needed to control hemorrhage. Hemodynamic instability mandates expeditious operative management or angiographic embolization (if the patient can be stabilized with volume resuscitation in order to make transportation to the radiographic suite less risky for the patient). The hemodynamically stable patient may be evaluated by any of the methods noted earlier. Minor grade I or II injuries frequently require no operative intervention. When diagnosed by CT scan, the surgeon must be cognizant of the magnitude and anatomy of the liver injury. Contusion contained within the liver capsule or minor lacerations, such as in grade I or II injuries, may be observed. These diagnoses together constitute most liver injury cases, accounting for ≈80% or 70%. Grade III injuries (deeper, larger wounds with more tissue destruction) occur in approximately 25% of cases. Grade IV and V injuries, involving large amounts of tissue destruction, have an incidence of 7% and 3%, respectively, and are highly lethal. It should be emphasized that evidence of blood in the peritoneal paracolic gutters, in the pelvis, or tracking along the preportal tissues is suggestive of a more significant injury than the liver anatomy may indicate and mandates exploration. Also, the concomitant existence of hollow viscus injury occurs in 5% to 15% of major hepatic injuries.

In addition, it is important to realize that massive parenchymal injuries can occur with surprisingly little bleeding and that minor lacerations may bleed profusely. An understanding of the tissue architecture of the liver is a prerequisite to successful management. Most blunt lacerations may occur along segmental fissures, as the vascular and biliary duct structures are moderately tissue resistant. This explains why a large midline or "four claw" laceration may be seen, with little or no intraperitoneal blood in a hemodynamically stable patient. This can be managed nonoperatively with observation and repeated CT scan. Nonoperative treatment of the stable patient sustaining a blunt liver injury is the management approach of choice today. Table 8 highlights the reported failure rates for nonoperative management of hepatic trauma.

Commonly, deceleration forces are responsible for a shear effect that can result in avulsion of the hepatic veins from the vena cava or major branches of the portal venous or hepatic venous systems. Hemorrhage is devastating, difficult to control, and responsible for the high mortality rate seen with such injuries.

Intraoperative Decisions: General Principles

Once the decision to operate has been made, the surgeon needs to proceed in an orderly fashion in a fully equipped operative theater with invasive monitoring capabilities. Before opening the abdomen, the surgeon must ensure that there is optimal venous access. Large bore central access is essential. The prudent, historical dictum is that access should be from the upper torso in the event there is a retrohepatic caval injury. The blood bank must be notified of the potential for massive transfusion of packed cells and blood components to treat the often associated coagulopathy. The development of blood salvage systems has greatly improved the care of these patients; shed blood from the operative field can be washed and reinfused, provided there is no evidence of gastrointestinal contamination. Infusion systems are available that allow rapid delivery of large volumes of warmed fluid to help minimize hypothermia and hypovolemia. Hypothermia is a common cause of coagulopathy and must be aggressively defended against. Invasive monitoring capabilities are essential in the management of these critically injured patients.

Optimal surgical exposure is essential and starts with performing a midline vertical incision for expedient entry into the abdominal cavity. The incision should extend from the xiphoid process to the symphysis pubis. Such an approach allows, if necessary, relatively easy extension into the thorax through either a median sternotomy or a lateral thoracotomy.

Performing a cholecystectomy could potentially decompress the gallbladder, thereby necessitating expeditious vascular control. The need to perform an emergency thoracotomy for vascular control of the aorta before opening the abdomen is rarely indicated. Such control of the bleeding can usually be obtained with the assistant's manual compression of the liver.

Once the abdomen is open, a rapid assessment of the injury is made and priority management begun. All clots are evacuated, and the four quadrants are packed to control bleeding. A sequential examination is then carried out with priority given to control of blood loss followed by control of any enteric content spillage.

The general approach to the liver injury requires adequate visualization of the anatomic features of the injury. This may require mobilization of the liver along the falciform and triangular ligaments. Full mobilization of the liver allows delivery into the abdominal wall that can often facilitate suture repair of a hepatic wound in a difficult area. While mobilizing the liver, care must be taken that the hepatic veins are

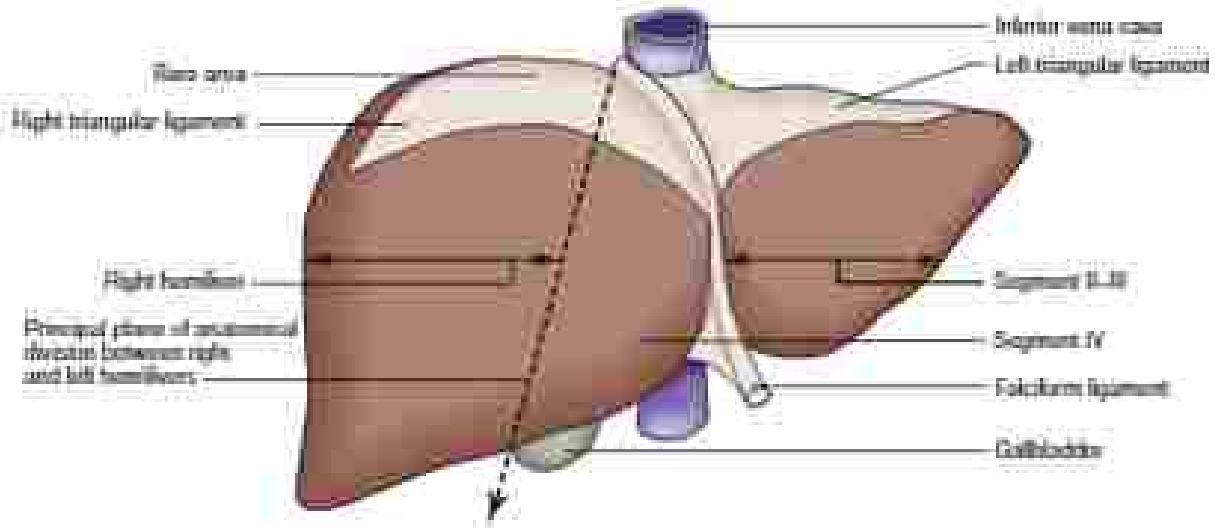

FIG. 8 Juxtahepatic (or retrohepatic) vena cava is in direct contact with the posterior aspect of the liver. (From Cantlie JJ, Parks AW: Historical and Practical Surgery [...]. Bristol, Bradshaw, 1898.)

TABLE 8 Failure Rates for Nonoperative Management of Liver Trauma

Study (year)	No. of Patients	Immediate Surgery (%)	Overall Failure Rate (%)	Liver Failure Rate (%)	Other Failure Rate* (%)
Meredith (1994)	116	8	3	3	0
Cmiel (1995)	156	18	11	5	6
Pachter (1996)	804	53	12	11.5	0.5
Malhotra (2000)	661	15	7	3	4
Velmahos (2003)	78	28†	15	9	15
Christmas (2005)	361	32‡	1.8	0.8	1.4

*Other failure refers to failure due to injuries from other intraabdominal organs such as the spleen, kidney, pancreas, or bowel.
†53% for liver bleeding.
‡13% for liver bleeding.

and injured. The coronary ligaments are in close proximity to hepatic veins. Also, the surgeon must be cautious during the mobilization of the liver that venous return through the vena cava is not obstructed for a prolonged period. Hemorrhage control during mobilization can often be done by the assistant applying direct pressure with laparotomy packs, compressing the liver between the hands.

As noted previously, most of the injuries encountered are grade I or II and require little more than simple suture repair. Grade III, IV, and V injuries require an organized approach for successful control of hemorrhage, which includes manual compression, direct ligation, or clipping of lacerated vessels, along with sophisticated techniques for more complex wounds.

Vascular occlusion of the portal triad (performing the Pringle maneuver) is a useful method of controlling hepatic arterial and portal venous inflow to the liver. A noncrushing or vascular clamp can be applied to the porta hepatis and safely left in place for approximately 45 minutes, although the specific duration threshold is not known for the hemodynamically labile patient. Also, an umbilical tape placed around the porta hepatis structures can be used for such control. If this maneuver markedly reduces the liver's bleeding, the parenchymal injury can be assessed and a method of repair decided on. However, if hemorrhage persists, then an intrahepatic portal vein injury or a major hepatic vein injury must be suspected.

Proceeding with laparotomy for localization and control of hemorrhage requires facilitous cooperation between the surgeon and the first assistant. With the depth of the hepatic wound exposed, it is usually the first assistant who controls the bleeding. The finger fracture technique for hepatectomy, with the first assistant compressing the liver, is very effective. The operating surgeon using the fingertips or the handle of a scalpel to separate the liver parenchyma and the assistant using a multiple loaded clip applier, made popular for laparoscopic cholecystectomy, ligate severed vessels. Nonabsorbable suture ligation can also be performed to control vessels as each is encountered. Knowledge of the anatomy of the liver (along with reported anatomic variants) is a prerequisite to this approach. The confluence of the left and middle hepatic veins must be kept in mind to avoid unrecognized ligation (Fig. 6). Likewise, the position of the inferior vena cava and the hepatic veins in the caudate lobe should be noted to avoid unnecessary injury that may complicate the surgical exposure. The placement of random deep sutures is fraught with difficulty. Failure of the above mentioned maneuvers to control hepatic bleeding means that the surgeon either has not adequately identified the source or is dealing with coagulopathic bleeding (or both).

Although specific ligation of the hepatic artery or portal vein branch supplying a specific portion of the liver is rarely needed, the suspected branch should be isolated, and its occlusion should control hemorrhage while the Pringle maneuver is released. If such is the case, then the identified branch should be ligated.

Being able to perform a resection of a needle wound should be in a surgeon's armamentarium when dealing with penetrating hepatic

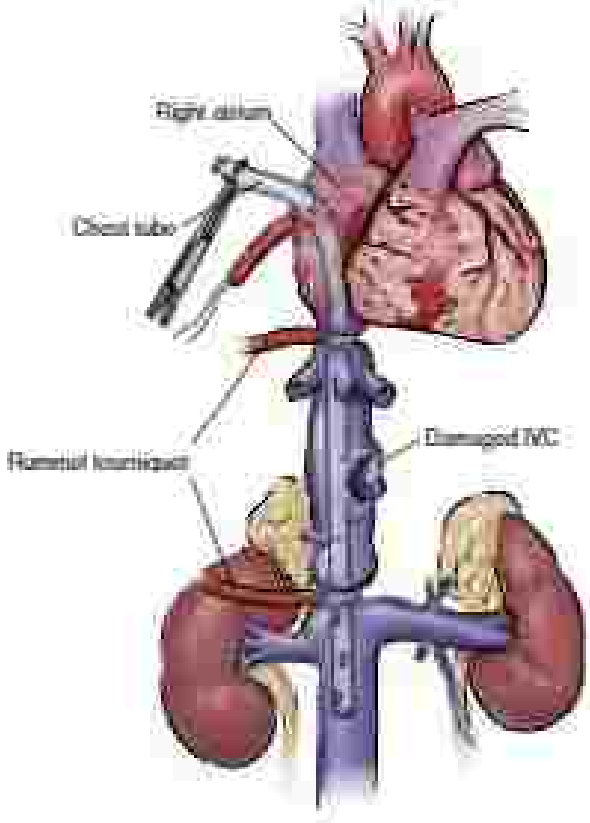

FIG. 4. After obtaining the necessary exposure (thoracotomy, median sternotomy), an opening, along with 2-0 Prolene purse-string sutures, is created in the right atrial appendage to provide the access needed for insertion of the atriocaval shunt, which is usually a No. 36 chest tube. An extra hole needs to be made at the level of the right atrium. With the chest tube holes being outside of umbilical tape occluders, blood is directed from the lower half of the body and the kidney through the atriocaval shunt. IVC, inferior vena cava. (From Richardson J., Kerwin AM, Rich's Vascular Trauma, 2nd ed. Philadelphia: Saunders; 2010.)

injury. In addition, a variety of methods designed for tamponade of the bleeding outside tract have been described, using various materials. Shuett, et al. described a tamponade device with multiple Penrose drains dragged through the liver tract. However, it is more preferable to open the liver and suture or clip control the bleeding site directly, if possible.

Liver injury, infrequently, follows the anatomic lines of demarcation delineating the right and left lobes, much less the segments. Anatomic resection, a once popular approach, is associated with high mortality rates. This technique has been, essentially, abandoned. Resectional debridement of devitalized liver is not formal lobectomy but rather a completion of the injury to remove unviable hepatic tissue and to facilitate vascular control. This usually entails a degree of larger fracture through uninjured liver, which allows visualization of the bleeding raw surface and more direct control. Application of specific liver clamps, such as the Lin clamp, designed to aid in lobectomy, is difficult because of positioning of the injury laceration and maneuvering around the clamp.

Once the bleeding has been controlled, the large, raw surface of the liver can be problematic, as persistent oozing of bile or blood continues. A viable omental patch sutured to the liver bed is an excellent hemostatic agent and internal drain. Stone and Lundy popularized the omental pack in their initial report. Pachter and Stone reported 90% successful hemostatic control with this procedure. For large, raw liver surfaces resulting from debridement or trachotomy, the omental patch held in place with several liver sutures is an excellent hemostatic agent. Also, utilization of the argon beam coagulator is another option in addressing bleeding of raw liver surfaces. The argon gas removes the blood from the hepatic tissue and ionizing energy is transmitted. A maximum of 110°C is achieved and an eschar is formed.

An alternative to surgical repair of the injured liver is a small wedge inserted to provide compression, to control bleeding, and to close parenchymal defects. Delaney et al. reported success in six liver injuries controlled in this manner. Stuart et al. reported 35 liver injuries wrapped for control. Sequential CT examination of the patients demonstrated progressive restoration of normal liver architecture.

The premise underlying much of the preceding discussion is that liver bleeding can be controlled. However, even when advanced techniques of liver control are used, hemorrhage control can be precarious, at best. A critical error that can be made when dealing with major liver injury is to continue operative intervention in the face of a hypothermic (less than 32°C), acidotic patient who has developed coagulopathy. Although the specific time to make a decision to pack the liver and initiate normothermia and coagulation factors is not always clear, the operating surgeon should always have a low threshold for temporary packing and prepare the patient to be expeditiously transferred to the intensive care unit for aggressive resuscitation and monitoring. Once a patient has required a 10 U transfusion, packing should be seriously considered. Patients with severe injuries, hypothermia, refractory hypotension, coagulopathy, and acidosis need early packing. It needs to be emphasized that large wound bleeding must be controlled before packing can be effective.

Perihepatic packing was popularized during World War II. The high incidence of complications, plus the advent of more sophisticated techniques for control of liver bleeding, led to the demise of packing until its revival in the 1970s. The major indications for perihepatic packing being persistent coagulopathy that developed as an extensive subcapsular hematoma or capsular avulsion. It is also a valuable adjunct to resectional debridement and tracheotomy. The use of a folded, disposable plastic drape is helpful. It is placed against the liver and the packs placed on it, preventing the laparotomy pads from adhering to the liver and possibly minimizing the recurrent bleeding upon removal of the packs. Gauze packs are then placed to compress the liver. The packs should be placed at both the superior and inferior surfaces of the liver. The packing should be tight enough to control the bleeding but not so tight that it unnecessarily compresses the renal vessels and possibly the inferior vena cava, resulting in intraabdominal hypertension. Patients who have undergone packing will require continued sedation with mechanical ventilation until pack removal because of the interference of optimal diaphragmatic excursion. Abdominal wall closure is rapid and is performed by towel clips or by running nylon suture in the skin. Utilization of silo like closures with sterile towels and plastic drapes should be used to minimize fluid loss and to maintain abdominal pressure. In addition, there should always be a high index of suspicion for the development of intraabdominal compartment syndrome.

Pack removal can be planned when the patient has required no vasopressors and coagulation parameters have been normalized. This usually occurs within 24 to 72 hours. Packs are then removed during a second operation, and the surgical team again must be prepared to manage bleeding. Repacking at the second operation might be indicated. The complication rate of packing is appreciable. There is an increased incidence of sepsis in a group of patients subjected to liver packing. An additional benefit of liver packing is that it may allow transport of a critically ill patient from one center to a definitive treatment center where the liver injury can be treated.

Juxtahepatic Venous Injuries

The lethality of juxtahepatic venous injuries to blunt hepatic trauma and the management challenges of definitively addressing such injuries have been well chronicled. Fortunately, such liver wounds are

seen infrequently. However, the downside is that very few acute care surgeons are familiar with and comfortable operating in this specific setting. Depending on the specific series, the mortality ranges from 50% to 80%, with massive hemorrhage being the overwhelming cause of death.

The deadly nature of this injury is a result of the difficulty in expeditiously getting access to the injury site. The retrohepatic vena cava and major hepatic veins are within the depth of the least midlife area of the liver—making exposure and direct control of bleeding very challenging. Attempting to rotate the liver in an effort to access the injury can actually extend the wound and cause increased bleeding. Also, such a misguided effort could result in a fatal air embolus.

Detailed knowledge of the pertinent anatomy is imperative for any surgeon attempting an operative management strategy. The juxtahepatic vena cava, which is within the "bare area" of the liver, extends for approximately 2 cm and is bordered by the phrenic veins and right adrenal vein—cephalad and caudad, respectively. Approximately 3 cm above the most superior aspect of the retrohepatic vena cava, the inferior vena cava enters the right atrium. The retrohepatic cava is an extrapericardial/intrapericardial structure. The three major hepatic veins, along with its tributaries, enter directly into the anterior aspect of the retrohepatic vena cava. This anatomy is relatively constant, with major anomalies being uncommon. While the course of the extrapericardial hepatic veins is short, the intrapericardial veins have a long course. Substantial blunt trauma can lacerate/avulse either or both.

Probably because of its highly lethal nature, juxtahepatic venous injuries are infrequently managed. Surrounding structures can provide a tamponade effect and contain juxtahepatic venous hemorrhage. Such structures include the liver, the diaphragm, and the suspensory ligaments of the liver. Adequate containment of hemorrhage by these structures might allow an attempt at expectant or minioperative management. However, if these supporting structures are disrupted, substantial bleeding will ensue. As a consequence, overly aggressive or injudicious hepatic mobilization can result in uncontrollable hemorrhage.

Juxtahepatic injuries, which can be caused by blunt or penetrating injuries, are often classified as type A or B, with the former being hepatic venous wounds that are intrapericardial and the latter being extrapericardial venous wounds. Both type A and B injuries can occur together. In addition, there can be associated injuries to the portal vein and its tributaries, which occur more frequently with type A wounds. Fortunately, the extrapericardial hepatic venous or the associated retrohepatic caval injuries are infrequent. Penetrating wounds to this anatomic region or the sheer forces from blunt injury are the predominant mechanisms of injury. Irrespective of the reported series on the management of juxtahepatic venous injuries, the mortality rates are overwhelmingly high.

There are, basically, three operative approaches in the management of juxtahepatic venous injuries: (1) direct repair of the venous wound(s), (2) surgical resection, and (3) pressure application (containment/tamponade measures) with reinforcement of the natural containment structures that have been disrupted. While there have been several reports of the specific strategy and efficacy of operative exposure and direct repair of juxtahepatic venous injuries, the success is sporadic and overall outcomes dismal. In 1966, Feldman was credited with reporting the first successful application of direct suture repair of a juxtahepatic venous injury. Schrock reintroduced, in 1968, the concept of vascular isolation with the utilization of an atriocaval shunt (see Fig. 4). However, the majority of surgeons have abandoned atriocaval shunting because of the challenges related to the technique and the overall dismal outcomes. The paramount or overarching principle in establishing vascular isolation is obtaining proximal and distal control of all vessels to totally isolate the liver. Heaney maneuver advocates a more expedient approach to achieve vascular isolation (Fig. 5) to surgically address juxtahepatic venous injuries and other complex liver wounds. At all times, it is imperative that the patient is optimally resuscitated and closely monitored. Another alternative, with respect to achieving vascular isolation in an effort to access retrohepatic wounds, is the establishment of a venovenous bypass (Fig. 6). This approach necessitates cannulation of the femoral vein and the axillary vein in the upper arm. The cannulas are connected by a heparin-coated tubing, with a flow assisted by a centrifugal pump. Both supra- and infrahepatic clamps are required for the venovenous bypass. Along with incompetence in the

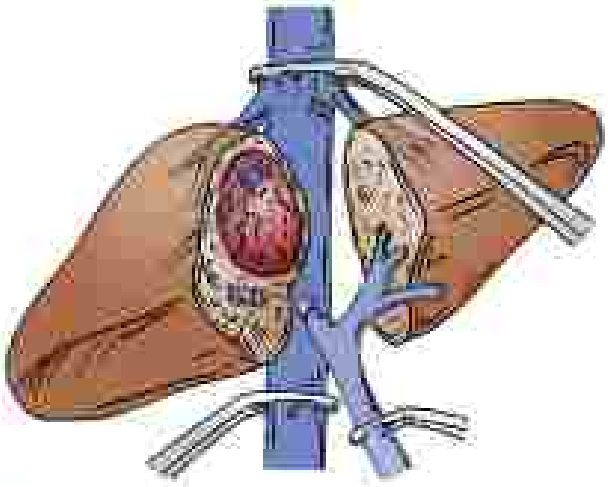

FIG. 5 The Heaney maneuver. Vascular isolation of the injured liver by applying vascular clamps to the suprahepatic and infrahepatic inferior vena cava, in addition to a Pringle maneuver. (From Blaisdell's Surgery of the Liver, Biliary Tract, and Pancreas, 4th ed. Philadelphia: Elsevier; 2007.)

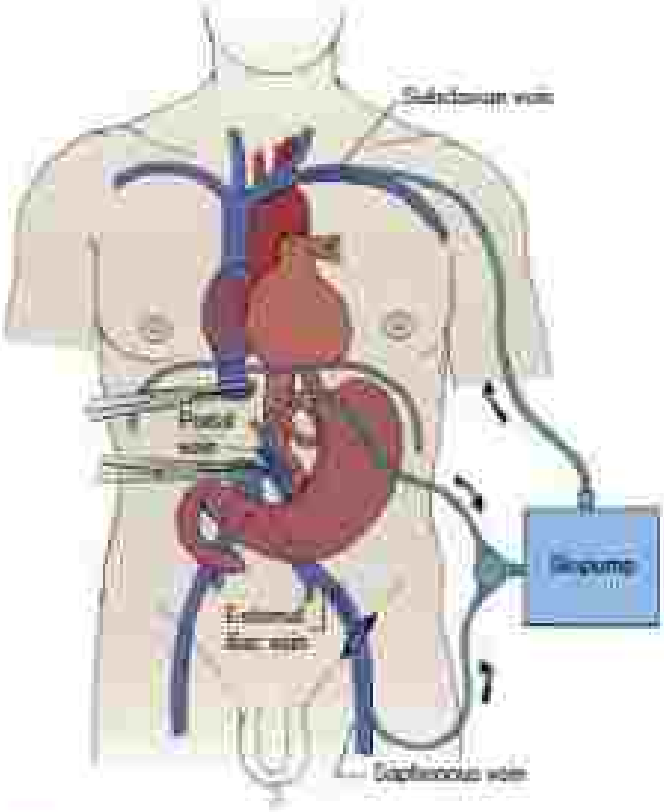

FIG. 6 The venovenous bypass requires cannulation of both the femoral vein and the axillary vein. A heparin-coated tubing connects the two cannulas. Flow is assisted by a centrifugal pump. (From Underhill G et al. Critical Care Nursing. 8th ed. Philadelphia: Elsevier; 2010.)

above techniques, major blood loss with associated coagulopathy precludes successful utilization of any of the shunting interventions. Operative hepatic resection, in an effort to access these retrohepatic wounds, is associated with a high mortality rate and should not be attempted.

Because of the inherent and overwhelming risks of surgical management of these complex injuries, tamponade with containment followed by angiography and possible embolization has become a stable option (when possible) in the management of juxtahepatic venous injuries. Such an approach often requires temporarily leaving the abdomen open. Although omentum has been proposed to create the tamponade effect, gauze packing is more expedient and effective. Pachter et al. described a "nonshunting approach," which consists of four components: (1) manual compression and aggressive fluid resuscitation; (2) prolonged portal triad occlusion (mean occlusion time, 91 min); (3) rapid and extensive finger fracture for vascular control, almost always through normal hepatic parenchyma to the site of injury; and (4) wide mobilization of the hepatic attachments with medial rotation of the liver to provide access to both the retrohepatic cava and the hepatic vein. In their series, six of the nine "nonshunted" patients survived.

Porta Hepatis

Injuries to the porta hepatis are rare, usually complex, and highly lethal. Review of the recent literature showed three large series that cumulatively report 180 patients treated between 1965 and 1994. These injuries are usually penetrating, occurring in 50% to 100% of the populations reported. Isolated injuries to the portal structures occur and are far more survivable than are multiple injuries. Overwhelming hemorrhage is the usual cause of death in all reported series.

The porta hepatis is composed of the hepatic artery, extrahepatic bile duct system, and the portal vein. The proximity of these structures to other major structures, and their relatively difficult exposure, explains their high lethality. In the multiinstitutional survey compiled by the Western Trauma Association and reported by Jurkovich et al., an overall 51% mortality rate was recorded. When broken down, the mortality rate in single structure injuries is still 45%, whereas the mortality rate in multiple structure injuries rises to 80%. This is in line with results in other reports in the literature.

Portal Vein

Injuries to the portal vein are responsible for most deaths ascribed to trauma to the portal structures. Once identified and the bleeding controlled, the question of repair versus ligation must be addressed. Ligation of the portal vein can be tolerated, in that there will be decompression of the portal hypertension by collateral vessels. Unfortunately, in patients subjected to ligation of the portal vein, the mortality rate is as high as 90%. This is in disagreement with survival rates of 50% to 80% reported previously by Pachter et al. and Jamie et al. Patients treated by ligation of the portal vein have greater circumferential disruption of the vein and overwhelming hemorrhage, and ligation is used as a rapid method of bleeding control. Repair of the portal vein is used with lesser degrees of injury—in circumferential injury less than 25%—and is reported to have increased survivability. Many of the deaths occur because of massive hemorrhage before a repair can be accomplished. When confronted with a portal venous injury, repair is preferable to ligation, although ligation is an acceptable option. Second look laparotomy to check for bowel viability has been advocated when the portal vein has been ligated.

Hepatic Artery

The liver receives a dual blood supply from the hepatic artery and the portal vein, allowing ligation of the hepatic artery without absolutely compromising hepatic blood supply. Lobar artery ligation is well tolerated, but overall mortality rate remains in excess of 40%.

Extrahepatic Biliary Ducts

Bile duct injuries are uncommon, even in this relatively uncommon injury cluster. Partial circumferential disruption can be treated by primary repair as well as demonstrated from the experience with iatrogenic bile duct injury at the time of cholecystectomy. Complete or complete disruption of the ductal tree is best managed by biliary enteric anastomosis tied to end anastomosis has an excessive stenosis rate. Adequate drainage of the area is essential, as bile leaks can occur. On rare occasions, stenting and external drainage have been used in an unstable patient, with biliary reconstruction accomplished at a later date.

The key to the diagnosis of bile duct injury is suspicion that the injury has occurred. Evidence of bile staining and the presence of a duodenal injury should prompt investigation that is best done by an intraoperative cholangiogram. Small injuries may be missed at initial exploration. Endoscopic retrograde cholangiopancreatogram with stenting may provide a diagnostic therapeutic answer if a patient develops a fistula subsequent to a missed injury.

Resuscitative Endovascular Balloon Occlusion of the Aorta

Bleeding remains the leading cause of preventable death in trauma patients who reach the hospital. Both penetrating and blunt trauma can lead to life-threatening injury of the abdominal vasculature. Traumatic injury to vessels may occur via direct laceration and transection or blunt injury resulting in dissection or thrombosis. While endovascular treatment of abdominal vascular injuries has become increasingly utilized, the unstable patient with active hemorrhage will still require open surgical intervention. Appropriate management of these patients centers on prompt recognition of the injury, rapid exposure, and control of hemorrhage. Despite advances in technology, mortality from abdominal vascular injury remains high and survival of these patients hinges on rapid exposure and control of the hemorrhage. Resuscitative endovascular balloon occlusion of the aorta, also known as REBOA, is gaining popularity as an adjunct for controlling major intraabdominal hemorrhage. The technique was first described in 1953 during the Korean War by Dr Lt Colonel Hughes on three soldiers in hemorrhagic shock. He surgeon placed a Foley through the femoral artery to provide proximal vascular control. Although some of the three patients survived, Lt Colonel Hughes noted temporary improvement with inflation of the balloon. However, the procedure was not widely adopted during this time, likely due to concerns regarding the technical difficulty of the procedure and availability of the equipment needed. It was not until 2006, when Ozenberg and colleagues first described the use of an aortic balloon occlusion device to control hemorrhage prior to endovascular repair for ruptured abdominal aortic aneurysms in three patients. As the use of REBOA has continued to increase in the field of vascular surgery, it has also recently gained momentum as an effective method of obtaining proximal control in the setting of life-threatening abdominal or pelvic trauma.

The goal of REBOA is to provide proximal control of abdominal vascular hemorrhage prior to transport to the operating room or angiography suite (Fig. 74). After the groin has been prepped, the common femoral artery is accessed with a standard hollow 18 gauge vascular access needle. It is important that incorrect placement, either too proximally into the iliac artery or too distally into the superficial femoral artery, be avoided. As many of these patients may not have a readily palpable femoral pulse, the artery can be accessed using standard anatomic landmarks, ultrasound guidance, or via direct exposure through an open cutdown. Once the artery is accessed, a 0.035-inch wire is fed through the needle in standard

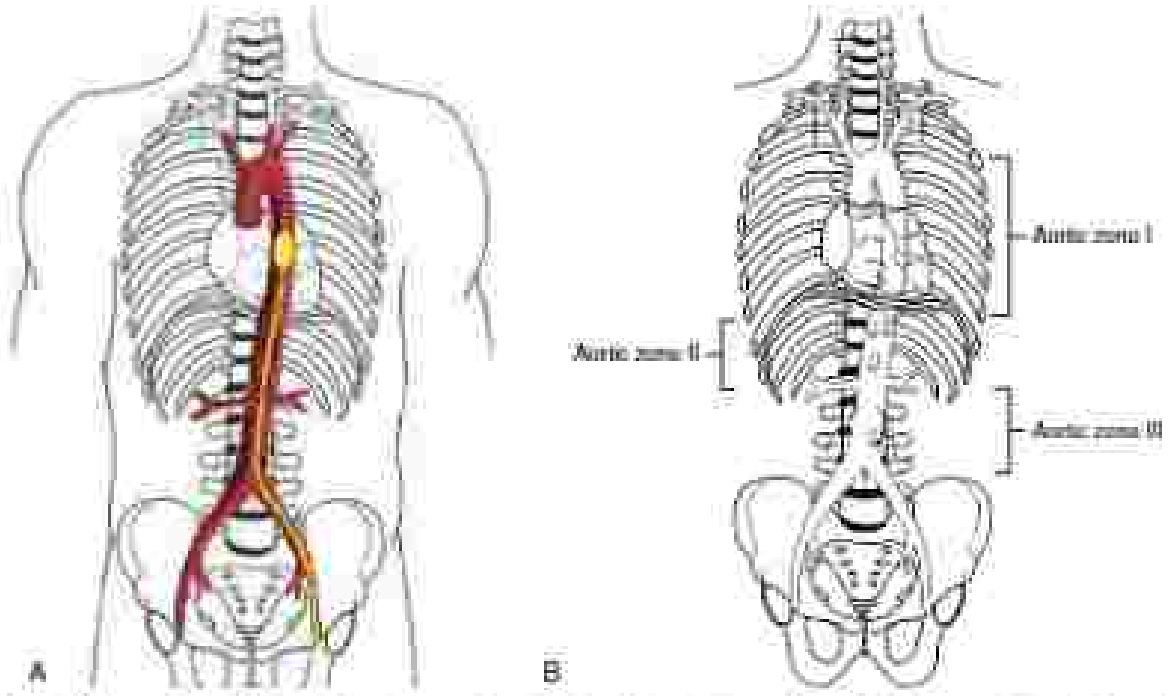

FIG. 7. (A) Aortic balloon occlusion device. (B) Aortic zones for positioning of Resuscitative endovascular balloon occlusion of the aorta device. Zone I between subclavian artery and celiac artery; zone II between the celiac artery and the lowest renal artery; and zone III between the lowest renal artery and the aortic bifurcation. (*Source:* A, Image B, from: [illegible] Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. J Trauma. 2011;71(1 Suppl 1):S48–S55.)

Seldinger fashion. Traditionally, a 6Fr vascular sheath and dilator are placed and then upsized to an 11Fr to 14Fr sheath depending on the size of the balloon being used; however, newer "low pass" sheaths and dilators are currently in production for the trauma setting. Once the appropriate size sheath is in place, a stiff Amplatz guidewire is placed through the sheath. The balloon device is then fed over the guidewire to the correct position.

The location of the balloon in the aorta is determined by the presumed location of the trauma, divided into three distinct zones (Fig. 7B). Zone I is the proximal zone of the descending aorta between the left subclavian and celiac trunk. Placement of the balloon in this zone is recommended for abdominal and visceral trauma. Zone II encompasses the abdominal vasculature from the celiac artery to the lowest renal artery. Placement of the balloon in zone II is contraindicated as it is possible to directly occlude the celiac artery, superior mesenteric artery, or renal arteries resulting in organ ischemia. Zone III extends from the lowest renal artery to the aorta bifurcation. Positioning of the balloon in this zone provides proximal control for pelvic hemorrhage while still maintaining perfusion to the abdominal organs. Correct positioning of the balloon can be accomplished with either fluoroscopy, plain film x-ray in the trauma bay, or by physical landmarks.

Once positioned, the balloon is then inflated with either saline or a 1:1 mixture of saline and contrast if fluoroscopy is being utilized. Appropriate filling of the balloon can be confirmed by either visualization of the balloon flattening against the wall of the aorta if using fluoroscopy or loss of a pulse in the contralateral femoral artery. Several animal studies have demonstrated that aortic occlusion times greater than 60 minutes may result in severe physiologic derangement and irreversible organ failure; thus it is imperative that the surgeon be mindful of the duration of balloon inflation and should limit this to less than 60 minutes. After hemorrhage has been controlled, the balloon should be slowly deflated with ongoing communication between the surgeon and the anesthesiologist, as there may be abrupt periods of hypotension as the balloon is deflated.

Concerns regarding the use of REBOA focus on incorrect placement of the device, effectiveness in controlling hemorrhage, and potential for organ ischemia. One of the initial case series in 1980 documented the use of REBOA in trauma patients and found that trauma surgeons were able to appropriately position and deploy the balloon and the balloon was able to control hemorrhage in 11 out of 21 patients with refractory hemorrhagic shock. Brenner and colleagues published a recent case series of six trauma patients with severe hemorrhagic shock in which REBOA was utilized prior to angiographic or surgical control of the hemorrhage. REBOA resulted in an average increase in systolic blood pressure of 55 mm Hg, and none of the patients died as a result of hemorrhage. Additional studies have shown similar rates of successful placement and control of hemorrhage in patients with both blunt and penetrating abdominal trauma.

While in many situations, the most effective method to control hemorrhage will be direct control via laparotomy or embolization, REBOA is a technically feasible and potentially life-saving adjunct in the patient with refractory and end-stage hemorrhagic shock. As the technology for the REBOA devices improves and more clinical research is performed, REBOA will likely become more widespread as a rapid and effective method of hemorrhage control prior to definitive surgical repair for life-threatening abdominal and pelvic trauma.

CONCLUSION

In addition to the management of abdominal trauma that has been underscored throughout the chapter for blunt trauma, there are several proposed treatment paradigms for many of the injuries sustained by trauma. However, the standard of care management for an individual is heavily dependent on the resources and personnel available, along with transport options, if any. There are resource rich

trauma systems throughout the country, with highly qualified personnel. However, these systems are not uniform throughout the nation and the concept of regionalization has not been perfected for all the regions in the country. The overarching goal remains the same: optimal management for everyone, irrespective of where the patient receives trauma care.

Suggested Readings

Burch M, Wellington L, Aitken A. Management of penetrating hepatic injury: A review of 102 consecutive patients. Am Surg 1994;60(3):132–142.

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Penetrating Abdominal Trauma

David V. Feliciano, MD

While blunt mechanisms account for 80% of injuries in the United States, patients with penetrating abdominal wounds continue to present to all trauma centers and emergency departments. The reasons for this have not changed over the past 75 years and include the following:

1. The tendency of young men to solve domestic and other interpersonal disputes with the use of the most lethal weapon available
2. The ready availability of handguns in the United States
3. Gang-related violence in urban areas and the sale of illicit drugs

TRANSPORT AND RESUSCITATION

Interventions in the field or emergency department do not control intraabdominal bleeding or gastrointestinal contamination in the patient with a penetrating abdominal wound that causes injury. Therefore transport and resuscitation in such patients is different than that used in patients with blunt multisystem trauma. For example, the application of a cervical collar or spinal immobilization in the field is unnecessary unless the patient has a specific complaint at the scene. Rapid transport takes precedence over the insertion of intravenous catheters at the scene in urban areas where a trauma center is only 15 to 25 minutes away. Even with longer transport times to the trauma center, the military concept of hypotensive resuscitation (limited or no resuscitation before operation) is now applied by many civilian emergency medical services during transport. Obviously, this would be inappropriate in a patient with an associated traumatic brain injury. The ideal perioperative systolic or mean arterial blood pressure during hypotensive resuscitation in the symptomatic patient with a penetrating abdominal wound is unknown.

In the emergency department, emergency intubation is indicated in patients with the following:

- Profound hypotension (ATLS class III or IV shock) or recent cardiopulmonary arrest
- Associated wounds to the neck or chest affecting the airway or breathing
- Depressed neurologic state secondary to shock, acute alcoholism or illicit drugs
- Extreme agitation preventing evaluation and resuscitation

Intravenous lines are inserted into the upper extremities, subclavian veins, or jugular veins, and venous blood is withdrawn for type and cross match and routine laboratory testing. In the patient with ATLS class III or IV shock, most level I trauma centers will initiate a massive transfusion protocol (MTP) and administer packed red blood cells immediately. Smaller centers or those without an MTP often still administer a crystalloid solution initially and then transfuse when type specific blood is available. Many centers have moved from *damage control resuscitation* with administration of rapid ratios of packed red blood cells, plasma, and platelets to *goal directed* hemostatic resuscitation. The latter is based on thromboelastography (TEG) or rotational thromboelastometry.

As resuscitation is ongoing, a surgeon performed ultrasound examination of the pericardium, peritoneal cavity and pleural cavities (expanded FAST or eFAST) is performed with a 3.5 MHz ultrasound probe in patients with multiple wounds, including the abdomen. Although this examination is primarily indicated in patients with blunt multisystem trauma, it has diagnostic advantages in patients with possible penetrating abdominal trauma, as well. For example, the presence of fluid (blood) in the pericardial sac might prompt a median sternotomy or anterolateral thoracotomy even before a needed laparotomy. Or the rapid diagnosis of a hemothorax or pneumothorax (without the need for emergency chest radiography) would prompt the insertion of a thoracostomy tube before a needed laparotomy. Finally, the presence of fluid (blood) in the peritoneal cavity

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confirms that a knife or gunshot wound has penetrated beyond the abdominal wall.

Patients who will be taken to surgery for an emergency or urgent laparotomy (see below) are administered an intravenous dose of a second- or third-generation cephalosporin antibiotic. As a general rule, patients with penetrating abdominal wounds and overt indications for an emergency laparotomy should be moved to the operating room within 10 minutes of arrival in the trauma room.

INDICATIONS FOR LAPAROTOMY AFTER PENETRATING ABDOMINAL TRAUMA

The timing of operation in such patients in a busy trauma center will depend on the patient's hemodynamic status and associated injuries, as well as the hemodynamic status of other patients with penetrating or blunt trauma who are being evaluated simultaneously (Box 1).

PATIENTS WITHOUT CLEAR-CUT INDICATIONS FOR LAPAROTOMY

Just as in patients with blunt abdominal trauma, the diagnosis of peritonitis on a physical examination after a penetrating abdominal wound, particularly a stab wound, may be difficult. This is particularly true in patients who are intoxicated, have impaired mental drugs, have associated injuries to the brain or spinal cord, or have multiple penetrating wounds in areas adjacent to the abdomen (thoracoabdomen, pelvis, flank, back). When serial physical examinations may not be helpful, standard diagnostic adjuncts are used, preferably in a sequence agreed on by staff trauma surgeons (Box 2).

In patients in whom contrast enhanced computed tomography (CT) will be part of the diagnostic workup, a 64 slice scanner should be used. A 64 slice scanner has a 4 cm scan width, and scanning of the trunk can be completed with a limited number of revolutions in a short period of time.

Dual energy CT in which images are acquired at two different energy levels simultaneously is now available in some hospitals, and attenuation differences allow for suppression of artifacts and enhanced images. This technology is now being used to image the brain and aorta and will soon have an impact on truncal imaging in injured patients.

The obvious goal of further diagnostic evaluation in patients without clear cut indications for an emergency or urgent laparotomy is to avoid an unnecessary or nontherapeutic laparotomy. Patients undergoing such procedures have a fixed rate of postoperative complications and an extended length of stay as compared with those managed with observation or further diagnostic testing.

POSSIBLE PENETRATING ABDOMINAL TRAUMA/HEMODYNAMICALLY UNSTABLE/MULTIPLE TRUNCAL AND EXTREMITY WOUNDS

One of the common sense observations about patients with multiple gunshot wounds is that associated hypotension is likely related to one wound ("one bad bullet"). When there is no external bleeding from an injured neck or extremity to explain the hypotension, surgeon performed ultrasonography is the diagnostic test of choice. As previously noted, an eFAST examination will document whether the hypotension is from pericardial tamponade, intraperitoneal hemorrhage, or intrapertoneal hemorrhage. An equivocal eFAST examination or lack of availability of an ultrasound machine should prompt an open diagnostic peritoneal tapvarage in the hypotensive patient, a rapidly performed diagnostic test in the modern era.

BOX 1 Indications for Laparotomy After Penetrating Abdominal Trauma*

- Hypotension in absence of other site of potential hemorrhage (i.e., penetrating cervical, thoracic or peripheral vascular wound with active hemorrhage)
- Peritonitis on initial or subsequent physical examination
- Evisceration of bowel and, in some centers, omentum (controversial)
- Bleeding from stomach (hematemesis or bloody return from nasogastric tube) or rectum (bright red blood or hematochezia on finger examination or proctoscopy)
- Bleeding from genitourinary tract (exception would be flank wound in stable patient and CT evidence of isolated nonhilar renal injury amenable to observation or angioembolization)
- Contrast enhanced CT demonstrates perforation of gastrointestinal tract, intraperitoneal bladder or severe (American Association for the Surgery of Trauma Organ Injury Scale Grade V) solid organ injury

*Modified from Nikolaou DV. Abdominal trauma revisited. Orv Hetil. 2007;148:1193–202.
CT, Computed tomography.

BOX 2 Diagnostic Adjuncts in Evaluating Patients with Possible Penetrating Abdominal Trauma

- Local exploration of anterior stab wounds
- Diagnostic peritoneal tapvarage
- Surgeon performed ultrasound examination (FAST)
- Contrast enhanced CT of the abdomen and pelvis
- Diagnostic laparoscopy

CT, Computed tomography.

POSSIBLE PENETRATING THORACOABDOMINAL TRAUMA/ HEMODYNAMICALLY STABLE

The thoracoabdomen is defined as the region to costal margin from the midline to the anterior axillary line. Penetration through the diaphragm into the peritoneal cavity from a wound in the thoracoabdomen will occur in approximately 15% of stab wounds and more than 65% of gunshot wounds (Fig. 1).

Once again, surgeon performed ultrasonography is the initial diagnostic test of choice in the patient without an obvious indication for a laparotomy. An ipsilateral pneumothorax or hemothorax can be confirmed, whereas the presence of intraperitoneal fluid (blood) documents that the hemidiaphragm and, possibly, intraabdominal viscera have been injured. An eFAST examination in which no intraperitoneal fluid is visualized is not helpful because only modest bleeding may result from a penetrating wound of the hemidiaphragm alone.

In the modern era, documentation of intraperitoneal fluid (blood) in the asymptomatic or mildly symptomatic patient) does not prompt an immediate laparotomy. With a wound in the right thoracoabdomen, triple contrast (intravenous, oral, rectal) CT is performed to evaluate the liver, right kidney, duodenum, and colon. This is a labor-intensive study for the radiology technician because all 3 contrast agents are administered simultaneously. In addition, metallic fragments from a bullet may create enough "scatter" to compromise the accuracy of one of the contrast studies. A patient with a wound to the liver or right kidney only without extravasation of contrast (no active bleeding) is managed nonoperatively with serial physical examinations for 24 to 36 hours. If desired, healing of the injury to the liver

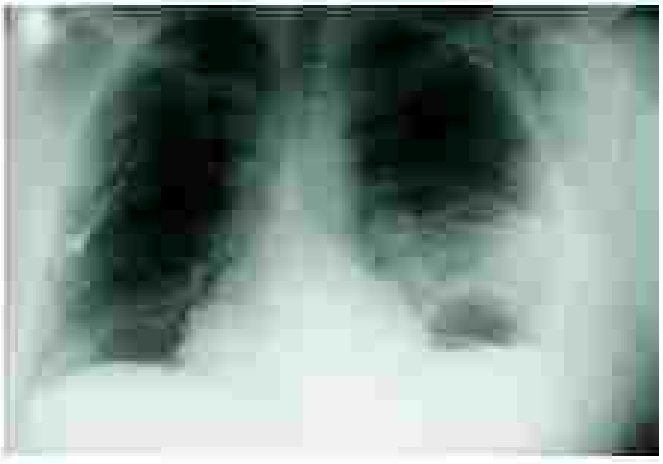

FIG. 1. Patient with left thoracoabdominal gunshot wound had 3-day delay before wounds to left hemidiaphragm and stomach were diagnosed.

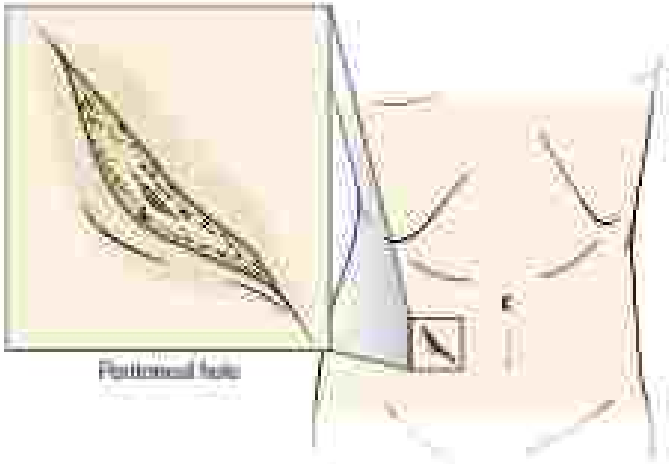

FIG. 2. Peritoneal perforation on a local wound exploration after a stab wound to the anterior abdominal wall mandates admission and serial physical examinations.

or right kidney can be evaluated on a follow-up CT examination in 5 to 7 days. In such a patient, the small penetrating wound to the right hemidiaphragm is not fatal. This is because omental herniation through the right-sided defect essentially never occurs, and the complication of a bronchobiliary fistula is so rare. A triple contrast CT is performed after a penetrating wound to the *left* thoracoabdomen as well, with the goal of evaluating the liver, spleen, left kidney, stomach, and colon. Even if a patient has a midintestinal wound to the left lobe of the liver, spleen, or left kidney and no extravasation of gastrointestinal contrast, the wound to the left hemidiaphragm must be repaired. This will prevent herniation of the omentum into the left hemithorax secondary to the negative intrapleural pressure of respiration. This can be accomplished via a laparoscopic approach depending on the surgeon's expertise.

Because of the labor intensive nature of triple contrast CT, some centers choose to perform diagnostic laparoscopy instead after a wound to the left thoracoabdomen. An equivocal triple contrast CT after a wound to either the right or left thoracoabdomen should be followed by diagnostic laparoscopy as well. Using a 30-degree laparoscope with the patient under general anesthesia in the operating room will allow for a careful inspection of the peritoneal hemidiaphragm and intraabdominal viscera.

PENETRATING ANTERIOR STAB WOUND/ HEMODYNAMICALLY STABLE

The anterior abdomen is defined as the area from the costal margins to the inguinal ligaments between the anterior axillary lines. Historic data have documented that stab wounds to this location penetrate the peritoneal cavity only 20% to 30% of the time. Even in patients with documented peritoneal penetration, only 50% to 55% will present with overt indications for a laparotomy. In the remaining 15% to 20% who undergo serial physical examinations, only half will eventually become symptomatic and require laparotomy.

A local wound exploration under sterile conditions and local anesthesia in the trauma room is the first diagnostic maneuver. Contraindications would include the agitated or uncooperative patient or one who is morbidly obese. A very localized layer-by-layer exploration will, at the least, document whether the anterior aponeurosis of the muscular abdominal wall has been penetrated. In many centers, the local wound exploration is terminated at this point and the patient admitted for serial physical examinations or further diagnostic testing. Other centers will continue the exploration through the muscular layers of the abdominal wall to determine whether the posterior aponeurosis, peritoneum, or both have been perforated (Fig. 2). If it can be confirmed that this has not occurred, the wound is irrigated and closed in layers, a tetanus immunization shot is administered, and the patient is discharged.

In most centers an asymptomatic or mildly symptomatic patient with penetration of the anterior aponeurosis or peritoneum will then undergo serial physical examinations every 6 to 8 hours for 24 hours. Almost all patients with continued bleeding from a solid organ, the mesentery, or omentum or peritonitis from a gastrointestinal wound will become symptomatic within 6 to 16 hours. Despite the delay to operative management that inevitably occurs in this small subset of patients, postoperative morbidity is surprisingly low.

Another option to the asymptomatic or mildly symptomatic patient is to perform an immediate diagnostic peritoneal tap/lavage. This option has become less popular over time because of false-positive examinations results from intraperitoneal blood related to the injury to the abdominal wall. Also, there has been continuing controversy about whether a red blood cell count of 100,000/mm^3 (as in patients with blunt trauma) or 5000/mm^3 (to pick up a small wound of the hemidiaphragm) should be used to mandate a laparotomy. The accuracy of this approach using a cell count of 100,000 red blood cells or 500 white blood cells/mm^3 ranges from 80% to 92%.

PENETRATING ANTERIOR STAB WOUND AWAY FROM LEFT HEMIDIAPHRAGM/ OMENTAL EVISCERATION

Evisceration of a large piece of omentum should prompt an emergency laparotomy. This allows for replacement of the omentum into the peritoneal cavity, a complete exploration for associated injuries (theoretically a higher incidence than if a smaller defect in the abdominal wall), and repair of the abdominal wall. Commonly exits, however, when a small piece of omentum is evisceration (Fig. 3). In such patients, an emergency laparotomy will be unnecessary in 20% to 60% of patients. Therefore some centers will ligate the base of the eviscerated omentum, excise it, return the remainder to the peritoneal cavity, close the defect in the abdominal wall, and perform serial physical examinations for 24 hours. This option is safe and has a ability to operative management essentially the same as if an omental evisceration had not occurred.

PENETRATING FLANK OR BACK TRAUMA/HEMODYNAMICALLY STABLE

The flank is defined as the sixth intercostal space to the iliac crest between the anterior and posterior axillary lines, whereas the back is the rest of

FIG. 3 Small external excoriation does not mandate laparotomy in all trauma centers.

the scapulae to the iliac crests posterior to the posterior axillary lines. Wounds in these areas may penetrate the peritoneal cavity or the visceral/vascular areas of the retroperitoneum. A historic policy of mandatory laparotomy for penetrating wounds [illegible] in symptomatic patients has been abandoned over the last 30 years because the negative [illegible] these areas.

The [illegible] patients are [illegible] serial physical examinations and triple contrast CT. The concern with serial physical examinations is that perforation of the retroperitoneal duodenum, ascending colon, or descending colon will cause retroperitonitis or a delayed onset of symptoms. [illegible] abdomen. [illegible] patients [illegible] hours after [illegible] serial physical examinations after penetrating stab wounds [illegible] applies to patients [illegible] or back [illegible] as well, and [illegible] the trauma surgeons in a given center extending the period for serial [illegible].

Triple contrast enhanced CT scans to evaluate patients with [illegible] in the 1990s. [illegible] with [illegible] intraperitoneal or [illegible] retroperitoneal visceral or vascular injury.

In summary, serial physical examinations [illegible] for surgical team, or triple contrast CT [illegible] for radiology technicians are acceptable diagnostic options, with a delayed diagnosis [illegible].

FLANK-ANTERIOR ABDOMINAL WALL GUNSHOT WOUNDS AND ANTERIOR ABDOMINAL WALL THROUGH-AND-THROUGH WOUNDS

In the modern era, there is a tendency for victims facing an assailant holding a handgun to turn away. Also, obesity is present in more than [illegible]% of adults in some states in the United States. This results in numerous patients having oblique missile tracts in proximity to the abdominal contents from the flank to the anterior abdominal wall, from the anterior abdominal wall to the flank, and from one location in the anterior abdominal wall to another.

When physical examination cannot rule out peritonitis, the diagnostic test of choice is abdominal CT with intravenous contrast. A preliminary [illegible] will often confirm that the gunshot wound is extraperitoneal. Because the kinetic (muzzle) energy of missiles from handguns is less than 1000 ft-lbs (with the exception of a .44 caliber), a shock wave injury to an intraabdominal viscus would be highly unlikely in such a patient. [illegible] of an intraperitoneal track in the patient with a persistent equivocal physical examination should be followed by a diagnostic laparoscopy in the operating room because 20% to [illegible]% of such patients will have an intraabdominal injury.

SELECTIVE NONOPERATIVE MANAGEMENT OF ABDOMINAL GUNSHOT WOUNDS

[illegible] and colleagues from Los Angeles County Hospital/University of Southern California reported on selective management of [illegible] patients with abdominal gunshot wounds [illegible] in 2001. The group of [illegible] patients ([illegible]%) who were selected for nonoperative management did not have any of the following: hypotension, associated injury to brain or spinal cord, intoxication, or need for sedation or intubation. Delayed laparotomy for new symptoms was performed in [illegible] patients ([illegible]%), and [illegible] patients ([illegible]%) did not have a laparotomy. The rate of unnecessary laparotomy in operated patients was 14[illegible]. The series presumably included many patients with oblique or extraperitoneal missile tracks as previously described. It confirmed, however, that the criteria used to choose nonoperative management in patients with stab wounds in proximity to the abdomen could be used in patients with gunshot wounds as well.

SUMMARY OF NONOPERATIVE MANAGEMENT

A patient with negative physical examination results (over 24 to [illegible] hours) or a normal contrast-enhanced CT after sustaining a possible or confirmed penetrating abdominal, flank, or back wound is given specific written instructions at the time of discharge. These state that a new onset of an elevated body temperature, abdominal pain, lightheadedness, hematemesis, rectal bleeding, hematochezia, or hematuria should prompt immediate return to the trauma center. The phone number of the trauma service is included, as well.

GENERAL PRINCIPLES OF TRAUMA LAPAROTOMY

The patient is placed in the supine position with the upper extremities at the sides unless there is a high likelihood of a simultaneous left anterolateral thoracotomy being performed. In such a patient, the left chest is elevated 30 degrees to allow for access to the descending thoracic aorta and thoracic esophagus, and the left upper extremity is rotated superior to the patient. Placing the upper extremities at the patient's sides allows for easy insertion of self-retaining abdominal retractors and ready access for a median sternotomy. Skin preparation and draping extends from the chin to the knees and encompasses the anterior and lateral trunk. This allows for ready access for removal of the greater saphenous vein from the groin and thigh, if needed. Throughout the trauma laparotomy, all the standard warming maneuvers are used to reverse or prevent hypothermia (increase room temperature; turn up heating cascade on anesthesia machine; cover patient's head and extremities with warming device; infuse blood and fluids through warming device; irrigate tubes, nasogastric, thoracostomy, and open body cavities with warm saline solution if hypothermia is persistent).

Depending on the patient's hemodynamic status, the midline incision is not opened until type-specific blood is available in the operating room. Once the peritoneal cavity is opened, blood, clots, and gastrointestinal contents are evacuated using laparotomy pads and a [illegible] suction device. Sites of hemorrhage in the mesentery, bowel, retroperitoneum or solid viscera are exposed and controlled with clamps or packing. Then, all perforations in the gastrointestinal tract are controlled with bowel, vascular, Babcock, or Allis clamps or

BOX 3 Rapid Operative Techniques After Penetrating Abdominal Trauma

Gastrointestinal Tract

Single layer closure of gastrointestinal perforations
Colon repair instead of colostomy
Delay gastrointestinal reconstruction

Solid Viscera

Hepatotomy, tractotomy, debridement, or perihepatic packing instead of formal hepatic resection
Topical agent, suture, or absorbable mesh splenorrhaphy for AAST OIS grade I–III injury instead of splenectomy
Avoiding placement of drains after stabilization or repair of grade I–II hepatic or pancreatic injuries, splenorrhaphy, splenectomy

Diaphragm

Single layer permanent suture repair

Named Arteries

Temporary intraluminal shunt instead of complex repair of proximal superior mesenteric artery, common iliac artery, or external iliac artery (these vessels are never ligated)

Named Veins

Ligation major injury to portal vein, superior mesenteric vein, splenic vein, left renal vein at midline, infrarenal inferior vena cava, common iliac vein, or external iliac vein

a stapling device. Depending on the patient's hemodynamic status, number and magnitude of gastrointestinal perforations and associated injuries, the perforations are repaired and the peritoneal cavity irrigated with a saline antibiotic solution. Then, treatment of injuries to solid organs or to retroperitoneal blood vessels is performed. This sequence is reversed in patients with active visceral or vascular hemorrhage.

As a general rule, the track of a knife or missile wound is followed first, with repair or resection of injuries as needed. Then, a formal exploration of every intraabdominal organ including retroperitoneal viscera and vessels, especially those in proximity to the track, is performed. The organs most commonly injured in patients with stab wounds to the abdomen are the liver, small bowel, diaphragm, colon, and stomach. In patients with gunshot wounds, injuries to the diaphragm fall by one half as compared with stab wounds, and injuries to named abdominal vessels are present in 20% to 25% of patients in large reviews. In any patient with multiple abdominal injuries from a penetrating wound, not just those undergoing a damage control laparotomy, rapid operative techniques are performed (Box 3).

A "damage control" laparotomy is indicated in patients with profound hypothermia (temperature 32°–34°C), a metabolic acidosis (pH <7.2), signs of an intraoperative coagulopathy, or some combination of these. This limited laparotomy controls hemorrhage and gastrointestinal contamination, only, and should be completed within 60 to 90 minutes. Leaving the abdominal wall open under a vacuum assist device or a plastic silo is appropriate after a damage control laparotomy, when distention of the midgut precludes a safe closure or when intraabdominal packs have been inserted. An early reoperation after a damage control laparotomy is occasionally necessary. This is

BOX 4 Goals at a First Reoperation After Damage Control Laparotomy

Remove and count packs and confirm absence of continued bleeding from liver or retroperitoneum
Inspect all repairs and search for missed injuries
Complete gastrointestinal anastomoses and/or create stoma
Insert nasojejunal feeding tube (or do gastrostomy or jejunostomy)
Irrigate abdominal cavity with saline solution containing antibiotic
Decide if formal suture closure of linea alba is safe

indicated when there is a continuing need for hourly transfusion of two units of red blood cells after a coagulopathy has been mostly corrected based on monitoring with TEG. Otherwise, a reoperation after an original damage control procedure is performed when the patient is normothermic, no longer acidotic, not coagulopathic, and has reasonable respiratory and cardiovascular function—usually at 48 to 72 hours. The goals of the first reoperation after a damage control laparotomy are listed in Box 4.

SUMMARY

In patients undergoing laparotomy after abdominal stab wounds, the survival rate is 98% and only 27% of patients required a blood transfusion in one large review. The most common postoperative complication was an infection in the incision (1.0%).

In patients undergoing laparotomy after abdominal gunshot wounds, the survival rate was 88% (97% in those without an abdominal vascular injury, 61% in those with an abdominal vascular injury) in one large review. The most common postoperative complications were an intraabdominal abscess (3.9%), infection in the incision (3.4%), and reoperation for persistent bleeding (2.2%).

Suggested Readings

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Velmahos GC, Demetriades D, Toutouzas KG, et al. Selective nonoperative management in 1,856 patients with abdominal gunshot wounds: should routine laparotomy still be the standard of care? Ann Surg. 2001;234:395–403.

Management of Diaphragmatic Injuries

Chair: [illegible] ... FACS, FCCM, Professor, Division of Trauma, Surgical Critical Care, Burns, and Acute Care Surgery, University of Arizona, Tucson, AZ

[illegible], MD, FACS

Traumatic diaphragmatic injuries (TDIs) continue to be a diagnostic and therapeutic challenge for surgeons who care for trauma patients. Clinical presentations are variable and associated thoracic and abdominal injuries often distract surgeons from the early identification and treatment of TDIs. In addition, missed diagnoses place patients at increased risk for visceral hernia and strangulation. The objectives of this chapter are to review the epidemiology, anatomy, and physiology of TDIs and provide current recommendations for diagnosing and managing TDIs in both the acute and chronic phases.

EPIDEMIOLOGY

The incidence of acute TDI after thoracoabdominal trauma ranges from 0.8% to 8% with TDI from blunt and penetrating injury accounting for 75% and 25%, respectively. Bilateral TDIs are uncommon, occurring in only 0.2% of patients with TDI. After either penetrating or blunt trauma, a higher incidence of left-sided TDI exists given the presence of a congenital weakness along the costal and lumbar portions of the left hemidiaphragm and because the liver provides some degree of protection along the right hemidiaphragm. Although TDI represents only 5% of all diaphragmatic hernias, it is responsible for 40% of hernias that eventually become incarcerated.

ANATOMY

An understanding of diaphragmatic anatomy is important to avoiding missed injuries and in minimizing iatrogenic phrenic nerve injury during operative repair. The diaphragm is a dome-shaped muscular-aponeurotic barrier that separates the thoracic from the abdominal cavity and is the main respiratory muscle of the body with expiratory and respiratory functions. Muscle fibers originate anteriorly from the sternum's xiphoid process, laterally, inferiorly, and posteriorly from the costal cartilages and osseous portions of the lower ribs and from the lumbar vertebral bodies and their intervertebral discs (Fig. 1). These fibers all insert into the diaphragm's aponeurotic portion known as the central tendon, which underlies the pericardium. The right dome is naturally 2 cm higher than the left due to the mass exerted by the underlying liver.

The diaphragm has three separate hiatuses, allowing for the passage of the inferior vena cava (IVC), esophagus, and aorta. Located at the T8 level, the aponeurotic canal opening allows the IVC and often the right phrenic nerve to traverse body cavities. The diaphragm's lumbar origin includes left and right crural fibers, which form the boundaries of the esophageal and aortic hiatus. The esophagus and the vagus nerves traverse the esophageal hiatus—a gap between the right crural fibers—at the T10 level. The aortic hiatus, formed by the fibers of the left and the right crura, is located at the T12 level, posterior and just to the left of midline, and allows for passage of the aorta, thoracic duct, and variably the azygos and the hemiazygos veins.

The diaphragm's blood supply comes from inferior and superior phrenic arteries, which arise directly from the thoracoabdominal aorta. Superior epigastric and intercostal arteries provide blood to the muscle's costal margins. Phrenic veins provide venous drainage directly into the IVC. The left and right phrenic nerves supply the diaphragm with its motor and sensory innervation. The left phrenic nerve passes through the muscular diaphragm more anteriorly than the right phrenic nerve, which passes through the aponeurotic central tendon through or close to the caval opening. The two main trunks typically divide into three main branches: anterior, intermediate, and posterior. Sensory innervation to the central tendon of the diaphragm and pericardium is through the phrenic nerves, whereas the intercostal nerves provide sensory nerve supply to the diaphragm periphery.

MECHANISMS OF INJURY AND ASSOCIATED INJURIES

The diaphragm is rarely injured in isolation. In fact, TDI is considered a marker for severe associated injuries, especially in the setting of high-grade blunt trauma. In patients sustaining blunt TDI, Meyers and McCabe reported a 60% incidence of associated pelvic fractures, a 25% incidence of associated hepatic and splenic injuries, and a 5% incidence of associated aortic tears. Thus, the presence of TDI in the setting of blunt trauma should alert the surgeon to a high probability of associated solid organ and pelvic injury.

DIAGNOSIS

Patients with missed or untreated TDIs often present in a delayed fashion with symptoms related to intestinal herniation or strangulation. Over time, small diaphragmatic defects can increase in size as a result of the constant activity of the muscle, and the pressure gradient between pleural and peritoneal cavities can result in herniation of intraperitoneal organs into the chest. Clinical presentations vary from mild nausea and vomiting from intermittent bowel obstructions, to severe pain from incarceration and intestinal ischemia, to septic shock and death from strangulated, necrotic, or perforated viscus. Undoubtedly, the consequences of an untreated TDI can be devastating and life threatening.

The diagnosis of a TDI in a patient who does not otherwise warrant immediate thoracic or abdominal surgical intervention can be challenging. Generally, the ability to make an accurate diagnosis outside an operating room relates to the size of the defect.

The physical examination is often unreliable for diagnosing TDIs because there are no highly sensitive signs to detect an underlying injury. However, there are certain signs that are suggestive of injury, including unilateral decreased breath sounds, bowel sounds in the chest, and respiratory distress. Although these signs are nonspecific findings, their presence should not be discounted in assessing for diaphragm injury. After penetrating injuries, the trajectory of the knife or bullet is more important than the actual location of the skin wound; the trajectory is usually difficult to accurately elicit. Probing a thoracoabdominal wound, especially one overlying the rib cage, is discouraged for fear of creating or exacerbating a pneumothorax or intercostal bleeding.

A focused assessment with sonography for trauma scan using a 5.5-MHz phased array ultrasound probe is the first screening tool used in the diagnosis of TDIs but has limited sensitivity; however, the presence of pleural fluid, subphrenic effusion, nonvisualization of the spleen, or the visualization of the spleen in the thorax can suggest TDI.

A chest radiograph is commonly performed but rarely diagnostic, especially for penetrating trauma where TDIs are small and plain films are seldom helpful. A chest radiograph more commonly contributes to the diagnosis after a blunt mechanism. Examples of such radiographic signs include air or an air–fluid level within a hollow viscus overlying the thorax or with the abdominal classic finding of the curling supradiaphragmatic nasogastric tube (Fig. 2). Suggestive findings include abnormality in the contour, shape, or position (e.g., elevation) of the hemidiaphragm, pleural effusion or atelectasis, and mediastinal shift (Fig. 3). However, the chances of seeing these signs in the intubated patient with TDI may be reduced because positive pressure ventilation causes the contour of the lower lobes of the lungs to expand, mimicking that of the intact diaphragm.

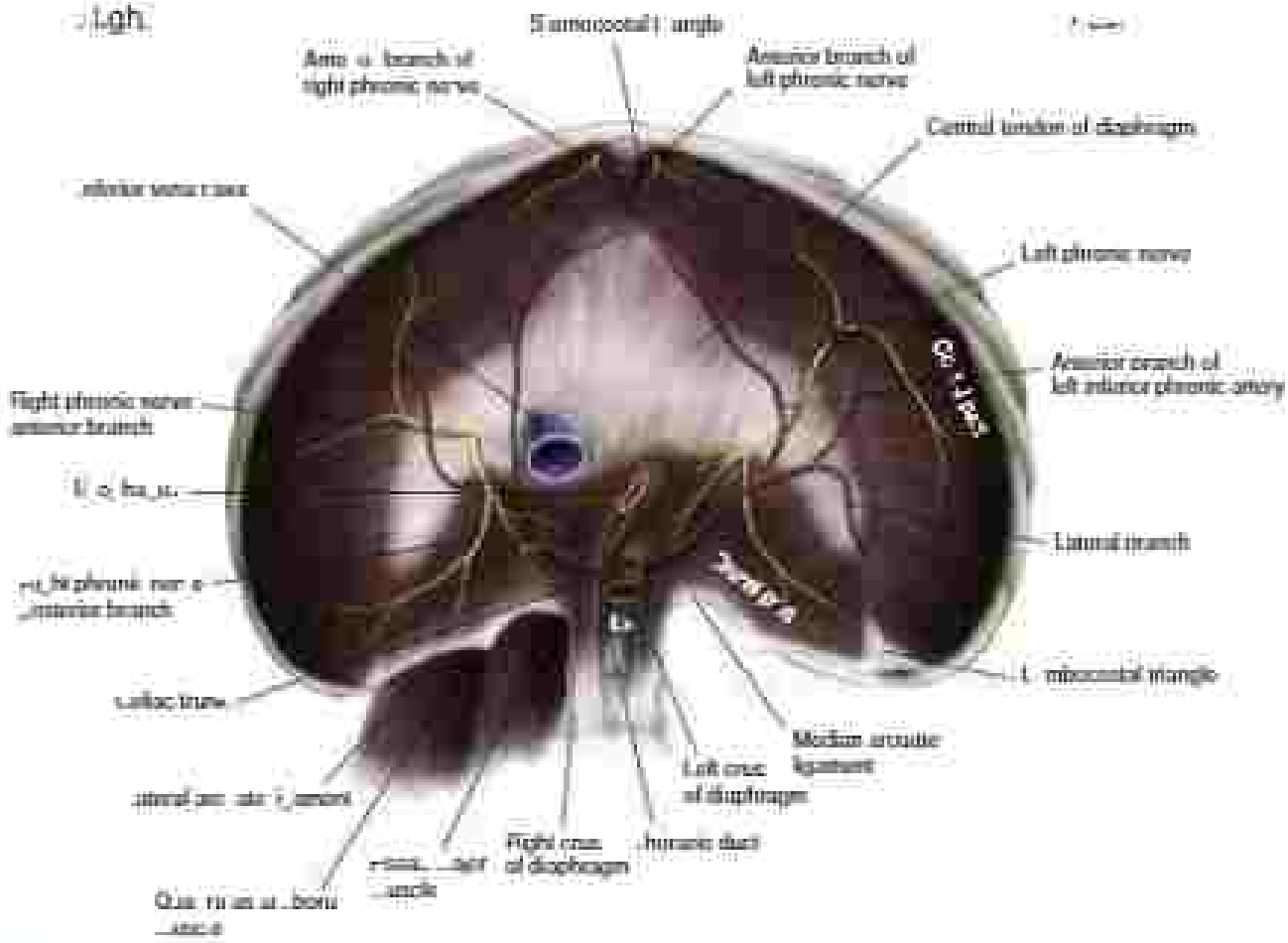

FIG. 1 Anatomy of the diaphragm (with additional structures). (From Anne G. M. Campbell, Clare Hall, Jonathan Ritchie, Gray's Surgical Anatomy, Philadelphia, 2020, Elsevier.)

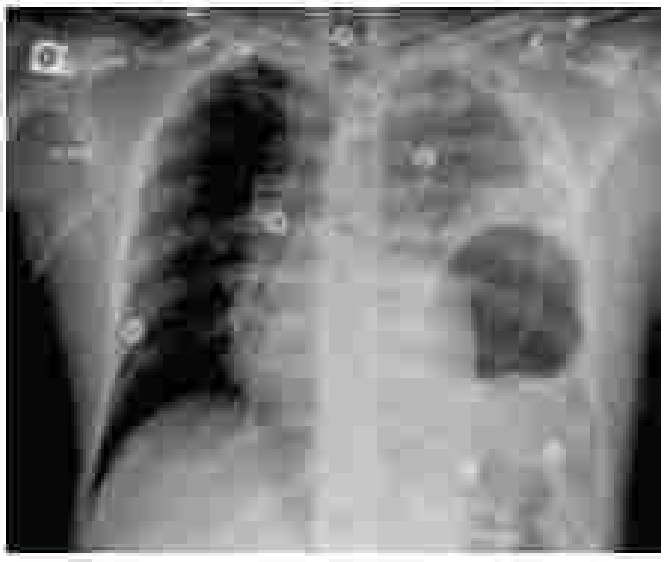

FIG. 2 Chest radiograph depicting typical findings of an acute traumatic diaphragmatic injury with a hernia containing stomach. Notice the left hemithorax, multiple rib fractures, an air-fluid level, and a curled nasogastric tube in the left side of the chest. (From Chason JK, Fox JC, Jr. Traumatic diaphragmatic injury. In: Tintinalli JE, Stapczynski JS, Ma OJ, Yealy DM, Meckler GD, Cline DM, eds. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. 8th ed. New York: McGraw-Hill Education; 2016.)

With its greater sensitivity and specificity, computed tomography (CT) scan may detect discontinuity of the diaphragm or a wound tract extending up to a hemidiaphragm, but conclusive evidence includes intrathoracic abdominal contents (Fig. 4). CT has a greater sensitivity for blunt trauma, where injuries tend to be larger, and is less helpful after penetrating mechanisms, where diaphragmatic defects are small and acute herniation is rare. Penetrating TDIs also present a spectrum of radiographic findings distinct from those in blunt trauma, with contiguous injury and transdiaphragmatic trajectory acting as best predictors. Diaphragmatic discontinuity, thickening, elevation, or segmental nonvisualization and intrathoracic herniation of abdominal viscera are strong predictors of blunt diaphragmatic rupture.

Surgery remains the gold standard for diagnosing an injury to the diaphragm. Diagnostic laparoscopy is the procedure of choice for assessing the diaphragm in hemodynamically stable patients who lack a clear indication for laparotomy. Laparoscopy provides excellent visual access as well as access for repair to areas that can be difficult to see and reach through standard laparotomy. However, during peritoneal insufflation, the surgeon must be cautious about introducing air into the pleural cavity and subsequently creating a tension pneumothorax. For this reason, in draping such a patient for laparoscopy, the chest should be prepared in case a thoracostomy tube needs to be inserted if not already present at time of laparoscopy. Given the risk for creating a tension pneumothorax, as pneumoperitoneum is introduced, it is imperative to monitor airway pressures, oxygen saturation, and tidal CO_2 and mean arterial pressure. Until the abdominal surface of the diaphragm is evaluated and deemed free of injury, insufflation pressures should not exceed 10 to 12 mm Hg.

With a strategy of low pressure pneumoperitoneum, careful attention to ventilatory parameters, and early diaphragmatic inspection, an iatrogenic tension pneumothorax may be considered a rare event.

As with laparoscopy, thoracoscopy may be used for the diagnosis of TDI and is an exceedingly sensitive modality. Diaphragm repair through the chest can be accomplished without concern for creating a tension pneumothorax. However, because the diaphragm is rarely injured in isolation, an intraperitoneal approach may be preferred in patients who would benefit from operative assessment for intraabdominal injuries. Whereas most pleural cavity injuries may be safely managed with a thoracostomy tube, a perforated intraabdominal hollow viscus or hemorrhage emanating from a solid viscus injury requires a timely diagnosis and expeditious surgical intervention.

Before the advent of minimally invasive scoping techniques, TDIs were most commonly detected at laparotomy. This remains the current mode of diagnosis in patients who require immediate abdominal exploration for hemodynamic instability or peritonitis. In patients who are acutely hemorrhaging from a chest injury with an indication for thoracotomy, an injured diaphragm may be detected and addressed from the chest as well. Concomitant abdominal injuries may be ruled out via an additional laparotomy or, in rare selected cases, by a transdiaphragmatic approach to the upper abdomen.

In patients with chronic diaphragmatic hernias related to trauma, a proper history and physical examination may be suggestive. These missed injuries often present with alimentary tract obstruction, incarceration, or strangulation. They are almost always found on the left hemidiaphragm and the diagnosis can usually be made with plain radiography, although CT scan is frequently used to better delineate size, location, and visceral involvement.

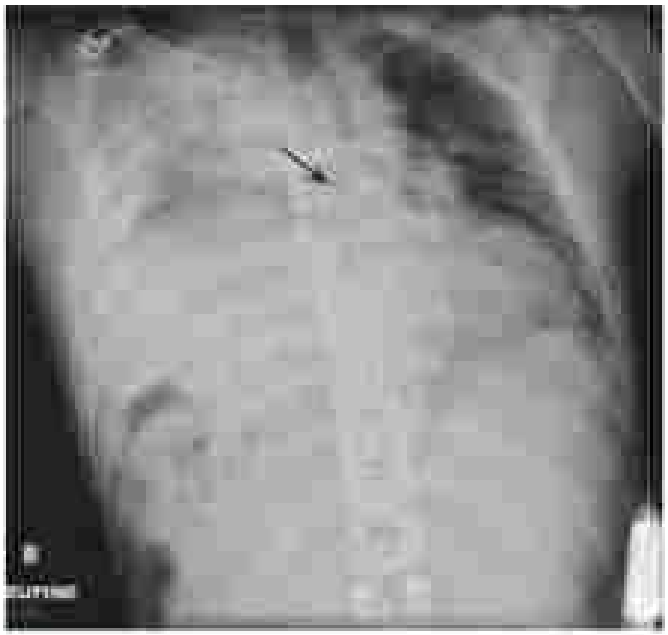

FIG. 3 Portable chest radiograph. Note complete opacification of the right hemithorax with only partial aeration of the anterior segment of the right upper lobe. There is collapse of the bronchus intermedius (arrow) and associated collapse of the right lower lobe. There is shift of the mediastinum and trachea to the left. Fluid is present along the right upper pleural surface, consistent with a hemothorax. The right hemidiaphragm is markedly elevated with indistinct margins. Although edema has secondary to a collapsed lung also caused elevation of the diaphragm, presence of contralateral mediastinal shift suggests a space occupying mass and favors diaphragmatic rupture. *From Coward S, Allen A, ... Smith M. Right sub-diaphragmatic injury resulting from blunt trauma. J Emerg ... Med. 2008;34(1):65–67.*)

MANAGEMENT

Acute Phase

TDIs are graded on a scale of I to V in the American Association for the Surgery of Trauma ... Injury Scale, developed in 1994 (Table 1).

Higher grade TDIs are typically from blunt trauma whereas lower grade injuries are from penetrating injuries. The treatment for an injured diaphragm is, for the most part, operative whether an injury is acute or chronic. Irrespective of localization, all acute diaphragmatic injuries encountered at surgery should always be repaired. Controversy exists regarding right sided injuries when there are no indications for operative intervention. Although most would agree that for large defects or for lower lateral or lower anterior wounds, which afford less protection from herniation by the liver, repair should be pursued. Regardless of mechanism, acute injuries can usually be repaired primarily. Repair may be achieved via laparoscopy/laparotomy or via thoracoscopy/thoracotomy, depending on the patient's hemodynamic stability and associated injuries and the surgeon's experience with

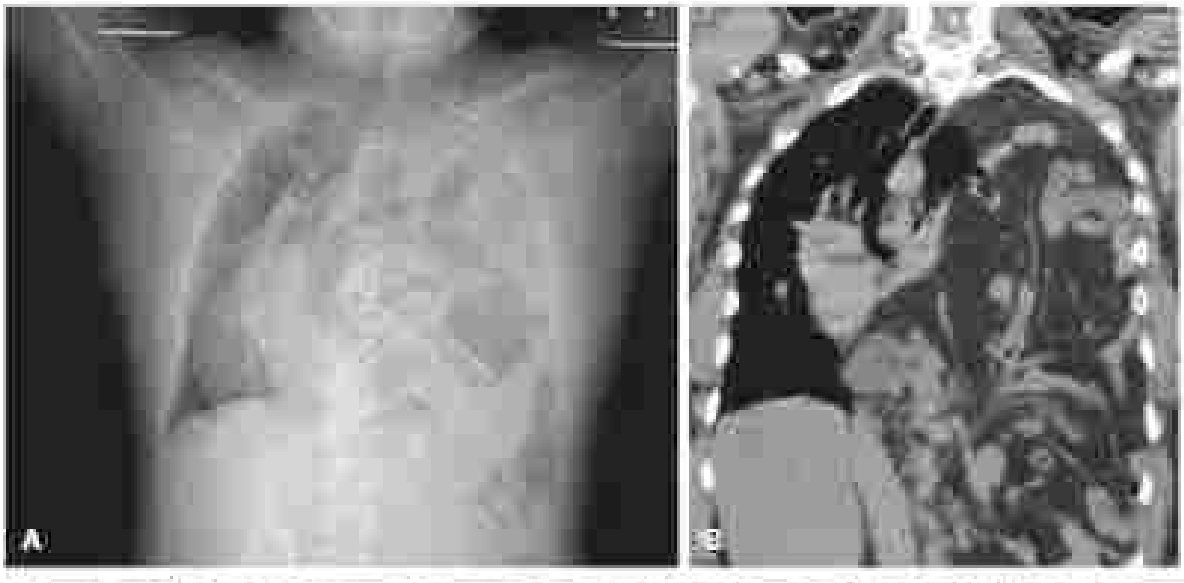

FIG. 4 (A) Chest radiograph followed by (B) computed tomography scan of the chest, abdomen, and pelvis showed a left-sided diaphragmatic hernia with stomach, pancreas, omentum, colon, and small bowel within the left hemithorax. *From Pikoulis E, Petsas ..., Spyrti ..., and Skiadas K. Late ... of chronic traumatic "slap" syndrome: Report of ... cases and review of the ... literature. Surg Case Rep. 2015;2:15. doi: ...*)

TABLE 1 American Association for the Surgery of Trauma Diaphragmatic Injury Grading Scale

Grade	Description
I	Contusion
II	Laceration <2 cm
III	Laceration 2–10 cm
IV	Laceration >10 cm with tissue loss <25 cm²
V	Laceration with tissue loss >25 cm²

Advance one grade for bilateral injuries.
From Moore EE, Malangoni MC, Cogbill TH, et al. Organ injury scaling IV: thoracic, vascular, lung, cardiac, diaphragm. J Trauma. 1994;36(3):299–308.

FIG. 5 Laparoscopic port placement for repair of diaphragmatic injury. Supraumbilical trocar used to insert the laparoscopic 30-degree camera. (From Lane J, Asensio JAM. Diaphragm injury. In: Cornwell EE, Asensio JA, Whitman E, eds. Atlas of Surgical Techniques in Trauma. 1st ed. Cambridge, UK: Cambridge University Press; 2015:216.)

minimally invasive technique (Figs. 5 and 6). Laparoscopic technique continues to gain traction for definitive exploration and repair, especially for penetrating acute diaphragmatic defects with low associated injuries. As with all surgical procedures, full exposure of the diaphragm is essential for repair. The upper abdominal viscera must be retracted in a way that allows for the entire intraperitoneal diaphragmatic surface to be evaluated, which may be difficult especially posteriorly on the left. Positioning the operating room table in reverse Trendelenburg with the right side down is indicated, as is the use of a 30-degree scope for improved visualization. If a nonpenetrating injury to the diaphragm is found, a chest tube should be placed not only to prevent a potential tension pneumothorax but also because a lung injury cannot be excluded.

When there is a large diaphragmatic defect, the ipsilateral lower lung lobe may be inspected for injury. If injury to the lung cannot be ruled out, it may be efficacious to copiously lavage the pleural cavity with sterile saline if there is a concomitant full-thickness bowel injury to reduce the incidence of an empyema.

Repair of the injured diaphragm involves debridement of devitalized tissues (Fig. 7). This is especially important for firearm injuries, where inadequate debridement may play a role in the breakdown of the repair. Nonabsorbable sutures should be placed and tied either intra- or extracorporeally. The type of repair—interrupted versus running, one layer versus two—has not been shown to matter in terms of recurrence. An interrupted suture repair may include a simple, figure of 8, or horizontal mattress technique (Figs. 8 and 9). Running repairs are often performed in a simple, locked fashion by grasping the lacerated edges with an Allis or Babcock clamp. Zero or No. 1 nonabsorbable suture material (e.g., polypropylene) is preferred. Most surgeons repair the diaphragm in a single layer, aiming for an airtight closure.

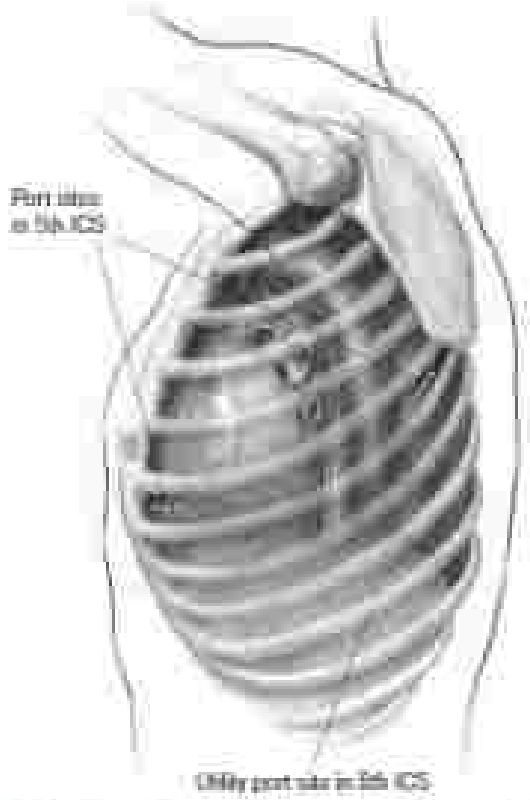

FIG. 6 Video-assisted thoracoscopic surgery port placement for repair of diaphragmatic injury. IC, intercostal space. (From Blackmon S, Schipper P. Video-assisted thoracoscopic surgery diaphragm plication. In: Shah A, Nason K, Cardoso R, Onaitis M, eds. Atlas of Thoracic Surgery. Philadelphia, PA: Elsevier; 2018:e1–e4.)

FIG. 7 Diaphragmatic defect of 4 × 3 cm seen after reduction of hernia contents showing ragged margins all around. (From Gupta G, Mandal D. Traumatic diaphragmatic hernia presenting late with nonspecific symptoms. Ann Int Surg. 2013;3:120–123.)

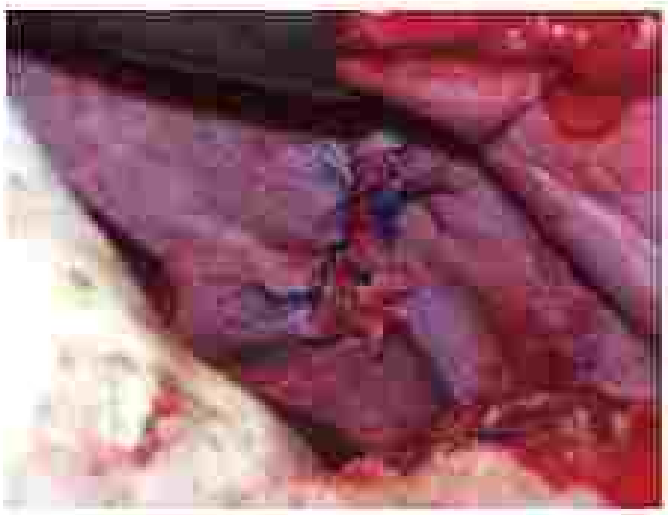

FIG. 8 Posterolateral diaphragmatic defect closed with interrupted polypropylene sutures. (From Dutta C, Morelli E. Traumatic diaphragmatic hernia presenting late with nonspecific symptoms. Arch Int Surg. 2011;1:108–109.)

FIG. 9 Laparoscopic repair of injured diaphragm using interrupted horizontal mattress sutures. (From Parker LB, Lange VC, Stone JE. Traumatic injury of the diaphragm. In Mattox KL, et al. Trauma. 9th ed. Philadelphia: McGraw-Hill Education; 2017:354.)

An experienced laparoscopist may perform the repair and address associated injuries without necessarily converting to an open procedure in the hemodynamically stable patient. If the repair is deemed technically difficult or the exploration deemed suboptimal, converting to laparotomy is indicated. Additionally, any instability should prompt consideration for conversion to laparotomy. In preparation for laparotomy, the supine patient is prepared and draped as for any trauma laparotomy. Principles of operative trauma are followed: packing, hemorrhage control, and minimization of contamination. Diaphragmatic evaluation should be thorough, especially for penetrating trauma. On the right, the *round ligament* can be clamped and ligated and the falciform ligament incised, allowing the liver to be retracted for better visualization. Division of the right triangular and coronary ligaments will allow the surgeon to mobilize the liver inferiorly and medially to expose the inferosurface of the right hemidiaphragm. On the left, the stomach and the spleen are retracted inferiorly and medially with gentle traction. Herniation through an injured diaphragm is usually readily apparent and should be immediately reduced to prevent respiratory insufficiency. Because associated injuries are likely to divert attention from an injured diaphragm intraoperatively, it is important to maintain a high index of suspicion and to thoroughly evaluate the entire undersurface on inspection and on palpation to prevent a missed injury.

Prosthetic mesh patches (Gore-Tex, Composix) and biologics (Strattice, AlloDerm) are preferred for large defects or for those where primary repair produces too much tension. Interrupted polypropylene sutures should be used to sew in the patch. In the event of an accompanying bowel injury, a nonabsorbable mesh is contraindicated and instead a biologic acellular tissue matrix such as AlloDerm or Strattice may be used. In the rare event that the diaphragm has avulsed from the chest wall, it may be reattached as a primary fashion using polypropylene sutures placed circumferentially around the ribs. Alternatively, bone suture anchors appropriately sized for rib thickness can also be used to secure the avulsed diaphragm to the chest wall.

Indications for thoracoscopic exploration remain undefined because intraabdominal organs can rarely be adequately assessed operatively without an additional laparotomy incision. However, several studies have found that for posterior and right sided TDI, thoracoscopy is a more appropriate screening tool and potentially better than laparoscopy. However, if a TDI is found, intraabdominal injury still needs to be excluded.

Chronic Phase

Surgery is indicated for chronic diaphragmatic hernias. Thoracotomy has a definite role in these patients because there is no concern for an associated intraabdominal injury. Additionally, reduction through the chest may be easier because adherent lung can make for a tedious and difficult dissection transabdominally. For the treatment of a chronic hernia, where primary approximation of the diaphragm would likely involve tension, producing suboptimal results, a mesh repair is warranted. After thoracotomy a chest tube should be used. If a laparotomy is performed, a red rubber catheter may be used to suction out air from the pleural cavity as the final stitches are tied to negate the need for a thoracostomy tube.

MORBIDITY AND MORTALITY

Patients with TDI from blunt trauma, as opposed to penetrating trauma, have higher mean injury severity scores and an increased mortality rate, primarily as a result of injuries to other organs including the brain and pelvis. As compared with left sided injuries, right sided TDI are associated with higher rates of death. Overall, mortality in patients with TDI approximates one in five. Additional morbidity may be incurred when TDIs are missed or not surgically addressed during the acute presentation; this usually presents in the form of symptomatic visceral herniation, obstruction, or strangulation.

Complications related to the diaphragm repair include a disruption of the repair, phrenic nerve injury, and peridiaphragmatic infection. Disruption of a repair is more common with large injuries or with those involving avulsion from the chest wall. Left or right phrenic nerve injuries may be caused by the diaphragmatic rupture at the time of impact or may be iatrogenic as a result of the repair. Peripheral injuries and repairs are much less likely to cause damage to main branches of the phrenic nerves. Diaphragmatic injuries just lateral to the esophageal and caval openings carry a high risk for left

and right nerve lesions, respectively, and must be repaired with the nerve distribution in mind to prevent an iatrogenic injury.

Subdiaphragmatic abscess and empyema are recognized postoperative infections and may be more common with associated hollow visceral injuries. These complications lengthen the duration of intensive care unit and hospital stay and increase morbidity and mortality. Pneumonia is also more common in patients with diaphragmatic rupture.

A missed or inadequately repaired right TDI often associated with a deep liver injury can lead to a bilateral pleural fistula. Although pigtail catheter thoracostomy and biliary stenting are often performed, they are frequently unsuccessful because negative intrapleural pressures maintain the output of the fistula. These patients often require a thoracotomy for diaphragm repair and lung decortication.

A missed TDI with subsequent herniation may lead to severe sequelae. Often in a delayed fashion, these patients may present with symptoms of bowel obstruction, sepsis secondary to strangulation and necrosis, or pulmonary insufficiency. A missed injury may result in sepsis, shock and death.

The repair of a chronic diaphragmatic hernia is more difficult than in the acute setting given the dense intrathoracic adhesions. Because the muscle edges have retracted and thinned over time and with pressure from the abdominal contents, these repairs are much more involved, routinely require mesh, and not uncommonly result in complicated hospital courses.

Selected Readings

Berg RJ, Inaba K, Okoye O, et al. The pattern of diaphragmatic injury in motor vehicle crash victims. J Trauma Acute Care Surg. 2014;77(5):684–691.

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Pelosi P, Ravagnan I, Mariani C. Diaphragmatic injuries and post-traumatic diaphragmatic hernias. Chir Ital. 2007;59(3):311–322.

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Asensio JAM, El Menyar A, Al Thani H, et al. Penetrating and outcomes in patients with traumatic diaphragmatic injury: a 15-year experience. J Trauma Acute Care Surg. 2015;79(4):592–598.

Management of Traumatic Liver Injury

Sandra R. DiStasio, MD, PhD, and Elliot R. Haut, MD, PhD, FACS

Although management of liver injury has evolved significantly over the past decade, including more nonoperative and interventional approaches, surgeons should still carry a healthy sense of respect for liver trauma. Treating a liver injury calls for an evidence-driven approach administered by trauma surgeons with both an experienced mind and skilled hands. It is imperative to employ the fundamentals of trauma care, sticking to a structured algorithm for initial evaluation and subsequent treatment, while maintaining a high index of suspicion for severe, lurking injuries that may not be obvious at the time of presentation. Regarding massive injury, the liver follows no rules, requiring the surgeon speed, fortitude, and teamwork to save the patient.

INITIAL EVALUATION

Trauma protocols call for a systematic approach to every patient, and those with liver injury are no exception. Evaluating the hemodynamic stability of the patient, the mechanism of injury, and findings on primary and secondary survey will guide decision making. In the unstable patient with a high index of suspicion of intraabdominal injury based on physical examination, history (i.e., high speed motor vehicle collision or gunshot to the abdomen), and rapid ultrasound evaluation, the surgeon should not hesitate to proceed with immediate operative management.

In the hemodynamically stable patient or one who responds well to initial fluid resuscitation, imaging is helpful. An early chest radiograph can inform the team about the severity of the mechanism (Fig. 1). For instance, after a motor vehicle collision, multiple rib fractures to the right side of the chest raise suspicion for liver injury. The focused assessment with sonography for trauma (FAST) examination, although convenient, is truly inadequate in evaluating for the presence and severity of liver trauma. A positive FAST with intraabdominal blood is helpful in the hypotensive trauma patient, driving immediate surgical intervention. However, a normal FAST should not put the team entirely at ease. The absence of fluid in Morrison's pouch does not rule out a liver injury and should not prevent the trauma team from proceeding with resuscitation or to computed tomography (CT) scan for a more thorough evaluation of possible liver injury (Fig. 2A). When obtaining a CT, it is imperative to include intravenous contrast to evaluate explicitly for arterial extravasation (Fig. 2B), which could be treated with interventional angioembolization. The most frequently used liver injury grading scale, developed by the American Association for the Surgery of Trauma, can help guide management based on the anatomic grade of injury (Table 1).

SELECTIVE NONOPERATIVE MANAGEMENT

Blunt Injury

Most blunt liver trauma can be managed nonoperatively with a combination of serial abdominal examinations and serial hemoglobin checks. Guidance from the Eastern Association for the Surgery of Trauma (EAST) and other groups suggest that nonoperative management is appropriate for hemodynamically stable patients, regardless of injury grade, age, neurologic status, or presence of other concomitant but nonoperative injuries. Historically, anecdotes suggested bed rest 1 day longer than the grade of injury to decrease the risk of further bleeding; however, newer data have shown earlier ambulation to be safe. In a recent series of more than 30,000 trauma admissions, only 1,412 patients had liver injuries, and less than 0.5% of these were grade IV or higher, and few even high grade injuries required operative intervention. Overall, compared with historical controls, studies show that a nonoperative approach and active monitoring have resulted in decreased utilization of transfusion and improved survival. EAST guidelines remind us that selective nonoperative management is appropriate only in environments where close clinical monitoring is feasible and where an operating room would be available for urgent laparotomy as needed.

Penetrating Injury

For nearly a century, surgical dogma has suggested that any penetrating injury violating the peritoneum merits operative exploration. However, in isolated penetrating injury to the liver, there are certain cases in which a selective, nonoperative approach can be appropriate.

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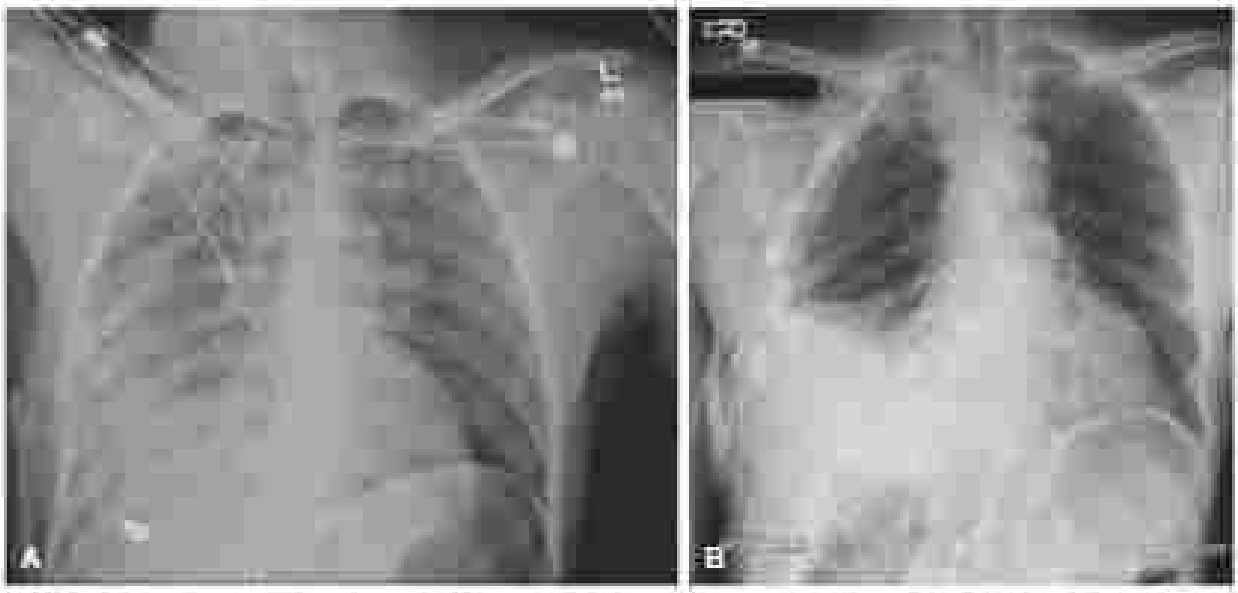

FIG. 1 (A) Chest radiograph to detect liver injury after gunshot wound to right thoracoabdominal region. (B) Chest radiograph to detect liver injury after blunt trauma to right thoracoabdominal region with multiple rib fractures and flail chest.

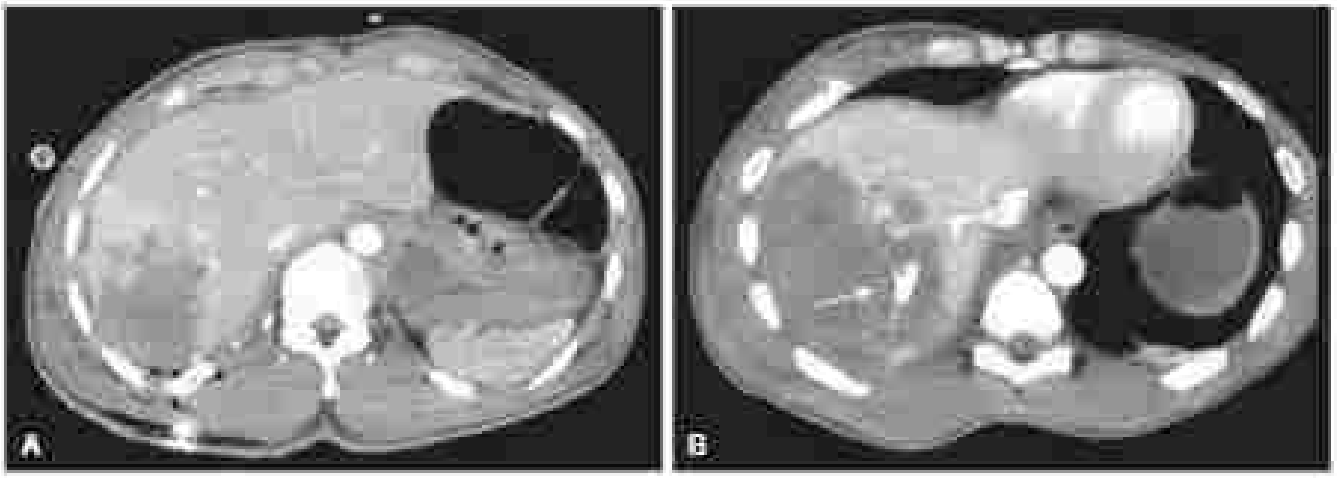

FIG. 2 (A) Computed tomography (CT) image demonstrating liver injury with bullet posteriorly below skin. (B) Gunshot wound to liver with active arterial extravasation on CT scan (arrow).

TABLE 1 American Association for the Surgery of Trauma Liver Injury Scale

Grade	Injury	Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area Intraparenchymal, <10 cm diameter
	Laceration	1–3 cm parenchymal depth, <10 cm length
III	Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma
	Laceration	>3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% of hepatic lobe or 1–3 Couinaud segments in a single lobe
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe
	Vascular	Juxtahepatic venous injuries (i.e., retrohepatic vena cava/central major hepatic veins)
VI	Vascular	Hepatic avulsion

From Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). J Trauma. 1995;38(3):323–324.

This approach has gained increasing traction in the last decade. EAST guidelines suggest that hemodynamically stable patients with penetrating trauma, particularly stab wounds to the right upper quadrant, who have no diffuse abdominal tenderness and who can provide a reliable physical examination do not necessarily require a laparotomy and can be closely observed. When undertaking this approach, we recommend the liberal, routine use of CT scan to help ensure the right patients get appropriate interventions in a timely fashion, even those for whom the physical examination results are normal. It should be noted that this management should be used selectively, and only in stable patients who can be monitored closely for development of subtle clinical changes or rapid deterioration.

INTERVENTIONAL TECHNIQUES TO AVOID THE OPERATING ROOM

Interventional radiology techniques are indispensable in the treatment of trauma to many organs including the liver and are important to have available at any trauma center. In a stable or transiently responsive patient with clear, active hemorrhage on CT, transarterial angioembolization can stop the bleeding and prevent the need for open operative management (Fig. 1). In patients undergoing embolization for other indications such as pelvic hemorrhage or splenic hemorrhage, relatively small bleeds from concomitant liver injury can be managed simultaneously. Angiography should be first-line therapy in cases where hemoglobin drops but the patient remains hemodynamically stable. Not all trauma centers have interventional radiology available at all hours, and this availability may drive decisions about which patients require transfer to higher levels of care.

Although interventional techniques are most often performed by interventional radiologists, some centers have vascular or trauma surgeons with this skill set. At some institutions, hybrid interventional operating room suites can accommodate intraoperative angioembolization. This would allow for operative exploration, injury identification, treatment of concomitant injuries, and immediate intraoperative angioembolization after packing, even with an open abdomen, all in the same trip to the main operating room.

FIG. 1 Angiographic imaging of active arterial extravasation from gunshot wound to liver (arrow).

Additionally, interventional techniques can be used in a delayed fashion for patients who have initially undergone either nonoperative or surgical management. They are frequently used to drain fluid collections, such as abscesses, hematomas, or bilomas. Other interventions include therapy targeted toward the biliary tree, via either percutaneous or endoscopic approaches, discussed later in this chapter.

OPERATIVE MANAGEMENT

For unstable patients presenting with signs of shock and a high suspicion for liver injury or intraabdominal hemorrhage, the immediate plan should be expeditious movement toward the operating room. The FAST examination can confirm hemoperitoneum and help finalize the operative plan. Although there has been a recent push toward resuscitative endovascular balloon occlusion of the aorta, it has not been adopted at all centers and is not yet in routine use. This procedure requires placing an arterial catheter into the femoral artery and advancing it above the level of injury where a balloon can be inflated to temporarily stop bleeding and allow more time for definitive repair. Although it is mostly utilized for pelvic bleeding, if placed proximally enough, it can impede liver blood flow.

In the operating room, it is of the utmost importance that the surgical, nursing, and anesthesia teams maintain excellent communication. Before starting the intervention, the anesthesia team should secure blood products and consider activating the massive transfusion protocol. The nursing team should be prepared with warming devices; operative equipment to tackle the liver bleeding, including packing materials and topical hemostatic agents; and specialized energy devices such as the argon beam, Cavitron ultrasonic surgical aspirator, and/or radiofrequency dissector (i.e., Tissuelink). In cases of major liver trauma, the primary surgeon should also anticipate complex surgical maneuvers and plan for adequate operative assistance. This may be from a nontrauma surgeon (e.g., surgical oncologist, hepatobiliary surgeon, or transplant surgeon), depending on local expertise. The patient should be prepared quickly and widely from clavicles to knees, leaving all options open including sternotomy, thoracotomy or sternotomy, which may be required for adjunctive procedures or control of the supradiaphragmatic vena cava.

Exposure is key in liver trauma. If a midline incision is chosen, it should be generous, extending to the xiphoid to allow for thorough evaluation of the liver. If high-grade liver or retrocaval injury is known or suspected, a bilateral subcostal (chevron) incision allows for excellent visualization and access to the entire liver and retrohepatic vena cava. This option is a great choice for rapid abdominal access if the patient has had prior midline incisions, allowing the team to avoid inadvertent injury to underlying bowel.

In keeping with standard trauma principles, all four quadrants should be packed, beginning with the suspected site of hemorrhage. This maneuver allows the anesthesia team time to catch up on the resuscitation and the surgical team time to evaluate the rest of the abdomen. The urge to approach the hemorrhage first must be resisted, and the landscape should be surveyed. If the packing is holding, spillage or contamination from hollow viscus injury can be addressed swiftly, with clamps, staples, or quick sutures. The surgeon should not feel compelled to definitively repair bowel injuries before evaluating the source of hemorrhage. After the rest of the abdomen has been evaluated, spillage is controlled, and the patient has been resuscitated, the surgical team should communicate their intention to approach the liver so everyone in the operating room can share their focus. If the packs are holding, having stopped the hemorrhage, the surgeon has two main choices to continue with the surgery for more definitive repair or to leave the packs in place for damage control and retreat to the intensive care unit (ICU) with an open abdomen. This damage control technique, with therapeutic packing in place, will allow the patient to be resuscitated and reverse coagulopathy, allowing the surgical team the opportunity to fight another day.

In most patients, further exploration is appropriate, starting with systematic pack removal to reveal the underlying source of hemorrhage. Hemostatic efforts should be proportional to the magnitude of injury. For minor injuries, compression alone may have solved the problem. Clots should be gently removed and the area can be further treated with superficial techniques. For small injuries, electrocautery or argon beam coagulation can be adequate.

Hepatorrhaphy requires a gentle touch and a somewhat intact liver capsule. We prefer a large absorbable suture (i.e., 0 chromic gut, 0 PDS) on a large blunt tip needle to place simple interrupted stitches, mimicking the curve of the needle, making sure to include capsule on entry and exit. The sutures must be tight enough to achieve hemostasis but not overly tight because that will pull through the tissue and cause worse bleeding. Pledgets are an option, but not necessarily required. The team should also be mindful of other, larger, more distinct injuries that may be lurking beneath the packing and should take care to perform any repair as expeditiously as possible.

For a moderate or severe injury, it is imperative to prevent an organized attack, all the while keeping in mind that managing severe liver injury may require damage control surgery maneuvers. First, inflow occlusion should be performed with a Pringle maneuver by first inserting fingers behind the portal triad and applying gentle pressure across the three structures—hepatic artery, portal vein, and common bile duct. A Rummel tourniquet or vascular clamp can be applied with an eye on the clock, intermittently loosening the device and allowing for reevaluation of the hemorrhage, venous decongestion of upstream organs (i.e., small bowel), and oxygenation of liver tissue. In addition to being therapeutic, the Pringle maneuver can be helpful to diagnose. If the Pringle does not control the hemorrhage, injury to extrahepatic venous structures such as the inferior vena cava or hepatic veins is most likely present.

The power of manual compression should not be underestimated, and if a liver injury is itself is the cause of hemorrhage, sturdy compression in combination with a Pringle maneuver can buy time for resuscitation. If therapeutic repacking is necessary, topical hemostatic gauze (i.e., QuikClot [*sic*] Medical, Wallingford, CT) can be used. These products come in different sizes and some are now approved by the US Food and Drug Administration for internal use in a damage control setting. One important caveat is that they must be removed in future procedures because they do not degrade. Other topical hemostatic agents are also available and have the benefit of not needing removal such as fibrin sealants (i.e., Evarrest, Ethicon) or oxidized cellulose (i.e., Surgicel, Johnson & Johnson, New Brunswick, NJ). If hemorrhage is under control with packing and the patient is severely physiologically deranged with the "lethal triad" of coagulopathy, hypothermia, and acidosis, damage control principles should be followed and the patient should be taken to the ICU with an open abdomen. An abdominal vacuum dressing can be applied and will augment the tamponade of packing in most cases. Data suggest that if interventional radiology resources are available, angiogram and subsequent angioembolization should be undertaken in most, if not all, of these patients. Upon return to the operating room, the field is often surprisingly dry after coagulopathy, hypothermia, and acidosis have been corrected (Fig. 4).

If a retrohepatic vena cava or hepatic vein injury is suspected, mobilization of the liver can release a valuable tamponade and result in rapid exsanguination. This is to say that mobilization should be pursued thoughtfully, not as a simple matter of course, in addition to deep right lobe or posterior liver injuries. A full mobilization and delivery of the liver toward the midline may be necessary to evaluate a deep posterior wound.

To repair deep hemorrhage, there are numerous possible techniques—which is a surefire sign that none are perfect. Selective vessel ligation is appropriate for individual large arteries or veins, but this technique is often more difficult than it sounds. Finger fracture deep into the wound should be performed, essentially extending the injury to identify and pursue actively bleeding vessels. When identified, they can be clamped and ligated with sutures. Clips are convenient and quick, but have the drawback of easily coming off in the course of operating when packs are placed or removed. After vessels are secured, packing the large defect with a pedicle of vascularized omentum can augment hemostasis of smaller vessels and help seal small biliary leaks. It is important to preserve the inflow and outflow of the omental pedicle so it does not simply break down and result in a large liver abscess. This is best done by tacking the omentum perpendicular to the greater curvature of the stomach, then tacking the omentum into the liver defect. The omentum can then be incorporated into the interrupted hepatorrhaphy sutures described previously or can be separately affixed to the liver with several loose stitches to preserve the blood flow.

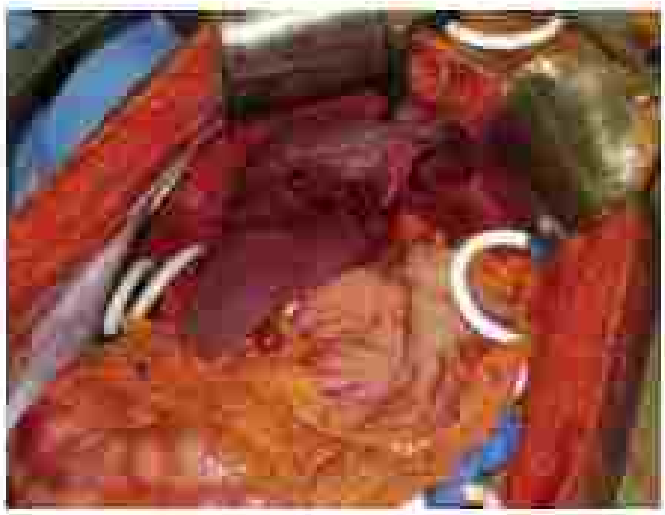

FIG. 4. Intraoperative image of liver after removal of packing at reoperation. Note the packs in place superior to the liver from initial damage control laparotomy.

For a transhepatic (through and through) penetrating injury, a balloon tamponade device can be lifesaving. Using either a Blakemore tube or a homemade red rubber catheter inside a Penrose drain, the device is inserted through the tract and inflated gently with saline until tamponade is achieved (Fig. 5*). The device can be left in place in a damage control setting and reevaluated after further resuscitation or angioembolization (Fig. 5B). For all surgeons taking trauma call, we suggest attending the Advanced Trauma Operative Management course sponsored by the American College of Surgeons Committee on Trauma to provide hands-on instruction on these techniques. Being facile with all available options allows surgeons to gain rapid control of bleeding and definitively repair injuries safely and effectively.

The role of major hepatectomy in liver trauma is an ongoing debate, and there are frequent swings of the pendulum. We continue to promote nonoperative therapy as a first line treatment, reserving major hepatectomy for delayed treatment in most cases. However, in certain instances expeditious resection is the only option for hemorrhage control or to access the site to control major bleeding. If it is deemed necessary, the resection line should be marked in healthy tissue using electrocautery. Finger fracture and selective vessel ligation can be used along the line of resection using one of many available specialized devices. The quickest, safest method often continues to be finger fracture, electrocautery, and vascular staplers. Many acute care surgeons encourage elective exposure to liver surgery to gain comfort in this area of practice, allowing them to brush up on skills and learn new techniques.

In rare cases in locations with the resources immediately available, venovenous bypass has been used to buy time needed to repair major liver injuries. Exceedingly rarer cases may require complete explant, back table repair, and immediate reimplantation or liver transplantation for the most severe grade V or VI injuries. Both of these techniques are highly resource intensive and are limited by availability of machinery, highly specialized personnel, and time.

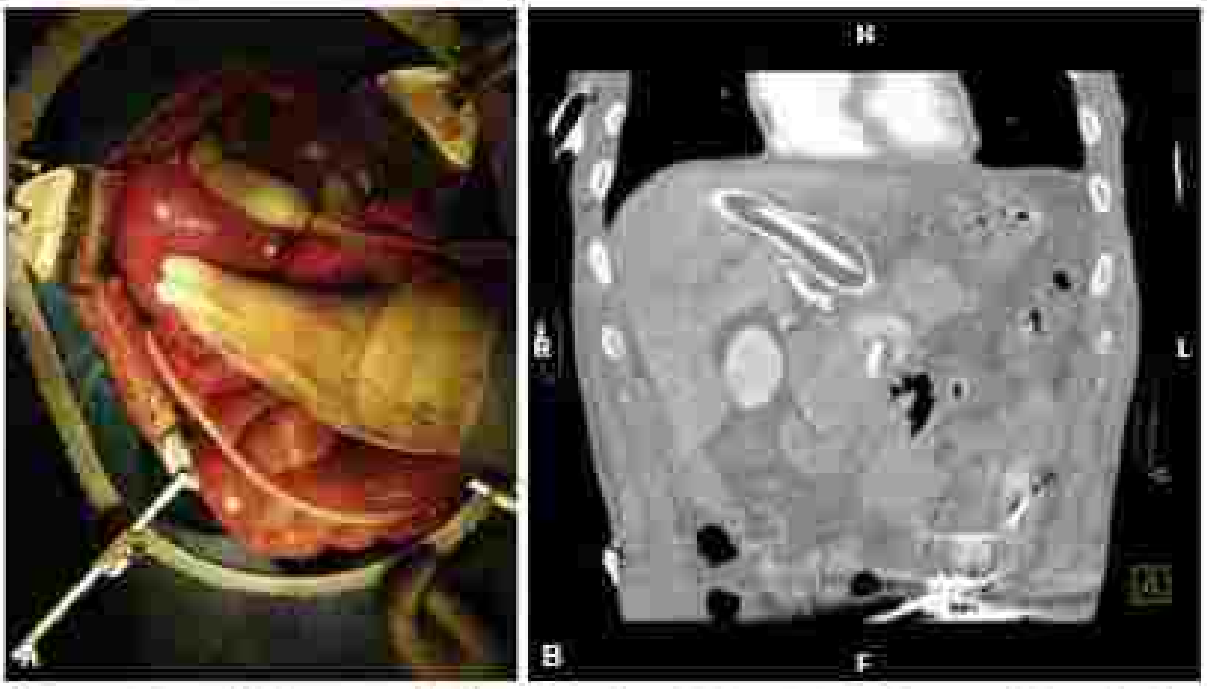

FIG. 5 (A) Intraoperative image of balloon tamponade in place across gunshot track in liver. (B) Computed tomography image of balloon tamponade in place for gunshot wound to liver.

EXTRAHEPATIC INJURY

Retrohepatic Inferior Vena Cava

Injury to the retrohepatic vena cava is every trauma surgeon's nightmare. To deal with this situation, it is imperative to proceed in a stepwise manner, but also to appreciate that outcomes after this injury are extremely poor and that, despite best efforts, the patient may not survive. The first principle to appreciate is that a contained retrohepatic hematoma does not require immediate exploration. However, the degree of containment is not always clear, and although it is easy to say in retrospect that one should not have explored the area, sometimes exploration is necessary. If a retrohepatic caval injury is suspected from the outset, mobilizing the liver is not recommended. Leaving the liver in situ will allow a natural tamponade and can aid in packing the injury. If the injury is identified after mobilization, the surgeon should restore containment with packing if possible. To gain exposure for suprahepatic control of the inferior vena cava (IVC), the laparotomy incision should be extended, often requiring a median sternotomy for control of the suprahepatic IVC within the pericardium. Total hepatic isolation, defined as control of the IVC above and below the liver and with a Pringle in place, may facilitate direct repair in a dry field. The atrocaval "Schrock" shunt is an important tool to have in the trauma surgery armamentarium, although the number of actual survivors is likely quite small. Once the vessels are isolated, a chest tube or endotracheal tube can be placed through a purse string made in the right atrium and down through the IVC, allowing flow through the tube and bypassing the injury in the IVC. To succeed, the decision to shunt must be made as *early* as possible, before the patient arrests or cannot be resuscitated. Using the shunt is only a temporizing measure to allow better visualization in a dry surgical field and allow attempts at hepatic vein or vena cava repair.

Extrahepatic Biliary Tree

The biliary tree is often an afterthought in most major liver trauma surgery or damage control operations. Patients will see the inconvenience of bile leaking, as opposed to bleeding, but the long-term outcomes can certainly be affected by thoughtful management of biliary injuries. In the moment, a quick whipstitch of an injured gallbladder is adequate to gain control of spillage and to move forward with the rest of a needed repair to the liver. In that case, a subsequent cholecystectomy is warranted. A major common bile duct injury can be clipped or controlled and drained externally to facilitate damage control, allowing reconstruction in the best possible circumstances. Placement of a choledochostomy tube can also allow control of biliary drainage if the downstream flow of the common bile duct is disrupted. In the most dire of circumstances, if the duct cannot be located, a drain can be left in Morison's pouch until the return operation. When it is time to repair a biliary injury, a T tube may be sufficient, for instance, in a clean stab wound injury. In larger more complex injuries, a Roux-en-Y hepaticojejunostomy is recommended for definitive reconstruction. Delayed workup with magnetic resonance cholangiopancreatography can provide more anatomic definition of the site and severity of injury. Endoscopic retrograde cholangiopancreatography (ERCP) or interventional radiology approaches can be considered for treatment if leaks are identified (Fig. 6). Definitive treatment may include long-term stent placement to allow the injury to heal with or without external biliary drainage via percutaneous tube.

COMPLICATIONS

Because the liver is such a highly vascular organ, traumatic injury to the liver carries risks of delayed venous or arterial bleeding. Teams should have a high suspicion of rebleed, particularly in the setting of new-onset pain, hypotension, tachycardia, change in drain output, or gastrointestinal bleeding. Arterial pseudoaneurysm can be a life-threatening complication that may not be recognized until it results in a massive bleed, even weeks or months after the original insult. Clinically evident gastrointestinal bleeding can be caused by a pseudoaneurysm bleeding into the biliary tree. Any small, unstable bleed, whether from a drain or gastrointestinal tract, should be investigated as possible hemobilia. The diagnosis can be confirmed on CT angiography and should be managed with interventional radiology as the first step.

After surgical repair or embolization of high grade liver injury, the liver frequently has some necrosis. Although it can be sterile, it

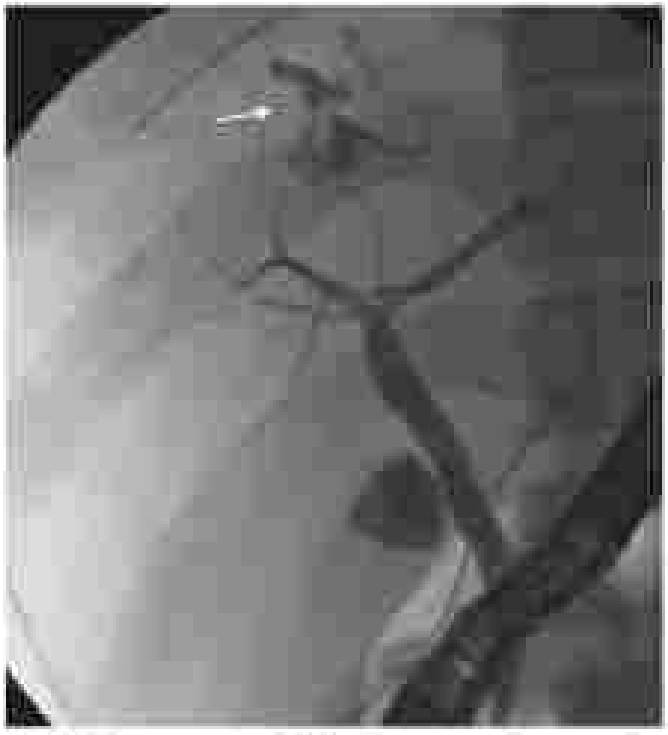

FIG. 6 Endoscopic retrograde cholangiopancreatography after gunshot to liver with resulting intrahepatic bile leak (arrow).

can become secondarily infected, particularly in patients with concomitant gastrointestinal injury or after biliary instrumentation during ERCP, which can seed the necrotic area with enteric organisms. Infected hematomas or other abscesses can be identified on CT scan and are best managed with percutaneous drainage as a first step, with surgical management only occasionally being needed.

Delayed biliary complications such as bile leak may require management as described earlier using combinations of surgical, interventional radiology, and/or advanced therapeutic endoscopic techniques.

CONCLUSION

Treatment of traumatic liver injury encompasses the spectrum from nonoperative watchful waiting with short hospital stay to massive open repair requiring damage control principles. In hemodynamically stable patients, selective nonoperative management is the treatment modality of choice but requires close monitoring and frequent reevaluations. For stable patients or those who are transiently responsive with arterial extravasation on CT, interventional angioembolization can provide excellent hemostasis. Hemodynamic instability and peritonitis necessitate immediate operative intervention. Surgeons should be encouraged to ask for assistance as needed, using any and all tools at their disposal to gain control of the field in an expeditious manner.

Suggested Readings

Como J, Bokhari F, Chiu W, Duane T, et al. Practice management guidelines for selective nonoperative management of penetrating abdominal trauma. J Trauma. 2010;68(3):721–733.

Kozar RA, Moore FA, Moore EE, et al. Western Trauma Association critical decisions in trauma: nonoperative management of adult blunt hepatic trauma. J Trauma. 2009;67:1143.

Kozar RA, Moore JB, Niles SE, et al. Complications in nonoperative management of high-grade blunt hepatic injuries. J Trauma. 2009;67(6):1304–1307.

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Pancreatic and Duodenal Injuries

Faris K. Azar, MD, Rachel L. Cheron, MD, and Joseph A. Salcedo, MD, MPH, FACS

Injuries to the pancreas and duodenum are challenging to diagnose and surgically manage. The first description of a duodenal injury was in 1814 by Larrey in France. Later in 1827, Travers described the first pancreatic injury in England. Although 200 years of surgical advancement have passed, these injuries continue to be associated with high morbidity and mortality. They remain difficult to manage because of their complex relationship with neighboring organs and vascular structures. A high index of suspicion must be maintained because delayed recognition of duodenal and pancreatic injuries results in increased morbidity and mortality. Early mortality in both injuries is a result of concomitant vascular trauma, whereas late mortality is typically related to infectious complications.

DUODENAL INJURIES

Outcomes

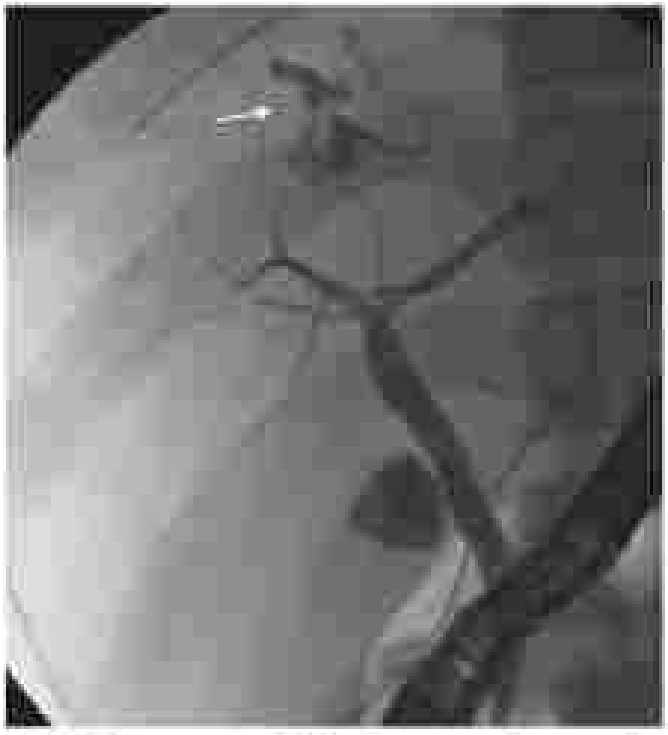
Although duodenal injuries are not common, they are associated with high morbidity and mortality. Overall mortality of patients with duodenal injuries ranges from 12% to 60%. Penetrating injuries are associated with higher mortality as compared with blunt injuries (25% vs 12%, respectively). Of those patients with delayed mortality, one third of the deaths are secondary to the duodenal injury itself.

Diagnosis

Early recognition is paramount in managing duodenal injuries to improve outcomes. The delayed identification of duodenal injuries beyond 24 hours is not uncommon and has even been described to occur in up to 20% of patients with duodenal injuries. Additionally, mortality rates of patients with delayed operative management beyond 24 hours are 40% compared with 10% of patients who undergo immediate surgical intervention.

The mechanism and pattern of injury should be considered when developing the differential of possible injuries. Blunt force trauma to the epigastrium from objects like seatbelts, handlebars, or steering wheels can result in injuries to the duodenum or pancreas, given their location deep to the abdominal wall against the spine.

A plain radiograph can reveal a right psoas stripe indicating retroperitoneal air, which signifies a duodenal injury, but this is rarely seen. Because early recognition is paramount, the fastest way to detect an injury is by computed tomography (CT) or operative exploration. Although CT scan has been shown to be the best radiologic method for early diagnosis, it is still associated with a high missed injury rate—reported as high as 22% in blunt injury. In patients with duodenal injuries identified beyond 24 hours, most of these patients actually have subtle findings on admission CT scan indicating the presence of injury. Although the use of oral and intravenous



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Pancreatic and Duodenal Injuries

Faris K. Azar, MD, Rachel L. Chevron, MD, and Joseph V. Sakran, MD, MPH, MPA

Injuries to the pancreas and duodenum are challenging to diagnose and surgically manage. The first description of a duodenal injury was in 1814 by Larrey in France. Later in 1827, Travers described the first pancreatic injury in England. Although 200 years of surgical advancement have passed, these injuries continue to be associated with high morbidity and mortality. They remain difficult to manage because of their complex relationship with neighboring organs and vascular structures. A high index of suspicion must be maintained because delayed recognition of duodenal and pancreatic injuries results in increased morbidity and mortality. Early mortality in both injuries is a result of concomitant vascular trauma, whereas late mortality is typically related to infectious complications.

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contrast is the best diagnostic test for duodenal injury, the sensitivity and specificity of noncontrast CT scans has recently been compared favorably to blunt hollow viscus injury.

Alternative diagnostic tools include upper gastrointestinal series using water soluble contrast, followed up barium contrast if the first is negative. Although this is a diagnostic option, it is not a good initial test in trauma patients. Diagnostic peritoneal lavage is also an option to identify hollow viscus injuries, but it is not a great study to isolate duodenal injuries, given that second and third portions reside in the retroperitoneum.

Surgical Exposure of the Duodenum

Operative exploration is also a diagnostic tool to identify duodenal injuries. During exploration, retroperitoneal air, staining, hematoma, or hematoma should raise suspicion for duodenal injury. In this setting, the duodenum should be investigated and examined. Additionally, in penetrating trauma, following the trajectory of the bullet, knife, or foreign object can help determine the injury pattern.

Kocher Maneuver

The first step of the Kocher maneuver is to mobilize the right colon off the inferior aspect of the duodenal C loop by dividing the white line of Toldt. The lateral peritoneal attachments are incised and the second portion of the duodenum is rolled medially (Fig. 1). This dissection can be carried to the first and third portions of the duodenum. Doing so elevates the pancreatic head and exposes most if not the retroperitoneum.

Cattell-Braasch Maneuver

The Cattell-Braasch maneuver medially retracts the viscera to expose retroperitoneal structures. To explore the duodenum, the Kocher maneuver should be extended and a Cattell-Braasch maneuver completed. The white line of Toldt should be divided down to the cecum and up the root of the small bowel mesentery (Fig. 2). This allows for further mobilization of the duodenal C loop and pancreatic head to expose some of the retroperitoneum.

Dividing the Ligament of Treitz

Finally, to complete duodenal exposure, the fourth portion of the duodenum is exposed by dividing the ligament of Treitz. Combining all three maneuvers allows the surgeon to inspect the entirety of the duodenum, from the pylorus to the proximal jejunum.

FIG. 1 Kocher maneuver. Anterior (A) and cross-sectional (B) views of the mobilization after takedown of the lateral duodenal attachments. (Courtesy Carter Stephen from Cameron J, Stephen C, Atlas of Gastrointestinal Surgery, vol 1. 3rd ed. Shelton, CT: People's Medical Publishing; 2007.)

Treatment

Duodenal Hematoma

Duodenal hematomas are usually seen in children; 50% of cases are secondary to abuse. Duodenal hematomas do not typically require operative management. About one third of patients present 48 hours from initial injury with symptoms of gastric outlet obstruction. Diagnosis can be made via CT scan or upper gastrointestinal series, although only 25% of patients have findings consistent with wall thickening, narrowed lumen, or displacement of the duodenum.

Duodenal hematomas can be managed nonoperatively with nasogastric suction and parenteral nutrition. Most do not require surgical management, but there is a 20% to 40% rate of concomitant pancreatic injury in both the pediatric and adult populations with duodenal hematomas. Therefore, exclusion of other injuries is imperative. A second upper gastrointestinal series with enteral contrast should be completed after 5 to 7 days of therapy to rule out continued obstruction or leak and ensure patency prior to resuming a diet.

If the nonoperative management fails after 2 weeks, operative intervention should be pursued to rule out stricture or pancreatic head injury. If the duodenal hematoma is identified on injury presentation intraoperatively, the duodenum should be thoroughly mobilized for exploration to rule out perforation. Once perforation is ruled out, a gastrojejunostomy or jejunostomy feeding tube should be considered.

Primary Repair

Injuries to the duodenum should be repaired primarily if possible. In cases of partial or complete duodenal transection without significant involvement and with little tissue loss, successful edge debridement and primary repair should be pursued. The goal is for a secure closure without compromise of the duodenal lumen. A two layer closure technique should be utilized if possible to include an inner layer of absorbable suture and an outer layer of silk Lembert sutures. If the second layer results in narrowing of the duodenum, a single layer closure can be buttressed with an omental pedicle. All patients with duodenal injuries should have wide drainage of the repair. Typical postoperative management includes nothing by mouth (NPO) with nasogastric drainage for 3 to 5 days and a dynamic enteral contrast study to evaluate the repair before reintroduction of a diet.

Many studies advocate for primary duodenal repair, even in grade III, IV, and V duodenal injuries (Table 1). No difference in morbidity, mortality, or length of stay is seen in patients repaired with duodenorrhaphy or resection with primary anastomosis when compared with pyloric exclusion. However, in cases of multiple duodenal injuries or those concomitant with pancreatic injuries, we prefer a more durable procedure with intraluminal drainage or enteric diversion to allow for healing.

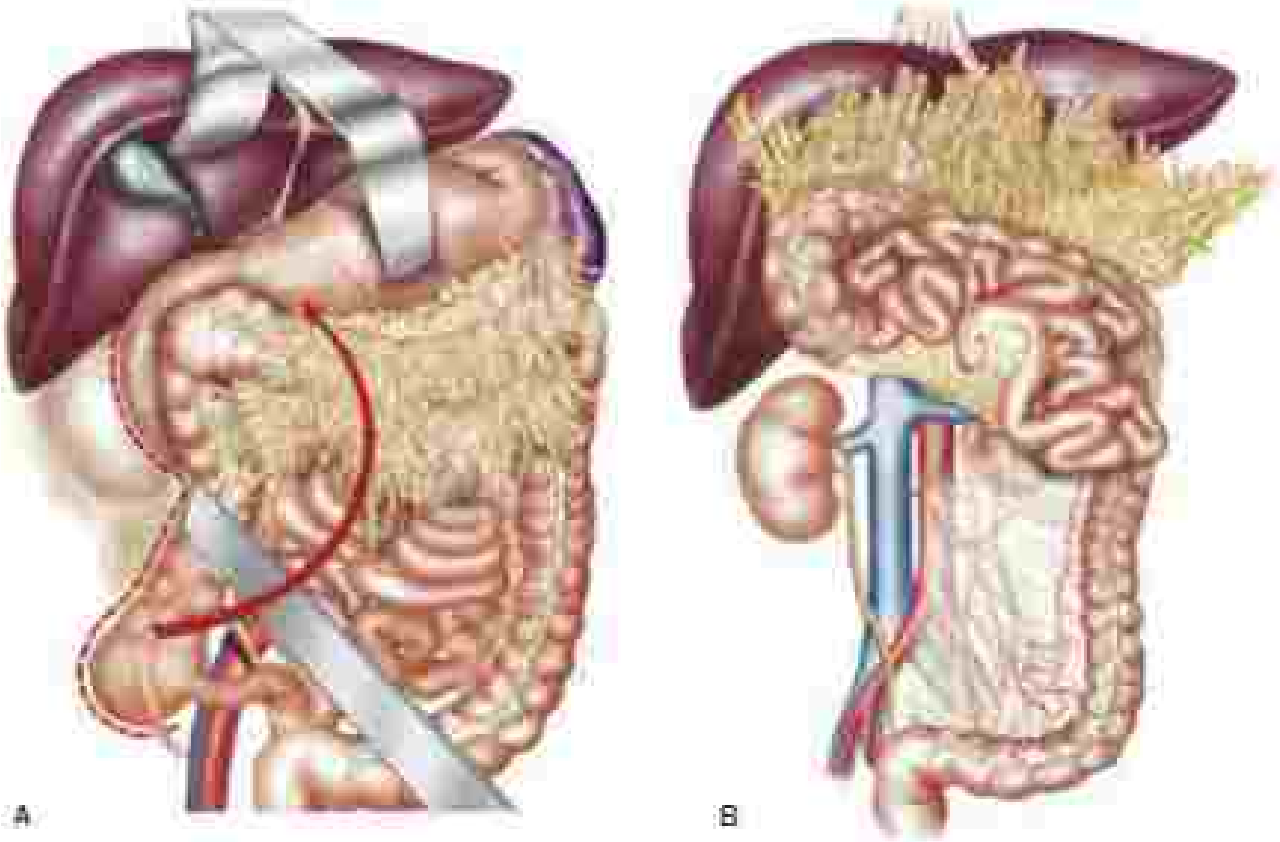


FIG. 2 Cattell-Braasch maneuver. Division of the lateral peritoneal attachments with extension up the root of the mesentery (A) and medial visceral rotation (B). (From Voigt J, Li M. Abdominal hysterotomy or damage control laparotomy: why when and how to do it? Vasc Surg. 2005;39:484 suppl.)

TABLE 1 American Association for the Surgery of Trauma Duodenum Injury Scale

Grade*	Injury	Description
I	Hematoma Laceration	Involving single portion of duodenum Partial thickness, no perforation
II	Hematoma Laceration	Involving more than one portion Disruption <50% of circumference
III	Laceration	Disruption 50%–75% of circumference of D2 Disruption 50%–100% of circumference of D1, D3, D4
IV	Laceration	Disruption >75% of circumference of D2 Involving ampulla or distal common bile duct
V	Laceration Vascular	Massive disruption of duodenopancreatic complex Devascularization of duodenum

*Advance one grade for multiple injuries up to grade III.
D1, first portion of duodenum; D2, second portion of duodenum; D3, third portion of duodenum; D4, fourth portion of duodenum.
From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990; 30(11):1427–1429.

Duodenal Diverticularization

Primary repair has been proven safe and acceptable but it is not always feasible. Duodenal diverticularization was first described in 1974 by Berne et al. It involves a gastric antrectomy with an end-to-side gastrojejunostomy, biliary T-tube placement, proximal duodenostomy tube placement, closure of the duodenal injury, and wide drainage (Fig. 3). This procedure results in permanent enteral diversion. We describe this for historic reasons but do not recommend its use in the traumatically injured patient. Duodenal diverticularization subjects patients to a larger physiologic insult and is associated with both increased operative time and complications.

Pyloric Exclusion with Gastrojejunostomy

Pyloric exclusion was first described by Summers in 1904. This technique diverts enteral contents away from the duodenal repair via a loop gastrojejunostomy and a temporary anatomic diversion. Pyloric exclusion can be completed with a transverse anastomosis stapler across the distal antrum, but we favor suturing the pylorus closed with absorbable suture through a gastrotomy (Fig. 4). Stapling of the gastric mucosa will result in recanalization of the distal stomach after several weeks.

Whereas some studies have suggested improved morbidity when using the pyloric exclusion technique in complex duodenal injuries, most studies have not shown a difference in outcomes when compared with primary repair even in severely injured patients.

Roux-en-Y Duodenojejunostomy

In the setting of severe duodenal injuries that cannot be repaired primarily, we favor the use of Roux-en-Y duodenojejunostomy reconstruction. Before reconstructing the duodenum, it is important to

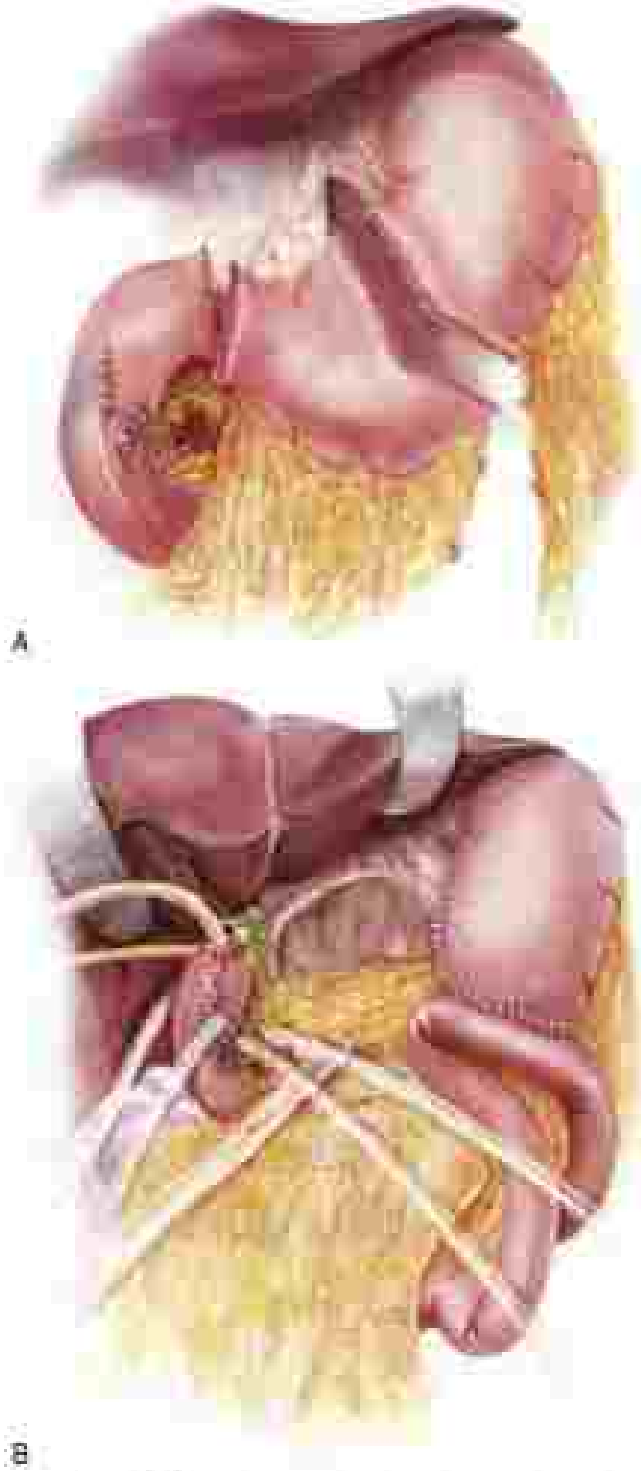


FIG. 3 Duodenal thoracostomy shown for lesions undermining. Gastric anastomosis (A) with a gastrojejunostomy, biliary T-tube, duodenostomy tube, and wide drainage (B). (Courtesy Carmine Sansone. From Cameron J, Sanfelice C. Atlas of Gastrointestinal Surgery, vol 1. 2nd ed. Shelton CT: People's Medical Publishing; 2007.)

understand the proximity of the injury and the ampulla of Vater because an enteric anastomosis impinging on unidentified ampulla could result in devastating consequences. If the ampulla cannot be visualized or identified via the duodenal injury itself, the gallbladder can be dissected off the liver bed and cannulated just above or through the cystic duct with a Fogarty catheter, which is manually guided down the common bile duct through the ampulla into the duodenum (Fig. 5).

If the ampulla is not immediately adjacent to the injury and its patency will not be compromised, a Roux-en-Y duodenojejunostomy should be fashioned. This anastomosis is ideally fixed securely in two layers in an end to side fashion (Fig. 6). However, a side to side anastomosis can also be done for injuries to the lateral aspect of the second portion of the duodenum. This repair is also favored in the setting of concomitant pancreatic injuries; primary duodenal repairs are at high risk for breakdown in the setting of pancreatic secretion.

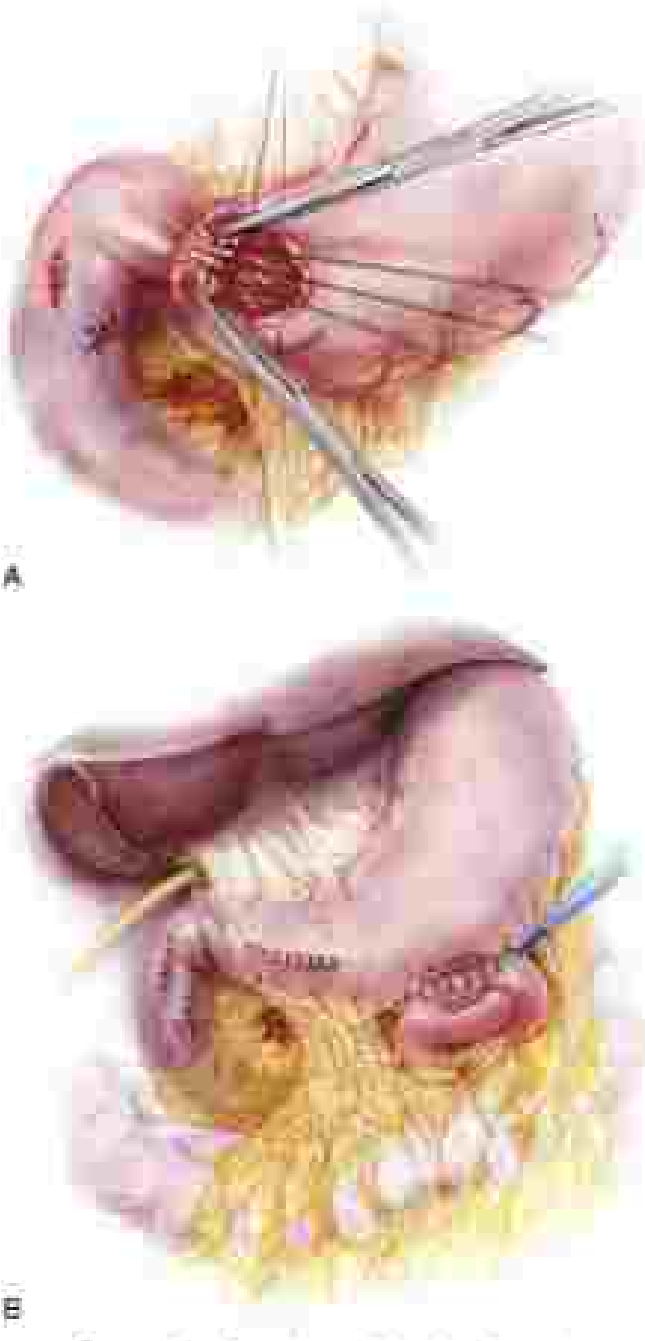


FIG. 4 Pyloric occlusion. Suture closure of the pylorus through a gastrotomy (A) and enteral diversion with a gastrojejunostomy (B). (Courtesy Carmine Sansone. From Cameron J, Sanfelice C. Atlas of Gastrointestinal Surgery, vol 1. 2nd ed. Shelton CT: People's Medical Publishing; 2007.)

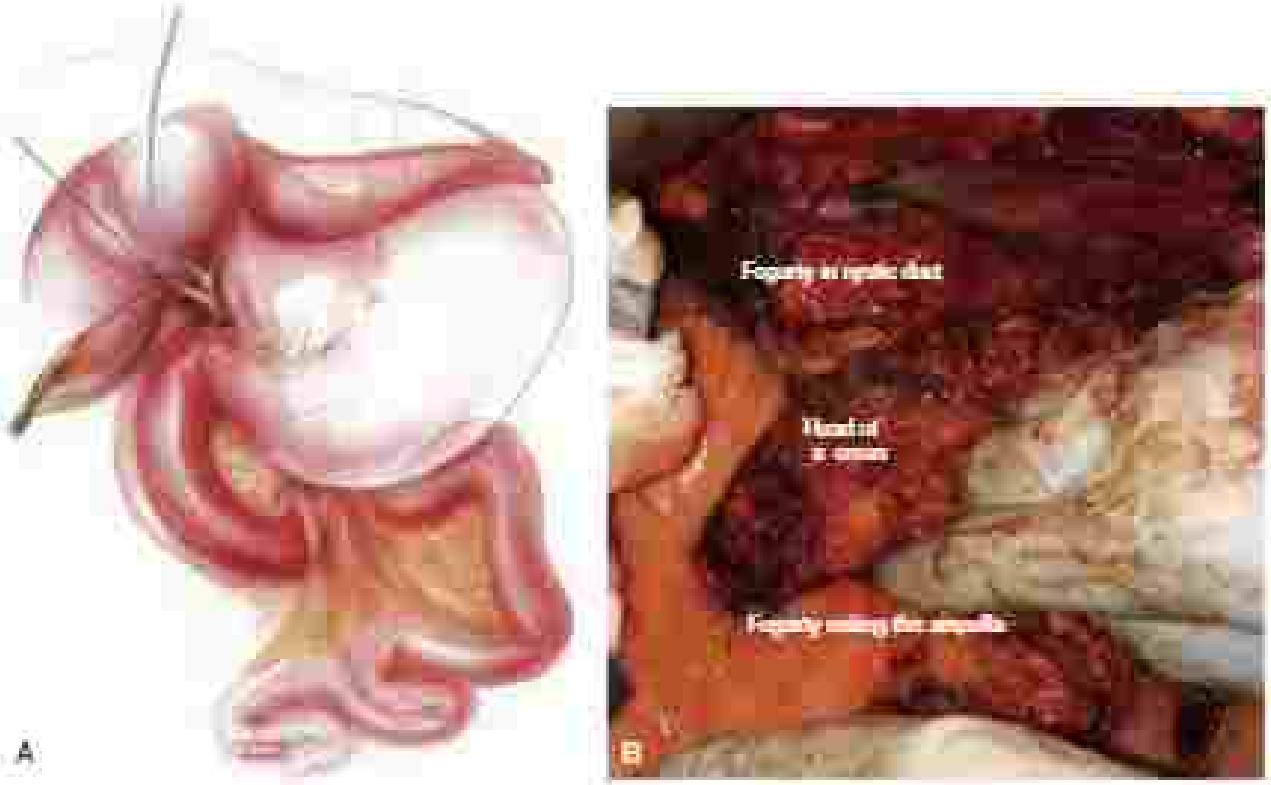


FIG. 1 Biliary injury passage to identify the ampulla. (A) Illustration. (B) Intraoperative photograph. (Courtesy Caitlin Sanders, Penn Germantown.) Sanders C. Atlas of Gastrointestinal Surgery, 2nd ed. Shelton, CT: People's Medical Publishing; 2014.

FIG. 2 End-to-side duodenojejunostomy, hand-sewn technique. (Courtesy Caitlin Sanders, Penn Germantown.) Sanders C. Atlas of Gastrointestinal Surgery, 2nd ed. Shelton, CT: People's Medical Publishing; 2014.

exposure, whereas a Roux-en-Y duodenojejunostomy provides more protection. Patching a duodenal injury with jejunal serosa has also been used, but our preference is for a more durable reconstructive procedure when possible.

Intraluminal Decompression Tubes

A duodenal leak after repair is a morbid complication that surgeons should avoid. Tenuous primary duodenal repairs that are not secure enough to warrant enteric diversion can be protected with internal drainage. Reducing the flow of biliopancreatic and gastric contents across the repair allows for healing.

Direct drainage of the duodenum through the duodenal suture line via a lateral duodenostomy tube should be avoided. This method of drainage is associated with high morbidity with direct complications including development of a difficult fistula.

A "triple tube" technique for decompression is favored by many surgeons. This provides duodenal decompression with both an antegrade gastrostomy tube and a retrograde jejunostomy tube; additionally, distal feeding jejunostomy is placed. Although this may provide thorough internal drainage, the antiperistaltic direction of the retrograde jejunostomy tube can cause it to fly out of place or become a possible point of obstruction or intussusception.

Our preferred method of internal drainage involves the use of a proprietary triple-lumen Mini gastrojejunostomy tube, which alone has the same functionality as the triple tube technique. It is a rigid 18F tube with large holes above and below the pylorus that allows for effective drainage of both the stomach and duodenum. Additionally, it is proprietatic, allowing for gastric and duodenal suctioning while having the capability for enteral feeding via a long distal port (Fig. 7).

More complex injuries to the duodenum such as those that involve the ampulla or pancreas, head are sometimes not salvageable; they may necessitate reconstruction via a pancreaticoduodenectomy, which is discussed later in this chapter.

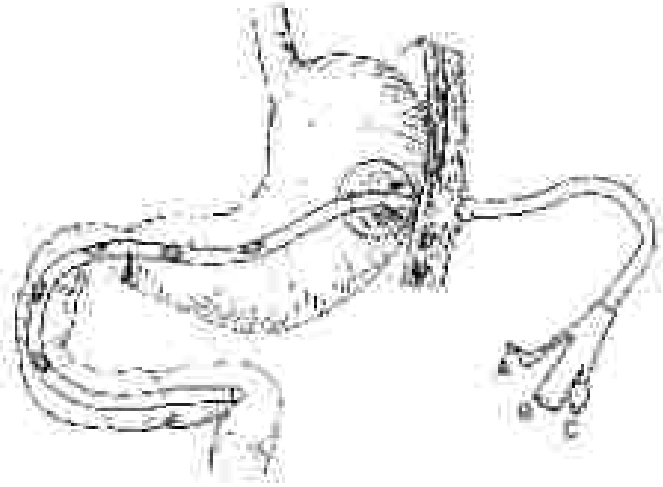


FIG. 7 Gastrojejunostomy tube. Internal drainage of the duodenum with a distal feeding port. (From Lloyd MD: abr J Cameron JM: Atlas of Surgical Oncology. Philadelphia: WB Saunders; 1995.)

FIG. 8 Anterior exposure of the pancreas. The gastrocolic ligament is divided and the pancreas is mobilized out of the retroperitoneum. (Courtesy George Sandblom, Jerrold Cameron, John Landau: C. Atlas of Gastrointestinal Surgery, ed 2. Decker, Hamilton, ON: People's Medical Publishing; 2004.)

PANCREATIC INJURIES

Outcomes

Pancreatic injuries are associated with high morbidity and mortality. Overall mortality of patients with pancreatic injuries range from 9% to 34% and rates of morbidity ranging from 30% to 60%. Early mortality is often a result of massive bleeding from an associated vascular or solid organ injury. The highest mortality is in patients with severe concomitant injuries requiring damage control laparotomy.

Diagnosis

It is critical to diagnose and manage pancreatic injuries immediately because delayed diagnosis and intervention leads to increased mortality. Physical examination in the trauma identifies area may reveal contusion to the epigastric region of the abdomen with pain out of proportion to the examination. An injury mechanism including high impact to the epigastrium from handlebars or a steering wheel should alert the surgeon to this possible injury pattern. Additionally, associated injuries, such as Chance fracture, have been associated with concomitant pancreatic injuries; suspicion for injury should increase in that setting. Laboratory testing resulting in elevated amylase and lipase is specific but not sensitive for predicting pancreatic injury. Importantly these laboratory values have been found to be nondiagnostic within the first 6 hours after injury, the most critical time to establish diagnosis.

CT scan is the radiographic test of choice in trauma patients. CT scan findings consistent with pancreatic injury include parenchymal disruption, intrapancreatic or peripancreatic hematoma, fluid in the lesser sac, peripancreatic edema, thickened left anterior renal fascia, and retroperitoneal fluid. Although CT scan is the test of choice in hemodynamically stable patients, the test still fails to identify all injuries, which can result in operative delay. The multicenter EuroSTAR CT study published in 2009 identified a 13% missed injury rate and a higher mortality in the patients with missed injuries.

Other tests can be time consuming and are not typically used in the acute workup after injury. However, in the hemodynamically stable trauma patient with an equivocal CT scan and an operative indication, endoscopic retrograde cholangiopancreatography can be both diagnostic and therapeutic for a pancreatic ductal disruption. Additionally, magnetic resonance cholangiopancreatography can also assess the integrity of the pancreatic duct.

Surgical Exposure of the Pancreas

Anterior Exposure

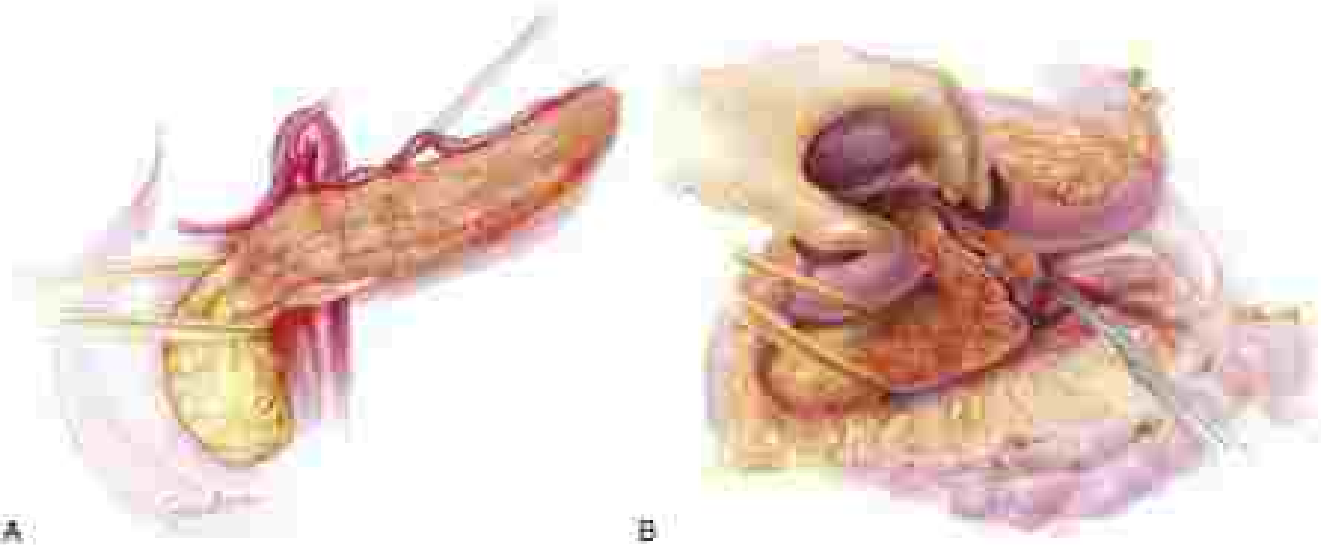
To gain anterior exposure of the pancreas, the right colon is mobilized inferiorly, the transverse mesocolon dissected free from the head of the pancreas, and the lesser sac is entered. The gastrocolic ligament is taken down with an energy device or clamps and tied to allow the omentum and transverse colon to be reflected inferiorly. This leaves the anterior aspect of the pancreas in view (Fig. 8). With the transverse mesocolon reflected inferiorly, venous tributaries can be followed down to identify the superior mesenteric vein (SMV) crossing anterior to the third portion of the duodenum.

Posterior Exposure

The posterior aspect of the pancreatic head is evaluated with the Kocher maneuver. The posterior aspect of the pancreatic body and tail can be exposed by medially rotating the spleen. Using the Attil maneuver, the spleen is detached from its attachments to the diaphragm, retroperitoneum, colon, and kidney. A plane is developed posterior to the splenic vessels and the organ is retracted medially to expose the posterior pancreatic body and tail (Fig. 9). This also serves as good exposure to identify injuries to zones I and II of the left retroperitoneum. Once all the maneuvers described for exposing the duodenum and pancreas have been completed, the only structures that remain tethering the pancreas to the retroperitoneum are the superior mesenteric vessels.

Interrogation of the Pancreatic Duct

The pancreas should be inspected for ductal injury. In cases where ductal injury is unclear, water soluble contrast with fluoroscopy or methylene blue dye can be used to look for pancreatic ductal injury. Using the same method described for passing a Foguty balloon to find the ampulla, a cholangiocatheter is passed with injection of the ductal system to radiographically or directly look for ductal disruption. Another method to perform a pancreatogram is to place a large bore intravenous line directly into the gallbladder with injection for



A B

FIG. 9 Posterior exposure of the pancreatic body and tail. Control of the splenic artery (A) before medial rotation of the pancreas out of the retroperitoneum (B). (Courtesy Corine Sandoval, from Cameron J, Sandoval C. Atlas of Gastrointestinal Surgery, ed 1. Shelton CT: People's Medical Publishing; 2001.)

fluoroscopy. Although this is less invasive and the defect in the gallbladder can be primarily repaired, it may not be best method to interrogate the pancreatic duct because contrast or dye is injected quite proximally and tends to pool in the gallbladder. These techniques can be time consuming and are only sometimes helpful in diagnosing a ductal injury.

Historically some advocated for interrogation of the pancreatic duct by direct cannulation after creating a duodenotomy or even performing a distal pancreatectomy. These procedures are not necessary, potentially dangerous, and result in additional injuries for enteric leak or pancreatic fistula formation. Direct cannulation of the pancreatic duct should be done only if a ductal injury already exists and provides easy access to the main pancreatic duct.

Treatment

Surgical Planning

The American Association for the Surgery of Trauma organ injury scoring classification for traumatic pancreatic injuries correlates and predicts morbidity and mortality (Table 2). In 2017, the Eastern Association for the Surgery of Trauma published practice management guidelines based on a systematic review of 37 articles. Grade I or II pancreatic injuries should have nonoperative or nonoperational management. For grade III or IV pancreatic injuries identified radiologically on CT scan or during intraoperative exploration, they conditionally recommend pancreatic resection. There were no conclusive recommendations for grade V injuries.

Surgical Intervention Based on Injury Grade

Grade I and II Injuries: Wide Drainage

Grade I and II injuries are consistent with lacerations or contusions to the pancreatic parenchyma without ductal involvement. Management of these injuries should consist of hemorrhage control and wide drainage. Parenchymal injuries should not be repaired, to avoid pancreatic fistula formation. Without concomitant injuries or contraindications, enteric nutrition should be given as soon as possible.

Grade III Injuries: Distal Pancreatectomy

Grade III injuries violate the pancreatic duct at the level of the pancreatic body or tail. A distal pancreatectomy is the procedure of choice in those patients with disruption of the main pancreatic duct.

TABLE 2 American Association for the Surgery of Trauma Pancreas Injury Scale

Grade*	Injury	Description
I	Hematoma Laceration	Minor contusion without duct injury Superficial laceration without duct injury
II	Hematoma Laceration	Major contusion without duct injury or tissue loss Major laceration without duct injury or tissue loss
III	Laceration	Distal transection or parenchymal injury with duct injury
IV	Laceration	Proximal† transection or parenchymal injury involving ampulla
V	Laceration	Massive disruption of pancreatic head

*Advance one grade for multiple injuries up to grade III.
†Proximal pancreas is to the patient's right of the superior mesenteric vein.
From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990;30(11):1427-1429.

Intraoperatively, the lesser sac is entered and the short gastric vessels divided. If the tortuous splenic artery is encountered along the superior aspect of the pancreas, it is encircled with a vessel loop for control. The spleen is elevated from the retroperitoneum on a plane deep to the splenic vessels (Fig. 9). Ideally the splenic artery and vein are dissected free from the pancreas and individually ligated with sutures. However, if the patient is hemodynamically unstable secondary to hemorrhagic shock, a distal pancreatectomy and splenectomy can be quickly achieved by firing a linear cutting stapler across the splenic vessels and again across the pancreas. The splenic vessels deep to the remaining pancreas should be inspected for hemostasis. Care should be given to the inferior mesenteric vein because it usually drains into the splenic vein.

After pancreatic division, we oversew the transected end of the pancreas using overlapping 3-0 absorbable figure of 8 or U stitch

sutures. Two factors that decrease the pancreatic leak rate after pancreatectomy are firm gland texture and visualization of the duct. Thus, if the duct is small, it should be oversewn with 5-0 synthetic absorbable suture. Distal pancreatic stumps should be widely drained, especially considering that the rate of pancreatic leak is higher in pts. (for distal pancreatectomy than for a pancreaticoduodenectomy (25% vs 15%, respectively).

Most trauma patients should undergo distal pancreatectomy with splenectomy because splenic preservation lengthens operating times significantly. With appropriate postoperative vaccinations, removal of the spleen in an adult patient rarely results in infectious complications. In fact, the operative morbidity associated with splenic preservation is higher. The splenic vessels must be meticulously dissected from the tail of the pancreas all the way to the splenic hilum, taking care to individually ligate small venous tributaries to the splenic vein. Splenic preservation should be done only by an experienced surgeon in a stable patient.

The goal of surgery for pancreatic injuries is to remove the segment of the pancreas with a violated duct and to preserve as much of the gland as possible. The exception to this dogma is for an injury to the body of the pancreas, which should not be treated with a segmental central pancreatectomy and pancreaticojejunostomy to the distal pancreas. We recommend against doing this in the trauma setting because this operation is morbid and yields two areas for potential pancreatic leak. We prefer an extended distal pancreatectomy with splenectomy for injuries to the pancreatic body. Even though this may waste pancreatic tissue and increase the likelihood of diabetes, it is a safer procedure with only one potential surface for pancreatic fistula formation.

Grade IV and V Injuries: Pancreaticoduodenectomy

Injuries consistent with proximal transection of the pancreatic head or parenchymal injury involving the ampulla are classified as grade IV pancreatic injuries. Massive disruption to the pancreatic head is consistent with a grade V pancreatic injury. It is not uncommon to have an associated duodenal injury in these patients as well. If these injuries cannot be managed by closed suction wide drainage alone, a Whipple operation may be necessary. In 2016, Krige et al. published a prospective study on 76 patients with grade V pancreatic and duodenal injuries. Nineteen of these patients underwent pancreaticoduodenectomy within this subpopulation there was a 16% mortality rate. If injuries are wide and dispersed throughout the pancreas, then a total pancreatectomy may be needed.

COMBINED DUODENAL AND PANCREATIC INJURIES

Complex injuries to the pancreatic head and duodenum or those duodenal injuries encroaching on the ampulla may necessitate a pancreaticoduodenectomy. These injuries are rare but can be seen with penetrating trauma and are usually associated with additional intra-abdominal injuries. The number one cause of mortality in patients with combined pancreatic and duodenal injuries is hemorrhagic shock from associated vascular injuries. Therefore, initial management is hemorrhage control.

After hemorrhage control, pancreatic and duodenal injuries need thorough evaluation with particular attention to the ampulla and biliopancreatic ductal structures. If the ampulla, distal common bile duct, or pancreatic duct is not intact in the setting of a severe duodenal injury, pancreaticoduodenectomy is the procedure of choice.

Damage Control Pancreaticoduodenectomy

Once a pancreaticoduodenectomy is determined to be necessary, deciding on a staged operation is critical. Trauma patients who undergo both resection and reconstruction during the initial operation are significantly more acidotic, hypothermic, and coagulopathic; additionally, they have significantly longer operative times. Therefore, the goals of the index operation are to achieve hemostasis and control contamination.

Once hemostasis is achieved, the right colon should be mobilized and the duodenum exposed using the Kocher maneuver. The transverse mesocolon is dissected from the pancreatic head and the lesser sac is entered by dividing the gastrocolic ligament. The SMV is dissected out over the third portion of the duodenum and the tunnel behind the pancreatic neck is initiated inferiorly.

The hepatoduodenal ligament is opened to reveal the portal triad. Care should be taken to avoid injuring aberrant vasculature such as a replaced right hepatic artery. The gastroduodenal artery (GDA) is encircled with a vessel loop. Our preference is to prevent spillage from the common hepatic duct by encircling it twice with the vessel loop using a Pilot technique and circling it down with a Rummel tourniquet. Next the gastrocolic arcade is divided and the distal stomach or proximal duodenum is divided. The common hepatic duct is then divided above the level of the cystic duct and a cholecystectomy is performed. The GDA is next clamped then divided using two 0 silk ties and the stump oversewn with a 3-0 Prolene suture. The underlying portal vein is exposed and the tunnel behind the pancreas can be completed from above. If time permits, stay sutures are placed superiorly and inferiorly to the pancreas before the gland is divided to control the pancreatic mesenteric vessels. The gland should then be divided with a stapler for temporary closure.

Ideally the pancreaticoduodenectomy specimen is removed as the index operation to remove any devitalized tissue. If possible, attention is turned to the intramesocolic compartment, where a segment of proximal jejunum is divided and the ligament of Treitz is taken down. Taking this down at a later operation risks bleeding from dilated mesenteric vein tributaries. The duodenum can then be passed below the mesenteric vessels. The final step is the dissection of the uncinate process off the portal vein and SMV. The liver stage of the damage control operation can be considered complete and a temporary abdominal closure device should be placed.

Reconstruction can be pursued in a second operation once resuscitation in the intensive care unit has been completed. Temporary closure of the hepatic and pancreatic ducts in the index operation allows them to dilate, making reconstruction easier in the subsequent operation. The jejunal limb is brought up in a retrocolic fashion through the base area of the transverse mesocolon. We perform an end-to-side duct-to-mucosa pancreaticojejunostomy in two layers. A posterior row of 3-0 silks is followed by a pancreatic duct to jejunal mucosal anastomosis with 5-0 absorbable monofilament sutures. An anterior row of interrupted 3-0 Lembert silk sutures is placed to complete the two layer anastomosis. Distal along the afferent limb, an end-to-side choledochojejunostomy is performed with a single layer of 4-0 absorbable monofilament sutures. Mesenteric defects are then closed.

A Hofmeister gastrojejunostomy is then created, our preference is a two layered hand-sewn anastomosis. We usually perform this anastomosis in an antecolic fashion in the trauma setting. Finally, a pedicle of omentum or falciform ligament is placed over the GDA to try to occlude it and prevent hemorrhagic complications in the case of a pancreatic fistula. Two closed suction drains should be placed above and below the anastomoses.

Ultimately, there are many ways to reconstruct during a Whipple operation (Fig. 103). The surgeon should utilize past experience and perform whichever technique are most comfortable.

OUTCOMES AND COMPLICATIONS

Complications after elective pancreatic and duodenal surgery are common, but when they are managed in high volume centers they usually do not lead to long-term consequences. In the trauma population, because of altered physiology and concomitant injuries, the complication rate is higher. Wide drainage of injuries and repairs cannot be overemphasized. More likely than not, a patient undergoing a

FIG. 18 Whipple procedure reconstruction: pancreaticojejunostomy, choledochojejunostomy and gastrojejunostomy. (Courtesy Carrie Stoltzfus, from Cameron J, Sandone C. Atlas of Gastrointestinal Surgery, vol 1, 2nd ed. Shelton CT: People's Medical Publishing; 2007.)

Whipple procedure for trauma will experience a complication. Our philosophy in dealing with this complex area of the body is that the simplest and safest techniques should be utilized.

Duodenal Leak

Leakage from a duodenal repair can be managed conservatively if the patient is adequately drained and clinically stable. These patients should be kept NPO and parenteral nutrition started. A dynamic contrast study should be done before an attempt at feeding to ensure that the leak has sealed.

Biliary Leak

While drainage is diagnostic and can be therapeutic as well. A biliary leak can be managed by interventional radiology with a percutaneous transhepatic catheter passed through the choledochojejunostomy to maintain the biliary leak. Endoscopic procedures should be avoided because insufflation of the afferent limb can lead to anastomotic disruption.

Pancreatic Fistula

Pancreatic fistula formation is higher for distal pancreatectomy than for pancreaticoduodenectomy, and usually drainage is sufficient. These are usually diagnosed by measuring drain amylase levels once the patient has resumed a diet. More clinically significant leaks may require NPO, intravenous nutrition, and possibly a somatostatin analogue like octreotide to promote closure. A leak from a distal pancreatectomy usually irritates the posterior wall of the stomach and can lead to ulcerating nausea.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) after pancreaticoduodenectomy can delay diet resumption. This phenomenon is poorly understood and is common after a Whipple operation. It is typically managed conservatively with prokinetic agents such as erythromycin and supportive care. DGE usually resolves over 2 to 3 weeks. Ultimately, if conservative management fails, a percutaneous gastrojejunostomy feeding tube may need to be placed for enteral feeds.

Hemorrhagic Complications

The most morbid of complications is postpancreatectomy hemorrhage. Subtle signs of bleeding and drain character should be followed closely. Early bleeding is the result of incomplete hemostasis and usually requires operative exploration. Delayed bleeds are usually the result of pseudoaneurysm formation from caustic GI/pancreatic secretions and are associated with high morbidity and mortality.

A change in drain output character to sanguineous indicates a wound bleed with several options; this can quickly lead to massive bleeding with exsanguination. If the patient is hemodynamically stable, the preferred course of action is to take the patient directly to interventional radiology for a diagnostic and potentially therapeutic procedure. Delayed bleeding after a Whipple operation is usually from a GDA pseudoaneurysm, whereas following a distal pancreatectomy, the splenic artery is usually the source. If bleeding is uncontrolled radiographically or the patient is unstable, the patient should be brought back to the operating room.

CONCLUSION

Duodenal and pancreatic injuries remain difficult to diagnose and treat. Although rare, they are associated with high morbidity and mortality. Early diagnosis along with a thorough understanding of hepatopancreaticobiliary anatomy and the techniques available to deal with such injuries are paramount to achieving the best outcomes.

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Injuries to Small and Large Bowel

Lily Tang, MD, and Carrie A. Sims, MD, PhD, FACS

The likelihood of sustaining injury to the small or large bowel depends greatly on the mechanism. With blunt abdominal trauma, the bowel can be crushed against the vertebrae, causing injury, or there can be a sudden increase in intraluminal pressure, leading to rupture. Injury can also occur with rapid deceleration, causing tangential tears at relatively fixed points (e.g., hepatic and splenic flexures). Overall, blunt abdominal trauma results in a fairly low incidence of bowel injury (1%–4%). In contrast, the small and large bowel are the most frequently injured organs in penetrating abdominal trauma. Abdominal stab wounds are associated with injury to the bowel in 20% of cases. The incidence dramatically increases to 80% after gunshot wounds.

If diagnosed promptly, the treatment of bowel injuries is fairly straightforward and results in minimal injury-specific morbidity. Missing an injury for more than 8 hours, however, has been shown to significantly increase not only morbidity but also mortality. A delay of 8 to 24 hours increases the mortality from 2% to 9.1% and a delay of more than 24 hours increases the risk of death to 30.8%. Unfortunately, there is no single diagnostic test, other than surgical exploration, that can definitively confirm or exclude a bowel injury. Given that routine laparotomy is nontherapeutic in roughly 50% of cases and carries up to a 4% lifetime risk of morbidity, there has been increasing interest in developing practice guidelines that utilize minimally invasive diagnostic adjuncts such as computed tomography or diagnostic laparoscopy.

DIAGNOSING BLUNT BOWEL INJURIES

The diagnosis of small bowel or colon injuries after blunt abdominal trauma can be challenging and requires a high index of suspicion. We have adopted the Eastern Association for the Surgery of Trauma algorithm for blunt abdominal trauma to standardize the evaluation of blunt bowel injury (Fig. 1). Although a physical examination should be performed, it lacks the necessary sensitivity and specificity needed to be a reliable screening tool. That being said, there are nonspecific clinical findings (e.g., tachycardia, abdominal tenderness, or peritonitis) that could be the result of a bowel injury and warrant further investigation. Additionally, identifying lower abdominal ecchymosis caused by the lap portion of the seatbelt ("seatbelt sign") or radiographic evidence of a lumbar vertebral body compression fracture (Chance fracture) should increase the suspected concern for bowel injuries. Nonspecific abnormal laboratory values, including elevated white blood cell (WBC) count, hypercoagulants, and lactic acidosis, may also suggest hollow viscus injury and warrant further investigation.

Imaging plays a critical role in diagnosing blunt intraabdominal injuries. Although focused assessment with sonography for trauma (FAST) is a good triage tool to assess intraabdominal bleeding in unstable patients, its use in evaluating bowel injury is remarkably limited. In addition to being operator dependent, the FAST cannot detect less than 100 mL of abdominal fluid and cannot distinguish between ascites, blood, or mucus. Similarly, radiographs are not useful for identifying intraabdominal injuries and only serve to delay the patient's evaluation and treatment.

Computed tomography (CT) scans are currently the best imaging modality available to evaluate intraabdominal injuries in the hemodynamically stable patient. Sensitivity and specificity for diagnosing blunt bowel or mesenteric injuries on CT scan is as high as 88.3% and 99.8%, respectively. CT findings that suggest a blunt bowel or mesenteric injury (Table 1) include intraperitoneal free fluid without signs of solid organ injury, pneumoperitoneum, stranding around the bowel or mesentery, bowel wall thickening, bowel wall ischemia, mesenteric hematoma, vascular blush, and oral (or rectal) contrast extravasation. Although CT scans have high sensitivity and specificity for intraabdominal injuries, segmental small bowel devascularization injuries secondary to mesenteric avulsion ("bucket handle") remain difficult to diagnose. This type of injury may present only with free fluid on imaging, which may be confounded by the presence of solid organ injuries and concomitant hemoperitoneum. As such, the surgeon must have a high clinical suspicion and a low threshold for going to the operating room. When CT scans are inconclusive for bowel injury and there are no other indications to go to the operating room, a nonoperative approach with serial abdominal examinations and serial laboratory work can be considered. If a nonoperative approach is pursued, patients with intraabdominal injuries will typically manifest signs or symptoms (e.g., tachycardia, hypotension, increased abdominal tenderness, development of peritonitis, increase in WBC or lactate) within 9 hours of observation.

When CT scans are unavailable, historically diagnostic peritoneal lavage (DPL) has been described as an option for diagnosing blunt bowel injury. DPL can also be used in patients who have free fluid on CT scan with no evidence of solid organ injury to help determine whether there is a hollow viscous injury that requires operative intervention. Although DPL has a high sensitivity for blunt bowel injuries (99%), it is an invasive procedure with low specificity (83%).

DIAGNOSING PENETRATING BOWEL INJURIES

Penetrating abdominal trauma is frequently associated with bowel injuries. In unstable patients, these injuries do not require imaging and should be identified on laparotomy. In stable patients, the diagnostic algorithm depends on the mechanism of wounding (Fig. 2).

Gunshot Wounds

Given that 80% of abdominal gunshot wounds are associated with bowel injuries, it should be assumed that patients with this mechanism of injury will require a laparotomy. This is particularly true if there is evidence of peritonitis, evisceration, hematemesis, gross blood per rectum, or hematuria. For hemodynamically stable patients who do not meet these criteria, radiographs of the chest, abdomen, and pelvis can be used to ascertain the bullet's trajectory, to determine whether retained fragments are present, and to help triage the thoracic cavity. Obviously, any evidence of free air mandates surgical exploration. Although the FAST examination cannot rule out a bowel or mesenteric injury, it can assess for the presence of intraabdominal free fluid. If these imaging modalities are negative (or inconclusive) or the patient does not have a reliable abdominal examination result, a CT of the abdomen/pelvis can be obtained. Findings on CT imaging that suggest small bowel or large bowel injury include intra-abdominal free air, free fluid without evidence of solid organ injury, bowel wall thickening, lack of bowel wall enhancement, mesenteric stranding or active extravasation, or extravasation of oral contrast. Although DPL has been historically performed, its role in the management of abdominal gunshot wounds is limited to situations where CT imaging is unavailable. Positive DPL findings include more than 10 mL of gross blood on initial aspiration, more than 100,000 red blood cells/mm^3, more than 500 WBC/mm^3, or the presence of bile, bacteria, or food particles.

Any concern for bowel injury should prompt operative exploration. However, there are two pathways for managing stable patients with negative (or inconclusive) CT imaging and reassuring clinical examination results. These patients can either be observed with

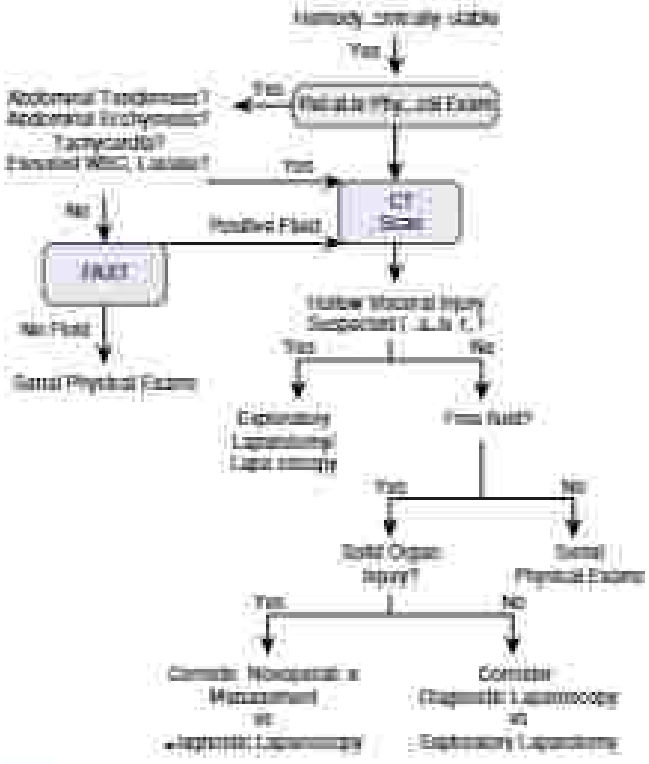

FIG. 1 Evaluation of blunt abdominal bowel injury. CT, Computed tomography; FAST, focused assessment with sonography for trauma; WBC, white blood cell count.

TABLE 1 Computed Tomography Findings Suggestive of Bowel Injury

CT Findings	Percentage With Findings
Free fluid	82.4%
Free fluid without solid organ injury	2.3%
Bowel wall thickening	10.2%
Pneumoperitoneum	7.2%
Mesenteric stranding	8.6%
Contrast extravasation	3.4%
Chance fracture	1.2%

CT, Computed tomography.
From Tahir MM, Wani OH, Lucheta JR, for the EAST Multi-Institutional 1993 Research Group. Current diagnostic approaches lack sensitivity in the diagnosis of perforated blunt small bowel injury: analysis from 275,557 trauma admissions from the EAST multi-institutional HVI trial. J Trauma. 2011;70(2):298–304.

serial examinations or undergo surgical exploration with a diagnostic laparoscopy or exploratory laparotomy. If injuries are identified on diagnostic laparoscopy, the procedure should be converted to a laparotomy.

Stab Wounds

Hemodynamically unstable patients with stab wounds to the abdomen warrant immediate surgical intervention (see Fig. 2). Evidence of evisceration, impalement, or peritonitis should also prompt surgical exploration. However, in contrast to gunshot wounds, stab wounds to the abdomen are less likely to result in bowel injuries and can be managed in a number of ways. A screening upright chest radiograph can be used to evaluate all abdominal stab wounds and the presence of free air mandates either laparoscopy or laparotomy. The absence of pneumoperitoneum, however, does not exclude a bowel injury, and further evaluation is guided by the location of the injury.

Anterior Abdominal Stab Wounds

Hemodynamically stable and reliable patients with anterior abdominal stab wounds can be managed nonoperatively with serial abdominal examinations or they can be evaluated for peritoneal violation using local wound exploration or diagnostic laparoscopy. If local wound exploration is positive for anterior fascial penetration, the patient should undergo diagnostic laparoscopy to rule out peritoneal violation. In the setting of peritoneal violation, either a therapeutic laparoscopy or exploratory laparotomy is indicated, depending on the surgeon's skill set. CT imaging can also be successfully used and has reported negative predictive value of 100%. CT scan findings that are suggestive of peritoneal penetration or bowel injury require abdominal exploration.

Flank and Back Stab Wounds

Stab wounds to the flank or back are less likely to cause small bowel injuries but may injure the colon. Unlike anterior stab wounds, physical examination and FAST are unreliable adjuncts for evaluating flank or back wounds given the retroperitoneal location of the ascending and descending colon. Thus CT imaging, with or without rectal contrast, has become the preferred diagnostic modality. Surgical exploration is warranted with any evidence of contrast extravasation from the colon, hematoma or stranding near the colon, free air in the retroperitoneum, pneumoperitoneum, or free fluid in the peritoneal cavity. The decision to proceed with laparoscopy or laparotomy should be dictated by patient stability and the surgeon's technical ability.

Thoracoabdominal or Upper Abdominal Stab Wounds

Although thoracoabdominal or upper abdominal stab wounds may result in bowel injuries, they are more frequently associated with injuries to the diaphragm. As such, the potential for diaphragm injury and herniation drives the management. Physical findings (e.g., hemothorax, pneumothorax) or CT scan findings suggestive of bowel injury (see Table 1) warrant immediate exploration. The presence of either pneumothorax or hemothorax on chest radiograph or CT scan strongly suggests diaphragm violation and warrants early laparoscopy. In all other cases, diagnostic laparoscopy should be performed within 8 to 12 hours to rule out a diaphragm injury.

MANAGEMENT OF SMALL-BOWEL INJURIES

Before incision, antibiotics with broad spectrum aerobic and anaerobic coverage should be given. If a hollow viscus injury is identified, antibiotics should be given for only an additional 24 hours. Regardless of mechanism of injury, the management of small bowel injuries begins with "running the bowel" from ligament of Treitz to cecum to identify all injuries. Free perforations can be temporarily managed with gentle occlusion using umbilical ties. All hematomas to the bowel wall or mesentery should be explored to ensure no injuries are missed. This is particularly true with stab wounds, where a hematoma can look deceptively benign. It is also worth noting that gunshot wounds will have a zone of injury that should be debrided before definitive repair. The management of small bowel injuries is dependent on the grading system cited by the American Association for the Surgery of Trauma (AAST) (Table 2). AAST grade I injuries (contusion or hematoma without devascularization, partial thickness laceration with no perforation) can be repaired by reapproximating the seromuscular layers with a single layer of 3-0 silk sutures (Lembert or Gehrken). Grade II (lacerations that comprise less than 50% of the bowel circumference) and grade III injuries (lacerations >50% of bowel circumference without transection) are repaired by limited

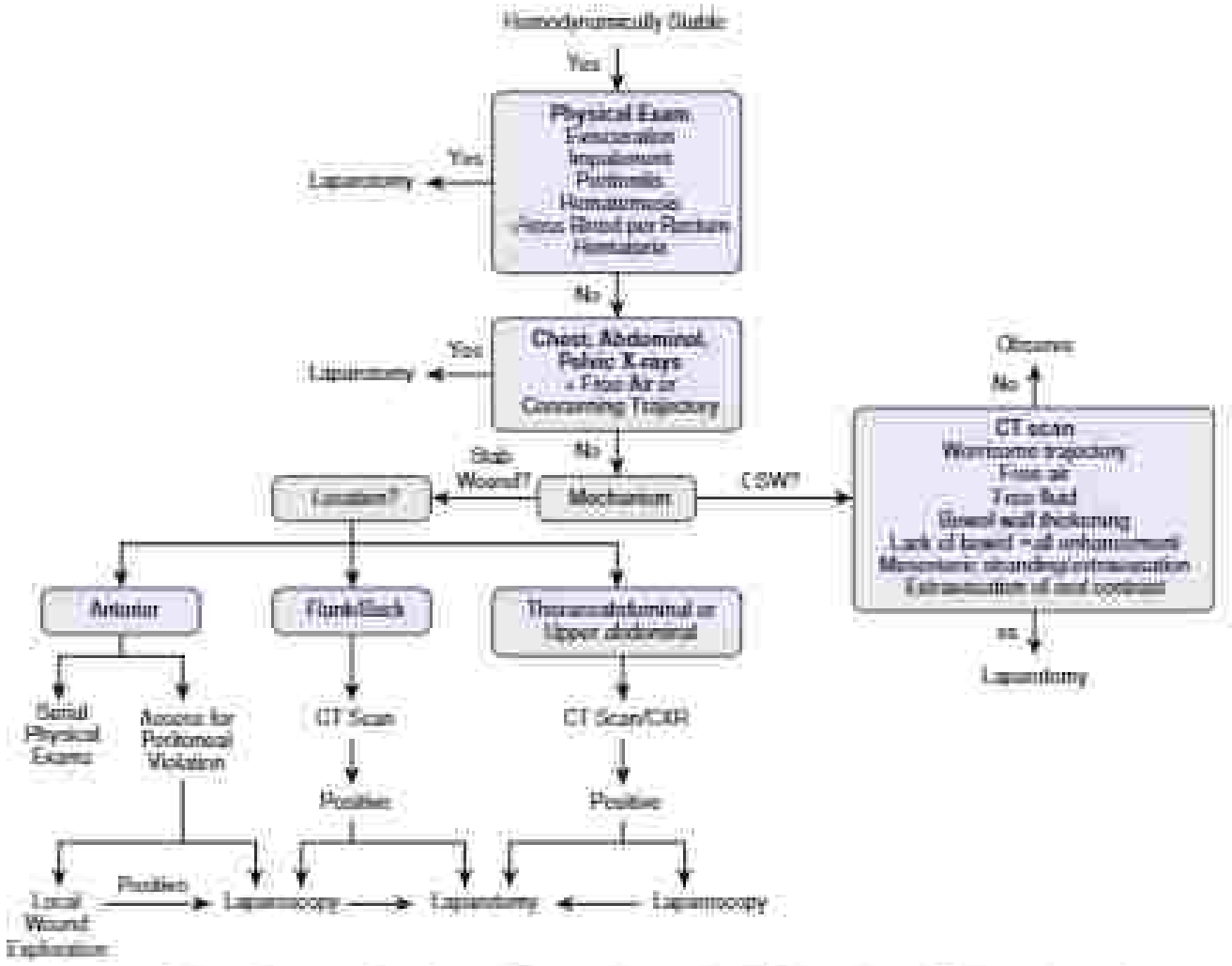

FIG. 2 Evaluation of penetrating bowel injury. CT, Computed tomography; CXR, chest radiograph; *GSW*, gunshot wound.

debridement and closure in two layers in a transverse manner to minimize any potential luminal narrowing. If there are multiple grade II or III injuries close to each other, a resection with primary anastomosis should be considered. Grade IV and V injuries require resection and reanastomosis. Damage control surgery should be considered if the patient is hemodynamically unstable, has had significant blood loss requiring multiple transfusions, is acidotic, coagulopathic, or hypothermic (Box 1). In such cases, the injured portion of bowel can be rapidly resected with a stapling device and the bowel left temporarily to discontinuity. It is imperative that a functioning nasogastric tube be placed to decompress the proximal bowel. After resuscitation, the patient should return to the operating room in approximately 24 hours for reanastomosis or the creation of an ostomy, depending on physiologic stability.

Whether to perform a hand-sewn or stapled anastomosis is a hotly debated topic. Although prospective studies have not been performed, a number of retrospective studies in trauma patients suggest that hand-sewn anastomoses have a significantly lower rate of anastomotic failure when compared with stapled anastomoses (0% vs 1.9%). In light of this, we recommend hand-sewn technique, particularly in patients with intraabdominal contamination.

As mentioned, penetrating abdominal trauma can be managed laparoscopically. With the right expertise, laparoscopy is safe and feasible. It is associated with decreased hospital length of stay and fewer perioperative complications. Importantly, although laparoscopic management of abdominal trauma can take longer, it is not associated with a higher rates of missed injuries. Thus, if the surgeon is comfortable with advanced laparoscopic techniques, we recommend therapeutic laparoscopy in stable patients be attempted, with a low threshold for conversion to open laparotomy.

MANAGEMENT OF LARGE BOWEL INJURIES

Antibiotic choice and duration are identical to those recommended for small bowel injuries and include broad-spectrum antibiotics for no more than 24 hours postoperatively. The colon should be carefully examined from the ileocecal valve to the rectum. If there is concern for a rectal injury below the peritoneum, a rigid proctoscopy should be performed. All bowel and mesenteric hematomas should be carefully explored to rule out underlying injury. The management of large bowel injuries depends on the stability of the patient and the destructiveness of the injury. Gunshot wounds leave a zone of injury in the bowel that should be debrided before definitive repair. As with small bowel injuries, the AAST grade of colon injuries can be used to guide operative decision-making (Table 3). AAST grade I colon injuries (serosal tears only) can be repaired with a single layer of Lembert sutures. Grade II colon injuries (laceration <50% of circumference) should be repaired primarily in two layers. Grade III, IV, and V injuries are considered destructive injuries and require a resection with either anastomosis or colostomy. The decision to create an anastomosis or an ostomy should be based on physiologic criteria. Patients

TABLE 2 American Association for the Surgery of Trauma Small Bowel Injury Scale

Grade*	Injury	Description
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration ≥50% of circumference
IV	Laceration	Transection of small bowel
V	Laceration	Transection of small bowel with segmental tissue loss
	Vascular	Devascularized segment

*Advance one grade for multiple injuries up to grade III.
From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling: III. pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990;30(11):1427-1429.

TABLE 3 American Association for the Surgery of Trauma Colon [Large Bowel] Injury Scale

Grade*	Injury	Description
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration ≥50% of circumference
IV	Laceration	Transection of colon
V	Laceration	Transection of colon with segmental tissue loss
	Vascular	Devascularized segment

*Advance one grade for multiple injuries up to grade III.
From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling: III. pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990;30(11):1427-1429.

BOX 1 Factors to Consider When Deciding to Pursue Damage Control Surgery

Hemodynamic instability
Any of the lethal triad: acidosis (pH <7.2), coagulopathy, hypothermia (<35°C)
Massive transfusion (>10 units packed red blood cells) or massive blood loss (>4 L)
Prolonged operative time (>90 min)
Lactate >5
Question of bowel viability
Massive intra-abdominal contamination requiring subsequent washout

without significant comorbidities, high dose steroid use, high blood transfusion requirements, acidosis, hypothermia, or significant intra-abdominal contamination may safely undergo colon resection with primary anastomosis. As with small bowel injuries, hand-sewn anastomoses are associated with fewer failures. In unstable patients, the colon can be tied off with umbilical ties or stapled with a stapling device. Definitive management of the colon injury can then be delivered until return to the surgical suite. It should be noted, however, that primary colonic anastomosis after damage control is associated with a 27% suture line failure rate. If a colostomy is performed, strong consideration should be given to creating a double barrel ostomy with afferent and efferent limbs exiting the same fascial defect. This will facilitate a less complex takedown procedure and obviate the need for reoperations.

Although the creation of a colostomy is often considered "safer" than primary anastomosis in patients with destructive colonic injuries, it is actually less morbid to perform a primary anastomosis in hemodynamically stable patients with minimal contamination or blood loss. Moreover, colostomies have their own acute and chronic postoperative complications, including ischemia, necrosis, obstruction, retraction, parastomal hernia, and subcutaneous abscess. Patients may also have difficulty with their colostomy appliance, particularly if the ostomy was placed near a wound or at a location where the patient cannot easily visualize it, such as below the belt line, in a skinfold, or under the pannus.

Traditionally, colostomy reversal was not considered for at least 3 to 6 months after hospital discharge. Recently, however, it has been shown that diverting colostomies can be safely reversed within 3 to 7 weeks after their creation. Regardless of timing, a contrast enema should be performed before reversal to rule out distal strictures and to assess colonic healing.

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Current Management of Rectal Injury

Andrew B. Peitzman, MD

The management of rectal injury has undergone several paradigm shifts over the past 100 years. Rectal injury is uncommon in civilian trauma practice, seen in 1% to 3% of civilian injuries. On the other hand, rectal injury occurs in 5% of military casualties. Thus, observations made during major conflicts have provided the clinical basis for most of this literature. During the American Civil War, colorectal injuries were treated nonoperatively, with surgical management limited to possible manual reduction of eviscerated bowel and closure of the fascial defect; mortality rates were greater than 90%. In World War I, treatment of rectal injuries consisted of wide local debridement and external drainage, with mortality rates of 70%. Mortality was reduced to 36% early in World War II by the incorporation of proximal colostomy for all injuries to the rectum; this was eventually mandated in the treatment guidelines issued by the Department of the Army (Letter 178). By the conclusion of World War II, mortality rates were as low as 8% with the addition of posterior drainage procedures. In the Vietnam War, changes in injury patterns with the severity of high-velocity firearm and mine-related injuries led to routine washout of the distal rectum as a component of the management of rectal injury. Mortality for rectal injury was reported as 12% for this conflict, aided by advances in resuscitation and antibiotic therapy, rapid evacuation, and increased usage of blood products. A report from military experience in Afghanistan described pelvperineal wounds as the signature injury in the conflict. Mortality, predominantly exsanguination, was 47% for perineal injury and 13% for perineal injury with associated pelvic fracture. During the decades of these wars, the key principles of the 4 Ds in the management of rectal injury have been supported, diversion of the fecal stream, distal washout, proximal drainage, and direct repair of the defect. The management concepts that are supported currently include closing the defect if readily accomplished and diversion. In very selected circumstances which we discuss here, proximal drainage and distal washout may still have a role.

As discussed, management of rectal injury in the civilian population over the past 50 years has mirrored the treatment strategies used by the military. The rectum can be injured from blunt injury (often associated with pelvic fracture), gunshot or stab (static) penetrating injury, impalement injury, foreign body injury, or blast injury. Two key principles must be acknowledged as we discuss rectal injury. First, rectal injury in wartime is produced by high-energy firearm injury or an explosive device. The destructive power is far greater than seen from a gunshot wound in civilian practice. Thus, extrapolation of management principles between military and civilian injury may not be valid. Second, management of rectal injury differs for intraperitoneal versus extraperitoneal rectal injury.

ANATOMIC CLASSIFICATION OF RECTAL INJURY

The rectum is a 12- to 15-cm segment of bowel that extends from the rectosigmoid junction to the dentate line and functions as a fecal reservoir. Associated vascular injury, urologic injury, or pelvic fracture is also a concern in managing the patient with rectal injury. Rectal injury is classified as intraperitoneal or extraperitoneal (Fig. 1). The extraperitoneal rectum comprises the posterior aspect, which is adherent to the presacral soft tissues along the curvature of the sacrum, and the lower one third of the anterior portion. Injuries to the anterior and lateral surface of the upper two-thirds of the anterior portion are classified as intraperitoneal. This is the only segment of the rectum that contains a serosal layer. Injury is graded on the basis of whether the injury is partial or full thickness, the percentage of rectal lumen compromised, and the extension into the peritoneum (Table 1). This classification is limited in clinical decision-making because it does not differentiate intraperitoneal from extraperitoneal rectum, nor does it account for differences in wounding energy that impact appropriate management. The rectum is well vascularized, with the upper third supplied by the superior rectal artery as it branches off the inferior mesenteric artery. The middle third is supplied by the middle rectal arteries from the internal iliac arteries, and the distal third is supplied by the internal pudendal arteries. The superior rectal veins drain into the portal system via the inferior mesenteric vein, whereas the middle and inferior rectal veins drain into the internal iliac and internal pudendal veins, respectively.

DIAGNOSIS

Recognition of a rectal injury requires a high index of suspicion when evaluating the patient with a penetrating wound to the lower abdomen, pelvis, perineum, buttock, or upper thigh. After the primary survey (Advanced Trauma Life Support) is done, complete exposure of the patient is critical to avoid missed injury to the folds and clefts. Digital rectal examination (DRE) is essential in evaluating the patient with potential rectal injury. Information gleaned on DRE is presence of gross blood in the rectal vault, palpable bony fragments within the rectum, defects within the rectal wall, and position of the prostate gland. When positive, DRE findings are generally nonspecific, revealing blood within the rectal vault. DRE is also insensitive and cannot reliably exclude rectal injury. Thus, proctosigmoidoscopy is an essential step in the workup of the patient suspected to have a rectal injury. In addition, a rectal injury may be obscured by blood or stool on proctosigmoidoscopy. Even if the rectal injury itself is not visualized on proctosigmoidoscopy, the finding of gross blood on examination confirms 90% of rectal injuries. Computed tomography (CT) obtained in the stable trauma patient may reveal the trajectory of a bullet/missile, demonstrate extraluminal air, or associated abdominal injuries. With the high likelihood of concomitant genitourinary injury, CT cystography may confirm a bladder injury preoperatively.

TREATMENT

The treatment protocol for rectal trauma is based on the anatomic classification of the injury. In addition to the anatomic distinction rather, characteristic extraperitoneal injuries as high or low based on whether they are proximal or distal to the peritoneal reflection. In addition, the hemodynamic status of the patient is a critical factor for decisions in the surgical management of these injuries. Patients should be placed on the operating table in the lithotomy position to facilitate rigid proctosigmoidoscopy and possible transanal repair of low-lying injury (Fig. 2). Before operation, broad-spectrum antibiotics with gram-negative and anaerobic coverage should be administered and continued for 24 hours postoperatively. The Eastern Association for the Surgery of Trauma published guidelines in 2011 for management of penetrating extraperitoneal rectal injury. The recommendations for patients with

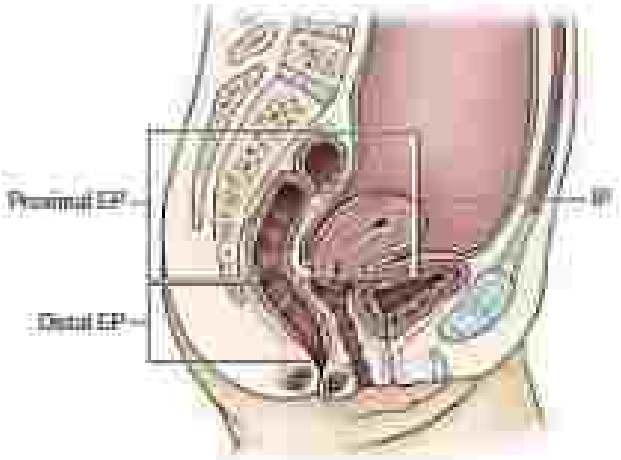

FIG. 1 The intraperitoneal (IP) and extraperitoneal (EP) divisions of the rectum. (From Weinberg JA, Fabian TC, Magnotti LJ, et al. Penetrating rectal trauma: management by proximal diversion, exposure, and closure. J Trauma Acute Care Surg. 2013;75:608–614.)

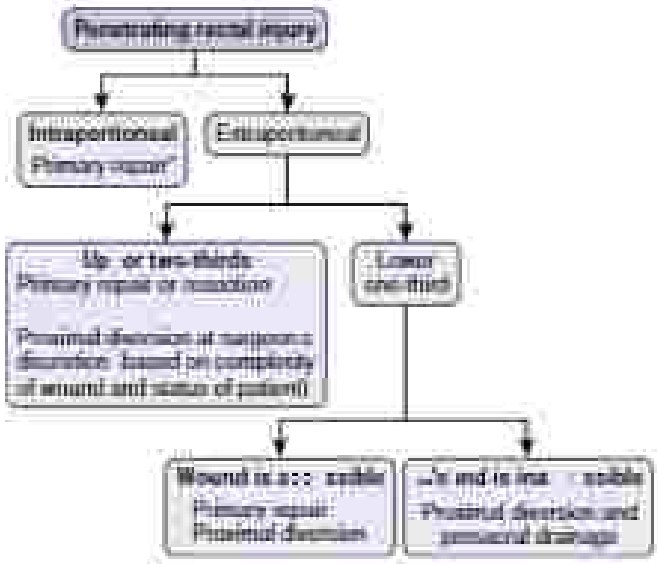

FIG. 2 Algorithm for the management of rectal injury. DRE, Digital rectal examination; CT, computed tomography. (From Clarens MF, Fraser RM, Jr. Rectal trauma: current based practice. Clin Colon Rectal Surg. 2010;23:101.)

TABLE 1 American Association for the Surgery of Trauma Rectal Injury Grading Scale

Grade*	Type of Injury	Description of Injury
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration >50% of circumference
IV	Laceration	Full thickness laceration with extension into perineum
V	Vascular	Devascularized segment

Modified from Moore EE, Cogbill T, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990;30(11):1427–1429.
*Advance one grade for multiple injuries up to grade III.

nondestructive extraperitoneal rectal injury (based on overall low-quality evidence) were:

1. perform proximal diversion
2. not place presacral drain
3. not perform distal rectal washout

Intraperitoneal Injury

The management strategies for intraperitoneal rectal injuries are similar to those used for colon wounds. The approach currently is that primary repair of a colon injury is safe in all but the sickest patient, regardless of location of the colon injury (right vs transverse vs left), degree of colon injury, or whether stapled or hand-sewn anastomosis. Nondestructive injuries without devitalization of tissue that do not require significant debridement (American Association for the Surgery of Trauma [AAST] Organ Injury Scaling grades I to III) can be repaired primarily. We perform a two-layer closure, using a full-thickness running absorbable suture followed by interrupted silk seromuscular sutures. With significant tissue loss or vascular compromise, resection of the injured segment is necessary. Consideration for primary anastomosis without diverting colostomy is appropriate in the presence of hemodynamic stability. On the other hand, with evidence of shock (prolonged hypotension, transfusion requirement greater than 4 to 6 units of packed red blood cells) or competing injuries (Injury Severity Score > 25), end colostomy with closure of the rectal stump is advised. The specific number of units of packed red cells transfused to push the decision to colostomy remains controversial. Interestingly, a recent AAST survey by Brown et al. reported that 82% of patients with intraperitoneal rectal injury underwent proximal diversion. Independent risk factors for abdominal complications with intraperitoneal injuries included high-grade injury and penetrating mechanism. Proximal diversion did not impact mortality. In this series, extraperitoneal rectal injuries were diverted in 76% of patients. Seventeen percent of extraperitoneal injuries underwent distal rectal washout and 27% had presacral drains placed. Independent risk factors for abdominal complications of extraperitoneal rectal injuries were presacral drainage and distal rectal washout. As with intraperitoneal rectal injuries, proximal diversion had no impact on mortality with extraperitoneal rectal injuries.

The posterior wall of the rectum must be assessed along the trajectory of the bullet if possible, to prevent missing injury to the posterior rectum. If a distal extraperitoneal wound cannot be definitively excluded, the patient should be managed as if a distal extraperitoneal injury were present.

Proximal Extraperitoneal Injury

Injury involving the extraperitoneal rectum proximal to the peritoneal reflection can be repaired with limited mobilization of the mesorectum. If injury is suspected, because of either crepitus of an anterior or lateral injury or the presence of a hematoma within the proximal mesorectum, perform primary repair using the two-layer technique described previously without the need for proximal diversion or presacral drainage. As with intraperitoneal injury, the decision to perform a diverting colostomy should be based on the patient's physiologic status, suspicion of a more distal injury, and

complexity of the surgical repair. Destructive rectal injuries not amenable to immediate primary repair should be treated with Hartmann's procedure.

Distal Extraperitoneal Injuries

Primary repair of extraperitoneal injury below the peritoneal reflection is hindered by difficult exposure, limited space (especially in males), proximity of neurovascular and genitourinary structures, and anatomic distortion secondary to associated injuries. If the wound is encountered while addressing another injury and is easily accessible, limited dissection and repair can be performed. However, only 20% of extraperitoneal wounds are amenable to repair, and extensive distal mobilization in search of a suspected wound is contraindicated because of risk for iatrogenic nerve, rectal, urologic, or vascular injury. Several authors have described irrigating laparotomy and performing laparoscopic assisted diverting loop sigmoid colostomy in hemodynamically stable patients without signs of peritonitis. However, we proceed with exploratory laparotomy and diversion of these patients, to allow assessment of the mesorectum and potential repair of proximal extraperitoneal injuries. Diversion is accomplished via a loop sigmoid colostomy. The sigmoid colon must be mobilized sufficiently to avoid tension and the posterior wall of the loop is maintained above the level of the skin. A Silastic rod or red rubber catheter is placed beneath the loop to prevent retraction. If fashioned properly, loop colostomy is effective for diversion of the fecal stream and outcomes are equivalent to those seen with end colostomy.

For wounds to the posterior portion of the distal extraperitoneal rectum, we practice presacral diversion. For injuries to the anterior portion of the distal extraperitoneal rectum, we do not routinely place a presacral drain, and injuries are managed primarily with proximal diversion. We place a presacral drain only in the setting of low anorectal injury with high likelihood that the drain will actually be in proximity to the posterior anorectal injury.

The presacral drain is inserted via a curvilinear incision between the coccyx and anus, followed by blunt dissection through Waldeyer's fascia to enter the presacral space. Place a closed suction or 1-inch Penrose drain within the space and gradually withdraw between postoperative days 5 and 7 (Fig. 3).

As mentioned, presacral drainage in these patients remains controversial. In a series of 32 patients, Armstrong and colleagues demonstrated a reduction in the pelvic abscess rate from 36% to 25% with the use of presacral drainage. Nash and colleagues also showed a significant decrease in infections within the presacral space, and a report by McGrath in 1998 also demonstrated a reduction in morbidity when drainage was used. Several subsequent reports have failed to demonstrate a reduction in morbidity or mortality. Gonzalez and colleagues published a prospective, randomized study evaluating 48 patients with rectal injuries and failed to demonstrate a reduction in infectious complications. They postulated that civilian injuries are different from the high velocity injuries encountered during combat and that violation of the presacral space actually may result in increased infectious complications.

Distal Rectal Washout

During the Vietnam War, irrigation of the distal colon and rectum was added to the treatment regimen for these injuries to reduce contamination and septic complications secondary to stool within the rectal vault. As the sigmoid colon is exteriorized for the creation of a diverting loop colostomy, a purse-string suture is placed on the distal segment of the sigmoid colon. A colostomy is made; a large-bore Foley or red rubber catheter is inserted into the colonic lumen, and 3 to 4 L of saline is instilled via gravity drainage into the colon. As the fluid is introduced, the distal rectum is dilated digitally to facilitate drainage, and drainage is continued until the effluent becomes clear.

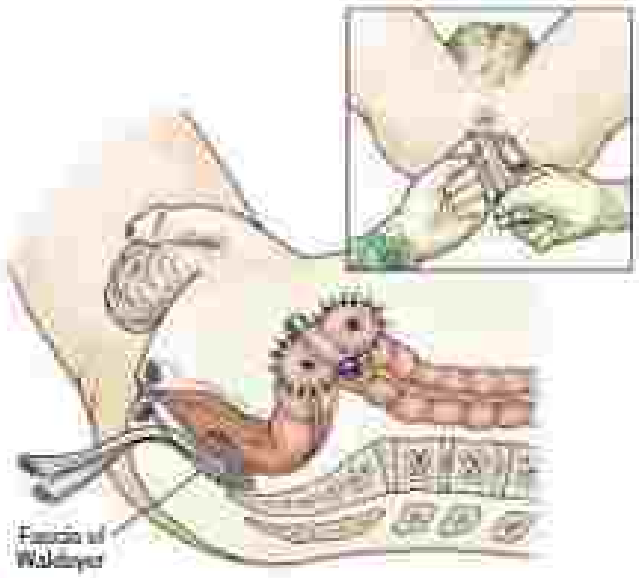

FIG. 3 Technique for presacral drainage and proximal diversion for low posterior anorectal injury. (*Courtesy Baylor College of Medicine, Houston, TX.*)

In 1988, Shannon and colleagues reported their experience with distal rectal washout in a series of 27 patients, demonstrating an incidence of pelvic abscess formation in 8% of patients who received rectal irrigation versus 36% in those who did not. The greatest benefit was observed in patients with high velocity gunshot wounds or other destructive injuries, such as pelvic crush injuries. Several authors have expressed concern that irrigation in patients who have not undergone primary repair may contaminate the surrounding soft tissues and increase the risk of pelvic abscess. Multiple subsequent studies have failed to demonstrate a benefit to the procedure. The benefit in combat situations may be related to the chronic debridement and contagion experienced by soldiers in the field combined with high velocity, destructive rectal and soft tissue injuries. We do not routinely include this procedure as a component of our treatment algorithm but will apply washout with wounds secondary to high-caliber weaponry or explosives.

Anorectal Injury

Most injuries to the anus and anal sphincters occur as iatrogenic injuries due to perineal tearing or midline episiotomy. Traumatic injury to the anal sphincter complex is often secondary to sexual assault, forceful introduction of a foreign body, or blunt injury due to complex pelvic fracture or straddle-type perineal injury. Injury also has been reported with insertion of enema tips or rectal thermometers and during anorectal procedures such as lateral internal sphincterotomy, hemorrhoidectomy, polypectomy, and endoscopic dilatation.

DRE is essential, palpating for mucosal defects, bony fragments, or gross blood. DRE should also include assessment of resting and squeeze sphincter tone. As mentioned earlier, DRE is insensitive to detection of anorectal injury. A simple laceration to the anal mucosa can be repaired primarily, but complex lesions involving the distal perineum and rectum may require diverting colostomy. With extensive perineal and anorectal injury, plan debridement of nonviable tissue and daily operative debridement and lavage for the first 3 days. If extensive tissue debridement is required, overlapping sphincteroplasty is the repair of choice; simple apposition of muscle is associated with a failure rate of 40%. In cases of complex injury to the pelvic floor with significant soft tissue defect, referral to a colorectal

operative for transposition of the gluteus or gracilis muscle with creation of a neosphincter is advised.

Rectal foreign bodies were first described in the sixteenth century. Household objects such as bottles and glasses are inserted most frequently. However, the full list of objects is long and imaginative. The patient may be embarrassed to discuss the situation. Remember that the object may have been placed as a method of assault. If the patient is clinically ill or has peritonitis, proceed for laparotomy with the patient in lithotomy. CBCT is an essential part of the evaluation. Abdominal films will demonstrate the foreign body and detect free air. A foreign body in the sigmoid colon is more likely to require operation than one more distal. Transanal extraction of a foreign body is successful in 70% of patients. The approach is with the patient in lithotomy, adequately sedated, and with adequate lubrication. If the object cannot be reached by this approach, then proceed with sigmoidoscopy. If this is unsuccessful, move to the operating room to assist via laparotomy or laparoscopy. On occasion, colotomy will be required to extract the foreign body. After extracting the foreign body, perform rigid sigmoidoscopy to evaluate for injury to the pararectal rectum.

TIMING OF COLOSTOMY CLOSURE

Colostomy closure is performed when the patient has recovered from the initial injury, subsequent operations, and associated morbidities. Resolution of inflammation, normalization of nutritional status, and proper healing of injuries are essential before performing colostomy reanastomosis. Rosa and colleagues have reported safe utilization colostomy closure on patients with rectal injuries, using contrast enema 5 to 10 days after injury to exclude a clinically occult leak. This was followed by closure as early as 9 days after injury without any reported complications related to leakage from the rectal wound. This approach has not been adopted widely. We perform several 2 to 3 months after hospital discharge to allow resolution of the chronic inflammatory adhesions resulting from laparotomy and healing of intraabdominal injuries.

MANAGEMENT OF COMPLICATIONS

Daily evaluation of the wounds, perineum, and presacral drain site (if performed) is essential to monitor the patient for possible pelvic infection or sepsis. The introduction of rectal thermometers or suppositories should be avoided. If the patient exhibits fever, leukocytosis, or other signs of infection 4 to 5 days after surgery, CT of the abdomen and pelvis is appropriate. The most common complication in these patients is intraabdominal abscess. Small abscesses (<2 cm) usually can be treated with intravenous antibiotic therapy alone. Larger abscesses can be treated with percutaneous drainage. If the collection is not amenable to drainage or if the patient has signs of sepsis, reexploration with irrigation and drainage is indicated. If feculent material is aspirated from the abscess cavity, the patient has a colonic fistula. Distal colonic fistulae generally resolve with time and adequate drainage. The catheter should be left in place and flushed twice daily with normal saline to prevent occlusion. Once drainage is minimal and there is radiographic confirmation that the abscess cavity has collapsed, the drain can be removed slowly over the course of several days.

The complication most directly attributable to initial injury is infection within the retrorectal space and the resulting pelvic sepsis. This may be seen as an isolated abscess within the presacral space or an extensive retroperitoneal infection tracking into the perineum and thighs. As with any necrotizing soft tissue infection, early broad-spectrum antibiotics and prompt surgical debridement are the mainstays of therapy, along with admission to an intensive care unit, hemodynamic monitoring, and crystalloid resuscitation.

Wound infections have been reported in up to 20% of patients with injuries to the colon and rectum. As such, the skin should not be closed at the time of fecal closure. Either the wound can be left to heal by secondary intention or delayed primary closure can be performed after 3 to 5 days. Given the contamination inherent in rectal trauma and stoma creation and the frequency of concomitant vascular, genitourinary, and orthopedic injuries, leaving the wound open is the preferred option.

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The Injured Spleen

Martin A. Croce, MD, and Michael Fitzgerald, MD

The spleen is one of the most commonly injured solid organs following blunt trauma. Its close relationship with the ribs and multiple attachments provide many locations for disruption of the capsule and injury to the parenchyma. In an adult, the spleen weighs approximately 100 to 250 grams, however, it can become enlarged due to various causes such as malaria, mononucleosis, hematologic diseases, and portal venous hypertension. This pathologic enlargement can make the spleen more susceptible to injury. Debate continues about the optimal management of patients with splenic injuries.

ANATOMY

Anatomically, the spleen is located in the left upper quadrant and is intimately related to the left hemidiaphragm and left ribs 9 through 12. Laterally, it is fixated by the splenophrenic ligament. Posteriorly, it is closely associated with the left adrenal gland and left kidney and is attached via the splenorenal ligament. Medially, it is closely associated with the tail of the pancreas. Identification of the tail of the pancreas is essential to safe mobilization of the spleen and splenectomy. Medially the spleen is adjacent to the greater curvature of the stomach and short gastric arteries, which must be ligated for total splenic mobilization. Inferiorly the spleen is in close proximity to the distal transverse colon and splenic flexure and is attached via the splenocolic ligament.

The blood supply of the spleen is provided by the splenic artery and the previously mentioned short gastric arteries. The splenic artery is a branch of the celiac axis and travels in a variably tortuous path along the superior aspect of the pancreas and terminates in the splenic hilum where it branches into the segmental blood supply of the spleen. It also receives blood from the short gastric arteries that come from the greater curve of the stomach and are an extension of the left gastroepiploic artery. The venous drainage of the spleen mirrors the arterial supply. The splenic vein joins the inferior mesenteric vein, which then joins the superior mesenteric vein to create the portal vein. The short gastric veins drain into the left gastroepiploic vein.

Functionally the spleen is divided into red and white pulp. The red pulp is responsible for filtration of old red blood cells, trapping bacteria and presenting the bacteria to the lymphocytes. The white pulp consists primarily of the lymphocytes, which are presented the bacterial antigens developed by the red pulp, and produce immunoglobulins to these antigens. The white pulp also plays a role in production of opsonins and complement activation.

CHILDREN

There are multiple differences between the adult and pediatric spleen that should be taken into consideration during management of splenic injuries. The spleen is larger in children due to its function in red blood cell production as well as its previously stated functions in the adult of filtering senescent red blood cells, trapping bacteria, developing antigens and presenting them to lymphocytes for the development of immunoglobulins. As children age and the bone marrow becomes more mature, the spleen does reduce in size relative to the other intraabdominal organs. In addition to the larger size of the spleen in children, the pediatric chest is much more flexible and allows for more significant force to be transferred without rib fractures. The capsule is thicker and parenchyma is firmer, which leads to lacerations in parallel with the vasculature. The orientation of laceration may be a reason for improved nonoperative success. Pediatric patients are excellent candidates for nonoperative management. They have lower incidences of delayed bleeding, are more likely to have isolated splenic injury secondary to one such mechanism, and the injured spleens are more likely to lacerate in a pattern parallel to the arterial supply secondary to the smaller composition. Children are also at a higher risk after splenectomy for overwhelming postsplenectomy infection. Thus, nonoperative management is not only more successful in children, it is preferred for long term functional immunity.

MANAGEMENT

Injury to the spleen can occur from either penetrating or blunt mechanisms. Regardless of mechanism, it is essential to carefully evaluate all other potentially injured structures given the spleen's close relationship with the pancreas, colon, kidney, stomach, and left hemidiaphragm.

Blunt Injury

The spleen is one of the most frequently injured solid organs after blunt trauma. The initial assessment of the patient will lead down one of two pathways. If upon initial evaluation the patient is found to have hemodynamic instability or evidence of peritonitis, the patient should be taken emergently to the operating room for exploratory laparotomy. In the setting of altered mental status or significant multisystem injuries, the abdomen should be evaluated using focused ultrasonographic evaluation (FAST) or diagnostic peritoneal aspirate/lavage. This can add a level of confirmation prior to heading to the operating room; however, if the patient is in extremis, time should not be wasted. Forty–five percent of patients with splenic injury present with hemodynamic instability and require emergent exploratory laparotomy.

If the patient is found to be hemodynamically stable the Eastern Association for the Surgery of Trauma guidelines state "Nonoperative management of blunt splenic injuries is now the treatment modality of choice in the hemodynamically stable patient, irrespective of grade of injury, patient age, or the presence of associated injuries." The initial assessment of the hemodynamically stable patient should always begin with assessing the airway, breathing and circulation, with keen attention to blood pressure and heart rate to not miss signs of reflective shock. Next, a detailed history of the event including mechanism should be obtained. A detailed past medical history including history of hematologic disease, preexisting conditions (malaria, mononucleosis, hepatic disease), anticoagulation, aspirin use, and previous abdominal surgeries should also be obtained. Physical examination should pay close attention to the left thorax and abdomen. Ecchymosis or abrasions to the abdomen should be noted. The presence of generalized abdominal pain, and, more specifically, left upper quadrant pain should raise suspicion of a possible injury. Left lower rib pain, specifically posterior rib pain can suggest a possible splenic injury as well. Left shoulder pain, known as Kehr's sign can also be present due to left hemidiaphragm irritation. Hemoglobin/hematocrit, coagulation studies and amylase and lipase should be evaluated for evidence of acute blood loss anemia, coagulopathy, and possible evidence of pancreatic injury. Imaging should begin with plain radiographs. Chest radiographs can offer clues to left upper quadrant trauma with evidence of left sided rib fractures, left sided hemothorax, or evidence of diaphragmatic rupture. Pelvic radiographs have minimal value beyond identifying additional locations of hemorrhage in the setting of pelvic fractures. A FAST exam can be performed and offers nonspecific information such as the presence of free fluid in the abdomen; however, in the setting of hemodynamic stability, the patient will be taken for computed tomographic (CT) scan of the abdomen and pelvis with intravenous (IV) contrast, which is the gold standard diagnostic test for splenic injury. With continued improvement of CT resolution, significant information can be gathered about the potential splenic injury. It is imperative that the study is done with

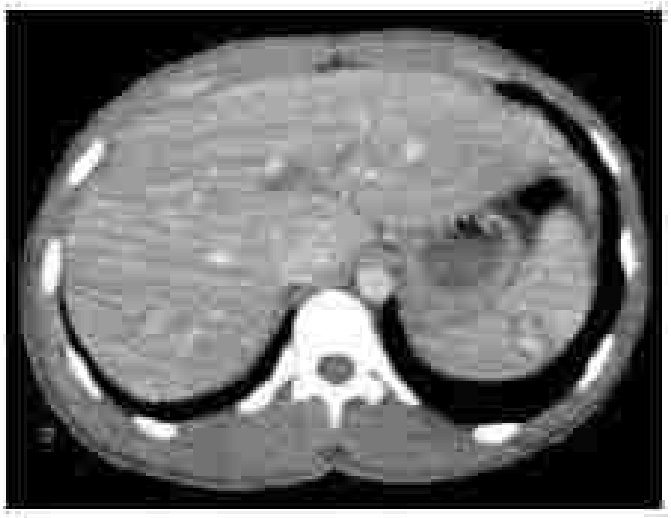

FIG. 1 Pseudoaneurysm on contrast computed tomographic scan.

IV contrast to help identify a contrast blush, which is indicative of a pseudoaneurysm (Fig. 1). Oral contrast has not been found to be helpful. Hematoma and parenchymal disruption appear as hypodense regions within the spleen. Free fluid suggestive of hemoperitoneum is often seen in Morison's pouch, the paracolic gutters, and the pelvis. Free fluid is a nonspecific finding and can also represent a bowel or mesenteric injury. The pancreas, left kidney, liver, and left hemidiaphragm should also be closely inspected. CT evidence of contrast extravasation, which appears as a hyperdense area of concentrated contrast, suggests a disruption of splenic parenchyma and ongoing bleeding. However, its significance is questionable in the setting of hemodynamic normalcy and does not necessarily mandate further intervention. Therapeutic possibilities include angiography with embolization, laparotomy, or continued close observation. A finding that should draw concern is evidence of pseudoaneurysm, which indicates vessel damage. The presence of a circumscribed extravascular contrast blush is diagnostic of a pseudoaneurysm. In a hemodynamically stable patient, this finding requires further evaluation with angiography since these patients have a higher incidence of delayed rupture.

Splenic injuries can be graded by various techniques. The most accepted grading scale is the American Association for the Surgery of Trauma Splenic Injury Scale, which grades the injury from I to V based on severity of splenic laceration and/or hematoma (Table 1). It is important to remember that these injury grades are not a perfect correlation with injury and can over- or underestimate the damage. The grade of injury and clinical course can be roughly correlated, but it is important to take into consideration factors such as pseudoaneurysms and bleeds. Angiography has been recommended for grade III or greater injuries, however, data to support this are conflicting. Angiography is a useful adjunct to nonoperative management, but it does have potential for complications, which include failure to control bleeding in up to 15% of patients, missed injury, and splenic abscess.

After completion of the workup, patients with nonoperative splenic injury should be admitted for close observation. As previously stated, regardless of patient's age, grade of injury, quantity of hemoperitoneum, or associated injuries, as long as the patients remains hemodynamically stable, nonoperative management is an appropriate treatment plan. However, lower threshold for surgical intervention may be considered in patients who are above the age of 55 or have significant traumatic brain injuries due to their increased sensitivity to hypotension. It is also essential that serial hematocrits and abdominal exams can be performed and in event of decompensation the operating room can be quickly mobilized for operative intervention.

Although research is bountiful in regard to nonoperative management of blunt splenic injury there are still details that have not been completely refined. There are no evidence based recommendations for the time interval between hematocrit checks or abdominal exams, and there is no set number of units of blood transfused that signal nonoperative failure. Also, the data are inductive on the need for repeat CT scans and appropriate time until resuming normal activity.

A consensus suggests an appropriate plan is admission to the intensive care unit (ICU) for grade II and above injuries, nothing by mouth (NPO) status, and serial hematocrit and abdominal exams at 6- to 8-hour intervals. Prompt angiography is recommended for patients with evidence of a pseudoaneurysm and may be considered in stable patients with confined contrast extravasation or higher grade injuries. Duration of ICU and NPO status have not been determined, but stable observation over 48 to 72 hours appears to be standard, followed by transfer to the floor, discontinuation of serial labs, and initiation of a diet. There are conflicting studies addressing the need for repeat CT; however, at our institution we routinely obtain 24 hour follow up CT scans on grade II or above injuries since some pseudoaneurysms appear later. There is currently no evidence for vaccinations in nonoperative blunt splenic injury. DVT prophylaxis may be started within 24 hours if the patient remains hemodynamically stable. The majority of nonoperative failure occurs within the first 8 days, and time until discharge mirrors this. Time to return to normal activity is also unclear. The spleen is not healed before 6 to 8 weeks and return to activity is at the physician's discretion, with time ranging between 2 and 6 months.

Failed nonoperative management can be marked by hemodynamic instability or peritonitis, which necessitates exploratory laparotomy for splenectomy and evaluation for potential missed hollow viscus injury.

Penetrating Injury

As with all penetrating injuries to the abdomen, it is essential to establish violation of the peritoneum. After this has been established, the patient should undergo surgical exploration. In the setting of a splenic injury, it is essential to evaluate the left hemidiaphragm, pancreas, and stomach to ensure there were no additional injuries. Operation for penetrating splenic injuries usually results in splenectomy, but splenic salvage may suffice in selected patients with minimal splenic injury.

OPERATION

To begin mobilization of the spleen the lateral attachments of the splenophrenic and splenorenal ligaments should be taken starting lateral to medial at the level of the esophageal hiatus. As the lateral attachments are taken down the spleen should be carefully elevated to the midline, it is important to ensure the appropriate plane is entered and the kidney stays in its retroperitoneal position. The short gastric arteries should be isolated and individually clamped and tied. Care should be taken to not tie to close to the stomach, which may lead to necrosis. If it too difficult to stay away from the stomach, the lateral short gastrics can then be oversewn. Once the spleen has been adequately mobilized, the kidney and distal pancreas can be completely evaluated. The splenocolic ligament connecting the inferior pole of the spleen and the transverse colon should then be divided. Lap pads can then be placed in the splenic fossa and the spleen can be further elevated and mobilized prior to ligation of the hilar vessels. With the spleen removed from the left upper quadrant, the left hemidiaphragm should be reevaluated. The pancreatic tail and splenic hilum should then be carefully inspected. The splenic artery and vein should be isolated and individually ligated to prevent arteriovenous fistula.

Once the spleen has been removed from the operative field, the surrounding structures should be reassessed and lap pads removed. The splenic fossa can be more carefully evaluated by placing a lap pad deep in the splenic fossa and slowly rolling it deep to superficial to

TABLE 1 American Association for the Surgery of Trauma (AAST) Splenic Injury Grade

AAST Grade/ AIS Severity	Imaging Criteria	Operative Criteria	Pathologic Criteria
I/1	Subcapsular hematoma <10% surface area Parenchymal laceration <1 cm depth Capsular tear	Subcapsular hematoma <10% surface area Parenchymal laceration <1 cm depth Capsular tear	Subcapsular hematoma <10% surface area Parenchymal laceration <1 cm depth Capsular tear
II/2	Subcapsular hematoma 10%–50% surface area; intraparenchymal hematoma <5 cm Parenchymal laceration 1–3 cm	Subcapsular hematoma 10%–50% surface area; intraparenchymal hematoma <5 cm Parenchymal laceration 1–3 cm	Subcapsular hematoma 10%–50% surface area; intraparenchymal hematoma <5 cm Parenchymal laceration 1–3 cm
III/3	Subcapsular hematoma >50% surface area; ruptured subcapsular or intraparenchymal hematoma ≥5 cm Parenchymal laceration >3 cm depth	Subcapsular hematoma >50% surface area or expanding; ruptured subcapsular or intraparenchymal hematoma ≥5 cm Parenchymal laceration >3 cm depth	Subcapsular hematoma >50% surface area; ruptured subcapsular or intraparenchymal hematoma ≥5 cm Parenchymal laceration >3 cm depth
IV/4	Any injury in the presence of splenic vascular injury or active bleeding confined within splenic capsule Parenchymal laceration involving segmental or hilar vessels producing >25% devascularization	Parenchymal laceration involving segmental or hilar vessels producing >25% devascularization	Parenchymal laceration involving segmental or hilar vessels producing >25% devascularization
V/5	Any injury in the presence of splenic vascular injury with active bleeding extending beyond the spleen into the peritoneum Shattered spleen	Hilar vascular injury that devascularizes the spleen Shattered spleen	Hilar vascular injury that devascularizes the spleen Shattered spleen

AIS, Abbreviated injury scale.

identify any missed short gastric vessels or overt bleeding. Drains are not routinely used unless a renal or pancreatic injury has been identified throughout the case.

POSTSPLENECTOMY AND COMPLICATIONS

Postoperative complications that occur can vary. Bleeding can occur from the short gastric arteries or the splenic fossa, which can be reduced with meticulous evaluation and individually ligating the short gastric arteries. Although rare, gastric distention can lead to the dislodgement of ties on the short gastric arteries. Gastric necrosis can occur at the site of short gastric artery ligation leading to gastric leaks and abscess formation. Inadequate dissection and mobilization can place the pancreatic tail on tension and lead to iatrogenic injury. Arteriovenous fistulas can occur when the splenic artery and vein are not ligated separately. Thrombocytosis can occur following splenectomy, but is usually managed expectantly. The loss of the spleen does remove an important filter of senescent red blood cells; however, this is well tolerated. The removal of the spleen also leads to reduction of antigen exposure to lymphocytes and compromises the immune system, which can present with significant postoperative complications.

Overwhelming post splenectomy infection is the most concerning and life threatening complication. It is extremely rare following splenectomy for trauma in adults compared to splenectomy for hematologic disease in young children, but it is still a potential concern. It is essential to have a low threshold for initiation of broad spectrum antibiotics and resuscitation in a patient who develops significant sepsis following splenectomy. Encapsulated organisms such as Pneumococcus, Meningococcus, and Haemophilus are the most common offenders. It is important to ensure the patient receives vaccines to these three bacteria postoperatively. The exact timing of vaccination is controversial, but it is essential that patients receive their vaccines prior to discharge.

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Retroperitoneal Injuries: Kidney and Ureter

Benjamin ... Breyer, MD, MAc., and Andrew J. Cohen, MD

URETER

Ureteral trauma is relatively rare. Genitourinary injury accounts for about 10% of trauma overall but ureteral injury accounts for only 1% of all genitourinary trauma. Although 96% of such traumatic injuries are related to penetrating trauma, less than 5% of all gunshot victims have ureteral involvement. Traumatic injuries affect the upper ureter two thirds of the time, and the middle and lower ureter are afflicted about equally.

The ureter is also subject to iatrogenic injury, with estimated rates during hysterectomy, for example, approximately 0.5% and during radiologic procedures about 1%. There is some evidence the risk of ureteral injury has increased with the utilization of laparoscopic surgery, but it remains unclear whether this is secondary to learning curves, patient selection, or other factors. With swift recognition, many low grade ureteral injuries may heal with ureteral stenting alone. True incidence rates of ureteral injury likely are underestimated given not all cases are reported and many resolve without investigation.

In the setting of multiple injuries, complex ureteral reconstruction may not be appropriate particularly if a patient is unstable or has other more pressing injuries. The focus in these cases is preserving renal function, which is easily accomplished by percutaneous nephrostomy tube. It is always appropriate to save complex reconstruction for a delayed setting because such cases may be prolonged and expose the patient to additional operative risk. For these more complex injuries, the armamentarium is plentiful with techniques to bridge any length of devitalized ureter. In recent years, especially in the delayed setting, robotic and laparoscopic techniques are increasingly used to repair these injuries. Intraoperative decision making is important, but careful tissue handling and a tension-free anastomosis will increase successful outcomes.

Anatomic Considerations

The ureter courses anteriorly from the renal pelvis posterior to the renal vasculature in the retroperitoneum. It is lateral to the gonadal vessels near its origin, but ultimately the gonadal vessels cross anterior to its surface on their course toward the gonads. The ureter courses medially and lies on top of the iliac vessels. The most reliable place to identify the ureter is just anterior to the bifurcation of the internal and external iliac arteries. In the male it courses deep to the vas deferens before inserting cephalad to the bladder neck on the posterior surface of the bladder. In females it runs deep to the uterine artery and ovarian ligament.

Because of the proximity of vertebrae and pelvic skeletal anatomy, the ureters are relatively protected from injury. The distal ureter's blood supply is lateral from branches of the iliac vessels and vesical pedicle, whereas the proximal ureter derives its supply medially from renal vessels.

Diagnosis

The first step to identifying ureteral injury in a stable patient already in the operating room is often cystoscopy with retrograde pyelogram. If injury was suspected during open or laparoscopic surgery, direct inspection of the ureter can be extremely valuable. Ureteral injury may be graded (Table 1). If no clear injury is seen, cystoscopy with retrograde pyelogram is appropriate. Ureteral stenting, even in cases of only suspected injury, has little downside and may protect the ureter from the sequela of thermal or crush injury, which may not be visually apparent. If stenting is not possible, percutaneous nephrostomy should be pursued. The extent of injury can be assessed with antegrade study or computed tomography (CT) urogram.

High resolution CT scan with delayed views provides excellent anatomic detail of the examined ureter. Medial extravasation of contrast from the hilum is the most common finding of renal ureteropelvic junction injury. In the setting of complete avulsion, the proximal ureter will not fill, a partial tear will likely show distal ureteral filling. The presence of a hematoma or extravasation may indicate the site of ureteral injury.

In cases of endourologic injury such as perforation during kidney stone treatment, endoscopic ureteral stent alone may be a viable treatment strategy. After stent removal, ultrasound to assess for distal hydronephrosis is paramount because ureteral strictures left untreated could lead to loss of renal function. Strictures can then be treated using endoscopic techniques or more complex surgery depending on stricture length and location and patient comorbidity and symptoms.

In the unstable patient, injuries to adjacent organs such as bowel, vena cava, major vascular, or injury to the kidney itself should be assessed first and addressed primarily. The ureter can be inspected in this setting but complex repair should not be attempted. Clipping the open end of the ureter, if identified, can aid in later localization. The patient should get a percutaneous nephrostomy tube to protect kidney function, and delayed repair of the ureter may be planned.

Diagnosis in Delayed Setting

Some patients may present 2 to 3 days after a traumatic event or surgery with symptoms of hematuria, dysuria, palpable flank mass, or peritonitis. Ureteric injury, if suspected, can be detected on CT urogram. Urinoma, urinary ascites, or new hydronephrosis may suggest ureteral injury, whereas extravasation of contrast from the ureter is pathognomonic. For postsurgical patients with a drain in place, sending fluid for creatinine analysis can identify urinary leakage, but further investigation will be required to identify the source.

Prevention

There is growing interest in preventing iatrogenic ureteral damage using preoperative stents for complex pelvic surgery such as removal of colorectal malignancy or complex gynecologic surgery. Prospective stenting has not been shown to decrease incidence of ureteral damage but may improve detection at the time of injury.

Surgical Approach to Repair

The location of ureteral injury dictates the options for repair (Table 2). Efforts should be made to maintain the blood supply during mobilization of the ureter; a fully skeletonized ureter is not desirable and likely prone to future stricture. Nonetheless, a tension-free anastomosis is vital, so careful ureteral mobilization will be required. Appropriate ureteral debridement to a bleeding edge is also key. Keep in mind that high velocity projectiles can result in blast injury and ischemia, which can produce occult injury up to 2 cm away from the transection.

Many ureteral injuries proximal to the iliac vessels may be repaired primarily over a stent in a tension free fashion. Using a 4-0 or 5-0 absorbable suture in spatulated suture is recommended. Spatulating both ends of the ureter is typical and ensures an mucosa apposition the gold standard (Fig. 1). Distal to the iliac vessels, a ureteral reimplantation with maneuvers such as psoas hitch or Boari flap are

recommended. Most distal injuries can be treated with a simple psoas hitch. The bladder is mobilized, particularly the contralateral side from the pelvic side wall. Occasionally the contralateral superior vesical pedicle must be ligated. The bladder is then affixed to the psoas muscle. The posting sutures are placed in the direction of the muscle fibers to minimize nerve entrapment.

Traditionally, a Boari flap in conjunction with a psoas hitch has been utilized to bridge a 6- to 8-cm gap of proximal ureter (Fig. 2). The base of the flap should be at least 4 cm wide to avoid flap necrosis. The base width must increase proportionally with planned length. Using umbilical tape or ruler the length of flap may be estimated. Small contracted bladders due to radiation or other causes are not suitable candidates for Boari reconstruction.

Other bladder flap shapes such as spiral flaps may allow for longer ureteral length at the expense of bladder capacity. If tension is still evident, the incision may be enlarged and mobilization of the kidney may provide enough ureteral length to proceed.

For trauma involving long segments of ureter, other reconstructive options include ileal ureter substitution, transureteroureterostomy/autotransplant, or nephrectomy. Consider referral to specialty center for complex injuries.

For cases when complex reconstruction is not attainable given patient comorbidity or status, clipping the ureter proximal to injury and obtaining percutaneous drainage is a reasonable alternative. At some point, ureteral reconstruction will become necessary. Given likely formation of adhesions this should be performed within the first 7 days of injury or delayed (typically for about 3 months). If reconstruction is planned in a delayed setting, percutaneous nephrostomy tubes are typically exchanged every 6 weeks. In a delayed setting, the reconstructive procedure can be attempted laparoscopically or robotically for the experienced surgeon.

TABLE 1 American Association for the Surgery of Trauma Ureteral Injury Scale

Grade	Injury
I	Hematoma, contusion or hematoma without devascularization
II	Laceration: <50% transection
III	Laceration: >50% transection
IV	Laceration, complete transection with <2 cm of devascularization
V	Laceration, avulsion with >2 cm of devascularization

Modified from Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling: III. Chest wall, abdominal vascular, ureter, bladder, and urethra. J Trauma. 1992;33(3):337–339.

Complications and Follow-up

Urine extravasation may continue despite repair. Such patients may present with urinoma or infected abscess best treated with antibiotics and percutaneous drainage. Ureteral stent, if already removed, should be replaced if extravasation is suspected. Long-term ureteral stenting can be successful in managing minor defects in repair.

Long-term sequelae from primary ureteral repair may include ureteral stricture. Patients should be followed with ultrasound imaging. Functional studies such as nuclear medicine Lasix renal scan can be pursued if hydronephrosis is noted. The goal of continued follow-up is to prevent renal disease secondary to asymptomatic obstruction. Strictures, if identified, can be repaired. High-volume centers have had recent success with the use of buccal mucosal graft placed at the site of focal ureteral stricture.

Future Directions

Application of robotic and laparoscopic techniques to reconstructive procedures has grown in the past decade. Other innovative techniques on the horizon include the use of injected indocyanine green to visualize a devitalized area of the ureter under near-infrared fluorescence. Attempts at utilizing engineered tissues in the urinary tract to replace or augment damaged areas remain in their infancy. In rare cases of complete ureteral loss, robotic autotransplantation or robotic ileal ureter interposition are reported at centers with extensive robotic expertise.

KIDNEY

Renal injury management has evolved in the past several decades toward conservative treatment for even high-grade injury. Renal trauma accounts for an estimated 3% of trauma cases. For these patients who experience abdominal trauma, renal injury occurs in about 10%. Given certain anatomic realities, pediatric patients may have higher risk of injury than adults. Luckily, only a small percentage of cases require surgical intervention.

With the refinement of endovascular technology, bleeding events that in past decades would have led to open surgery and sometimes nephrectomy can now be salvaged. Injuries such as artery leak often

TABLE 2 Strategies for Ureteral Repair Based on Injury Location

Injury Location	Injury Length	Primary Procedure	Fallback Procedure
Common (any)	1–2 cm	Retrograde and stent	Percutaneous nephrostomy tube
Upper one-third	1–3 cm	Pyeloplasty Ureteroureterostomy	Renal pelvic flap Downward nephropexy Autotransplant
Middle one-third	1–3 cm	Ureteroureterostomy Transureteroureterostomy	Downward nephropexy Appendix substitution (right) Ileal ureter Autotransplant
Distal one-third	Up to 8 cm	Reimplantation Ureteroneocystostomy	Psoas hitch Boari flap
Complete loss	Complete	Ileal ureter Autotransplant	Nephrectomy

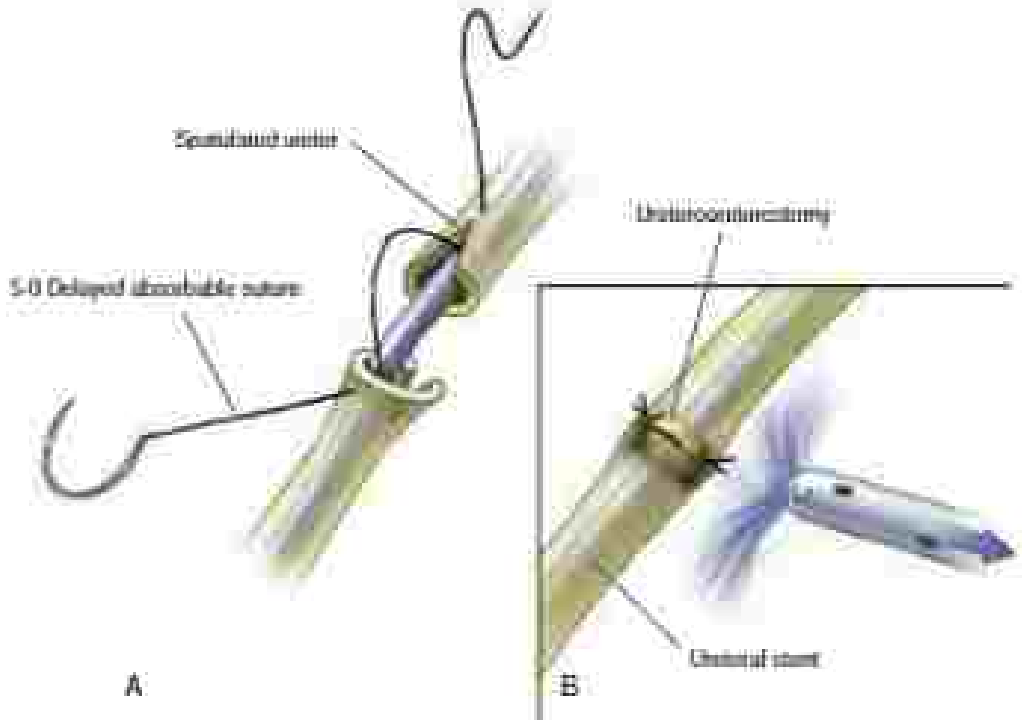

FIG. 1 (A) Spatulation performed before anastomosis to increase surface area at the anastomosis. (B) Completed anastomosis with protecting stent.

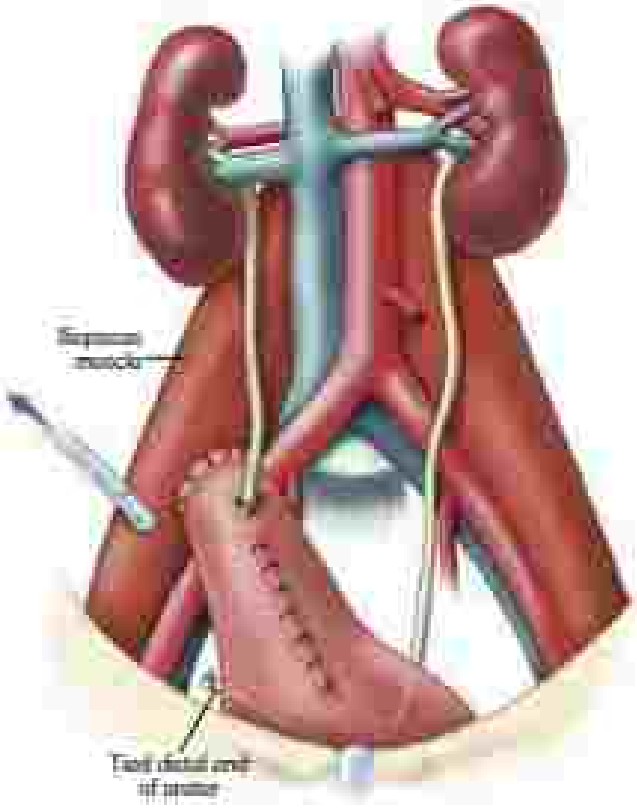

FIG. 2 Completed Boari flap with stent. (From Ingelfinger M, Gotto M, eds. *Atlas of Pelvic Anatomy and Gynecologic Surgery*. 4th ed. Philadelphia: Elsevier; 2015.)

studies on their own or, at worst, require arterial stent or percutaneous drain. Operative renal trauma at present is reserved for cases of complex, multiorgan injury or penetrating trauma. The key to proper management is proper staging of injury (Table 3, Fig. 3). The American Association for the Surgery of Trauma Kidney Injury Scale has been prospectively evaluated and injury stage is predictive for the need for interventions.

General principles of surgery in the traumatic abdomen such as packing quadrants and systematically identifying areas of injury apply to these situations. A key consideration before renal intervention is identifying whether the retroperitoneum has been violated or expanding hematoma is present. Many methods have been devised to repair renal parenchyma and avoid nephrectomy, however, with ongoing and severe hemorrhage, nephrectomy may be prudent. The primary objective of managing these patients is to control life-threatening bleeding while preserving enough nephron mass to avoid renal disease.

Anatomic Considerations

The kidneys are paired compartmental structures. The psoas muscle lies posterior to each kidney and the colon lies on the anterior surface. The kidneys are surrounded by perirenal fat and Gerota's fascia, which encapsulates the adrenal glands and kidneys. The lower poles of the kidney are inferior to the 11th rib and are somewhat more prone to injury, whereas the superior aspect and hilum are more protected by the ribs.

The kidneys have a segmental arterial supply. In general, blunt injuries fracture along the planes between the segmental vessels, whereas penetrating injuries may involve and cross segmental arteries. Varied vascular anatomy may be encountered. The most common variant is an accessory lower pole renal artery, which may be present in about 10% of patients. Ureteral duplications and pelvic and horseshoe kidneys are also possible and make subsequent surgical exploration complex.

The anterior axillary line is an important landmark to consider during the kidney. This is the vertical line that runs along the anterior axillary fold. Abdominal side wounds anterior to the anterior axillary

TABLE 3 American Association for the Surgery of Trauma Kidney Injury Scale

Grade*	Injury
I	Contusion or nonexpanding subcapsular perirenal hematoma and no lacerations
II	Superficial laceration <1 cm depth and does not involve the collecting system (no evidence of urine extravasation) Nonexpanding perirenal hematoma confined to retroperitoneum
III	Laceration >1 cm without extension into the renal pelvis or collecting system (no evidence of urine extravasation)
IV	Laceration extends to renal pelvis or urinary extravasation Injury to main renal artery or vein with contained hemorrhage Segmental infarctions without associated lacerations Expanding subcapsular hematomas compromising the kidney
V	Shattered kidney Avulsion of renal hilum: devascularization of a kidney due to hilar injury Uncategorized: avulsion Complete laceration or thrombus of the main renal artery or vein

Modified from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma*. 1989;29(12):1664–1666. Advance one grade for bilateral injuries up to grade III.

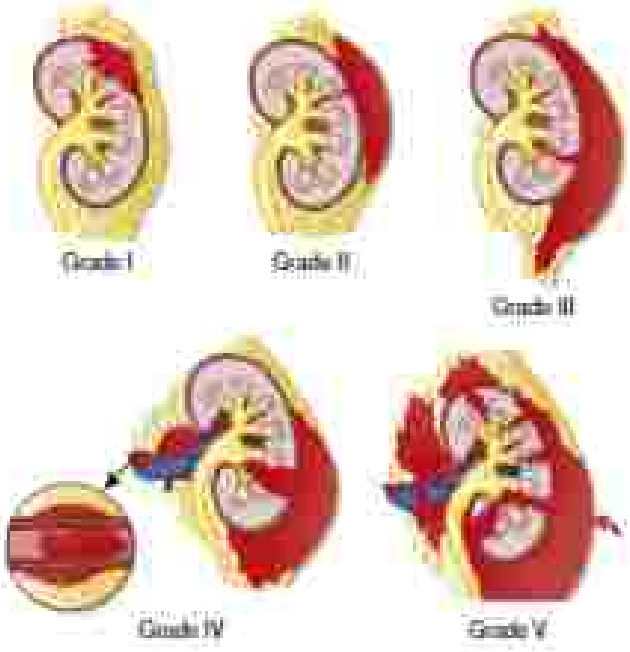

FIG. 3 Trauma kidney injury scale. (From Adams JG, Auster J, Collings J, Dibbell DM, Cassidy MA, Nadel ES, eds. *Emergency Medicine: Clinical Essentials, 2nd ed*. Philadelphia: Elsevier; 2013.)

[ion are often associated with concomitant abdominal injuries. Renal injuries posterior to this line rarely impact the colon but in general are much less likely to involve intraabdominal organs.

Children under 16 are vulnerable to renal injury. They have relatively large kidneys with underdeveloped Gerota's fascia and less perirenal fat, which is protective in adults. Because of incomplete ossification of the lower ribs, children's kidneys are more likely located in the true abdomen. Moreover, shock is an unreliable indicator of injury extent in children because they can have a robust catecholaminergic response to stress that may mask severe blood loss.

Diagnosis

Physical manifestations of possible injury generally include flank ecchymosis, rib fractures, and transverse spinal process fractures. Hematuria is also a common sign of trauma to the kidneys; however, the presence and degree of hematuria does not correlate with injury severity. Likewise, the absence of hematuria does not rule out injury. If possible, the patient should be instructed to void before resuscitation efforts because mild hematuria may clear quickly in the setting of aggressive fluid resuscitation. The presence of hematuria can guide whether further imaging is indicated.

Decisions on diagnostic imaging are predicated on mechanism of injury (blunt vs penetrating), the presence of hematuria (gross vs microscopic), and shock (blood pressure <90 mm Hg). In adults, blunt trauma with gross hematuria requires further imaging. In contrast, adults with blunt trauma and microscopic hematuria require no imaging because no associated significant injury is expected. These patients with suspected blunt trauma, microscopic hematuria, and shock do require imaging. The mechanism of injury itself can prompt imaging; for example, major acceleration or deceleration injuries such as a fall from height or high-speed motor vehicle accident should prompt imaging. In penetrating injuries, any degree of hematuria or an injury location suspicious for renal trauma should prompt imaging. Patients who do not initially undergo renal imaging who later develop hematuria should also be imaged.

Given their abnormal blood differences, lower imaging thresholds for children exist. Any pediatric trauma (<16 years) with any degree of significant hematuria (>50 red blood cells per high-powered field) should be imaged.

Contrast-enhanced CT with additional 10 minute delay scans is the gold-standard imaging modality to stage the stable renal trauma patient and is both sensitive and specific for renal injuries.

There are some situations in which CT scan is not possible or ill-advised given patient instability. For these patients, a single-shot high-dose intravenous urography (IVU) can provide some useful information. Briefly, it confirms the presence of two functional kidneys, may show extravasation of the collecting system, and, in penetrating injuries, may show the course of the projectile. One-shot trauma IVU consists of 2 mL/kg of body weight of standard 60% intravenous contrast injected intravenously, followed by an abdominal radiograph 10 minutes later. The patient requires a suitable blood pressure (usually about 90 mm Hg) for satisfactory study.

Nonoperative Management

Numerous years of research have demonstrated that most renal injuries can safely be managed nonoperatively. Lower grade injuries are typically managed with bed rest, hemodynamic monitoring, and serial hemoglobin measurement. New evidence has emerged suggesting bed rest may not be required, especially in patients without hematuria. Transfusions may be given as needed. If hemodynamic instability develops, additional imaging with angiography and possible embolization or surgical exploration may be required. One exception for angiography is if a patient requires two units of blood. We also strongly consider angiography if any patient has persistent gross hematuria or develops suspected pseudoaneurysm or arteriovenous malformation.

Angiography with superselective embolization therapy for renal trauma has evolved. It is a minimally invasive approach and can be

TABLE 4 Indications for Operative Management of Renal Trauma

Absolute indications	Relative indications
Expanding pulsatile retroperitoneal hematoma	Urinary extravasation without visible ureter
Renal pedicle avulsion	Concurrent colon/pancreas trauma: exploration with incomplete staging or grade III or greater concurrent renal injury
Persistent life-threatening shock or hemorrhage	Renovascular hypertension
Ureteropelvic junction disruption or avulsion	Failed embolization

effective in stopping bleeding, because there is no significant collateral arterial blood supply to the kidney, embolization stops hemorrhage at the expense of nephrons.

Those patients with high-grade injuries should be managed with second CT urogram 3 to 5 days after initial presentation to evaluate for persistent urine leak or urinoma. While being managed conservatively, patients may develop new fever or flank pain which should prompt earlier restaging. On additional imaging, large urine leaks should prompt indwelling stent placement. It is prudent to leave a urethral catheter in such cases to prevent reflux of urine. Antibiotics should also be considered to prevent infected urinoma. Large or infected urinomas seen on subsequent imaging without ongoing extravasation can be drained percutaneously.

Surgical Approach to Repair

A critical decision in renal trauma is when to proceed to operative intervention (Table 4). The approach to renal trauma can be accomplished with proximal vascular control or in a lateral to medial approach. Although some prefer proximal control in most settings that require exploration, the lateral approach involves mobilizing the overlying colon, and dissecting the kidney from Gerota's fascia. The vasculature is approached in a lateral to medial direction. During this work, a Satinsky clamp, sponge stick, or manual pressure can be used to stop bleeding while the kidney is repaired. Particularly for lateral parenchymal injuries, isolating each vessel for possible clamping may not be necessary.

Particularly if there is a medial hematoma, we believe early vascular control ultimately decreases the nephrectomy rate. Uncontrolled hemorrhage may lead to unplanned nephrectomy, when approached in a systematic fashion, vascular control can be done quickly and efficiently. Such control should reduce unplanned nephrectomy in trauma.

We approach the injured kidney through a standard trauma laparotomy midline incision from the pubic symphysis to the xiphoid. A fixed retractor such as the Bookwalter may be employed, but surgical assistants may perform manual retraction effectively with such an incision. The transverse colon is wrapped in moist sponges and placed on the chest or in ample abdominal is can be packed. The small intestine can be placed in a bowel bag or protected with moist lap sponges and retracted superiorly or placed on the chest to the right. Ultimately, all the bowel must be moved to the root of the mesentery and the ligament of Treitz are exposed.

With great care, the retroperitoneum is incised over the aorta superior to the inferior mesenteric artery and the incision is extended to the ligament of Treitz (Fig. 6). If a retroperitoneal hematoma prevents palpation of the aorta, consider an incision medial to the inferior mesenteric vein (IMV). The IMV runs a few centimeters to the left of the aorta and is usually easily identifiable, even if aortic pulsations are not. Continue to open the retroperitoneum along the anterior surface of the aorta until the left renal vein is encountered at its crossing. In less than 1% of cases, the left renal vein will be retroaortic. Once identified, a vessel loop should be placed around the left renal vein. This vessel can be used as a guide to help find the remaining renal vasculature. Once found, they too may be encircled with vessel loops. Most bleeding can be controlled during repair with manual compression of the kidney; rarely will vessel occlusion be necessary. But with this dissection complete, the vasculature can quickly be occluded with building clamps or other means as necessary.

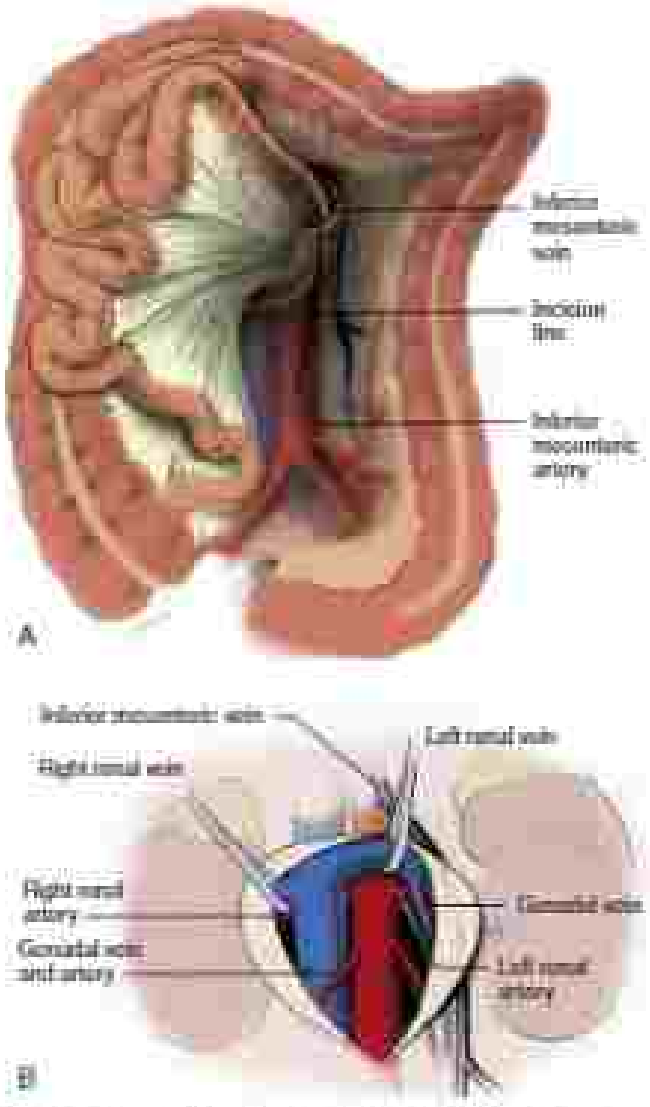

FIG. 6 Technique to obtain vascular control. (A) Exposure of the major vessels. (B) Relationship of the renal vasculature after incision of the posterior peritoneum over the aorta. (From Mc, Inc JW Surgery for renal trauma. In Novick AC, Streem S., Pierce JF., eds. Stewart's Operative Urology. Baltimore: Williams and White; 1989.)

Next, the injured kidney may be exposed in the typical fashion by mobilizing the ipsilateral colon along the white line of Toldt and reflecting it medially. Gerota's fascia is then incised along its lateral aspect. We prefer a lateral approach at this point to avoid renal vein thrombosis, subcapsular dissection or ureteric injury. It also may help preserve perinephric fat for later reconstruction. Renal capsule preservation is particularly important because this fascia is a strength layer needed during reconstruction and tearing it results in more bleeding.

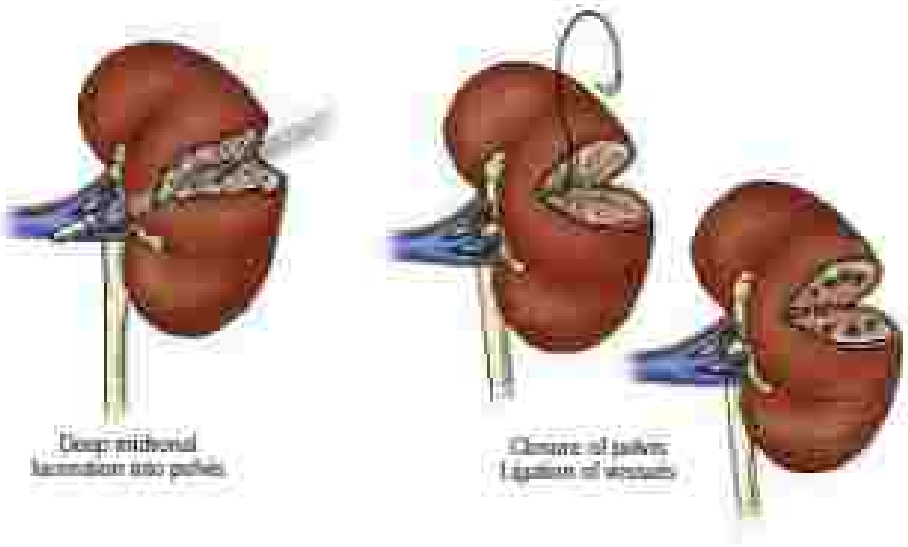

FIG. 5 Example of closure for traumatic penetrating renal injury from *[Grant Kim H, Mullens WK, Hill W. Kidney trauma [penetrating and vascular injuries] repair and nephrectomy. In: Gill WC, Asensio JA, Adams CA, et al., eds. Atlas of Traumatic Emergency Surgical Techniques. Philadelphia: Elsevier, 2018.]*

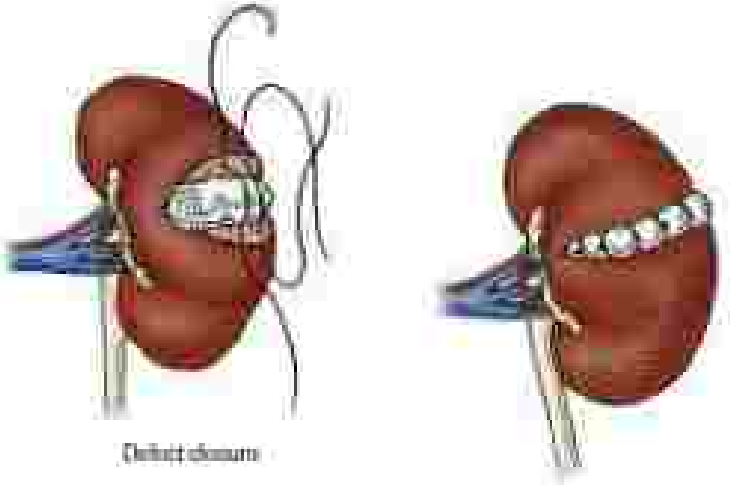

FIG. 6 Example of closure for traumatic penetrating renal injury with buttress *[Grant Kim H, Mullens WK, Hill W. Kidney trauma [penetrating and vascular injuries] repair and nephrectomy. In: Gill WC, Asensio JA, Adams CA, et al., eds. Atlas of Traumatic Emergency Surgical Techniques. Philadelphia: Elsevier, 2018.]*

Generally, in a hemodynamically stable patient, renal reconstruction should be employed. Coagulopathic patients or those with life-threatening hemodynamic signs should be monitored for nephrectomy. In some cases, after controlling hemorrhage and packing the retroperitoneum, further resuscitation is required and a planned return to the operating room should be arranged. Heroic reconstructive measures should be employed for patients with solitary kidneys. Renal injury reconstruction is analogous to the repairs performed during a partial nephrectomy for cancer. First, perform sharp excision of all nonviable parenchyma. Meticulous hemostasis of individual bleeding vessels can be obtained with sutures, cautery, or argon beam. In particular, the collecting system should be closed to a watertight fashion with absorbable sutures to prevent urinoma or ongoing extravasation (Fig. 5). It is prudent to place an antegrade ureteral stent for significant collecting system reconstructions. Parenchymal defects can also be reconstructed by approximating capsular edges over a hemostatic absorbable buttress such as Surgicel, or thrombin soaked Gelfoam (Fig. 6). In some cases, heminephrectomy may be required due to extent of injury. Omental interposition can be used to separate the injured kidney from any concurrently injured abdominal organs. Placing omentum between the lower pole and ureter can also help prevent perinephric fibrosis (Fig. 7).

It is important to recognize situations in which reconstruction may be counterproductive and nephrectomy preferred: shattered kidneys, kidneys with major vascular lacerations, or an unstable patient.

Complications and Follow-up

Complications typically occur early and are most often related to the collecting system. In particular, urinoma formation and prolonged urinary extravasation are most common. Infected urinomas may become symptomatic. Patients may present with fevers, flank pain, or sepsis. Such abscesses typically require percutaneous drainage and antibiotics. Prolonged urinary extravasation can typically be managed with a ureteral stent. Ongoing or delayed hemorrhage after repair can be evaluated via angiography and consideration given to embolization if continued transfusions are required.

Delayed bleeding, abscess formation, urinary fistula, hypertension, and hydronephrosis are considered late complications. Pseudoaneurysm or arteriovenous fistula either from the initial injury or the repair may result in delayed bleeding about 2 to 4 weeks after surgery. Embolization typically can effectively treat this issue. As stated previously, abscess formation is treated by percutaneous drainage and systemic antibiotics. A delayed urinary fistula requires further evaluation to determine its location either via CT urogram

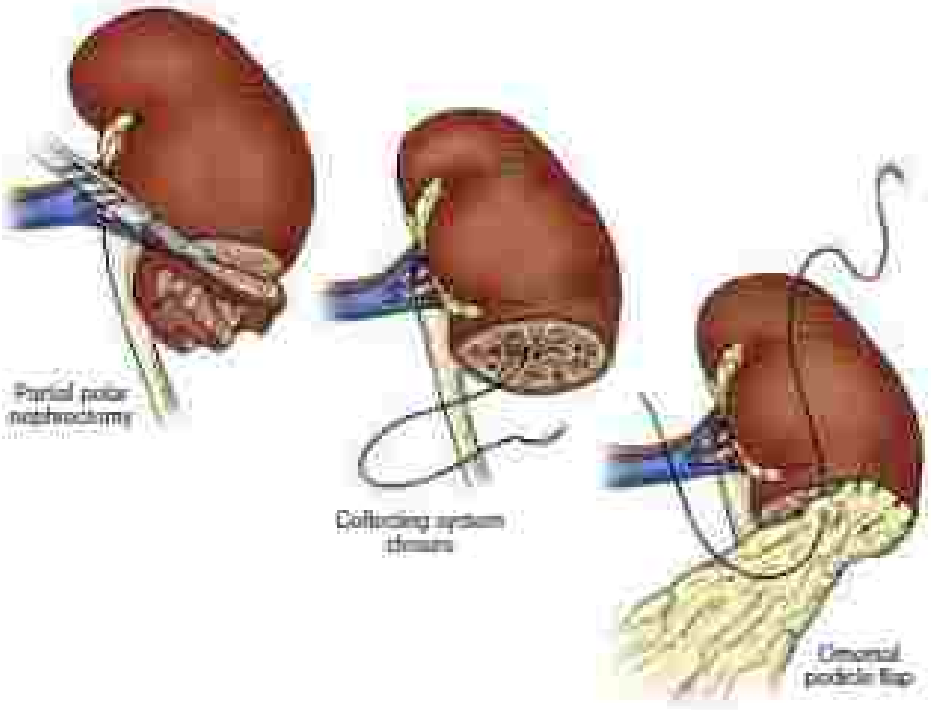

FIG 1. Hemostasis/control for extensive injury. *From Gin H, Hubert MG, Joly HM. Kidney trauma [parenchymal and vascular injury]: repair and nephrectomy. In: Cadeddu JC, Novick AC, Partin AW, Adams LA, et al, eds. Atlas of trauma surgery. Surgical techniques. Philadelphia: Elsevier; 2010.*

or retrograde study. Concurrent ureteral stricture or injury may be identified at this time. An indwelling stent and/or percutaneous drainage of the kidney should be attempted with planned repair 3 to 4 months in the future.

Hypertension is a rare long-term complication that results from either arterial stenosis (Goldblatt kidney) and chronic upregulation of the renin/angiotensin axis or direct parenchyma compression (Page kidney). If hematoma causing renal compression is the possible cause, surgical decompression may be useful but hypertension is ideally controlled medically. Hydronephrosis may develop due to unrecognized ureteral injury or after perinephric fibrosis resulting from injuries to the ureteropelvic junction or lower pole of the kidney. Interposition of omentum or perinephric fat between the injured kidney and the ureter at the time of repair may prevent this issue. Ultimately, it may be prudent to pursue renal ultrasound and blood pressure measurement for patients who have undergone renal reconstruction in the setting of trauma.

Suggested Readings

Brandt S, Coburn M, Armenakis N, et al. Diagnosis and management of ureteric injury: an evidence-based analysis. *J Urol Int*. 2004;68:577–584.

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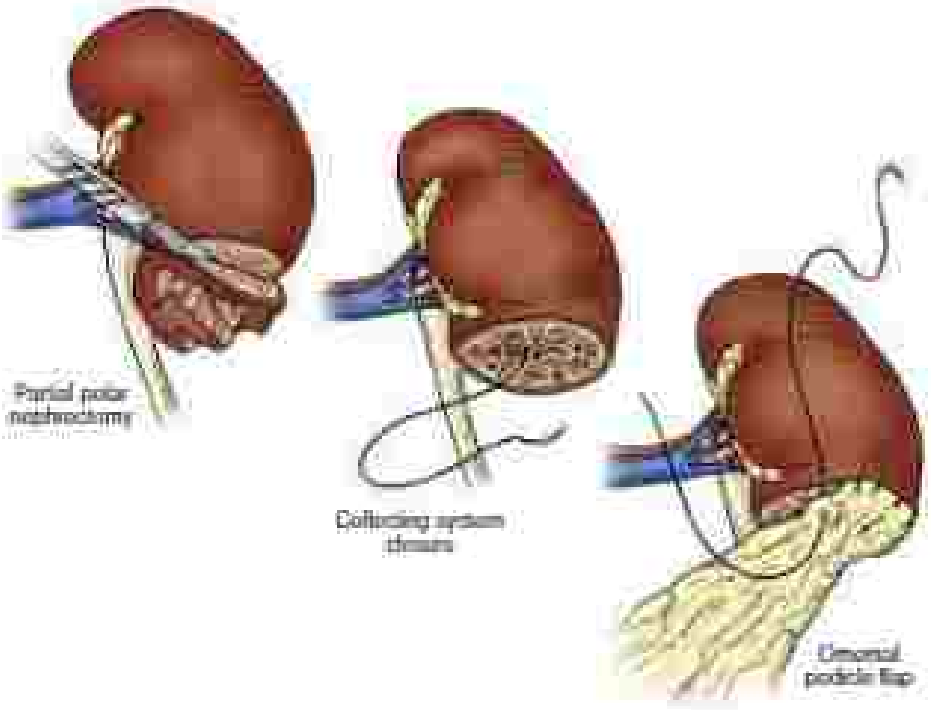
Tenets of Damage Control

J. David Richardson, MD, and Nicholas A. Nash, MD

Classical surgical teaching espoused the principles that once an operation had been undertaken, it should be continued to completion with an attempt to correct all the issues or problems encountered even in the setting of physiologic derangements. The mantra "do it right the first time" often prevailed. In the situation of the severely injured patient with major hemorrhage, this approach often resulted in a lethal triad of hypothermia, profound metabolic acidosis, and coagulopathy. This triad usually resulted in a death spiral from which the patient could not be salvaged, with a mortality approaching 90%.

The term *damage control* was adopted from the Warfare Manual of the Department of the Navy. It was stated as "the capacity of a ship to absorb damage and maintain mission integrity." Although the principal tenets of damage control had been espoused earlier, in 1983 Rotondo and Schwab described their experience with what could be termed *abbreviated laparotomy* when with abdominal packing and subsequent reoperation in an attempt to decrease the mortality in penetrating injuries causing exsanguination. Using this mindset, they reported greatly improved survival with a strategy to rapidly control bleeding and stabilize the patient before attempting definitive treatment.

The central tenets of damage control surgery are (1) control the threatening hemorrhage, (2) limit or prevent contamination, and (3) maintain end organ perfusion. The improved results of this concept led to its widespread adoption, but efforts to codify improved resuscitative strategies lagged behind the utilization of damage control operative techniques. Major conflicts in the Middle East led combat surgeons



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The central tenets of damage control surgery are (1) control the life-threatening hemorrhage, (2) limit or prevent contamination, and (3) maintain vital organ perfusion. The improved results of this concept led to its widespread adoption, but efforts to codify improved resuscitative strategies lagged behind the utilization of damage control operative techniques. Major conflicts in the Middle East led combat surgeons

to develop the concept of *damage control resuscitation*, emphasizing the earlier and greater use of the components of whole blood instead of traditional crystalloid infusion for initial resuscitation.

The term *damage control* and its underlying tenets have now been applied to virtually all aspects of emergency surgical procedures, including orthopedic surgery and neurosurgery. However, the scope of this chapter is limited to five basic themes: (1) the proper mindset and recognition of patients who might require damage control procedures, (2) damage control resuscitation, (3) damage control laparotomy for trauma or general surgical emergencies, (4) abbreviated thoracotomy, and (5) pitfalls or downsides to possible overuse of these techniques.

DAMAGE CONTROL MINDSET

To properly implement successful damage control strategies, it is imperative that surgeons have the proper mindset. This mindset should initiate an early thought process that triggers a set of responses that will begin immediately. Therefore, a successful damage control strategy in a patient who presents with hypotension should begin in the emergency department. The mindset should include a rapid assessment, a comprehensive resuscitation strategy, and a plan for early operative or radiologic intervention, depending on the type of injury.

Many patients who will require a damage control laparotomy or thoracotomy present to the emergency department with obvious signs of physiologic derangement on admission. They may be actively bleeding, have altered coagulation profiles early (if studied), and signs of hypoperfusion. Certainly surgeons with adequate experience in the care of the injured may recognize these signs immediately and proceed with a proper mindset; those with less experience may not do so, leading to delays in appropriate resuscitation and poor operative management. For example, damage control resuscitation (see later in this chapter) should not be initiated after the patient is already coagulopathic. Likewise, relying on abdominal packing to control bleeding after the patient is well into the coagulopathy phase of the triad will generally have an unsatisfactory outcome.

Making these decisions requires sound judgment, which usually comes from experience. One obviously should not initiate massive blood transfusion on a patient who has transient mild hypotension but does not otherwise appear seriously injured, nor should the surgeon pack an abdomen immediately when hemorrhage could be controlled using time-honored surgical techniques. However, in a patient who is clearly severely injured, timely treatment is vital and delays may lead to the patient's eventual death.

The principles for the use of abbreviated thoracotomy are less clear to our practice, and the consequences of strategies, such as packing the thorax, may be more deleterious. With these considerations in mind, we are somewhat more reluctant to employ this technique for thoracic injuries. However, in appropriately selected patients, it may be lifesaving. Recently, damage control vascular surgery has been promulgated. In our experience where most injuries can be repaired expeditiously, these techniques are not widely used, whereas in a combat zone, in a rural hospital, or when there is no experienced surgeon available to treat the injured blood vessel, vascular damage control techniques may be appropriate.

In summary, a proper mindset regarding damage control surgery means one must be able to rapidly assess the individual situation and apply proper judgment as to the treatment needed.

The proper mindset for damage control procedures in emergency general surgery or the occasional elective operation that proceeds badly is often different from that needed in hemorrhage from trauma situations. In our experience, there are generally three scenarios within the abdomen in which damage control techniques may be useful: (1) the patient has an obvious intra-abdominal catastrophe that may be manifested by sepsis, hypotension, or major physiologic derangement; (2) the patient may have an obvious abdominal problem but the extent of the situation and remedy required are not obvious until the procedure commences; or (3) the patient has an elective operation in which an untoward event occurs that is usually manifested as major hemorrhage. In the first scenario (obvious intra-abdominal catastrophe and altered physiology), the surgeon should have a damage control strategy at the top of their mind. This may involve source control of infection if possible, drainage of purulent material, and an abbreviated procedure that likely will require reoperation. Temporary abdominal closure may be indicated, particularly if the patient is unstable.

In the second scenario the surgeon may be unprepared for the extent of the problem and may be tempted to overreach in an attempt to solve the problem completely. Provided the patient is hemodynamically stable, complete correction is desirable, but occasionally in complex problems unrecognized preoperatively, temporization is a preferable option. In such situations, early planned reoperation may permit a better outcome. We have been involved in many cases through the years where the third scenario of major unanticipated hemorrhage occurs during an elective operation. Examples include abdominal trocars placed into the vena cava, aorta, or iliac vessels or major pelvic bleeding from oncologic or gynecologic procedures. Because these events were not anticipated, a different mindset is necessary. Temporary packing while blood is obtained and appropriate consultation achieved is mandatory. Notification of family members with the patient should be done promptly. If major bleeding is encountered, then a shift in mindset from operative completion to patient salvage should occur.

Although the considerations about mindset may appear self-evident, in our experience the reality may be different. Even surgeons who virtually never encounter significant bleeding in their elective procedures should have a default option in the unlikely event that the unthinkable occurs. The lead author of this chapter was once consulted intraoperatively by a plastic surgeon who transfused seven units of blood after encountering bleeding from an unnamed large vein on the chest wall during a breast procedure. The safe practice of surgery requires a prepared mind and a proper mindset to deal with the myriad of situations that may be encountered in both elective and emergent procedures.

DAMAGE CONTROL ASSESSMENT AND RESUSCITATION IN TRAUMA PATIENTS

After initial triage by prehospital providers, patients at risk for major hemorrhage should be rapidly identified. The principles of the Advanced Trauma Life Support manual should be followed, but in an extremely timely manner. Failure to identify a problem may be catastrophic, but the assessment cannot be done at a leisurely pace in high-risk patients. Once the airway is secure, a rapid diagnostic evaluation should be performed, which may include a focused assessment with sonography for trauma (FAST), and a chest and pelvic radiograph (if indicated). Although diagnostic peritoneal lavage is not used commonly, it still can have value in the patient with unexplained hypotension and an equivocal FAST examination. The hospital's massive transfusion protocol should be initiated to alert the blood bank regarding the potential for a patient with major blood requirements.

Damage control resuscitation (DCR) should ideally be used in tandem with a damage control operation. While the hemorrhage may be easily controlled with standard surgical techniques, such as a splenectomy, the nature of an abbreviated procedure should be reconsidered from the outset if the bleeding is not readily controlled. DCR, as currently practiced, has a three-pronged strategy: (1) permissive hypotension, (2) limitation of crystalloid infusion, and (3) hemostatic resuscitation. Permissive hypotension is the concept of ensuring circulation adequately to perfuse vital organs without complete resuscitation, which may actually increase bleeding. The adequacy of circulation in the practice of permissive hypotension can potentially be judged on two factors: preservation of sensation and the ability to palpate at least a weak radial pulse. The practice of permissive hypotension was initially found to be beneficial in treating patients with

ruptured abdominal aortic aneurysms. The Ben Taub group in Houston demonstrated its safety and efficacy in patients with penetrating trauma and short transport times to a trauma center.

The second limit to DCR involves limiting the infusion of crystalloid solutions. Although crystalloid infusions have great value in certain situations, in patients with major hemorrhage their overuse before surgery may cause a dilution of clotting factors with subsequent clot disruption. Additionally, crystalloid solutions, especially when administered in large volumes, have a proinflammatory effect that may potentiate organ failure. In severe hemorrhage, the early use of blood components appear to be advantageous.

The third limit revolves around the early use of what is termed *hemostatic resuscitation*. For several decades before the ongoing Middle East conflicts, the use of blood products for hemorrhage control was a foreign concept. Blood components were replaced as needed, often based on measuring the hematocrit, obtaining a platelet count, or using other laboratory measurements for calculating the need for component replacement. However, the seminal work by United States military surgeons demonstrated that early replacement of whole blood or its constituent parts decreased transfusion requirements and resulted in a decreased mortality. These experiences have been replicated in numerous civilian experiences. Although the use of fresh whole blood is not feasible in nonmilitary settings, the replacement of its constituent components is feasible. The initial mantra for component replacement was 1:1:1 with a unit of platelets and fresh frozen plasma (FFP) for each unit of packed red blood cells. Although there has been some debate about the correct ratio of components and there has been no randomized control trials for DCR, there is an overwhelming clinical experience supporting these concepts in patients with major blood loss. There are theoretical reasons to avoid the transfusion of "old" blood in massive blood situations. Storage of blood leads to various degradative products over time and these storage lesions are likely proinflammatory. The practicality of this approach in clinical settings is less clear.

In addition to the aforementioned principles, there are other considerations that may need to be addressed, especially in patients with major blood loss.

Hypothermia Prevention

Hypothermia is a part of the lethal triad, but some of its effects may be partially ameliorated if addressed early. After the patient has been fully exposed to exclude associated injuries, warm blankets and forced air warming devices should be applied to decrease heat loss. Fluids and blood products should ideally be warmed during infusion. Supplemental oxygen should be maximally titrated. However, if the patient cannot be promptly resuscitated, hypothermia may continue despite warming efforts.

Acidosis Prevention

This topic remains controversial. Normal saline has a pH of approximately 5.5, whereas Ringer's lactate is more physiologic. Hence, large volume infusion of normal saline should be avoided.

Pharmacologic Adjuncts

Medications are available for rapid infusion that may aid in reversing the effects of coagulopathic bleeding and aid in the DCR process. Prothrombin complex concentrates (PCCs) are drugs consisting of clotting factors (three factor PCCs consist of clotting factors II, IX, and X; four factor PCCs add clotting factor VII). These products mimic the effects of FFP but act more rapidly and are much easier to deliver to the patient with less volume required (the drug comes in powder form). Antifibrinolytics (tranexamic acid [TXA] or aminocaproic acid) have also become a mainstay of most DCR situations with massive blood loss. They act to prevent hyperfibrinolysis, whereby the body's natural breakdown of clots occur in a pathologic, accelerated process. Some centers are able to quickly decide which patients would best benefit from this therapy with thromboelastogram evaluations. Others without this technology can use TXA based on clinical judgment (hypotension, presumed need of massive transfusion protocol) given the overall safety profile of the drug and its proven ability to decrease the amount of blood transfusions necessary in such circumstances.

DAMAGE CONTROL LAPAROTOMY FOR TRAUMA

A surgeon attempting to perform damage control laparotomy should have the proper mindset, as previously mentioned. Most patients who will need a damage control operation for bleeding will present with evidence of significant blood loss, preoperative acidosis, abysmal lactate, hypothermia, or other suggestive signs. There are other situations where the level of hemorrhage may not be readily apparent but becomes so after clots are dislodged or visceral structures are manipulated. In our opinion, a midline incision should always be used in exploration (laparotomy) for trauma. Blood and clots must be evacuated and the source of the hemorrhage isolated as rapidly as possible. Our teaching is to attempt to locate the source of bleeding by quadrants, if possible, while realizing that some patients will have multiple bleeding sites. The targeted areas should have abdominal packs placed rapidly for tamponade in all four quadrants, including the pelvis.

In patients with significant ongoing hypotension, the aorta may be occluded at the diaphragm by manual compression or may be controlled with a metallic aortic occluder or cross-clamped with a vascular clamp. The cross clamping of the aorta is one of those techniques that is much easier to describe than to actually do, even for the experienced surgeon. It can be accomplished by rotating the esophagus slightly to the left after rapidly and safely encircling it. The muscular fibers overlying the aorta may be rapidly divided, and a large noncrushing vascular clamp can then be used to cross clamp the aorta. Our teaching is to actually attempt to clamp the spine and, in that case, one is more likely to actually have the aorta clamped. Although aortic clamping is more difficult than simply compressing the aorta, if it can be accomplished rapidly and successfully it does allow for better hemostasis and facilitates exposure in the upper abdomen without the need for an assistant to provide continuous manual compression. Control of the aorta at the hiatus allows resuscitation by the anesthesia team. Aortic control may be obtained in the prehospital or emergency department setting, with the use of a technique called *resuscitative endovascular balloon occlusion of the aorta*, in which a balloon catheter is passed retrograde through the femoral artery into the aorta. The balloon is then inflated, resulting in aortic occlusion. This technique is useful in skilled, experienced hands, but is of doubtful utility for the novice who might consider its use. Packs should then be removed serially. Our practice is to remove those that are not bleeding initially, leaving the suspected site of hemorrhage until the final pack removal.

The areas that are most problematic for hemorrhage control in our experience are the liver and major vascular structures.

Hepatic Hemorrhage

Liver injuries may present in all shapes and sizes. If there are visible arterial and/or venous vessels bleeding from within a crack in the liver, these may be able to be safely controlled with direct vessel ligation. In our experience, putting clips on hepatic bleeding is not efficacious because they tend to fall off and rarely is there an accessible vessel to be adequately clipped. Although there are those who have condemned the use of hepatorrhaphy by using a large blunt liver needle to suppositionate crevices in the wound, we have occasionally found this to be a successful strategy. One should not strangulate tissue to the point that it becomes necrotic, but coaptating tissue may facilitate hemorrhage control, even if packing is necessary.

If there is a nonbleeding, contained hematoma in the retrohepatic region, under no circumstances should that hematoma be opened. Retrohepatic venous bleeding, which could come from a torn hepatic vein, is by definition a low-pressure system. Many of these will heal and not cause long-term sequelae if they are unopened.

Major arterial bleeding from deep within the liver must be stopped. Although packing is efficacious for venous bleeding, it does not control arterial hemorrhage. There is controversy about whether a patient should be taken from the operating suite to a hybrid operating room or an angiography suite to radiologically control major hepatic arterial bleeding. Such decisions would depend on the resources available within the facility, the expertise of both the surgeon and the radiologist who might be available to care for the patient, as well as the inherent stability of the patient at the time.

The use of control of the portal triad through cross clamping with the Pringle maneuver may be valuable while attempting to obtain control of hepatorrhaphy. Generally we request that our cross-clamp time be measured and, in 15- to 30-minute increments, we then remove the clamp for a few minutes to allow liver reperfusion, even if the clamp needs to be reapplied.

In our experience, a generalized venous bleeding from the hepatic parenchyma itself is extremely difficult to control with suture techniques. If there is a segment of liver that is amenable to resection, newer resective techniques using staple devices are efficacious in nonanatomic resections to control hemorrhage. Ongoing venous bleeding that is not rapidly controlled by either sutures or staple techniques should be considered for perihepatic packing.

We attempt to count the number of packs used to avoid having a retained sponge. As in many aspects of surgery, perihepatic packing may be a bit of an art. Simply stuffing packs in an insertion to posterior direction to compress the liver may effectively decrease bleeding, but it also may compress the vena cava and impede venous return to the heart, not allowing the patient to ever be adequately resuscitated. Rather, the packs should be placed in a superior to inferior position, such that the liver is compressed from top to bottom as opposed to the anterior to posterior direction. Whereas some surgeons advocate placing a nonadherent dressing over the wound before packing, we prefer to pack directly on the wound, believing the tamponade effect is actually greatest by direct sponge contact.

Spleen

A ruptured spleen causing major hemorrhage, whether as an isolated injury or in combination of others, should be treated with a rapid splenectomy. Attempts to salvage splenic injuries by splenorrhaphy or partial splenectomy should be strongly discouraged and a rapid splenectomy performed.

Renal

Any small, nonpulsatile, and nonexpansive hematomas involving the kidney should not be opened. If the patient has active, ongoing bleeding with an expanding perirenal hematoma, the treatment is more controversial. In a totally isolated situation, there are occasions where one may actually be able to salvage a portion of the kidney by a variety of techniques after control of the renal artery proximally. However, in our experience, this has been exceedingly rare and generally, once the hematoma is opened, a nephrectomy will be required. Before opening a hematoma, one should ensure presence of the contralateral normal-sized kidney.

Pancreas

Hemorrhage control of the pancreas is typically achieved with simple suture ligation or packing. It is important to remember contamination from a pancreatic duct injury. This can be controlled with simple drainage at the index operation, and more definitively with formal resection at the second look laparotomy (distal pancreatectomy, subtotal pancreatectomy, or Whipple, depending on the site of injury), if needed.

Pelvic Hematoma with Associated Pelvic Fracture

There can be significant amounts of blood in the pelvis and even further layering in the retroperitoneum with significant pelvic fractures. Intraperitoneal packing of the pelvis may provide some benefit. Depending on the extent the laparotomy incision, a separate incision can be made in the suprapubic area and the preperitoneal space of Retzius can be accessed and expanded toward the sacrum. Three laparotomy pads can be placed in both sides of the pelvis to help tamponade bleeding. Efforts at embolization of the internal iliac arteries can be made immediately after the operation and the interventional radiology or vascular teams should be mobilized during the operative phase.

Vascular Injuries

There are myriad types of vascular injuries. As previously stated, major arterial bleeding will require control through suture, staples, shunts, or some type of mechanical hemostasis. Likewise, most major venous injuries will require a primary repair as well. Venous bleeding from armored vessels or small vessels may be controlled by packing.

Control of hemorrhage is the initial priority in damage control surgery for trauma, but a secondary issue is the control of contamination from hollow viscus injuries. The source of visceral contamination should be isolated, identified, and may be controlled initially with a noncrushing clamp. If the intestine is devitalized, it may need to be rapidly resected using staple devices with a secondary anastomosis or ostomy creation at a later time with a planned reoperation. Some have advocated simply using a whipstitch to close visceral injuries, but in our experiences some of these will leak and cause major problems with sepsis and intestinal fistula at a later date. If the hemorrhage can be rapidly controlled, then taking a few additional minutes to perform a secure closure of bowel injuries is worthwhile. The decision required in terms of rapid cessation of the operation versus ensuring a secure closure depends on the judgment of the surgeon.

In damage control operations for emergency general surgical procedures where hemorrhage is not the concern, the use of an abbreviated laparotomy will generally be dictated by the physiologic state of the patient. Devitalized tissue should be removed, purulent collections drained, and necrotic intestines resected. Primary anastomoses may be delayed if the patient's condition warrants.

Whether the damage control laparotomy is performed for injury or an emergent nontrauma problem, the abdominal fascia will rarely be able to be closed primarily. Although the abdominal contents need to be adequately packed to control venous bleeding, closure of the fascia or skin may result in a deleterious increase in intraabdominal pressure and subsequent abdominal compartment syndrome. There are commercial systems available for an open abdomen that rely on negative pressure (e.g., ABThera), but we often use a homemade system with suction drains placed under the fascia to control the drainage of fluid from the open abdomen (this is important to prevent moisture on the body surface, which accelerates bowel loss). A layer of a nonadherent material is placed over the viscera, followed by a layer of sterile towels or packs.

Finally, an occlusive dressing (e.g., Ioban) is placed over the wound (Fig. 1). The patient is then returned to the operating theater for an attempt at definitive repair 24 to 72 hours later. A vigorous attempt should be made for primary fascial closure at the second procedure, or as early as feasible.

There are situations in which the abdomen cannot be closed during the initial hospitalization. Although this problem was once very common, we are encountering it much less frequently. Limiting crystalloid resuscitation and the use of DCR has decreased the problem of abdominal swelling somewhat. Negative pressure systems may allow more rapid fascial reapproximation.

FIG. 1 This patient has undergone a damage control laparotomy. The abdominal dressing consists of suction tubes for fluid evacuation, sponges to facilitate negative pressure therapy, and an iodine-impregnated sealing dressing.

Our unit has also championed the use of "direct peritoneal resuscitation" in which 2.5% glucose based dialysis fluid (Delflex) is used to irrigate the abdominal cavity and decrease visceral edema. Our results showed an increased ability to accomplish earlier fascial closure.

DAMAGE CONTROL THORACIC SURGERY

There are several indications for a thoracotomy for trauma. These include cardiac tamponade or evidence of cardiac injuries on FAST scan, massive thoracic hemorrhage or ongoing bleeding from the chest, or persistent or high likelihood of injuries to other intrathoracic structures, such as the bronchus or esophagus. Here we confine our remarks to patients who need an abbreviated operation for major thoracic hemorrhage.

Intrathoracic hemorrhage results from cardiac injuries, pulmonary injuries, or chest wall bleeding in most circumstances. On occasion, vascular injuries of the thoracic outlet may produce intrathoracic hemorrhage as well. This latter category of injuries must be controlled by appropriate operative or endovascular techniques. However, the principles of care for pulmonary injuries have changed somewhat in the past decade. With the increase in caliber and velocity of firearms, destructive pulmonary injuries are currently much more common than those encountered several decades ago, when the simple placement of a tube thoracostomy and reexpansion of the lung often led to the arrest of bleeding.

Major pulmonary hemorrhage should be controlled when possible by the minimum amount of pulmonary resection. However, devitalized tissue that tends to ooze may be difficult to control with simple suture closure. Nonanatomic resection with a stapling device often will suffice to controlling pulmonary bleeding. If the bleeding is massive, the hilum may need to be controlled to facilitate exposure of the bleeding vessels. Hilar control may be accomplished by placing a noncrushing clamp across the hilum or simply twisting the lung 180 degrees to occlude blood flow. The latter maneuver will capture tension of the inferior pulmonary ligament to the level of the inferior pulmonary vein. Anatomic lobectomy may be the standard for a cancer patient with good pulmonary function, but it is rarely indicated in most situations of pulmonary hemorrhage. On occasions, when bleeding from deep within the parenchyma is encountered, a "tractotomy" may be used to expose the bleeding vessel. Although this appears to be a simple technique when illustrated on a two-dimensional diagram in a textbook, in the cylindrical shape of the lung it sometimes is more difficult. Placing a stapling device within the minitract and firing it to expose the deeper portion of the lung may facilitate visualization of the bleeding vessel within the parenchyma, which can then be sutured. Major pulmonary resection, such as a pneumonectomy, should be avoided unless it is the only measure that will not result in an operative death. The results of a pneumonectomy for trauma are usually poor, with postoperative mortality resulting from delayed right heart failure.

Bleeding from chest wall vessels may occur from destructive missile wounds, such as a shotgun wound or from blunt trauma with multiple rib fractures, which may shear intercostal vessels. In the latter situation, the use of encircling sutures around the ribs may control bleeding. On rare occasions, we have actually taken the patient to our hybrid room for angiographic control of intercostal vessels that were not amenable to suture ligation. Occasionally, a patient is encountered who has continuous oozing from the chest wall that is not amenable to either suture or angiographic control. In this instance, packing the chest wall and performing an abbreviated thoracotomy may be lifesaving. We have also found occasional instances of significant diaphragmatic bleeding, where packing the inferior thorax may help temporarily quell hemorrhage. Cardiac wounds exposed by a median sternotomy may not, on occasion, be amenable to normal closure. The system used for managing the open abdomen is employed in these cases.

Although the principles of abdominal packing are now well recognized, the indications for packing the chest are less well defined, and the outcome is not always predictable. The use of significant packing within the thorax may limit pulmonary excursion and lead to ventilatory problems. Unlike the abdomen, in our experience, some type of closure of the chest is generally indicated to prevent herniation of the lung through the open thoracic cavity with subsequent lung entrapment and a poor ventilatory status. We have not found that packing the pulmonary parenchyma itself is practical or feasible. The use of towel clips or rapid suture closure of the skin of the thorax to prevent pulmonary herniation is useful. Similarly, the principles of oxygenation after adequate resuscitation and correction of physiologic derangements would mirror those of damage control surgery of abdominal injuries.

DAMAGE CONTROL VASCULAR SURGERY

Much has been written about damage control vascular surgery, particularly in a review of injuries suffered in combat. In war theaters, the ability to do vascular repair is limited by a number of factors, including the availability of skilled surgeons and the necessity for treatment of other injuries. In managing civilian injuries, the need for damage control vascular surgery may differ significantly. In our experience, the two primary indications for the necessity of damage control vascular surgery in civilian trauma are the need to (1) transport a patient from an initial managing facility to a more sophisticated level of care; and (2) temporize the effects of ischemia due to arterial injury, primarily in the extremities, while more urgent, life-threatening injuries are managed. If the patient is stable, other life-threatening injuries are not present, and there are adequate surgical capabilities for primary vascular repair, then the use of damage control strategies is not indicated, in our opinion. In situations where there is not adequate surgical capability, we rarely encounter patient transfers to us of ischemic wounds. Generally, these patients

are simply transported in the most compact manner possible, rather than attempting to open the extremity, place a shunt, and then transfer the patient. The judgment required in these types of decisions are extremely complex and would vary greatly from one institution and individual surgeon to another. However, in patients where bleeding is minimized from an extremity or cervical injury, such that operative control was mandatory, the use of a shunt may be an excellent bridge while the patient is transferred to a facility where a definitive repair can be undertaken. That said, however, our general impression is that if surgeons are able to place the shunt, they often are able to do a repair. In our trauma center, we use shunting on occasion in patients who have other severe injuries that must be managed, and the shunt is then used as a temporizing device. In such a situation, it is imperative that one closely monitors the distal flow to ensure the shunt has not clotted and is functioning properly. The principles that we attempt to follow for shunt placement are as follows.

- As one attempts to place a shunt, we recommend that the vessels be tested for backbleeding in the distal artery. If there is inadequate flow or poor backbleeding, a balloon catheter embolectomy should be performed to ensure no clots are present proximally or distally or that any existing clots are removed. We then follow this with the instillation of heparinized saline into both the proximal and distal limb of the transected vessels. Vessels then can be occluded using a vessel loop or Rumel tourniquet. We do not advise systemic heparinization in patients who are multiply injured.
- An appropriately sized shunt is then used by cutting to a length adequate to ensure it is secure at both the proximal and distal ends of the vessel. Blood flow can then be reestablished as the shunt is placed within the vessel. The shunt should be secured in place by using a sturdy ligature of heavy silk or nonabsorbable suture. We recommend that the vessel not be dilated or resected to normal artery because this can be better accomplished at the time of definitive repair.
- Distal perfusion must be assessed with Doppler ultrasound. Flow should be biphasic, or optimally triphasic. In our experience, pulses are generally not palpable in these patients.
- In patients with ischemic injuries, a rapid fasciotomy may need to be undertaken to ensure that compartment syndrome does not abrogate the effects of perfusion to the extremity with the shunt.

In these situations, definitive repair should be performed within 24 hours once resuscitation is complete. On occasion, shunts may be left in place for 2 to 3 days, but it is imperative that distal perfusion be adequately monitored.

DEFINITIVE OPERATION AFTER DAMAGE CONTROL SURGERY

Once the patient has been adequately resuscitated and normal hemodynamic and clotting status restored, the patient should be returned to the operating room as early as reasonably possible for definitive repair of injuries. In some situations, such as major hepatic bleeding, which has been controlled by packing, we prefer to leave the patient at least 24 hours, even if the resuscitation is complete within 6 to 8 hours. The mechanical effects of the packing itself on local coagulation is often important.

Regardless of which type of damage control operation is performed, the wound (and any subsequent) procedure performed must be meticulous. The potential for wound injuries due to a hurried initial operation is always a threat. Therefore, a comprehensive reexploration is mandatory.

Our practice is to radiograph the body cavity (chest or abdomen) of any patient who has had a damage control operation. Although we attempt to count sponges at the first operation, such sponge counts may often be inaccurate, thus the need for thorough radiologic evaluation of the cavity is vital. On more than one occasion, we have encountered situations where an inadequate radiograph failed to detect a sponge that was hidden in the recesses of a body cavity that was not properly evaluated. Thus, multiple views of the chest and abdomen may be required to ascertain that no foreign body is still in place.

MISUSE OF DAMAGE CONTROL OPERATIONS

There is a tremendous amount of literature on the *efficacy* of damage control operations (DCOs), particularly with abbreviated laparotomy.[1] Although the principles for these techniques are continually being refined, the basic elements of management of these patients is relatively well established. However, it is important to note that there are no randomized control trials demonstrating the efficacy of DCOs, regardless of the type of injury being treated. Given the nature of these types of problems encountered, there will almost certainly never be level one evidence proving the efficacy of these techniques.

When damage control strategies are appropriately applied, it is our strong belief that they may be life- or limb-saving, depending on the situation. However, these techniques present problems in and of themselves, including the potential of infection, life-limiting ventral hernias, and enterocutaneous fistula. Additionally, all will require at least one reoperation. As in all surgical situations, patients and their family must be made aware, when feasible, of the reasons for employing these radical but potentially lifesaving approaches.

One element of concern for us has been the potential overuse of techniques, such as abdominal packing. We have encountered patients transferred to us who have had gauze packing stuffed into their abdomen or chest, with no attempt made to definitively manage the problem. A review of records of some of these patients demonstrates that none of the hallmarks of the patient requiring a damage control procedure was initially present. As in all surgical procedures, the judgment required in these situations is a delicate balance between not doing enough and doing too much. When properly applied, damage control procedures are now one of the most important adjuncts for surgeons who take care of trauma and emergency general surgical patients.

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Early Management of Pelvic Ring Disruption

J. Greg Mears, MD, and Greg M. Osgood, MD

Simply stated, early detection and appropriate basic early intervention can save a life. Pelvic fractures can bleed significantly; first responders can prompt life-threatening bleeding without sophisticated technology or advanced training. Appropriately managed, a patient with a complex pelvic fracture may not require intensive care unit (ICU) admission and may not place undue stress on a health system. In the past 20 years, improvements to understanding simple interventions and teaching these to front line providers have allowed primary emergency responders to care for prior to orthopedic consultation. For this reason, expanded dissemination of these techniques to all trauma responders is integral to improving trauma outcomes.

EARLY MANAGEMENT OF PELVIS FRACTURES

Early management of pelvic fractures involves detection of patients at risk of sustaining this injury, appropriate radiographic evaluation and fracture classification, and rapid assessment of patients with life-threatening patterns. This early triage aids in efficient utilization of resources and immediate intervention in the appropriate patients. Most pelvic fractures are not life threatening. Discerning the subset of patients with high-energy patterns with high degrees of morbidity and mortality within this diagnosis is imperative.

Mechanism of Injury in Pelvis Fractures

Pelvic fractures occur through both low energy and high energy mechanisms. The most common fractures of pelvic bones occur in falls from standing height. These fractures primarily occur in elderly people with osteopenic or osteoporotic bone. The mechanism of injury is a direct impact through the greater trochanter or iliac crest, placing a lateral compression (LC) force across the pelvis. Typically, this generates a compression fracture through the sacral alar area and a corresponding, more displaced, anterior pelvic ring fracture through the superior and inferior ramus (Fig. 1). This fracture type occurs because of significant osteopenia. Although these are low-energy fractures and are rarely life threatening, they may be devastating to the individual patient due to medical comorbidities and difficulty to mobilizing after the fracture.

In contrast, high-energy fractures to the pelvic ring occur through motor vehicle collisions, motorcycle injuries, falls from a height, and other mechanisms in which the pelvis is subjected to high velocity sudden impact. These fractures are characterized by larger degrees of displacement and generally occur in younger patients. They may involve LC, anteroposterior compression (APC), or vertical loading of the pelvic ring. Typically, these fractures occur through high energy direct impact to the symphysis or greater trochanter, or indirect loading through the femur and femoral head, although crushing mechanisms also occur. Associated injuries and significant bleeding characterize these fractures; a high index of suspicion for this injury is required when patient presents with high energy trauma to the abdomen and pelvic regions.

Relevant Patient History at the Time of Pelvic Trauma

Detection of pelvic trauma begins as the patient rolls into the trauma room. Pelvic trauma should be suspected after motor vehicle and motorcycle trauma, equestrian trauma, industrial injury, history of crushing mechanism, fall from a height, and other high-velocity injuries. The external signs of pelvic trauma include gross lower limb deformity, open wounds of the perineum and lumbosacral posterior torso (Fig. 2), bruising around the genitor trochanters and thighs, and subcutaneous swelling about the pelvis. Internal dysfunction or separation of the skin from underlying fascia, the Morel-Lavallée lesion, often occurs about the thigh at the time of pelvic trauma (Fig. 3). This can cause significant unrecognized blood loss and may also complicate surgery if not addressed appropriately. Compressive dressings are the first intervention when this associated injury is detected. Another common presenting complaint on immediate presentation is lower limb neurologic dysfunction. Motor and sensory loss below the hips should raise suspicion of lumbosacral trauma. The disturbing nature of this symptom to the patient makes it one of the first symptoms identified as the patient arrives at the trauma bay.

First responders should conduct a primary survey of the patient, assessing the ABCs of trauma response. Initial evaluation of the patient for sources of bleeding, the most common cause of hypotension in trauma, includes establishing whether there is pelvic and retroperitoneal bleeding. Bleeding from pelvic trauma occurs at lacerated vessels, but also from the large surface area of the fracture. Although providers often focus on arresting arterial blood loss, uncontrolled venous bleeding is a common source of hypotension. Veins do not contract or constrict, are thin walled, and are difficult to access; therefore venous bleeding is difficult to address directly without surgical intervention. Bleeding at fracture surfaces and venous bleeding can only be controlled by compression and stabilization of the fracture hematoma. Class III hemorrhage, with depression of systolic pressure, signifies a blood volume loss of 30%; in these cases, pelvic hemorrhage must be strongly considered. Focused abdominal sonography in trauma poorly identifies pelvic and retroperitoneal bleeding; therefore a high index of suspicion of this problem is indicated. Computed tomography (CT) and angiography may be required to identify discrete vascular sources of hemorrhage.

The events at the trauma scene are critical to patient outcome. Providers must know if there was associated external or perineal bleeding identified when the trauma occurred. In rushing to stabilize a patient with pelvic trauma, the clinician must identify all sources of external bleeding and open wounds as part of the initial survey; perineal and posterior wounds are often overlooked at the patient's peril (Fig. 4).

Prior to performing any surgical interventions, it is critical that the team assess the patient for prior abdominal and pelvic trauma, prior surgery to this area, prior laparoscopic or minimally invasive interventions, or radiation dosing to this area. These prior activities complicate all surgical procedures that address pelvic trauma.

IMMEDIATE ACTION SAVES LIVES: PRIMARY INTERVENTIONS

Advanced Trauma Life Support protocol mandates anteroposterior (AP) radiographs of the pelvis as part of the primary survey. Increasingly, CT of the body, and importantly the pelvis, is performed to identify life threatening injury. The primary responder to pelvic trauma therefore should have preliminary radiographic imaging that identifies a pelvic fracture, allows some important generalizations on patient hemodynamic status, and signals the need for orthopedic consultation. If the patient's history and emergency radiographs suggest pelvic trauma, fracture, or dislocation, orthopedic consultation is warranted. The specialist's experience with immediate interventions and knowledge of common protocols for management is important to decreasing mortality and morbidity.

The next step in intervention is identifying the patient at risk from life threatening hemorrhage from pelvic trauma. As stated, the combination of patient complaints, the history of the injury, and

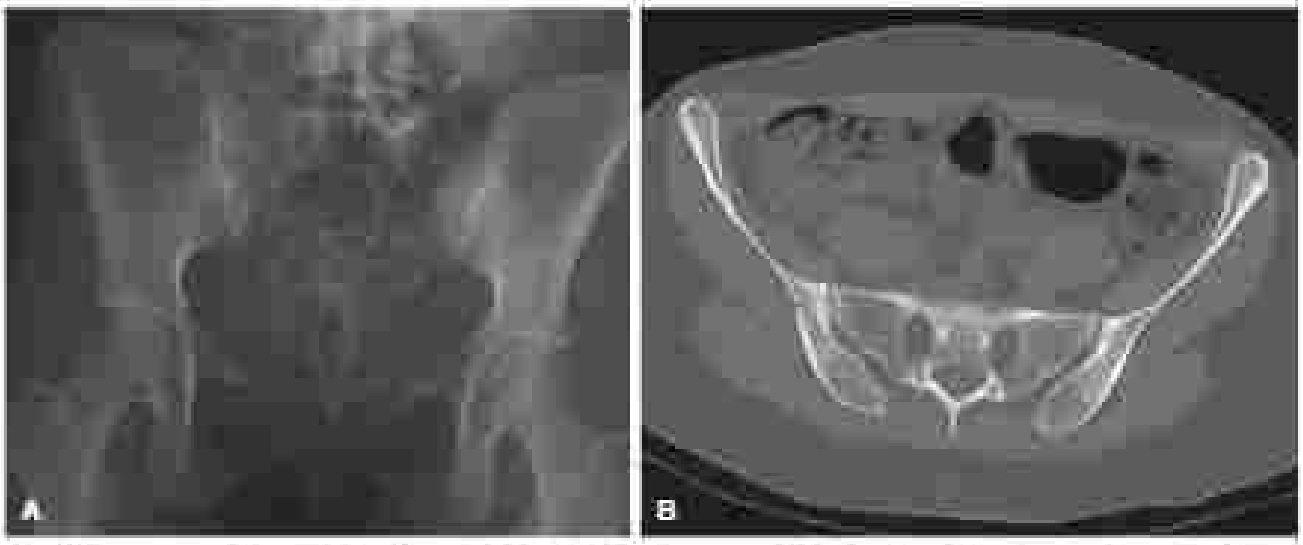

FIG. 1 (A) Anteroposterior radiograph of stable minimally displaced lateral compression pelvic fracture. (B) Axial computed tomography image of sacrum shows left sacral alar compression fracture.

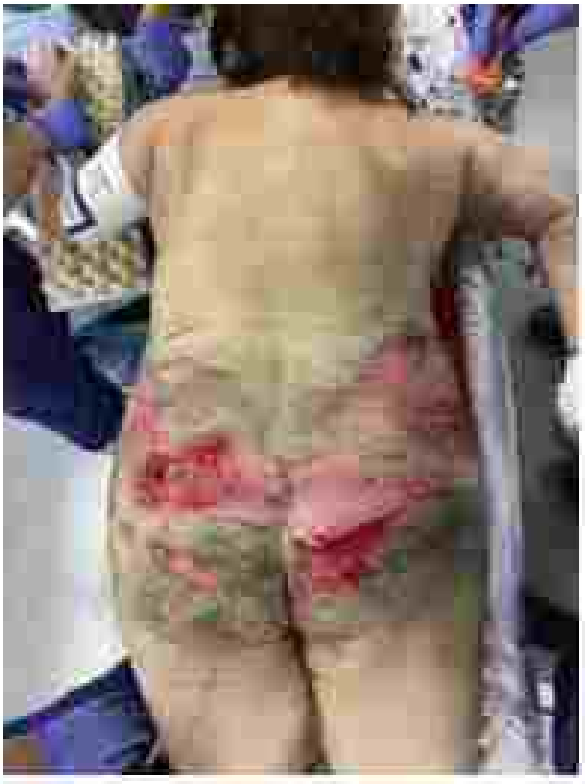

FIG. 2 Posterior lumbosacral abrasions related to pelvic trauma.

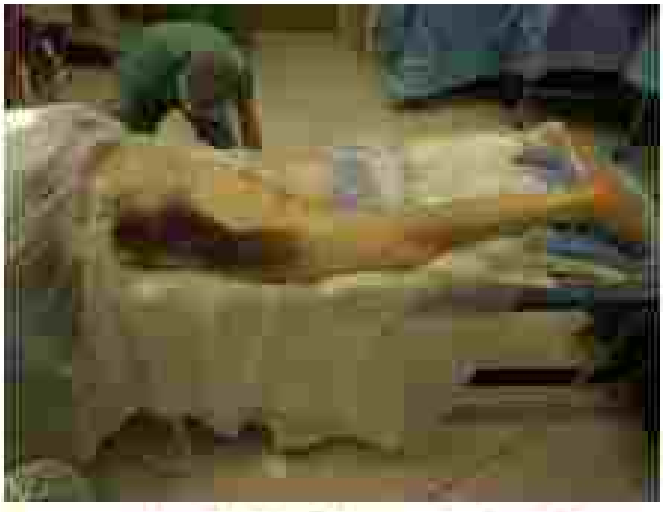

FIG. 3 Large Pelvic Cradle binder on the lateral thigh.

immediate visualization of the patient provide significant clues to this end. Radiographs that show gross displacement of the pelvis, gross asymmetry of pelvic bones, vertical shifting of the ilium on one side, and gross open book deformity of the pelvis warrant emergent placement of a circumferential pelvic sheet or binder; therefore efficient circumferential physical examination of the anterior and posterior lumbopelvic area and perineum (described later) is expedited and the compressive binder is applied. Rapid irrigation of large perineal wounds and packing improves the effect of a binder because large open wounds permit ongoing hemorrhage that cannot form a stable hematoma. The application of a pelvic compressive wrap or binder is lifesaving and should not be delayed (Fig. 3). It decreases the pelvic volume allowed for hemorrhage and applies a stabilizing compressive force at bleeding fracture surfaces and wounds. The technique of binder application is important to optimizing its effect and to minimizing the need for adjustment or reapplication.

Gentle realignment of the lower limbs with gross manual traction can improve binder effect. Bringing the feet together and internally rotating the lower extremities places the pelvis in optimal position. Commercially available binders attempt to simplify the steps of application; however, the principles of safe binder application must be followed. The first principle of binder application is centering the binder over the greater trochanters so that a compressive force is applied through toward force at the femoral heads. Improperly applied binders centered on the prominent iliac crest do not provide the best compression. The second principle is a wide, smooth surface of force application, roughly 20 cm in width, to distribute the required force over a large surface area of vulnerable skin. Wrinkles in sheets or binders must be avoided. Third, adequate compression should be applied; this often requires 2 to 3 responders to apply an effective binder when the patient is large. Two providers apply force at the greater trochanter, then one secures the binder. Finally, the patient

FIG. 4 Perineal wound associated with open fracture.

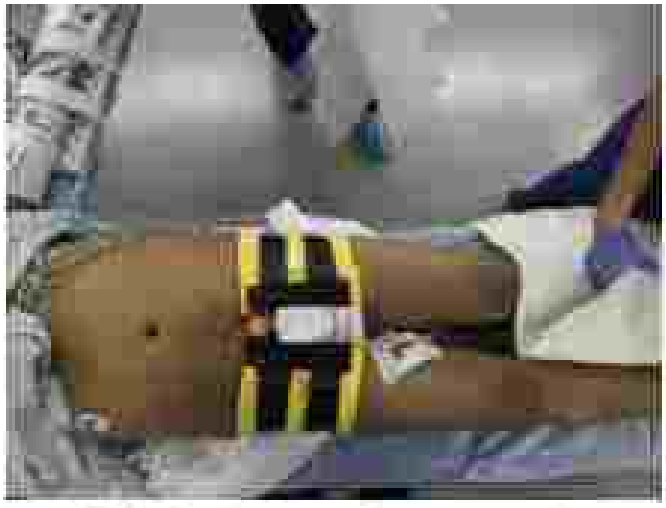

FIG. 5 Pelvic binder applied appropriately over greater trochanters and tightened.

with a binder must not be neglected. The skin beneath a binder is at risk due to initial trauma and then also due to binder compression.

There are few case reports of a binder causing or worsening a patient's injury. The question often arises if binders should be applied in the setting of LC injury, considering that the compressive force of the binder seems to only add to the internal rotation force of the patient's injury. If the patient's injury only involves internal rotation into hemipelvis (LC1 and LC2 injuries discussed later) the binder can be removed because it most likely does little to assist in hemorrhage control. If the patient's injury is a windswept pattern (LC3), the binder most likely can provide some benefit in stabilizing the pelvis and minimizing bleeding. A pelvic binder should always therefore be considered when pelvic fracture and hemorrhage is suspected as the source of hemorrhagic shock. Once the pelvic fracture pattern is appropriately identified, the binder may be removed if the provider determines it is not helping in the patient's care.

FIG. 6 Early skin breakdown is seen directly over the right greater trochanter 24 hours after binder application.

A binder may be left in place for 24 hours to allow fracture hematoma stabilization, but the skin must be checked around this time to assess for ongoing compromise. A binder may be left on after this point only if it is necessary for life-threatening injury. Prolonged application causes skin necrosis (Fig. 6) that can greatly affect surgical planning and patient outcomes.

A simple bed sheet is an effective universally available resource that all providers can learn to apply as a pelvic binder. Applied in this manner, it is referred to as a circumferential pelvic antishock sheet (CPAS). The same principles apply for sheet application: centering over the greater trochanters, wide surface of force application, effective compression and application, and tightness (Fig. 7A,B). When these principles are followed, pelvic hemorrhage can be effectively controlled on the scene wherever pelvic trauma occurs. Access for internal fixation can be obtained by strategically cutting windows in the sheet prior to surgical preparation (Fig. 7C).

Physical Examination vs Radiographs

The emergency imaging of the skeleton following high-energy trauma involves an AP pelvis radiograph, with or without axial CT of the pelvis. Although a great deal of information about a pelvic injury can be obtained through these standard radiographs, these images are merely snapshots of pelvic geometry that may belie the amount of pelvic instability and threat to the patient. A well-aligned pelvis on initial imaging may be the result of clothing, dressings, a compressive wrap or binder, or positioning at the time of radiograph, such as the cradling bed of the CT scanner. The pelvic injury and instability may be much greater than what appears on the films (Fig. 8). Stability of the pelvic ring should not be assumed when the history of injury suggests pelvic ring fracture, even when radiographs show a normal appearing pelvis. Therefore, a careful physical examination is critical.

Physical examination follows in a standardized manner, involving circumferential inspection, palpation, gentle motion of the extremities, and complete neurovascular examination including examination of both lower extremities.

In the setting of high-energy trauma, multiple caregivers should be recruited to safely logroll the patient to inspect the posterior spine and pelvic region. The perineal area must be inspected with great care, looking for small puncture areas where bony fragments may have perforated the skin. Additionally, open fractures can occur through perforation through the rectum and genitourinary system. For this reason, inspection and palpation of these sensitive areas is imperative,

FIG. 7 (A) Correct application of a circumferential pelvic antishock sheet. (B) A well-applied sheet secured with Kocher clamps compresses the pelvis. (C) Windows in the pelvic sheet allow access for conversion to anterior pelvic external fixation.

a speculum examination is warranted in women. Blood at the urethral meatus usually indicates urethral injury; this is best further investigated with retrograde urethrogram prior to Foley catheter insertion. The lower extremities should be inspected for subtle leg length inequality or abnormal rotational in either lower extremity. This may indicate significant displacement of one hemipelvis or upward displacement of one side of the pelvic ring, which allows limb shortening.

Palpation, specifically manipulative assessment of the pelvis, is important for these patients as well. AP compressive force is applied to patients in the supine position to detect subtle open book instability of the pelvic ring that is not identified on initial plain radiographs. In a similar manner LC, as the greater trochanters, detecting rotational instability of one hemipelvis, is essential. These maneuvers may disrupt pelvic hematoma, and therefore should not be executed repetitively. Gentle range of motion of the hips is indicated for these patients to detect fractures, soft tissue injury, or dislocation around the hip.

The neurovascular examination of a traumatized pelvis includes assessment of motor function and sensation from the waist down. Active hip, knee, ankle, and toe flexion and extension should be assessed. Lumbar and sacral roots must be tested for motor and sensory function. Rectal tone and perianal sensation should be tested at the time of rectal examination for open injury and hemostasis testing. Timely documentation of the neurovascular examination on presentation is important because the patient's examination may evolve after arrival.

Treatment of Open Pelvic Fracture Wounds

Open wounds may occur externally or rectally, as previously mentioned. Antibiotics are first and foremost in treatment of open wounds. Timely administration of antibiotics within 1 hour is essential in preventing infections at open fractures. First generation

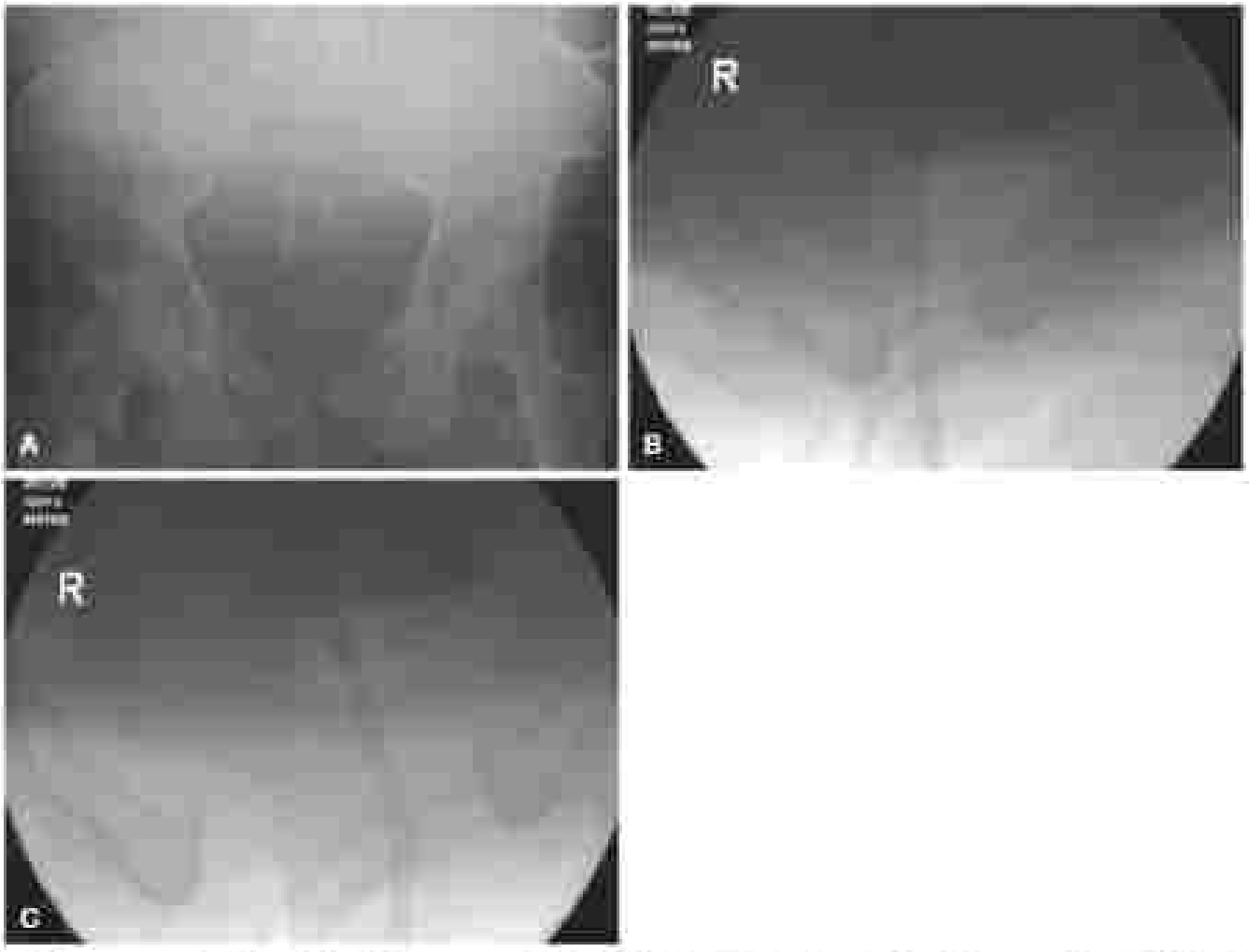

FIG. 8. (A) Anteroposterior pelvis radiograph on presentation in a binder. (B) Fluoroscopic examination under anesthesia demonstrates approximated symphysis at rest. (C) A moderate anterior force is applied, displacing the left hemipelvis laterally.

cephalosporin should be administered for simple wounds; patients with large degloving injuries and wounds communicating with the bowel should also receive gram-negative coverage. External skin lacerations that do not extend to the abdomen, rectum, or vagina should be irrigated and closed, if small. Larger wounds may require operative exploration and treatment. Open wounds may allow significant ongoing bleeding. This may prevent stabilization of a pelvic hematoma. An open wound may also defeat the compressive forces of a pelvic binder, despite the binder's effect of decreasing the potential volume into which bleeding can occur. Bleeding may continue through the open wound if it is not examined. Careful emergency packing of open wounds should therefore precede application of the binder.

Traction Pins and Closed Reduction

Extremity traction can assist in stabilization of pelvic fractures by reducing and realigning anatomy and reapproximating surfaces that fit together. In the same manner, it can decrease the amount of bleeding at bony surfaces. Realignment and stabilization help to decrease patients' pain. Establishing normal anatomic relationships also helps in definitive treatment of the injury, considering that limbs will be more easily reassessed at the time of definitive fixation if traction has been in place.

Traction is most effective through application of skeletal traction pins through the distal femur, proximal or distal tibia, or calcaneus. Pin placement should be performed by skilled personnel only, considering that neurovascular structures are at risk in the locations of all properly placed pins. If skeletal traction is not possible, manual traction through the displaced extremity at the time of binder application, internal rotation of the extremities, and taping the toes together assist in accomplishing the previously stated goals. Although skin traction apparatuses exist, they are generally ineffective at maintaining length and may cause soft tissue compromise if not appropriately applied and vigilantly attended to.

Binder Removal

Although a CPAS or binder provides essential support in minimizing pelvic hemorrhage, continued use beyond 24 hours can be detrimental. It obscures femoral access points, may impede access to the abdomen, and puts sustained pressure on skin, which inevitably leads to necrosis. For this reason, the skin beneath the binder should be inspected after 24 hours of application and the position must be altered, if binder use is to continue.

Removal of CPAS or binder can exacerbate hypotension, so removal should usually be performed with supervision. This is easiest in the ICU setting, where the strap can be removed, and the immediate effect can be observed on continuous monitors. Outside of the ICU, the provider should be ready to measure vital signs a few minutes after removal, and then later detecting tachycardic response or hypotension in response to the decreased pelvic pressure and

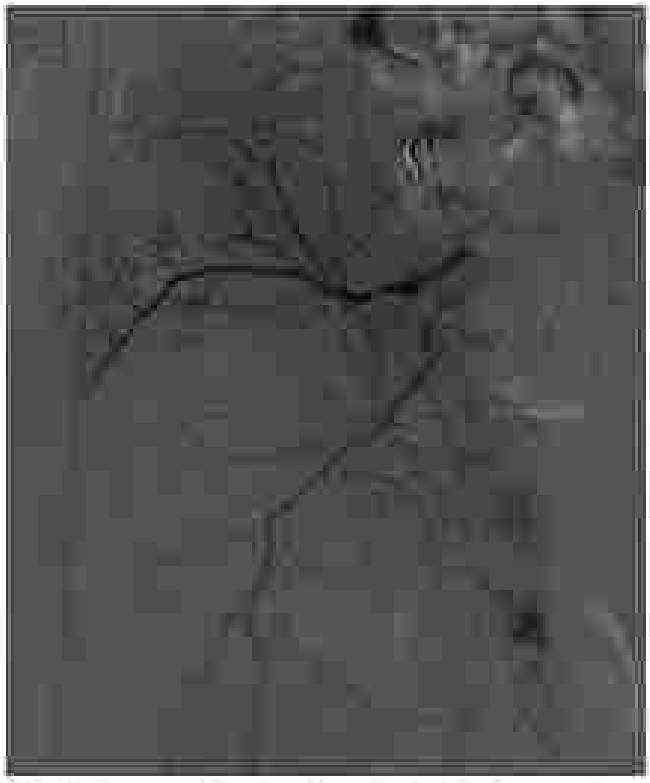

FIG. 9 Angiogram of the patient shown in Figure 10 demonstrating small anterior right pelvic bleed.

increased volume. The binder is removed slowly and left in place beneath the patient, in case it needs to be rapidly reapplied. If the binder must be reapplied because of persistent initial hypotension, adjusting the binder to a slightly different position may decrease skin injury. External fixation placed in the operating room setting should also be considered at this point to provide adequate pelvic stabilization, compression of the pelvic hematoma, and to minimize external soft tissue injury. Documenting the condition of the skin beneath the binder assists the providers in the patient's continuity of care, to communicate the risk of ongoing soft tissue injury.

Role of Pelvic Angiography

The role of pelvic angiography is multifactorial in each trauma hospital. The availability of resources and the timing of availability are important factors in determining its use. Each trauma hospital must establish the potential role of angiography in treating pelvic hemorrhage. The success of pelvic binders in early management of hemorrhagic shock caused by gross pelvic hemorrhage has helped establish the role of angiography as an intervention that should be performed after the pelvic binder application, and after the emergency need for abdominopelvic surgery has been ruled out. Interventional radiography and specifically pelvic angiography have a role in addressing persistent arterial bleeding in patients who are persistently unresponsive to resuscitative efforts, who are already placed in a binder or external fixator, and who do not require surgical hemorrhage control (Fig. 9). Each hospital determines its decision tree or algorithm identifying the order of interventions and role of angiography based on available resources.

Role of Pelvic Packing in Emergency Control of Pelvic Hemorrhage

Some hospitals have access to surgeons educated in pelvic packing. When retroperitoneal hemorrhage is suspected as a source of hypotension and the patient is not responsive to binder application and primary resuscitative response with intravenous fluid and blood, pelvic packing can be considered. Especially in the setting in which exploratory laparotomy is underway for hemorrhage control, pelvic packing is a straightforward next step. The role of this step is predetermined, much the same as angiography, based on resources available within each institution. Understanding of the pathoanatomy of pelvic hemorrhage is critical for successful pelvic packing. Retroperitoneal veins in the space of Retzius and retroperitoneum are responsible for much of pelvic hemorrhage and this pathology is addressed with pelvic packing. These pads are forcibly packed against the hemorrhage on each side, along the pelvic brim and into the true pelvis, and posteriorly near the sacroiliac joint. The pelvis must be stabilized with a binder or an efficient pelvic external fixator for this method to succeed.

Systematic Radiographic Evaluation

The AP pelvis radiograph (Fig. 10A), when carefully inspected, reveals tremendous information about pelvic anatomy and pathology, its implications for instability and associated injury, and potential surgical challenges that can impede surgical stabilization. The first step in analysis is assessment of normal alignment of the body at the time of the radiograph. Central position of the sacrum proximate to symphysis and similar appearing pedicles in the lumbar spine are the best indicators that the alignment of the body is normal at the time of x-ray exposure. Gross asymmetry is easily perceived, when present. Subtle asymmetry must be searched for through critical comparison of density and clarity of the sacral ala at the sacroiliac joint, appearance of sacral foramen, area/volume of the iliac fossa, visibility of the sacral spine, density of the quadrilateral surface, the shape of the obturator foramen, and midline position of the pubic symphysis. When a subtle difference is detected on a well-centered film, small posterior fractures and displacements and hidden anterior fracture lines are more easily perceived and explained.

A systematic evaluation of the AP radiograph includes inspection of the lumbopelvic junction, the brim of the iliac crests, the brim of the true pelvis, the foramen of the sacrum, the quadrilateral surfaces, iliac spines and tuberosities, superior and inferior rami, and the pubic symphysis. The evaluator looks for blurring of bone and joints at the lateral sacrum near the sacroiliac joint, and vertical and transverse fracture lines in the front of the pelvis. On a well-centered pelvic radiograph, displacement of the pubic symphysis generally occurs away from the side of the posterior injury on an LC fracture. Soft tissue shadows, often unappreciated on plain radiography, may show thigh and retroperitoneal hematoma, bladder displacement, and intraperitoneal air.

The CT scan solidifies diagnoses and suspicions drawn from the AP radiograph. The same anatomic regions previously reviewed on plain radiographs must be inspected on axial or reconstructed views. Visualizing sequences of images assists in localizing and measuring pathological features. The bony volume of the sacrum and fixation corridors is best appreciated on CT. Fracture extensions into the lumbopelvic facet joints, that indicate increased lumbopelvic instability, are detected here as well. Three-dimensional reconstruction image quality is improving to the point that most features of pelvic fracture-dislocations can be clearly seen. It must be understood that most algorithms for reconstruction cause blurring of subtle fracture lines to the point of concealment. Soft tissues are further delineated with different contrast settings. Intravenous contrast medium that may have obscured plain radiography is better localized in CT planes. Despite the important information gleaned from the CT scan, advanced plain radiographs further assist the primary responder in quantifying risk of the injury to the patient and aid the orthopedic surgeon in operative planning.

The inlet pelvic radiograph (Fig. 10B) is performed by aiming the x-ray beam from anteroposterior to posteroinferior across the pelvis. The volume of the pelvis is best appreciated from this anterior cephalad viewpoint. This view best delineates the brim of the true

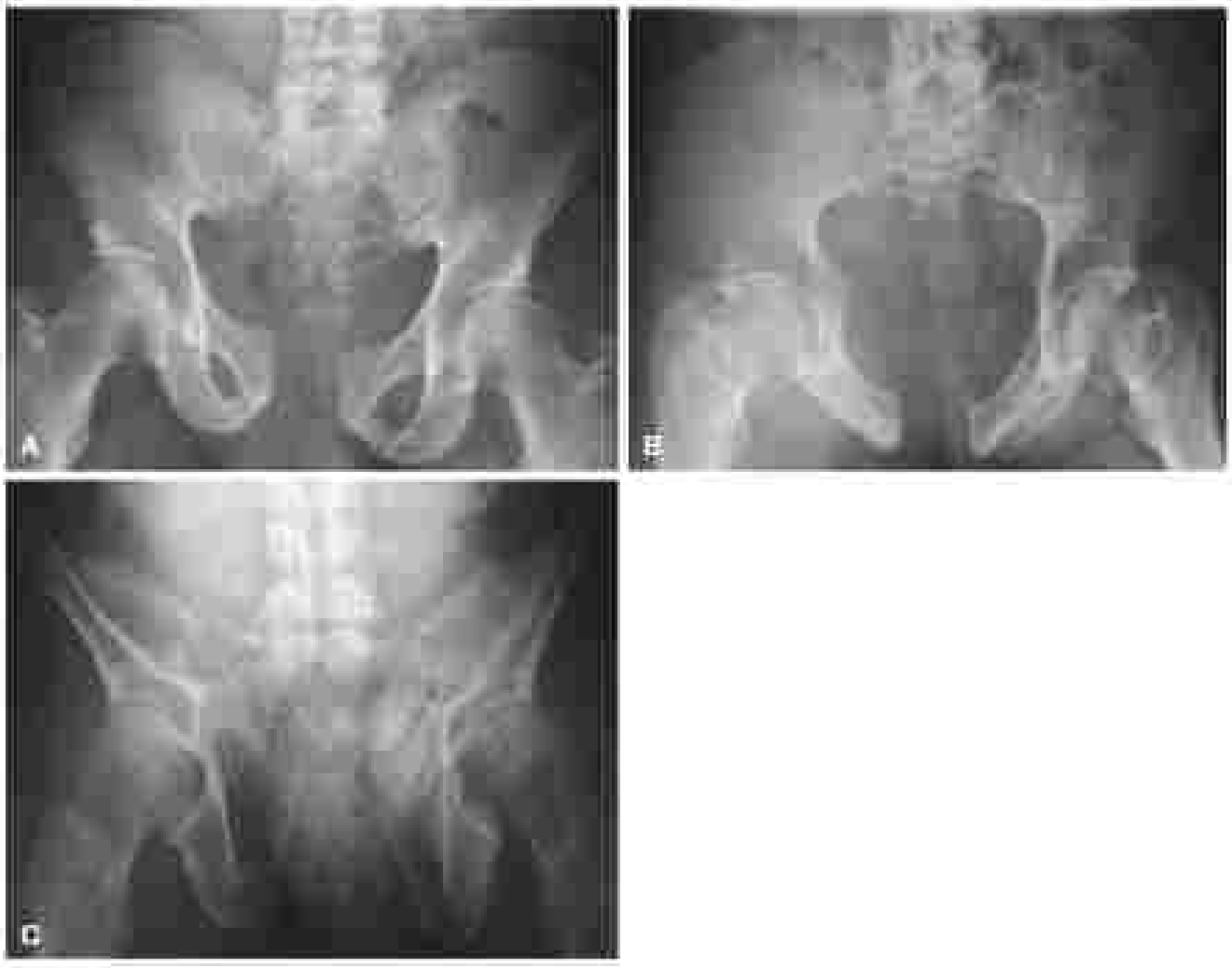

FIG. 10 (A) Anteroposterior pelvic radiograph. (B) Inlet radiograph of the pelvis. (C) Outlet radiograph of the pelvis.

pelvis. It demonstrates internal and external rotational deformities and anterior or posterior displacement of the pelvis at the time of injury. Evaluation of this radiograph, like the AP view above and outlet below, starts by assuring if the patient is well centered on the image. Visualization of compression fractures at the sacroiliac joint is improved from this perspective. Anterior pelvic fractures at the superior and inferior ramus and parasymphyseal region and their orientation (transverse to H, fractures, and cephalocaudad to APC fractures) are more easily understood.

The outlet pelvic radiograph (Fig. 10C) is performed by aiming the x-ray beam from anteroinferior to posteriosuperior across the pelvis. A true outlet superimposes the cephalad aspect of the symphysis over the S2 sacral body. Underappreciated on this view is the visualization of the sacral anatomy (necessary for surgical planning). Common features of sacral dysmorphism (accessory processes, crescent sacral foramen, persistent sacral disk disorder, and undulating sacroiliac joints). This view highlights the vertical displacement of one hemipelvis in relation to the other and the body during trauma. This can be measured by comparing the relative heights of the iliac crests, femoral heads, or ischial spines. Widening of the symphysis can be easily measured on this view. Appreciation of rotational deformity is also enhanced by comparing the symmetry of each obturator foramen oval.

The lateral sacral view or lateral reconstruction of the lumbosacral pelvic region from the CT scan may prove important in assessment of injury. This projection allows improved evaluation when sacral fractures or hemipelvic dissociations without pelvic ring disruption are suspected. U shaped and H shaped sacral fractures, among other isolated sacral patterns, and their associated sagittal plane (kyphotic) deformities are detected from this perspective.

Judet oblique radiographs, taken with 45-degree elevation of each hip, allow assessment of the acetabulum if fractures in the hip socket are detected on the AP projection. Fractures of the acetabulum can occur in combination with pelvic ring disruptions, most commonly when a lateral compressive or trajectory force is applied through the greater trochanter as the mechanism of injury. If a patient's pelvic fracture does not extend to the acetabulum, Judet projections do not add significantly to the diagnosis and treatment of pelvic ring injury.

Classification of Pelvic Fractures

Several pelvic fracture classifications have evolved in an effort to improve communication and decrease morbidity and mortality rate in patients. Unfortunately, no classification is complete; some pelvic ring injuries escape classification.

The best classification system in the emergency department (ED) setting and among all trauma team subspecialties is the Young Burgess classification of pelvic fractures (Table 1). This scheme correlates the trauma history and vector of force application against the pelvic ring to the radiographic findings of bony and soft tissue displacement on standard films. The force of displacement on the anatomy is linked to common patterns of fracture and dislocation. The classification

TABLE 1 Young-Burgess Classification of Pelvic Fractures

Category	Common Characteristic	Differentiating Characteristic
LC1	Anterior transverse fracture (pubic ramus)	Sacral compression on side of impact
LC2	Anterior transverse fracture (pubic ramus)	Crescent (iliac wing) fracture
LC3	Anterior transverse fracture (pubic ramus)	Contralateral open book (APC) injury
APC1	Symphyseal diastasis	Slight widening of pubic symphysis and/or sacroiliac joint, stretched but intact anterior and posterior ligaments
APC2	Symphyseal diastasis or anterior vertical fracture	Widened sacroiliac joint, disrupted anterior ligaments, intact posterior ligaments
APC3	Symphyseal diastasis or anterior vertical fracture	Vertical displacement anteriorly and posteriorly usually through sacroiliac joint, occasionally through iliac wing and/or sacrum
VS	Symphyseal diastasis or anterior vertical fracture	Vertical displacement anteriorly and posteriorly, usually through sacroiliac joint, occasionally through iliac wing and/or sacrum
CM	Anterior and/or posterior, vertical and/or transverse components	Combination of other injury patterns: LC/VS or LC/APC

From Burgess AR, Eastridge BJ, Young JW, Ellison TS, Ellison PS, Poka A, Bathon GH, Brumback RJ. Pelvic ring disruptions: effective classification system and treatment protocols. J Trauma. 1990;30:848–856.
APC, Anteroposterior compression; LC, lateral compression; VS, vertical shear.

disruption vectors in those from APC, LC, or forces causing vertical displacement of one side of the pelvis anatomy (vertical shear [VS]).

Certain injuries are associated with each vector of force application. APC injuries are commonly associated with severe life-threatening hemorrhage, especially in the elderly. LC injuries commonly have associated head and thoracic trauma.

APC and LC injuries are divided into three subsets of increasing severity. APC1 fractures have minimal anterior widening at the symphysis or anterior pelvis, with insignificant ligamentous or bony disruption; these do not require surgery. APC2 injuries can be identified by more than 2.5 cm of anterior symphysial widening. They have disruption of the bone ligaments of the pelvis (sacrospinous and sacrotuberous ligaments) and anterior sacroiliac ligaments, but the strong posterior sacroiliac ligaments are intact. It is important to confirm that the posterior sacroiliac ligaments are intact on advanced imaging. APC3 injuries have ruptured all anterior and posterior pelvic ligaments; they are grossly unstable at one or both hemipelvis, have significant intrapelvic hemorrhage, and require immediate intervention. A binder is indicated in the initial resuscitation of all APC injuries.

LC1 injuries have fractures through the sacral foramen or ala and corresponding anterior pelvic fractures of the superior and inferior rami, with internal rotation of one hemipelvis. This fracture is the most common pattern because it occurs when elderly fall from standing onto their hip. Young patients who sustain fractures in these anatomic regions, and therefore are classified as LC1, commonly have significant displacement and instability. Although elderly LC1 fractures are commonly stable and do not require surgery, young patients or those with good bone stock often have instability that can be confirmed on examination of the pelvis under anesthesia. LC2 disruptions have posterior fractures through the iliac wing and corresponding anterior rami fractures. LC3 patterns are fracture-dislocations known as the "wind swept" pelvis. They have the greatest instability due to internal rotation of one hemipelvis and external (APC type) rotation of the opposite hemipelvis. LC3 injuries also have appreciable hemorrhage and this is appropriately managed in the ED with a binder.

VS fractures are one large subset that demonstrates predominating vertical displacement of an entire hemipelvis proximally or distally. Distal displacement is very rare but it is associated with significant nerve injury and often vascular trauma. Proximal vertical displacement is associated with proportional vascular injury and soft tissue damage to the abdominal ligaments, anterior and posterior sacroiliac ligaments, and anterior pelvic ligaments. Associated vascular injury is common, especially with significant displacement. Therefore, longitudinal traction on the shortened limb and binder application aids in management of pelvic hemorrhage in these patients.

It is clear from the Young Burgess classification that APC, LC3, and VS patterns (Fig. 1) are at the greatest risk of hemorrhage in general. These patients respond best to early pelvic binder application. APC injuries have a clear indication for binder protocol until surgical management. LC3 and LC2 injuries, once appropriately confirmed, probably do not benefit significantly from prolonged binder application.

Role of External Fixation

External fixation was often applied in the ED for pelvic ring fractures. With the rapid acceptance of pelvic binders and CPAS, ED external fixation is obsolete. Compressive wraps are reliable initial treatment, sheets are universally available and inexpensive. External fixation therefore only has a significant role once 24 hours have passed. At this time, the patient is usually able to transport to the operating room for thoracoscopic imaging and controlled sterile technique. External fixation applied in this environment is much more reliable than a frame applied in the ED. Additionally, recent acceptance of supra-acetabular two pin external fixation as a stronger compressive frame makes this the frame of choice (Fig. 12A); it must, however, be placed under fluoroscopic guidance. Definitive treatment of anterior pelvic instability can be effectively accomplished with external fixation (Fig. 12B). This is usually done once the patient is stable enough for surgery. This mode of fixation is usually selected over internal fixation when prior surgery or radiation complicates anterior open approaches, when an open fracture or gross contamination contaminate the anticipated surgical approach, or when other surgical incisions make standard approaches difficult.

Need for Definitive Surgical Stabilization of Pelvic Fractures

Definitive fixation of pelvic fractures should occur when the patient is stable enough for the approaches that are required for fixation. If limited open or percutaneous techniques are utilized, surgery does not have to be delayed. Large open approaches, including

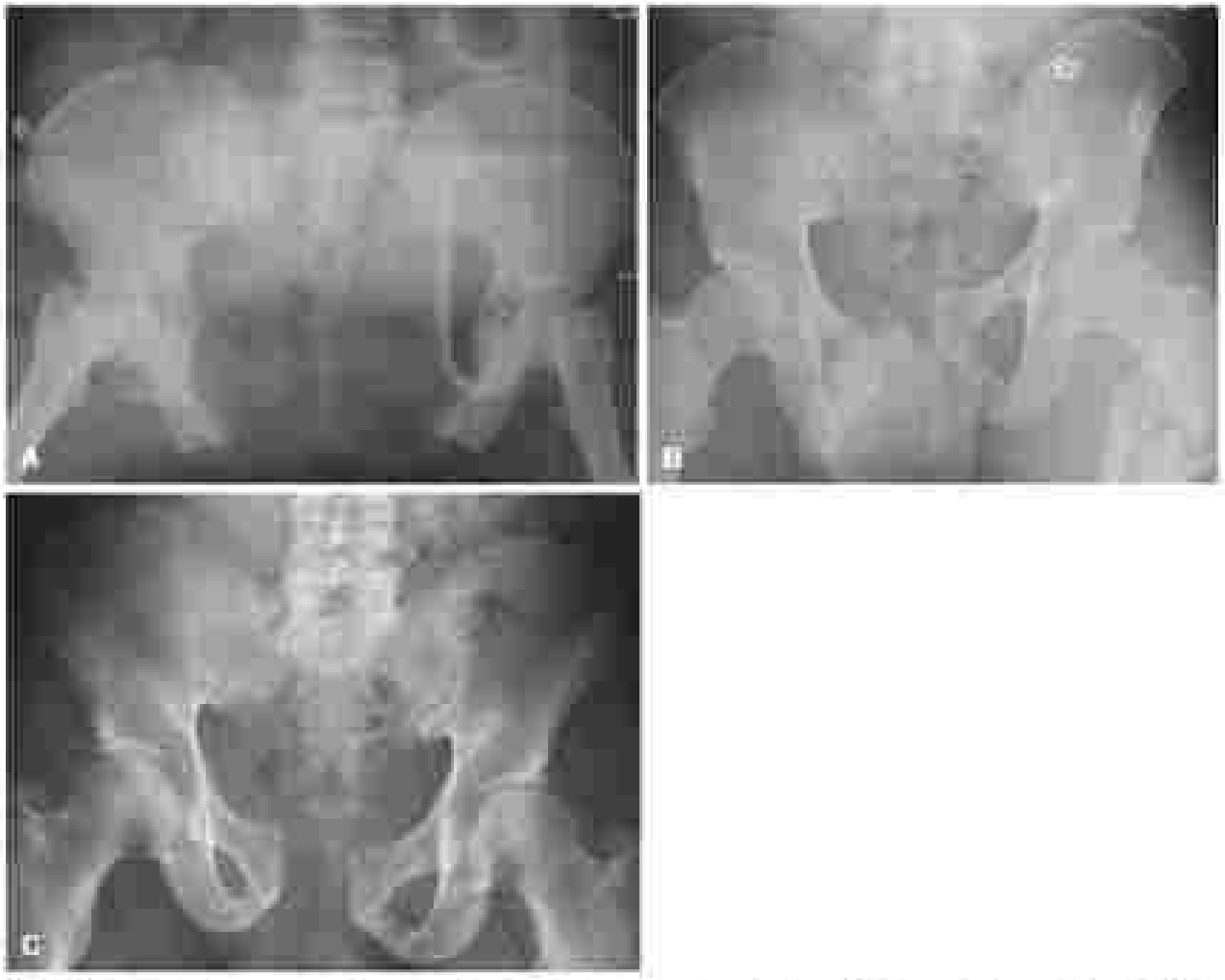

FIG. 11 (A) Anteroposterior compression 3 pelvic ring disruption. (B) Lateral compression 3 injury shows internal rotation of left hemipelvis and external rotation of right hemipelvis. (C) Vertical shear pattern.

FIG. 12 (A) Clinical example of how rotation signs accurately external fixation frame. (B) Definitive treatment radiograph of patient in figure 10 using external fixation.

lateral windswept iliac fixation approach, Pfannenstiel/Stoppa approach, and prone posterior open approach to the posterior ilium require consideration of other lines and tubes (diverting colostomy or chest tube) and the ability of the patient to be placed in the proper position for surgery. The patient should be adequately resuscitated, signified by a normalized lactate less than 2.5. Finally, stabilization of a complex pelvic injury may require more than one surgery as staged procedures to allow recovery from each component of surgical stabilization.

Hospital Admission in Pelvic Fracture

Although many pelvic ring fractures are indicated for surgery, minimally displaced fractures and fractures in relatively healthy individuals may not require hospitalization or operative fixation. Many LC1 and APC1 fractures can be observed briefly and discharged from the ED. Disposition to home requires that a patient have adequate assistance to mobilize out of bed, ambulate with some assistance, and accomplish activities of daily living. Pain must be adequately controlled and breathing should not be labored. Elderly patients often require brief social admissions to plan safe discharge and teach mobilization skills with physical therapy. Once a patient is appropriately dealing with the fracture discomfort and equipped to return home, he or she can be discharged.

Definitive Nonoperative Pelvis Fracture Care

Nonoperative care of a pelvic fracture requires demonstration that the fracture will not displace under physiologic loading during activities of daily living. Usually the injury AP, inlet, and outlet radiographs are repeated after the patient mobilizes out of bed. Most APC1 injuries allow bilateral lower extremity weight bearing as tolerated (WBAT) with crutches or walker. Most LC1 injuries can accommodate partial/foot flat weight bearing or WBAT on the injured side. The key to nonoperative management of pelvic fractures is serial radiographs demonstrating that minimal displacement occurs over the course of healing. This requires frequent office visits so that unacceptable displacement is detected prior to healing.

CONCLUSIONS

Management of pelvic fractures requires urgent recognition of life-threatening fracture patterns, which respond well to pelvic binder application in the setting of hypotension (APC2, APC3, LC2, VS). Many physical examination findings lead the clinician to suspect these injury patterns. The diagnosis is confirmed on systematic radiographic evaluation. Urgent gentle manipulative reduction and application of a compressive sheet or binder is accepted as the best first line defense against life threatening hemorrhage. The key to success in management of these injuries is a systematic approach to physical examination and patient evaluation, followed by expeditious use of resources to resuscitate the patient in anticipation of surgical stabilization.

SUGGESTED READINGS

Burgess AR, Eastridge BJ, Young JW, et al. Pelvic ring disruptions: effective classification system and treatment protocols. J Trauma. 1990;30(7):848–856.

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UROLOGIC COMPLICATIONS OF PELVIC FRACTURE

Hunter Wessells, MD, FACS

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—RICHARD TURNER-WARWICK, UNIVERSITY COLLEGE HOSPITAL, LONDON, ONTARIO, CANADA, 1982[1]

Pelvic injuries cause a significant disease burden in the United States, representing 7.3% of all traumatic injuries. Nonfatal injuries, based on most recent estimates by the US Centers for Disease Control and Prevention, totaled 2.3 million annually in the United States, which translates to approximately 180,000 pelvic injuries every year. Patients with pelvic trauma are severely injured, the majority having injury severity scores exceeding 16. Significant mortality arises from associated head injury, genitourinary and gastrointestinal organ injury with pelvic fracture can cause acute life threatening complications as well as lifelong disability and reduced quality of life.

Pelvic trauma, as with many unintentional injuries, has a male preponderance, with approximately two thirds of injuries occurring in men. The proportion of patients with bladder and urethral injury differ between women and men as follows: overall, 6% experience bladder injuries, whereas, in men, 3% exhibit urethral injury and, in women, nearly 7% have injury to the bladder neck and urethra. Notably, these figures represent rates of injury at large trauma centers and may not be representative of the experience in community hospitals or centers without trauma designation.

The American Urological Association (AUA) developed Practice Guidelines for Urotrauma in 2014 that provide a systematic evidence review that allowed for evidence based recommendations for the diagnosis and treatment of lower urinary tract injuries after pelvic fracture. These build on prior Guidelines and Consensus Statements from other organizations.

BLADDER INJURY

Identification of pelvic fracture bladder injury requires a detailed history, physical examination, urinalysis, and appropriate imaging. A total of 95% of patients with a bladder rupture will have gross hematuria, and the remaining few with microhematuria can be detected during the initial trauma evaluation with appropriate algorithms. There is no clinical prediction rule to identify patients requiring cystography after pelvic fracture other than the degree of hematuria. Recent studies suggest that patients with microscopic hematuria are unlikely to suffer bladder injury. Thus, AUA Guidelines state that clinicians must perform retrograde cystography to image the bladder after any blunt trauma with gross hematuria. Similarly, clinicians should perform retrograde cystography in stable patients with pelvic ring fractures and clinical indications of bladder rupture. At our institution, this translates into imaging all patients with pelvic fracture and greater than 30 red blood cells per high power field on urinalysis. All penetrating trauma patients with any degree of hematuria and an injury in the pelvis require assessment of the bladder either with imaging or operative exploration. Fracture patterns associated with bladder and urethral injuries are similar, namely, diastasis of the pubis and obturator ring fractures. The greater the displacement of these fractures, the more likely a genitourinary injury.

Imaging is important because failure to recognize a bladder injury can lead to significant complications including urinary ascites, infection

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Imaging is important because failure to recognize a bladder injury can lead to significant complications including urinary ascites, infection

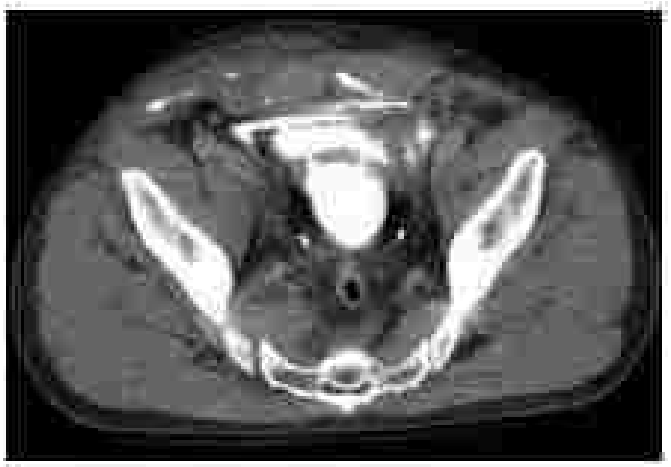

FIG. 1. Computed tomography cystogram demonstrating extraperitoneal bladder rupture with two defects in the anterior bladder wall.

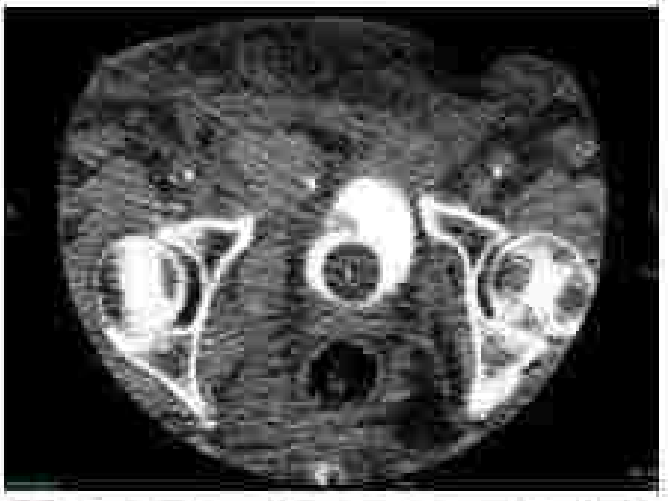

FIG. 2. Computed tomography cystogram demonstrating bony spicule in bladder lumen in a patient with unrecognized bladder injury.

of pelvic hematoma, chronic bladder dysfunction, and sepsis. Spiral computed tomography (CT) with 5-min cuts obtained after complete filling of the bladder will delineate all intra- and extraperitoneal bladder injuries. The degree of bladder filling is important and should be in the tolerance to a responsive patient. In the unresponsive patient, the contrast is hung at 40 cm of water and a volume of 350 mL infused. With CT, there is no need for scout or postevacuation imaging because the cross-sectional nature of the imaging identifies both anterior and posterior leaks. Conversely, with plain film cystography, scout and postevacuation films are required. Because of these differences, CT cystogram is more expedient and now the standard in most trauma centers.

The classic extraperitoneal bladder rupture, whether identified by CT or plain film cystography, will outline loops of bowel consistent with extraperitoneal location. Extraperitoneal bladder ruptures leads to extravasation of contrast in the retroperitoneum including the space of Retzius, the lateral pelvic regions, and into the groin and thigh. Typically, the dome defect in the bladder wall can be visualized with CT (Fig. 1). Combined intra- and extraperitoneal bladder ruptures can be missed when a large injury in one location makes it difficult to distend the bladder. These are rare, occurring in only 3% to 8% of all bladder ruptures.

The sensitivity and specificity of CT and cystography has been determined for blunt trauma and is 95% and 100%, respectively, using operative findings as a gold standard. CT of intraperitoneal rupture has a lower sensitivity, possibly because of the aforementioned confounding due to multiple sites of rupture.

Surgeons treat repair intraperitoneal bladder rupture in the setting of blunt trauma because the ruptures are large, and untreated can lead to ascites, azotemia, and sepsis. In contrast, management of extraperitoneal bladder injuries can be nonoperative with catheter drainage as long as the rupture is considered uncomplicated. These injuries do not involve open pelvic fractures, urinary infection, bony fragments (Fig. 2), or a foreign body to the bladder. Use of an appropriately sized catheter is essential to avoid obstruction by clots and poor bladder drainage. Other absolute indications for bladder repair include a bladder neck injury (Fig. 3), concomitant rectal injury, urethral injury, and major vaginal laceration. A relative indication for repair would be the need for open reduction and internal fixation of the pubis or anterior pelvic ring, to which case bladder exploration is often advocated.

Operative management of bladder rupture requires exposure based on whether the lesion is felt to be intra- or extraperitoneal. With extraperitoneal bladder rupture (Fig. 1), a lower midline or transverse Pfannenstiel-type incision provides sufficient access to the bladder and allows primary closure of injuries. The incision choice may be dictated by orthopedic or other considerations. For intraperitoneal bladder ruptures, which tend to be located at the dome, be midline in nature, and large, a midline incision slightly higher on the abdominal wall gives good access to the dome of the bladder.

Bladder exploration must be thorough to identify associated injuries to the genitourinary tract. Most common will be additional injuries to the bladder, including unrecognized or additional extraperitoneal injuries as well as bladder neck injuries. The bladder neck should be assessed by visual inspection, palpation, or endoscopic evaluation. Although ureteral injury is very uncommon in pelvic fractures, when the bladder is open, as long as visualization is adequate, assessment of the ureteral orifices is mandatory. This can be achieved by observing a jet of clear urine out of each orifice, intubation of the orifice with a feeding tube or other small (e.g., 3F/5) catheter, or administration intravenous indigo carmine and observing blue dye excreted in the urine.

Bladder lacerations should be repaired in a standard two-layer closure with running slowly absorbable suture such as 2-0 polyglycolic acid. The first layer incorporates the mucosa and the muscularis. The second layer incorporates the muscularis and overlying serosa. In the region of the bladder neck, where access to the urinary canal behind the pubis bone may be difficult, a single layer of well-placed interrupted absorbable sutures is sufficient to allow appropriate healing. When coordinating bladder exploration with other issues, it is advisable to explore and repair bladder neck injuries before orthopedic pelvic fracture fixation because exposure is worse after plating. In patients with multiple bladder lacerations, smaller lacerations can be fixed from within the bladder with a single layer of slowly absorbable suture. A closed suction drain is placed adjacent to the bladder to prevent collections. Urinary drainage after bladder repair may be carried out either with suprapubic cystostomy or usually with urethral catheter drainage alone. There is no evidence that suprapubic (SP) cystostomy improves outcomes compared to urethral catheterization alone, and the use of SP tubes is discouraged.

Follow-up imaging is required when nonoperative management by catheter drainage is selected, and after operative repair. Cystography (usually via plain film imaging) should be carried out 10 to 14 days after injury to confirm the integrity of the bladder before initiating voiding trials. This is true whether the patient has been under nonoperative management or underwent operative repair. Once bladder integrity has been confirmed, the catheter can then be removed based on patient's other injury status and mobility. If extravasation persists, repeat cystography is recommended at appropriate intervals until healing occurs. Overall, only a very small subset of patients with bladder injury will require re-operation or epiloyal closure.

URETHRAL INJURY

Pelvic fracture urethral injury (PFUI) is a rare but significant injury, associated with potential genitourinary morbidity including urethral stricture, urinary incontinence, sexual dysfunction, and chronic pain.

The signs and symptoms of these injuries are nonspecific and include blood at the urethral meatus; difficulty or inability to void after injury; a palpable bladder; butterfly perineal hematoma; high-riding prostate on digital prostate examination; fracture of the pubic symphysis; pelvic hematoma; or associated bladder injury. Thus, AUA Guidelines state that that patients with blood at the urethral meatus should undergo retrograde urethrogram (Fig. 1).

PFUI is suspected in cases of pelvic diastasis or fracture of the inferior pubic ramus. Such straddle fractures lead to a significantly greater odds of injury. Urethral injuries are classified using American Association for the Surgery of Trauma grades 1 to 5. Grades 1 and 2 (contusion and stretch injuries respectively) only need urethral catheter drainage until the patient recovers from other injuries. Grade 3 PFUI (partial disruptions) are easily managed with catheter realignment, whereas grades 4 and 5 complete disruptions with or without extensive separation or involvement of the prostate or vagina, may be treated with early endoscopic realignment or suprapubic cystostomy. There is debate as to the benefit of early endoscopic realignment, and suprapubic cystostomy remains the most commonly *elected* treatment nationwide.

Male urethral injuries after pelvic fracture are first delineated with retrograde urethrogram. However, when patients have blood at the urethral meatus and immediate catheter drainage is required, a single attempt at urethral catheterization may be considered. There is no strong evidence to suggest that this maneuver will convert a partial urethral injury to a complete injury. Nevertheless, in stable patients without immediate need for catheter drainage, retrograde urethrogram remains the recommended diagnostic modality. Cystoscopy can provide additional information, and may be performed in the emergency department, but overall it is not favored as a primary diagnostic modality. Female urethral and bladder neck injuries are more difficult to identify and diagnose compared with male injuries. These injuries may only be identified with intraoperative physical examination or incidentally in the intraoperative setting (40% of injuries). Thus, with all such patients, a thorough history and physical examination, laboratory studies, and imaging as indicated remain important.

The decision whether to perform suprapubic cystostomy or urethral realignment for PFUI depends on the patient's stability and associated injury status. Suprapubic cystostomy urinary diversion is appropriate as the initial step to securing prompt urinary drainage after PFUI, either in the emergency department or the operating room. AUA Guidelines state that clinicians may perform primary realignment in hemodynamically stable patients with PFUI. This may be deferred for up to 7 days, pending orthopedic coordination for ORIF, and does not need to be done in the middle of the night when equipment and support staff may be lacking. When attempting realignment, prolonged attempts at endoscopic realignment in patients should be avoided. Other rare indications for urethral realignment include the presence of a bladder rupture (which would complicate SP tube placement), rectal and vaginal lacerations, bladder neck injury, severe cephalad bladder displacement ("pie in the sky") and concomitant open reduction and internal fixation with the placement of orthopedic hardware.

Unfortunately, little evidence exists about the risk of bone or hardware infection in the face of suprapubic cystostomy, leading to discrepancy in expert opinion between urologic surgeons and their orthopedic colleagues. Our practice is to accommodate the preferences of our orthopedic colleagues when possible, preferentially realigning the urethra and thus removing the SP tube before pelvic fixation.

Stricture rates will be higher after suprapubic cystostomy compared with primary urethral realignment; realignment allows healing without strictures in 10% to 30% of patients versus less than 5% with suprapubic diversion. The standard approach for realignment uses two flexible endoscopes inserted per urethra and per SP tract, respectively. Typically, this requires two urologists skilled in flexible endoscopy, fluoroscopy, and coordination with orthopedic surgery. As long as SP cystostomy can temporize urinary drainage, realignment can be performed in an elective or semielective fashion when appropriate resources can be brought to bear, up to a week after injury.

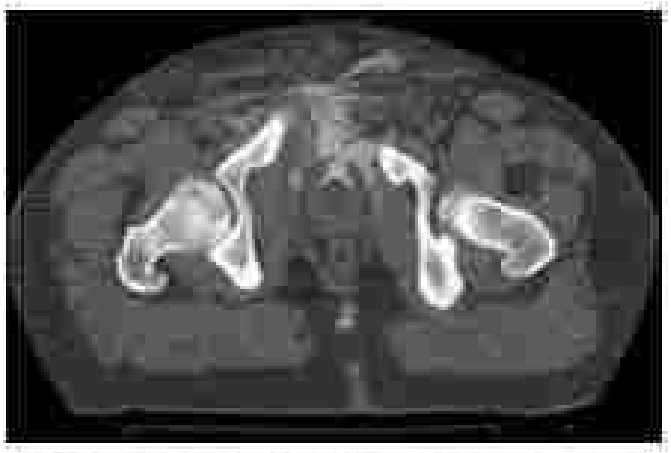

FIG. 1 Computed tomography cystogram demonstrating extravasation at level of catheter balloon consistent with a bladder neck injury.

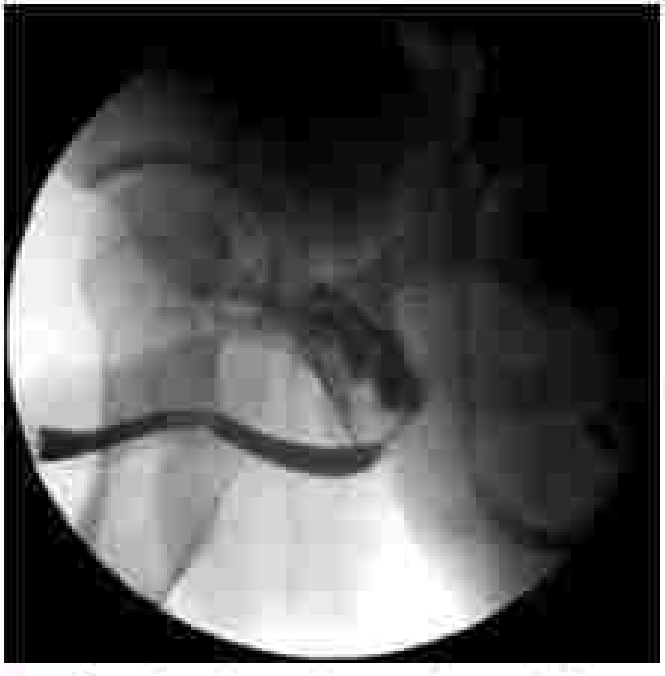

FIG. 2 Retrograde urethrogram showing complete urethral disruption.

After urethral realignment, periurethral retrograde urethrogram is recommended at 4 weeks after injury to assess for persisting leak. If leaks persist, repeat imaging is required until healing. The impact and prevalence of urethral stricture, erectile dysfunction, and urinary incontinence after PFUI require close surveillance for at least 1 year after injury.

CONCLUSIONS

Immediate identification of acute genitourinary injuries and appropriate urinary drainage is essential to prevent early septic complications and to ensure subsequent normal organ function. Coordination with the trauma team early, and orthopedic surgery later, allows appropriate operative or nonoperative management based on the injury severity and presence of associated injuries. Continued controversy about

cost of urethral realignment after PFUI may be answered by trials currently under way through the American Association for the Surgery of Trauma. Close follow-up is required to identify bladder, urethral, urinary incontinence, and sexual dysfunction resulting from injury to the bladder, urethra, and pelvic vascular structures. Importantly, even in the absence of overt genitourinary organ injury, soft tissue and vascular damage may lead to delayed complications including urinary and sexual dysfunction and cause significant impairment of quality of life.

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Spine and Spinal Cord Injuries

Khaled M. Kobashi, MD, FRCS, and Andrew Harris, BS

INTRODUCTION AND EPIDEMIOLOGY

The incidence of spinal cord injury (SCI) is between 25 and 50 cases per million in the United States, a rate that is higher than other developed countries. Among the general population, most cases of SCI are caused by motor vehicle accidents (40.8%), followed by acts of violence (12%), and sports-related injuries (9%). In those older than 65 years, however, falls are the leading cause of SCI. Recent trends show that overall, 55% of SCI cases occur in the cervical spine, with a rising predominance of upper cervical lesions (C1 to C3), that patients being discharged from the hospital as ventilator dependent. Current estimates suggest that 48.7% of SCI is neurologically complete at presentation, a number that has been decreasing slightly as the prevalence of gunshot related injuries decreases and falls in the elderly increases.

Although comparisons of affected age groups is complicated by differences in reporting, several predominant trends are clear. Men are the most commonly affected at approximately 80% of cases, and a 4:1 incidence ratio compared with women—a disparity that has remained constant over time. In addition, the highest risk age groups are the late teens and 20s, although recent data have shown that the mean age of patients affected by SCI is increasing in line with the increasing age of the US population.

INITIAL EVALUATION AND MANAGEMENT

Because of the magnitude of injury necessary to damage the spinal cord, SCI is commonly comorbid with multiorgan injury, which can complicate or even prohibit a thorough history and physical examination. Nonetheless, the initial evaluation of a patient with SCI is identical to other trauma patients in accordance with Advanced Trauma Life Support guidelines. Airway, breathing, and circulation are assessed as part of the primary survey, followed by complete evaluation in a secondary survey. Overt signs of SCI in the secondary survey include flaccid paralysis, hemodynamic instability with bradycardia, priapism, lack of response to painful stimuli to the lower extremities, and paradoxical breathing, all of which require prompt evaluation and application of appropriate algorithms to determine if imaging and/or surgical treatment is warranted.

Aside from the maintenance of airway, breathing, and circulation, the immediate chief concerns in patients with SCI are (1) avoiding movements that could worsen the condition by pathologic motion of displaced vertebral elements, and (2) minimizing deleterious effects of the secondary injury cascade by maximizing blood oxygenation and tissue perfusion. Within 2 to 3 hours after injury, disruption of arterioles by mechanical disruption and vasoconstriction causes ischemia in the gray matter of the cord. Following this result in fragile tissue of the central nervous system is the release of cytokines, inflammation, and apoptotic cell death primarily over the next 24 to 48 hours, although these processes can continue to cause damage for up to 3 weeks after injury.

In the acute phase of injury, maintaining an appropriate airway is essential to maintaining oxygen delivery to the damaged spinal cord. Patients with cervical spine injury are at increased risk of airway compromise both because of the risk of development of localized edema, neck hematoma, disruption of the innervation to respiratory musculature, and concomitant pulmonary injury. Thus throughout the acute evaluation, one should remain vigilant in monitoring for signs of acute respiratory failure and consider prompt intervention. Hypotension (<90 mm Hg systolic), even for brief periods of time, should be avoided as it is associated with significantly worse outcomes, although this can be especially difficult in the setting of neurogenic shock. Attention should also be given to transfer these patients to an appropriately specialized center that is equipped to treat patients with SCIs, as early transfers to such centers has been associated with improved outcomes and reduced complications.

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TABLE 1 American Spinal Injury Associations International Standards for Neurologic Classification of Spinal Cord Injury Impairment Scale

Grade	Classification	Motor	Sensory
A	Complete	No motor function	Complete deficit
B	Incomplete	No motor function	Incomplete deficit
C	Incomplete	Motor function is preserved—more than half of key muscles below the neurologic levels have a grade <3/5	Incomplete deficit
D	Incomplete	Motor function is preserved—more than half of key muscles below the neurologic levels have a grade >=3/5	Incomplete deficit
E	Normal	Normal motor	Normal

After completion of the primary and secondary survey, the National Emergency X-Radiography Utilization Study (NEXUS) criteria are commonly used to determine if radiographic imaging is warranted for patients with suspected cervical SCI. According to these criteria, patients who are alert and communicated, and who lack midline cervical pain, neurologic symptoms, or distracting injury do not require further imaging. The negative predictive value of these criteria is 99.8% for ruling out a cervical spine injury. No such validated criteria exist for ruling out the need for imaging in cases of suspected lumbar SCI; however, the same concepts can intuitively apply to the thoracolumbar spine as above the level of the spinal cord.

Patients with neurologic symptoms, or who fail the NEXUS criteria, will usually require imaging, which will be discussed later in this chapter. Symptomatic patients should also receive a thorough physical examination to identify motor and sensory deficits that can aid in localizing the injury. Detailing specific deficits in these patients is important and has shown to be associated with prognostic value and decreased complications. The American Spinal Injury Association (ASIA) classification system is widely used for classifying physical examination symptoms in these patients. This scale uses a 0 to 5 point scale to evaluate 10 different muscle groups bilaterally, and each of the resulting 20 scores are added to determine the total ASIA motor score. Sensation is also evaluated on a 0 to 2 scale in all dermatomes. Finally, the ASIA scale classifies SCI overall as complete SCI (A), sensory incomplete (B), motor incomplete (C and D), and normal (E) (Table 1). The combination of the ASIA impairment scale with the ASIA motor score comprises the best description of a patient's neurologic status after SCI.

Incomplete SCI is also commonly classified into syndromes based on the level of injury and neurologic tracts involved. Central cord syndrome is the most common, accounting for 9% of SCI overall. The defining characteristics of this syndrome include symptoms with arms weaker than the legs, and a variable amount of sensory loss that does not affect the face. Corticomedullary syndrome results from injury from the lower medulla to C4, and presents with respiratory difficulty, spinal shock, sensory deficit between C1 and C4, and facial sensory loss from damage to the ascending tract of the spinal trigeminal nerve. Space occupying lesions such as disk fragments, hematoma, or fractured vertebrae can cause anterior cord syndrome, which presents with complete paralysis owing to disruption of the corticospinal tract and preservation of vibration and light touch. Posterior cord syndrome is more rare and presents with tetraparesis and profound sensory loss with preservation of pain and temperature sensation. Brown-Séquard syndrome is another commonly described syndrome involving hemisection of the spinal cord, classically in patients with penetrating injury. The syndrome presents with ipsilateral paralysis, ipsilateral vibration and loss of light touch sensation, contralateral pain, and temperature loss. Conus medullaris syndrome can be caused by burst fractures of T12 or L1 and will result in paraparesis along with loss of bowel and bladder function, sensory loss in the legs, and sparing of perianal sensation. With lower third lumbar injury, cauda equina syndrome can also occur as a traumatic injury presenting with saddle anesthesia, bowel and bladder dysfunction. Of note, the prognosis for cauda equina syndrome caused by traumatic injury to the spinal column has a higher rate of recovery owing to the higher resistance to injury found in lower motor neurons. In addition to the classically described syndromes, SCI can also be caused by prolonged hypotension and watershed infarction. Although rare, SCI due to hypotension and ischemia can occur in the absence of cerebral ischemia and is best diagnosed by magnetic resonance imaging (MRI).

IMAGING

Computed tomographic (CT) scanning is the imaging modality of choice in acute SCI and has proven to be more sensitive and specific than radiographs in diagnosing vertebral column fracture or dislocation following blunt trauma. In patients who are found to have SCI at a single level, imaging of the entire spinal column should be obtained as 10% to 80% of patients will present with multiple noncontiguous fractures. In patients with cervical spine injury, if high-quality CT scans are available, three-view radiographs are not required; however, if high-quality CT is not available, level I evidence supports three-view radiographs (anteroposterior, lateral, odontoid views) as an additional test.

Performing MRI in trauma patients is challenging, time intensive, and not readily available at all centers. In patients who have clearly defined symptoms that correlate with CT findings, most would argue against the use of MRI in the acute setting. In patients who have neurologic symptoms without findings on CT scan, however, MRI may be useful to identify occult cord compression from dynamic pathologies such as critical disk herniation or epidural hematoma. Because MRI can accurately depict cord compression and signs of cord injury (hemorrhage, transection, edema, hemorrhage, ischemia), current recommendations suggest that MRI may be performed, when feasible, prior to surgical intervention for a potential addition to surgical decision-making, although evidence is weak to support this recommendation. In patients who have pain without neurologic findings, MRI may identify ligamentous injury as the cause of pain, although ligamentous injury does not necessarily imply spinal instability. MRI has also shown use in predicting long-term neurologic outcomes through a prognostication score when correlated with clinical symptoms, although the validity of these predictions have yet to be established.

SCI without radiographic abnormality (SCIWORA) is a syndrome that presents almost exclusively in children. The most accepted current definition of SCIWORA has come to encompass CT and radiographs only as cases of SCI almost always have pathologic findings on MRI. Nonetheless, both complete and incomplete SCI may present as SCIWORA, and surgeons should be aware of this presentation of SCI. Current recommendations involve up to 12 weeks of bracing, and MRI in this population of patients has been shown to hold prognostic value.

SELECTION OF SURGICAL CANDIDATES AND TIMING OF SURGERY

Disruption of musculoligamentous structures associated with the majority of SCIs has the potential to cause permanent neurologic impairment. Therefore the goal of surgical intervention in patients with SCI is to reduce compressive forces on the spinal cord and restore normal anatomic alignment. Although a variety of injury patterns may occur, we will describe the classic isolated injuries. Patients with multiple fracture patterns or cord compression present at multiple levels may warrant more complex treatment algorithms.

Cervical Spine

Injuries to the cervical spine can be classified as craniocervical (occiput to C2) or subaxial (C3-T1) injuries. The most cranial of these injuries is atlanto-occipital dislocations. Although usually fatal because of the level of the injury or associated vertebral artery injury, patients who survive this traumatic dislocation are treated with occiput to cervical fusion. Infrequently, these traumatic dislocations may also require decompression of associated damaged nerves. Unilateral fractures of the occipital condyle can be treated with a cervical collar for 6 to 12 weeks. C1 fractures commonly occur as a burst type fracture of the anterior and posterior arches, originally described as double fractures through each arch and known by the eponym Jefferson's fracture. Although other variations of C1 fractures exist, they are typically treated by halo vest immobilization for 6 to 12 weeks. C2 fractures are divided between those affecting the odontoid process and all other fractures. Type I odontoid fractures occur at the tip of the dens. Type II fractures occur at the base, and type III fractures occur at the body of the axis. Type I fractures are stable and can be treated with immobilization with a cervical collar. The management of type II odontoid fractures is somewhat controversial, as there is a high risk for nonunion without surgical treatment, but surgical treatment is both risky and invasive at this level. Current accepted indications for surgical management of type II odontoid fractures include patients with instability, cord compression with neurologic deficits, and high risk of nonunion (smoking, osteoporosis, etc.). Surgical treatment options include odontoid screw fixation and posterior atlantoaxial arthrodesis. Nonoperative management may be considered for patients without these symptoms and <5 mm displacement. Nonoperative treatment options include nonrigid orthosis (collar, cervicothoracic orthosis) or rigid cervical orthosis (halo vest). Type III odontoid fractures may be treated effectively with cervical collar immobilization. Hangman's fractures (HF) are bilateral fractures of the C2 pars interarticularis and are similarly classified into three types based on the degree of subluxation of C2 on C3 and angulation of the C2 vertebral body. Type I HF exhibit less than 3 mm translation and may be successfully treated with a cervical collar. Type II HF are defined as those with more than 11 degrees of angulation and more than 3 degrees of translation, and may require surgical fixation if deemed unstable, although the definition of stability varies between authors. There is no consensus. Type III HF are defined by severe angulation and facet dislocation of C2-C3, and generally require surgical fixation. Nonoperative management of these fractures include either cervical collar or halo vest, and surgical treatment options include anterior C2-C3 interbody fusion, posterior C1-C3 fusion, and bilateral C2 pars screw osteosynthesis (Table 2).

Subaxial cervical spine fractures can be classified using several classification schemes. The Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification and subaxial cervical spine injury classification (SLIC) system are the most commonly used. The SLIC system is shown in (Table 3) and considers the morphology of the fracture, integrity of the discoligamentous complex, and neurologic status of the patient. Each of these domains are scored from 0 to 2/4 from intact to most severely damaged, and the decision to operate is dictated by the overall summative score. Overall score of less than 4 indicates nonoperative management, whereas overall score of more

TABLE 2 Craniocervical Fracture Types and Recommendations for Treatment

Fracture Location	Recommended Treatment
Atlanto-occipital dislocation	Occiput to cervical fusion
Unilateral occipital condyle fracture	Cervical collar for 6–12 weeks
C1 fracture	Halo vest immobilization for 6–12 weeks
C2 fracture:	
Odontoid (type I)	Cervical collar immobilization
Odontoid (type II)	Surgical vs nonsurgical treatment depending on displacement and patient comorbidities
Odontoid (type III)	Cervical collar immobilization
Hangman's (type I)	Cervical collar immobilization
Hangman's (type II)	Surgical fixation if unstable
Hangman's (type III)	Surgical fixation

TABLE 3 Subaxial Cervical Spine Injury Classification System

Characteristic	Points
MORPHOLOGY	
No abnormality	0
Compression	1
Burst	+1 = 2
DISTRACTION (E.G., FACET PERCH, HYPEREXTENSION)	
Rotation/translation (e.g., facet dislocation, unstable teardrop, or advanced-stage flexion compression injury)	4
DISCO-LIGAMENTOUS COMPLEX	
Intact	0
Indeterminate (e.g., isolated interspinous widening, magnetic resonance imaging signal change only)	1
Disrupted	2
NEUROLOGIC STATUS	
Intact	0
Root injury	1
Complete cord injury	2
Incomplete cord injury	3
Continuous cord compression in setting of neurodeficit	+1
SCORE	
≤4	Nonoperative treatment
4	Operative vs nonoperative
≥5	Operative treatment

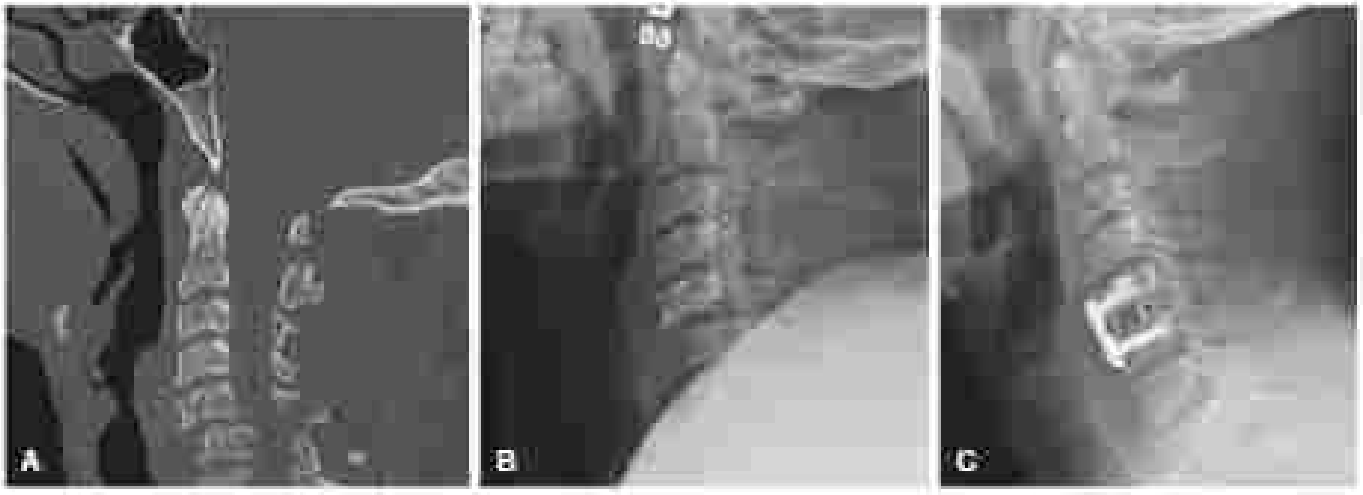

FIG. 1 Subaxial cervical spinal cord injury. This patient presented to the emergency department (ED) as a pedestrian versus motor vehicle accident. Computed tomography scan (A) and radiographs (B and C) demonstrated C5–C6 bilateral jumped facets with relative anterolisthesis of C5 on C6 with complete spinal cord injury at C6 level (American Spinal Injury Association score A). The injury was reduced in the ED using serial traction. Later that day, the patient had definitive fixation with a C5–C6 anterior cervical discectomy and fusion.

than 5 nonoperative operative treatment. Fractures with a score of 4 using the SLIC system may be treated operatively or nonoperatively. Nonoperative management of these fractures is similar to craniocervical fractures. When indicated, surgical fixation for subaxial fractures may be performed through an anterior, posterior, or combined approach, considering the need for decompression, stabilization, and reconstruction (Fig. 1).

Ideally, surgical decompression should be performed prior to 24 hours after injury in cases of cervical SCI. To date, the 2012 Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) is the largest study to evaluate the effect of early surgical decompression after SCI on long-term outcomes. The results of the STASCIS showed that decompression prior to 24 hours was associated with a grade 2 improvement on the ASIA scale at 6 months. These findings are backed by a large amount of preclinical evidence supporting the advantages of early surgical decompression. When feasible, given the limitations of the treatment facility and comorbid injuries in these patients, the goal should be for surgical decompression to be performed in less than 24 hours.

Thoracolumbar Spine

Traumatic injury at the level of the thoracic spine is less common, owing to the added structural support of the ribs and sternum. Thus when injury at this level does occur, it is frequently severe and associated with neurologic deficits, and most thoracic injuries occur in the thoracolumbar junction. Isolated lumbar SCI is less common, mainly because the spinal cord typically ends between L1 and L2. Surgical decision making in thoracolumbar SCI is also dependent on the stability at the level of the injury.

The three-column model of the spine proposed by Denis in 1983 is the basis for conceptualizing variations in thoracolumbar injury and the resulting loss in mechanical stability (Fig. 2). The three-column model has subsequently been used to develop the AO classification of spinal injury (1994), and more recently, the Thoracolumbar Injury Classification and Severity Score (TLICS) (2005). Unlike the AO classification, thoracolumbar spinal injuries are classified as compression injury (group A), distraction injury (group B), and translation or rotation injury (group C) (Fig. 3). This classification system depicts increasing injury severity from category A to C and associated increased likelihood of requiring surgical stabilization. In general, type A injuries are limited to the anterior column and type B and C injuries affect two or three columns. Considering that type A injuries

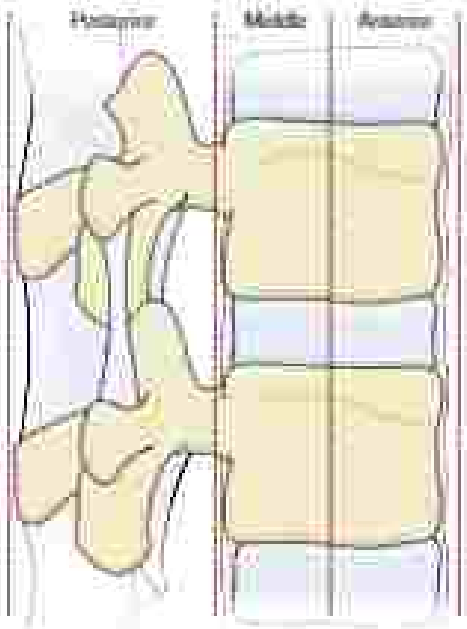

FIG. 2 Three-column model of Denis. The three-column model divides the spinal column into anterior, middle, and posterior columns. The anterior column is composed of the anterior portion of the annulus fibrosus, anterior annulus, and anterior portion of the vertebral body. The middle column is composed of the posterior portion of the vertebral body, posterior annulus, and posterior longitudinal ligament. The posterior column is composed of the posterior bony elements (pedicles, facets, spinous process, lamina) and interspinous ligaments.

are generally stable, they can be treated with a thoracic lumbar sacral orthosis (TLSO) brace, whereas type B and C injuries are inherently less stable and will usually require operative management. The TLICS score considers injury morphology, posterior ligamentous complex injury, and the patients' neurologic status. The score of each domain is added, with a higher score indicating more severe injury, and the total score determines if surgical versus nonsurgical management is warranted.

In stable fractures that are treated with TLSO bracing, patients are followed with radiographic imaging to ensure bony union across the

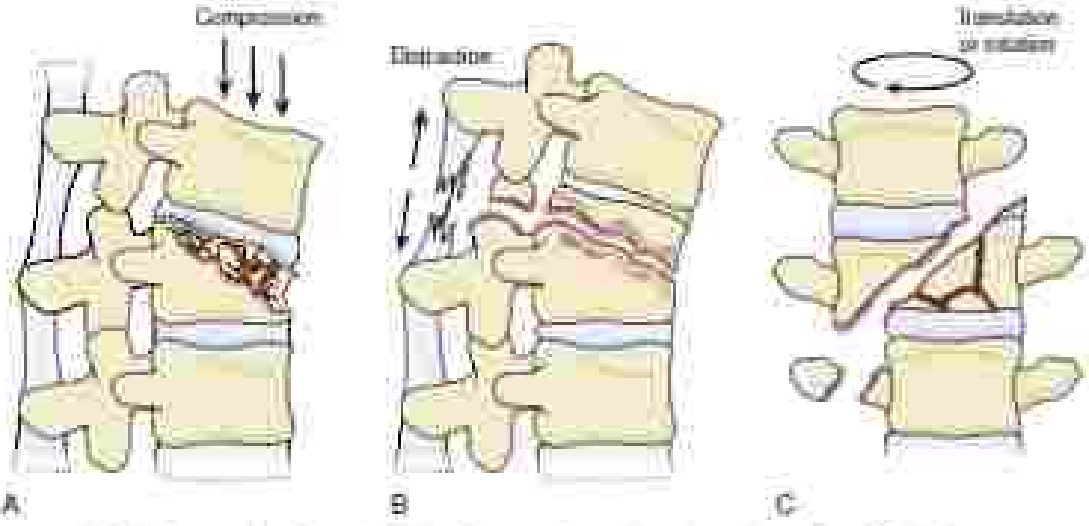

FIG. 2 Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification of thoracolumbar spinal injury. The AO classification is semi categorical and evaluates the mechanism of compression (A), distraction (B), and translation or rotation in any (C).

fracture site. Follow-up visits should include surveillance of psychosocial issues, pressure ulcers, urinary tract infections, and bowel and bladder dysfunction. Patients should be screened for depression and suicidal ideation, and referrals to psychiatry should be made as needed. Patients should be educated on the importance of skin inspection and pressure relief, and should be instructed to perform self-catheterization if necessary. Patients should be screened for spasticity, and treatment should be initiated if it is interfering with activities of daily living or causing pain. Patients should be screened for neuropathic pain, and treatment should be initiated if it is interfering with activities of daily living or causing pain. Patients should be screened for bowel dysfunction, and treatment should be initiated if it is interfering with activities of daily living or causing pain. Patients should be screened for sexual dysfunction, and treatment should be initiated if it is interfering with activities of daily living or causing pain.

MEDICAL MANAGEMENT

Hemodynamic Support

Hypotension (SBP < 90 mm Hg) should be avoided in the acute setting of SCI. Hypotension can result from hemorrhagic shock and concomitant hemothorax, tension pneumothorax, cardiac tamponade, or sepsis, and all can contribute to hypotension. As such, substantial evidence supports the use of intravenous fluids and vasopressors to maintain MAP between 85 and 90 mm Hg for the first 7 days after injury. Intravenous fluids should be titrated judiciously, as these patients are at high risk of pulmonary edema, and early consideration should be given to vasoactive agents. Lactate has yet to be a preferred algorithm developed to guide fluid resuscitation in patients with SCI.

Corticosteroids

Among the most controversial topics within the field of SCI is the use of methylprednisolone sodium succinate (MPSS) in the treatment of acute SCI. MPSS is a synthetic glucocorticoid that exhibits anti-inflammatory effects through interference with cytokine signaling and arachidonic acid metabolites. The theoretical basis for its use in SCI comes from numerous studies in animal models that have shown enhanced neuron survival after the use of MPSS; however, high dose glucocorticoids come with increased risk of infection and gastrointestinal bleeding in patients with SCI. For many years, it was common practice to administer MPSS within 8 hours of SCI, but this has proven to be a complex issue that continues to be debated even when faced with several large randomized trials, and the subsequent debate has brought to light the heterogeneity of the population of SCI patients. The National Acute Spinal Cord Injury Study (NASCIS) has conducted three trials (NASCIS I, II, and III) spanning from 1.84 to 7, and the findings of these trials have served as the basis for other prospective studies and current guidelines. The most recent guidelines are the result of a joint statement between AANS, the American Academy of Neurological Surgeons, and the Congress of Neurological Surgeons published in 2013. These recommendations are to consider a 24 hour infusion of high dose MPSS within 8 hours of SCI (30 mg/kg bolus + 5.4 mg/kg per hour for 23 hours). In addition, the AANS/CNS recommendations are to avoid MPSS after 8 hours of SCI, and to avoid the 48 hour bolus infusions that were once recommended. These recommendations are based on evidence suggesting a small benefit in motor recovery when MPSS is administered within 8 hours of injury, and that the possible drawbacks (gastrointestinal bleeding, infection) outweigh the benefits after 8 hours and with 48 hour infusions.

Alternative Neuroprotective and Neuroregenerative Agents

Several alternative neuroprotective agents have been studied in SCI, including minocycline, riluzole, GM-1, 21, 1118, and Cethrin. Although there has been promising preclinical evidence, several phase III clinical trials have failed to demonstrate significant clinical benefit of these agents.

COMPLICATIONS AND REHABILITATION

Patients with SCI are at risk for a handful of short- and long-term complications, owing to both direct neurologic injury and concomitant injuries. In the subacute setting, patients may experience spinal shock, neurogenic shock, or respiratory failure that may require fluids, vasopressors, and/or mechanical ventilation. In the intensive care unit, common complications include dysphagia, venous thromboembolism, infections, and stress gastrointestinal ulcers—all of which are managed in line with standard medical therapy. Long-term complications include complications owing to immobility, pressure sores, hypokinesia, obesity,

denervation [illegible], urinary retention, constipation, [illegible] and [illegible] premorbid condition (depression, anxiety, [illegible]) [illegible] setting to the rehabilitation [illegible] [illegible]

PROGNOSIS

[illegible] injury [illegible] grade, age at injury [illegible] [illegible] severe neurologic deficits [illegible] [illegible] and the [illegible] independence [illegible] ranging from 0 to 100. The mortality rate of patients with SCI is difficult to generalize [illegible] systematic review showing [illegible] survival between [illegible] days and [illegible] years. [illegible] the mortality associated with SCI is highest between 6 and 12 months after injury with the [illegible] [illegible] that [illegible] of patients are employed at 1 year following the initial insult. The average lifetime costs attributed to the care for patients with SCI vary from [illegible] in elderly patients with less severe injuries [illegible] younger patients with high cervical injuries.

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Evaluation and Management of Facial Injuries

Michael P. Grant, MD, [illegible], PhD

Facial injuries consist of damage to bone and soft tissue and disruption of the attachments between the two. The facial injury may be isolated or part of a multiple system injury pattern. Multiple system injuries that include a facial injury often require a coordinated effort by general surgeons, trauma surgeons, and specialty teams. Even isolated high-energy maxillofacial injuries warrant a complete evaluation preferably by a trauma team.

EMERGENCY TREATMENT OF MAXILLOFACIAL TRAUMA

The presence of a facial injury implies a geographic (simultaneous) injury to the head, face, and neck, including the brain and cervical spinal regions. Evaluation for brain injury, skull fracture, and cervical spine injury is mandatory in any patient with a maxillofacial injury to exclude serious injuries to adjacent anatomic regions.

Maxillofacial trauma presents three life-threatening emergencies: (1) airway obstruction, (2) hemorrhage, and (3) aspiration.

Airway Obstruction

Airway obstruction is expected in patients with comminuted fractures of the upper and lower jaws and injuries that result in swelling or bleeding into the airway spaces (neck, pharynx, larynx, mouth, floor of the mouth, and nose). The onset of stridor, hoarseness,

denervation (spasticity, urinary retention, constipation, temperature dysregulation, autonomic dysreflexia, and orthostatic hypotension), and the development of psychiatric conditions (depression, anxiety, and sleep disorders). Rehabilitation goals are often complex and should be individualized to each patient. Physical and occupational therapists should be an integral part of caring for these patients even before transferring to the rehabilitation unit, and both patients and their families should be educated on the importance and goals of rehabilitation efforts on maximizing the potential for long-term recovery.

PROGNOSIS

Providing a reliable prognosis to patients and their families is an important component of caring for patients with SCI. The most important prognostic factors to consider are the level of neurologic injury, AIS impairment scale grade, age at injury, and appearance of the spinal cord on MRI—with early mortality seen in high cervical lesions, increased age, more severe neurologic deficits, and edema or hemorrhage on T2 MRI. A handful of disability measurement scales exist for categorizing patient's impairments and monitoring improvement, and the Spinal Cord Independence Measure (SCIM) is among the most common. The SCIM considers self-care (0 to 20 score), respiratory and sphincter management (0 to 40), and mobility (0 to 40) with the final score ranging from 0 to 100. The mortality rate of patients with SCI is difficult to generalize overall, with a large systematic review showing median survival between 35.4 days and 56.5 years. On average, however, the mortality associated with SCI is highest between 4 and 12 months after injury with the greatest threat being pneumonia and sepsis. It is estimated that 13% of patients are employed at 1 year following the initial insult. The average lifetime costs attributed to the care for patients with SCI vary from $1.1 million in elderly patients with less severe injuries to $4.8 million in younger patients with high cervical injuries.

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EVALUATION AND MANAGEMENT OF FACIAL INJURIES

Michael P. Grant, MD, PhD, FACS, and Paul N. Manson, MD

Facial injuries consist of damage to bone and soft tissue and disruption of the attachments between the two. The facial injury may be isolated or part of a multiple system injury pattern. Multiple system injuries that include a facial injury often require a coordinated effort by general surgeons, trauma surgeons, and specialty teams. Even isolated high-energy maxillofacial injuries warrant a complete evaluation periodically by a trauma team.

EMERGENCY TREATMENT OF MAXILLOFACIAL TRAUMA

The presence of a facial injury implies a geographic (simultaneous) injury to the head, face, and neck (including the brain and cervical spine) regions. Evaluation for brain injury, skull fracture, and cervical spine injury is mandatory in any patient with a maxillofacial injury to exclude serious injuries to adjacent anatomic regions.

Maxillofacial trauma presents three life-threatening emergencies: (1) airway obstruction, (2) hemorrhage, and (3) aspiration.

Airway Obstruction

Airway obstruction is expected in patients with comminuted fractures of the upper and lower jaws and injuries that result in swelling or bleeding into the airway spaces (neck, pharynx, larynx, mouth, floor of the mouth, and nose). The onset of stridor, hoarseness,

drooling, inability to swallow, and noisy respirations should prompt an alert clinician to urgently intubate the patient or in some cases perform a tracheostomy. Cricothyroidotomy is an emergency maneuver to access the airway through the cricothyroid membrane. It should always be converted to tracheostomy as soon as feasible.

Life-Threatening Hemorrhage

Life-threatening hemorrhage results from several categories of injury. (1) facial and scalp lacerations, (2) closed fractures of the sinus and midface, (3) arterial injuries of the sinuses and skull base with internal carotid or venous sinus (cavernous sinus) hemorrhage.

Facial Lacerations

Bleeding from facial lacerations is usually the result of partially or fully transected major arteries. These are controlled by direct ligation, carefully avoiding branches of the facial nerve, which are many times adjacent to arteries. The partially transected artery cannot retract and will continue to bleed until effectively manually controlled.

Closed Fractures, Sinus Injuries, and Midface Injuries

Midface and orbital fractures produce hemorrhage from lacerations of arteries and veins in the walls of the sinus cavities or adjacent structures. In the majority of cases, manual repositioning of the maxilla or zygoma combined with intermaxillary mandibular fixation controls the bleeding. The maxilla is first placed at rest in intermaxillary fixation (IMF). Angiographic embolization is the usual method of control in those few patients (<5%) who continue to bleed. Selective embolization or ligation of the internal maxillary artery, accessed through the posterior wall of the maxillary sinus, or bilateral external carotid and superficial temporal artery ligation can be performed. These procedures are seldom necessary.

Aspiration

Aspiration of oral secretions, gastric contents, or blood frequently accompanies fractures of the middle and lower face, especially with cerebral injury or depressed mental status secondary to injury or drug or alcohol ingestion. Rapid, noisy respirations, low arterial oxygen content, and a decrease in pulmonary compliance are seen. Intubation prevents aspiration and should be performed urgently when it becomes evident that the airway is not being protected.

Occult and Ancillary Injuries

The possibility of occult injuries demands a thorough, multisystem examination in every patient. Observations of other organ systems must be continued throughout the entire period of facial injury treatment. In patients with multisystem injuries, the status of all injuries must be continuously assessed.

EARLY MANAGEMENT OF MAXILLOFACIAL TRAUMA

The early management of maxillofacial trauma comprises (1) clinical examination, (2) appropriate diagnostic imaging, and (3) definitive wound and/or fracture management.

Clinical Examination

The diagnosis of most facial injuries is accomplished by a thorough clinical examination, noting the pattern of contusion, bruises, discolorations, crepitus, pain, localized tenderness, numbness, paralysis, malocclusion, diplopia, visual acuity loss, facial asymmetry, deformity, and changes in eye position and facial contour. The care provider should assume that a fracture underlies any contusion bruise or laceration until proved otherwise. Any laceration or wound should be suspect for containing a foreign body.

The physical examination should be both sequential and direct, starting with an orderly examination of the facial structures in sequence from top to bottom, followed by a careful, sequential examination to those areas suspect or obviously injured. A digital examination of the critical areas is then performed. Palpation of all bony surfaces begins at the supraorbital rims, continues around the orbit, and extends to the infraorbital rims and nose, includes the zygomatic arches and molar prominences, and concludes with an examination of the maxilla and mandible, both intraorally and externally to position and movement. Any deformity, malocclusion, crepitus, bone irregularity, inability to bring the teeth together to occlusion, or tenderness is noted. It is essential to confirm the proper interrelation of the teeth in occlusion; any deviation to the expected pattern implies the possibility of a fracture/dislocation. Intraoral or extraoral lacerations or bleeding from a tooth socket imply the possibility of an accompanying fracture.

An evaluation of facial nerve (facial motoric muscle system) and trigeminal (sensory nerve and motor nerve) function compares the two sides of the face. Facial sensation is documented in the supraorbital, corneal, infraorbital, and mental distributions (anesthesia or hypoesthesia). A search for occult lacerations in the ear canal, nose, mouth, floor of mouth, and pharynx should be conducted. The occlusion of the jaws, the relation of the teeth to occlusion, and the stability of the teeth in sockets are noted, looking for irregular arch forms and abnormalities of interrelation of the teeth. Fractured or missing teeth, intraoral and gingival lacerations, bleeding tooth sockets and gaps or level discrepancies in the maxillary and mandibular dentition indicate the possibility of fractures. Lacerations of the lips, chin, floor of the mouth, and palate are accompany anterior jaw fractures.

Visual and sensory function should be evaluated in all patients with orbital, upper facial, or frontal bone trauma. Visual acuity and range of extraocular motility should be evaluated, and the presence of a relative afferent pupillary defect, visual field defect, diplopia, hyphema (bleeding in the anterior chamber), periorbital ecchymosis, or subconjunctival hemorrhage imply the possibility of an orbital fracture or globe injury. In a partially injured optic nerve, a light swinging back and forth between both eyes will cause the usually intact pupil to constrict, whereas the partially compromised optic nerve causes that pupil to paradoxically dilate while the contralateral pupil constricts.

Alginate impressions of the dentition are taken, and most models are set up prepared to provide a dental record. In the physical examination, any grossly displaced midfacial or mandibular fractures can be manually repositioned, which often stops bleeding, and if desired, IMF can be applied with wire loops between the teeth to temporarily stabilize jaw fractures. The airway must be protected at all times, and intubation is frequently the best technique.

Radiographs

Plain radiographs are of little value in the evaluation of facial injuries, except when they may be necessary to exclude the presence of a radiopaque foreign body. The ideal radiographic examination is computed tomography (CT). Multiply injured patients should not be transported for extensive radiographic evaluation, and such studies supplement, but do not replace, the findings of a physical examination. For most fractures, the best radiographic evaluation consists of images in three axes—axial, sagittal, and coronal plane CT scans, to include the frontal sinus, nasoethmoid, orbital, maxillary, and mandibular regions. Both bone and soft tissue windows should be obtained, so that all structures may be assessed. If the patient cannot be positioned for direct coronal images, coronal images may usually be reconstructed from the axial CT format. A rapid soft tissue window CT examination of the brain or skull does not replace the need for a specific maxillofacial CT because needed detail is not provided and soft tissue windows miss fractures.

WOUND AND FRACTURE MANAGEMENT

Soft Tissue Injuries

Soft tissue injuries include lacerations, bruises, contusions, and hematomas. Cutaneous wounds are inspected for foreign material and assessed for depth and direction to predict deep structure involvement (probing with a cotton tipped applicator, not sharp instruments) and to detect contamination or foreign material. Lacerations require inspection for damaged structures, followed by cleansing by scrubbing, gentle irrigation, and removal, judicious sharp debridement of the uneven, contused tissue edge before closure (and when tolerated by entire tissue). A millimeter or two is usually a sufficient edge resection of a laceration, and achieves a clean, even minimum-trauma margin. A layered repair achieves a flat wound, resulting in minimal scar formation. Antibiotics are indicated when a clean wound (defined by surgical debridement) cannot be created, especially in the presence of heavier contamination, such as an animal bite. Direct primary closure of facial wounds is always preferred, with second-look procedures at 48-hour intervals, when concern about infection, hematoma, or continued devitalized tissue is an issue, as in the case of large degloving or avulsive wounds. We use the benefits of second-look procedures frequently, obtaining the benefits of primary healing and early opportunities for detection of hematoma, infection, or devitalized tissue by secondarily opening a portion of the wound.

Open wound management is almost never used, with the possible exception of human bites, and second-look procedures are preferred. Debridement should be quite conservative in the region of the vermillion, oral commissure, eyelids, eyebrows, distal nose, and nostrils. All foreign material must be meticulously removed at the time of the initial examination and treatment, because it cannot be satisfactorily removed after healing. Postoperative wound laceration surface hygiene is accomplished four times daily with a 10-15 cc peroxide saline solution on cotton tipped applicators and the application of either a liberal lubricating ointment and or a topical antiseptic ointment such as bacitracin (facial sutures) or a combination steroid antibiotic ophthalmic ointment (Lacri-Lube) (periorbital sutures). Intraoral repairs are cleansed with mouthwash and standard oral hygiene three times daily. The toothbrush remains the best cleaning mechanism for the gums and the dentition.

Any localized facial hematoma should be drained by incision, and a soft compressive dressing should be applied. Localized hematomas most commonly occur in the ear region and may involve the forehead or buccal areas. Laceration of the lacrimal system should be suspected in any wound on the nasal aspect of the upper or lower eyelids. Eyelid or periorbital lacerations raise the possibility of globe rupture or penetrating injury, which must be excluded by direct palpation and thorough inspection and eye evaluation.

Lacerations of the facial nerve and parotid duct are managed by direct repair using loupe magnification. Parotid duct lacerations are diagnosed by inserting a No. 22 Angiocath sleeve (Becton Dickinson) into the duct orifice (opposite the second maxillary bicuspid tooth necessarily) after dilating it with a lacrimal punctum dilator and irrigating with saline. The presence of saline in the wound implies duct and or parotid gland laceration.

Because duct is a short structure that extends from the anterior margin of the parotid gland 1.5 inches anterior to the tragus on a line between the tragus and floor of the nostril, to the second maxillary bicuspid. Facial lacerations are usually accompanied by buccal branch facial paralysis because the two structures are adjacent. Nerve and duct transections should be repaired.

Cerebrospinal Fluid Rhinorrhea

Fractures involving the frontal or basilar skull may lacerate the dura, allowing cerebrospinal fluid (CSF) to exit from the nose (rhinorrhea), or fractures with dural lacerations may allow air to enter the intracranial area (pneumocephalus). Either condition permits entry of organisms through the meninges with the possibility of meningitis. Generally prophylactic antibiotics are used to a pulse rather than a prolonged course in these conditions; perioperative antibiotics will generally accompany operative treatment of either condition when indicated. CSF rhinorrhea is detected by the presence of clear fluid exiting from the nose or pharynx. Often CSF is mixed with blood, making its detection more difficult. The double ring sign, absorption of blood and CSF onto a paper towel, produces a small, central blood ring with a large, peripheral, clearer fluid ring surrounding it. A detailed CT scan is mandatory if CSF leak or pneumocephalus is suspected. Chemical tests confirming the CSF leak include beta transferrin and intrathecal fluorescein.

Definitive Fracture Management by Region

Nasal Fractures

Nasal fractures produce dislocation either laterally, posteriorly, or in combination. The diagnosis is suggested by epistaxis, bruising, swelling, and deformity: lateral deviation/dislocation, or recession, and flattening of the nose in frontal impact injuries of the nasal pyramid (Fig. 1). Intranasal inspection shows dislocation, deviation, or laceration of the mucous membranes or septum and possibly the turbinates with difficulty breathing because of blood, mucosal swelling, and the narrowed airway. Nasal and periorbital hematomas generally accompany nasal fractures, and at least one third have a small laceration over the nasal bridge. Nasal fracture hematomas do not observe the precise boundaries seen in orbital fractures, which are confined to the distribution and insertion of the orbital septum (Fig. 4.8).

Clinically, radiographic evaluation of nasal fractures consists of plain films, a nasal series, a Waters view, and sinus films. These are not very definitive, and a CT scan is the best examination, making plain radiographs of no utility. The value of nasal images to isolated low-energy injuries is both methodical and clinical. Injuries to adjacent bony structures are excluded, and the exact fracture extent and displacement of nasal structures, including the septum, nasal bones, and turbinates are identified.

Treatment

Closed reduction of the septum and nasal pyramid is performed under anesthesia; less ideally, an external field block and intranasal topical Afrin are used. Reduction maneuvers may occasionally create

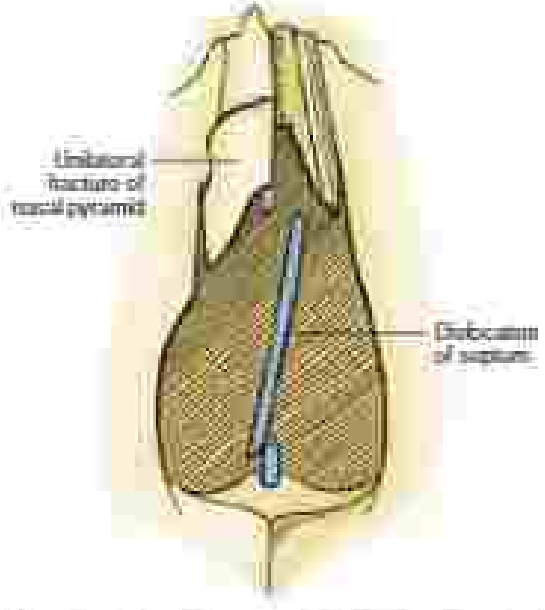


FIG. 1 Nasal fractures are characterized by lateral or posterior displacement, and sometimes both. Each displacement requires a specific reduction maneuver.

profuse nasal hemorrhage, and one must be prepared for this and protect the airway. Isolating patients when the airway is unprotected is not recommended.

Laterally deviated nasal fractures first have any greenstick components of the fracture completed by bilateral intranasal mobilization of the nasal pyramids laterally and the septum centrally, establishing them to the midline and supporting them with external and internal nasal splints. The septum is straightened and centralized with an Asch forceps and supported with antiprotic, laminated Doyle nasal splints. Frontal impact nasal injuries produce varying degrees of nasal retrusion and may require open reduction and bone or cartilage grafting to restore projection and achieve the nasal profile and support necessary to produce an adequate aesthetic result.

Zygomatic Fractures

The zygoma constitutes the malar prominence and forms the lateral and inferior walls and rims of the orbit. The zygoma has five attachments to adjacent structures: laterally to the temporal bone through

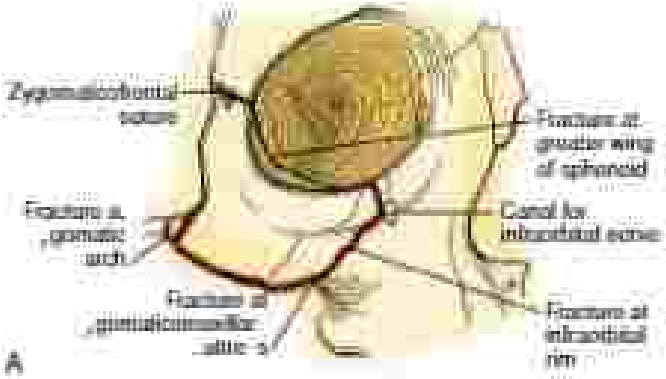


FIG. 1 (A) The zygomatic bone constitutes the lateral and inferior portions of the orbit and malar eminence. It attaches to the frontal bone superiorly, the temporal bone posteriorly, and the maxilla medially and inferiorly. In the orbit, the alignment of the orbital process of the zygomatic bone with the greater wing of the sphenoid provides an accurate clue to reduction. (B) The combination of a periorbital and subconjunctival hemorrhage implies a bone fracture somewhere; when the orbital periorbital hematoma is confined to the orbit by the insertion of the orbital septum,

the zygomatic arch, superiorly to the frontal bone through the frontal process, medially to the maxilla through the infraorbital rim, inferiorly to the maxillary alveolus through the zygomaticomaxillary buttress, and to the lateral orbit to the greater wing of the sphenoid through the orbital process of the zygoma (Fig. 1). The diagnosis of a zygomatic fracture is suggested by the combination of a periorbital and lateral subconjunctival hematoma (Fig. 1B). These are sensitive but nonspecific signs that may accompany any orbital fracture. If the frontal process of the zygoma is dislocated inferomedially, the lateral canthus is inferiorly displaced by its attachment to the lateral orbit at Whitnall's tubercle. Depression of the malar eminence accompanies posterior displacement of the body of the zygoma. Steps, or level discrepancies, may be palpated in the bone forming the inferior or lateral orbital rim or at the zygomaticofrontal suture. Intraorally, a hematoma is present in the upper buccal sulcus, and intraoral irregularity of the maxillary buttress may be palpated. Unilateral epistaxis is secondary to hemorrhage exuding through the ipsilateral maxillary antrum. If the zygoma is posteriorly or medially dislocated, difficult or painful chewing or difficulty bringing the teeth into occlusion may result from impingement of the zygomatic body or zygomatic arch on the coronoid process of the mandible, from bruising to the temporalis muscle, or from hemorrhage into the temporomandibular joint.

Orbital extraocular muscle entrapment symptoms (diplopia) result from the orbital floor fracture component and depend on the mechanism and degree of involvement of extraocular muscles, with restriction of their motion by actual muscle incarceration and/or entrapment of adjacent soft tissue in the fracture. Infraorbital nerve numbness accompanies most zygomatic fractures and is related to bruising or injury of the infraorbital nerve at the infraorbital foramen. In the case of a significant orbital fracture, globe dystopia, enophthalmos, and double vision may be present. The definitive radiographic examination of the zygomatic fractures is axial, sagittal, and coronal CT scans with bone and soft tissue windows.

Indications for surgery include the functional symptoms produced by bone displacement, which include deformity, enophthalmos, double vision resulting from incarceration of an extraocular muscle or its surrounding fat or fascia, vertical malposition of the globe, loss of malar prominence, anesthesia of the infraorbital nerve (in medially dislocated zygomatic fractures that compress the nerve at the infraorbital foramen), radiographically extensive orbital floor fracture, and interference with the excursion of the coronoid process by medial depression of the zygomatic arch or posterior depression of the body of the zygoma.

Treatment

Displaced fractures isolated to the zygomatic arch are treated by elevation through a Gillies approach. An incision in the temporal hair permits insertion of an elevator under the deep temporal fascia on the temporalis muscle to elevate the zygomatic arch. Because of periosteal continuity, medially displaced arch fractures are generally stable following closed reduction. Displaced zygomatic fractures not isolated to the arch are managed by open reduction and internal plate and screw fixation (Fig. 3). Incisions for zygomatic fracture reduction consist of lower eyelid incisions (subciliary, subtarsal, or transconjunctival), gingivobuccal intraoral sulcus incisions (the lateral limb of an upper blepharoplasty incision and, in extensive fractures, a coronal incision. Simple fractures with incomplete fractures at some buttresses may often be reduced with a single approach. Comminuted zygomatic fractures, especially those with lateral displacement of the zygomatic arch and body of the zygoma, require three incisions: coronal, intraoral, and eyelid.

Temporary alignment is initially achieved by placing interfragmentary wires at the zygomaticofrontal suture and infraorbital rim. The zygomaticomaxillary buttress, exposed through an intraoral gingivobuccal sulcus incision, is then stabilized by reduction and fixation. If the zygoma is laterally displaced, an open reduction of the zygoma, orbit, and arch are directly approached through a coronal incision. The orbital floor is explored through a lid incision and following

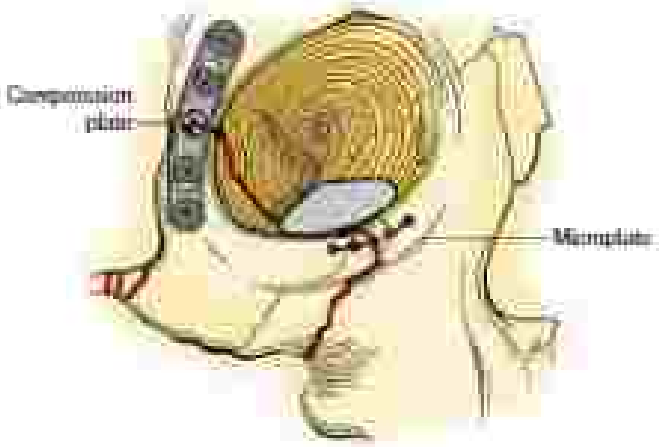


FIG. 1. Right internal fixation of a zygomatic fracture has been performed by applying plates and screws to the junction of the zygoma with the frontal bone and maxilla. The bone is manipulated into position and temporarily secured with interfragment wires before rigid internal fixation is applied.

retrieval of soft tissue contents of the orbit from the antrum, the orbital floor is reconstituted with either alloplastic materials (polyethylene or titanium) or a thin, curved bone graft such as a split rib, or the external table of the skull.

Nasoethmoid-Orbital Fractures

Nasoethmoid orbital fractures are comminuted fractures of the central upper midface: the nose and medial orbital rims. They result either directly from a blow to the glabella and upper nasal area that shatters the medial orbital rims, nose, and frontal sinus, or indirectly by the extension of other midface or frontal fractures (forehead or zygomatic/Le Fort's maxillary areas). One-third of these fractures are unilateral, one side of the nose and the medial orbital rim, and two-thirds are bilateral. One-third are isolated to the central midface alone (ipsilateral nose and medial orbital rim), and two-thirds are extended to other areas of the central midface or forehead. Commonly, a unilateral nasoethmoid fracture exists with a midface Le Fort's fracture. The *sine qua non* of this fracture is the presence of fractures that isolate the lower two-thirds of the medial orbital rim with its attached medial canthal ligament from adjacent bones, which allows migration laterally of the entire medial eyelid commissure (Fig. 3A).

The diagnosis of a nasoethmoid orbital fracture is suggested by the presence of a severely depressed, comminuted, frontal impact nasal fracture (Fig. 4B). Pain and tenderness are present with direct finger pressure over the medial canthal ligament. Unilateral or bilateral eyelid (spectacle) hematomas are usually present. Nasal lacerations are present in 50% of patients, and epistaxis is invariably accompanies this injury. A forehead contusion, depressed nose is usually accompanied by telecanthus, which is increased distance between the medial eyelid commissures. Crepitation is present on palpating the nose, and a CSF leak, pneumocephalus, or orbital emphysema may be present.

Traumatic telecanthus is measured by an increase in the distance between the medial commissures of the eyelids. This distance normally equals the length of a palpebral fissure. A high index of suspicion is necessary to confirm the diagnosis of traumatic telecanthus in patients with minimal displacement or impacted fractures. Mobility of the medial orbital rim may also be detected on bimanual examination with simultaneous intranasal-extranasal examination. A palpating finger placed externally against the bone bearing the medial canthal ligament attachment detects movement of the bone produced by the tip of a clamp placed in the nose directly under the canthal ligament. Movement of the medial orbital rim confirms the presence of a fracture that will require open reduction. The definitive radiographic examination consists of axial, sagittal, and coronal CT scans with bone and soft tissue windows (Fig. 4C).

Treatment

Treatment should generally be accomplished as soon as reasonably possible because of the possibility of an associated CSF leak, frontal sinus fractures with associated duct obstruction, and pneumocephalus. The fracture is exposed with three incisions: coronal, lower eyelid, and gingivobuccal sulcus incisions, so that the entire frontal-nasomaxillary fracture is visualized. Initially, fracture fragments are linked together with interosseous wires and then stabilized by plate and screw fixation (Fig. 5). Reconstruction of the majority of the internal orbit and nose are accomplished by inserting shaped bone grafts to the nose and either bone graft or alloplastic material to replace orbital wall defects. The repair will reconstitute the orbital volume, nasal height, contour, and projection of the central upper face. Bone grafts replace critical areas of structural bone loss. If the medial canthus is detached from the frontal process of the maxilla, it is reattached by trans-nasal canthopexy wires attached posttimed posterior and superior to the lacrimal fossa.

Frontosinus Fractures

Frontosinus fractures include fractures of the frontal bone, frontal sinus, supraorbital rims, and anterior cranial base (Fig. 6A). Anterior cranial base fractures often accompany frontal vault skull fractures and supraorbital, nasoethmoid, and frontal sinus fractures. High Le Fort's (II or III) fractures are often accompanied by a fracture of the frontosinus region.

The diagnosis of frontosinus fracture is suggested by frontal contusion and laceration, periorbital hematoma, or swelling (*question mark—sinus* [Fig. 6B], is a classic symptom of an anterior cranial base fracture), which also may include a dural tear and a CSF leak, pneumocephalus, frontal lobe injury symptoms (confusion, coma, and seizures), epistaxis, anosmia, and visual impairment. Hemotympanum occurs in middle cranial base fractures, and a Battle's sign (hematoma of the mastoid) occurs in posterior cranial fossa fractures. The definitive radiographic examination is an axial and coronal CT scan of the frontal bone, frontal sinus, and anterior cranial fossa and cranial base.

Frontal Sinus Fractures

The frontal sinus consists of two asymmetric cavities separated by one or more bony partitions. The size of the frontal sinus is quite variable, from almost nothing to pneumatization of the entire frontal bone and orbital roof. The most common symptoms of a frontal sinus fracture are lacerations, contusion, or bruises in the forehead area. Often, these are the only physical signs of a fracture, and their presence with tenderness should prompt a CT scan. Epistaxis is usually present. In severe cases, a deformity or depression of the glabellar area may be seen, especially after resolution of the swelling. A CSF leak, pneumocephalus, or orbital emphysema may be noted. Radiographic examination consists of axial and coronal CT scans.

Treatment

Nondisplaced anterior wall fractures without duct obstruction require only observation. Depressed fractures of the anterior wall that do not obstruct patency of the nasofrontal duct (Fig. 6A) can be treated by elevation and concentrative mucosal debridement. Fractures blocking the nasofrontal ducts are treated either by obliteration of the entire sinus with bone after thoroughly stripping the mucosa and plugging the nasofrontal duct with a bone graft, or cranialization of the sinus cavity after removing the mucosa and posterior wall. Posterior wall frontal sinus fractures imply the possibility of a dural laceration if there is more than several millimeters' displacement. Nondisplaced posterior wall fractures can be observed if duct obstruction is not present; however, posterior wall fractures displaced more than the thickness of the inner table may require surgical exploration. If the posterior wall of the frontal sinus is fractured and displaced more than several millimeters, the integrity of the dura must be confirmed.

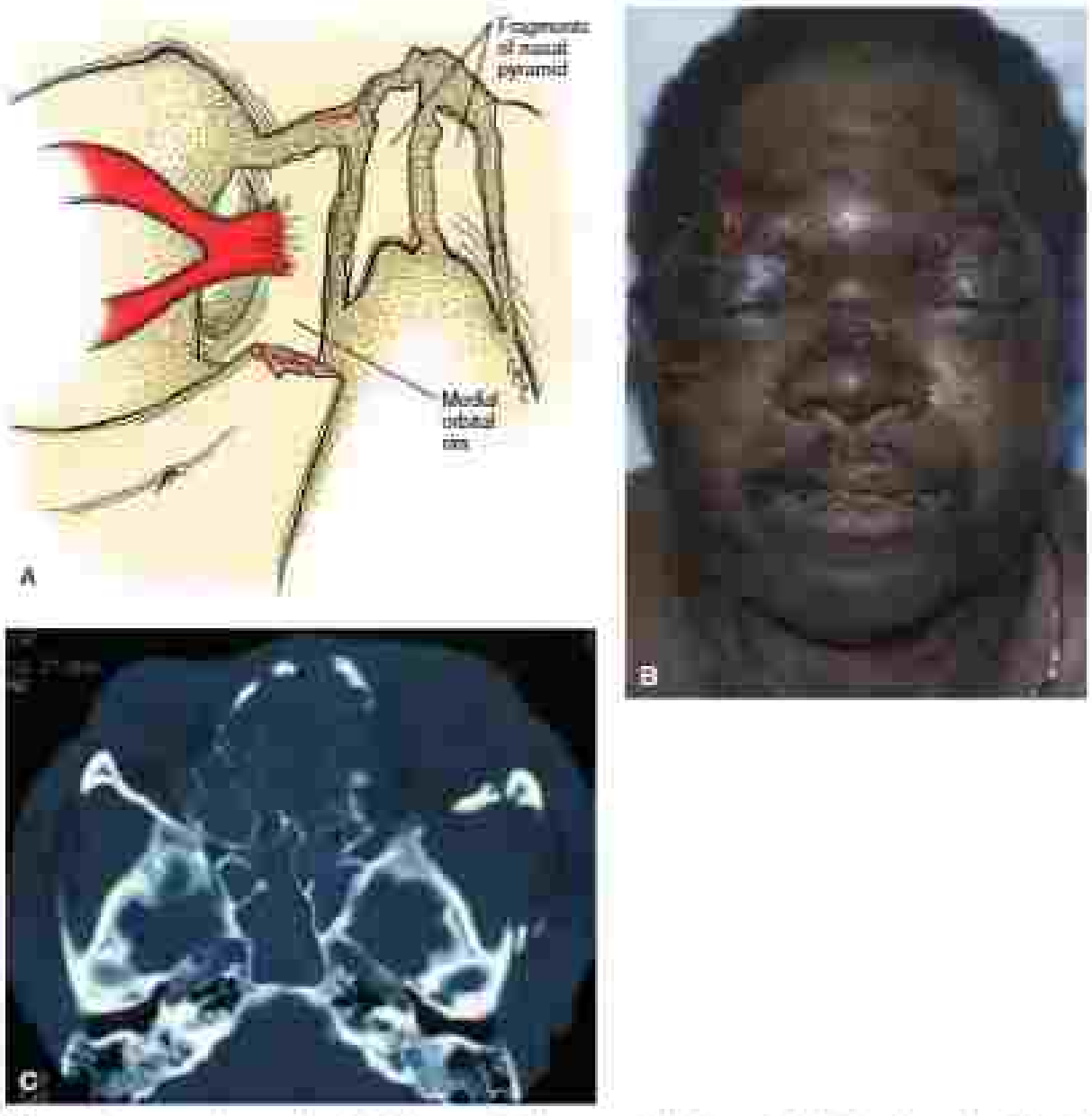


FIG. 8 (A) The central segment of a naso-orbital orbital fracture is the lower two-thirds of the medial orbital rim. Here, the medial canthal ligament attaches to the frontal process of the maxilla. Dislocation of the frontal process of the maxilla dislocates the entire canthal complex. (B) A patient with naso-orbital orbital and Le Fort III fractures. Flattening of the nose and bilateral periorbital hematomas are seen. (C) Radiograph computed tomography scan of the patient's nose in panel

When enough of the sinus is destroyed (and especially if the nasofrontal duct is not patent), the likelihood is that the sinus will not function and will form an abscess. Sinus mucosa may be removed both by stripping and light burring of the bony walls of the sinus cavity to eliminate microscopic invaginations of mucosal membrane into the bone. Both nasofrontal ducts are then plugged with fascia or fat or calvarial bone grafts. The remainder of the sinus may then be obliterated with bone shaving sinus obliteration. The procedure of cranialization implies more thorough removal of the frontal sinus and accompanying ethmoid sinus remnants, and osteoplasty of the anterior posterior wall, sealing the nasofrontal ducts with calvarial bone grafts following thorough removal of the mucosal membrane and posterior sinus wall, and reconstruction of the anterior wall. In effect, the procedure of cranialization converts the sinus to a portion of the intracranial cavity (Fig. 7). The anterior bony wall of the sinus may be reconstructed by bone replacement or grafts where appropriate.

Supraorbital Fractures

Supraorbital fractures are suggested by the presence of lesions or lacerations in the area, a depression of the supraorbital region, a downward and forward protrusion of the globe, ptosis, and possible components of the superior orbital fissure or orbital apex syndromes. In some cases, a superior gaze paresis that may mimic inferior rectus entrapment (Fig. 8). A step or fracture discontinuity may be palpated in the supraorbital rim, and numbness may occur in the distribution of the supraorbital or supratrochlear nerves. Radiographic examination consists of axial, sagittal, and coronal CT scans.

Treatment

The treatment of displaced supraorbital fractures involves confirmation of the integrity of the dura, replacement of bone pieces into their proper position, and direct stabilization by interosseous wiring or plate and screw fixation. Damaged segments of the orbital roof are

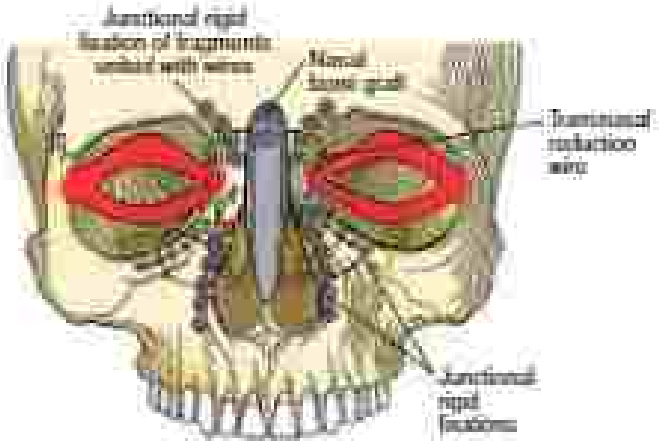


FIG. 5 Scheme for open reduction and internal fixation of a naso-orbital fracture. Initially the fracture fragments are maintained into position and temporarily held with transnasal wires. Plate and screw fixation is then applied. The two frontal processes of the maxilla are linked by a transnasal reduction wire and paired from one frontal process of the maxilla to the other at the posterior and superior edge of the lacrimal fossa.

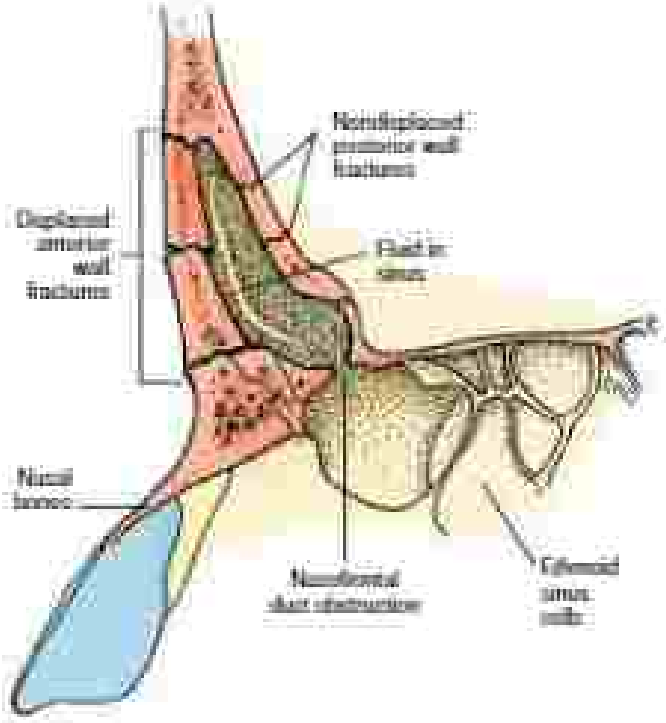
replaced by repositioning or substituted with a shaped bone graft. Frontal sinus involvement is frequent in supraorbital fractures and is managed as previously described. Exposure for operative reduction may occasionally be accomplished through a local laceration, but it generally requires a coronal incision.

Fractures of the Orbit

Isolated fractures of the internal portion of the orbit are accompanied by globe injury in 30% of patients. The minimal visual sensory examination consists of an assessment of visual acuity, pupillary reaction to light, confrontation fields, extraocular motility, examination of the anterior and posterior chambers, and a determination of intraocular pressure. The pupillary size and reaction must be assessed and compared bilaterally to exclude the presence of a relative afferent pupillary defect. Subtle physical signs of an optic nerve injury are a decreased red saturation test and decreased color vision, with more significant injuries, a relative afferent pupillary defect and a reduction in central visual acuity occur.

Orbital Floor Fractures

The diagnosis of an orbital floor fracture is suggested by periorbital and subconjunctival hemostasis. Anesthesia is invariably present in the infraorbital sensory nerve distribution, which produces cutaneous anesthesia of the ipsilateral nose, cheek, and upper lip and anesthesia of the anterior maxillary teeth on the affected side. Diplopia can be present in primary (central) gaze or in looking up or down or left or right, by virtue of contusion or entrapment of the fascial sheath of the rectus muscles. Enophthalmos is often present initially because of swelling, and it is followed by enophthalmos when enlargement of the bony orbital cavity allows extrusion of the globe into the enlarged orbit as the swelling resolves. Acute posttraumatic enophthalmos implies a significant orbital expansion injury that will require an early surgical repair. With orbital floor fractures, inferior and medial displacement of the globe accompanies posterior displacement. Orbital emphysema and ipsilateral epistaxis are usually present. Topical anesthesia, instilled into the conjunctival sac, allows the performance of a forced duction examination when indicated: the globe is manually rotated after grasping the insertion of the inferior rectus muscle through the conjunctiva with a forceps. Difficulty or absence of globe rotation implies incarceration of an extraocular muscle or its ligament system, which would often benefit from operative reduction and repair.



A

FIG. 6 (A) Depressed fractures of the anterior wall of the frontal sinus are created by alteration. Fractures blocking the duct are treated by obliteration of the sinus cavity because absence of duct function would create an abscess. Fractures of the posterior wall of the frontal sinus imply the possibility of a dural laceration. Generally, significantly displaced fractures of the posterior wall of the frontal sinus (>3–5 mm) require surgical exploration. (B) A spectacle hematoma is seen in the upper lid and implies a fracture of the frontal region: frontal bone, frontal sinus, or supraorbital area. The fracture hematoma is confined by the insertion of the orbital septum in the internal orbit with a sharp demarcation.

The radiographic examination consists of axial, sagittal, and coronal CT scans with soft tissue and bone windows. Indications for surgery are enophthalmos, entrapment of a muscle (diagnosed by restrictive strabismus producing double vision in a field of gaze controlled by the muscle), positive forced duction examination and/or CT confirmation of muscle or fascial entrapment, and vertical

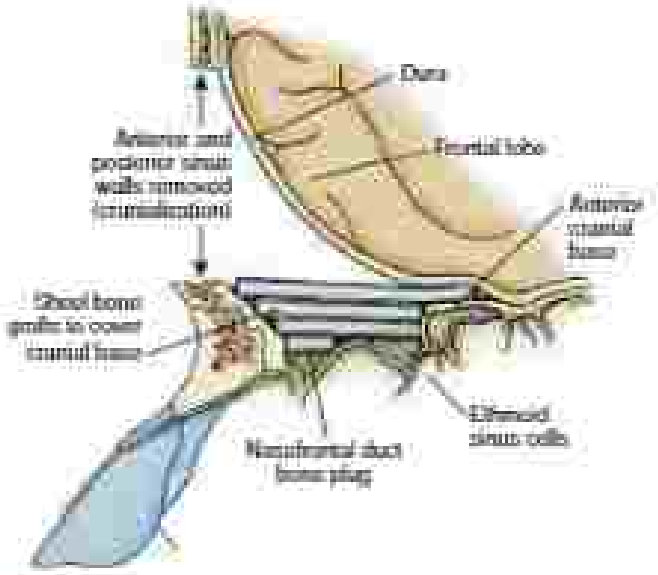


FIG. 7 The procedure of cranialization of the frontal sinus involves removal of the posterior sinus wall and all of the sinus mucosa, sealing the nasal frontal ducts with bone grafts, and using bone grafting to the defects in the anterior cranial fossa (floor of the frontal sinus) and anterior cranial fossa. In effect, the sinus is obliterated and converted to a portion of the intracranial cavity. The anterior wall of the sinus is then reconstructed, either with the preserved fracture fragments of the anterior wall or with bone grafts. Intracranial sinus is being cranialized with the reconstruction of the anterior wall to follow.

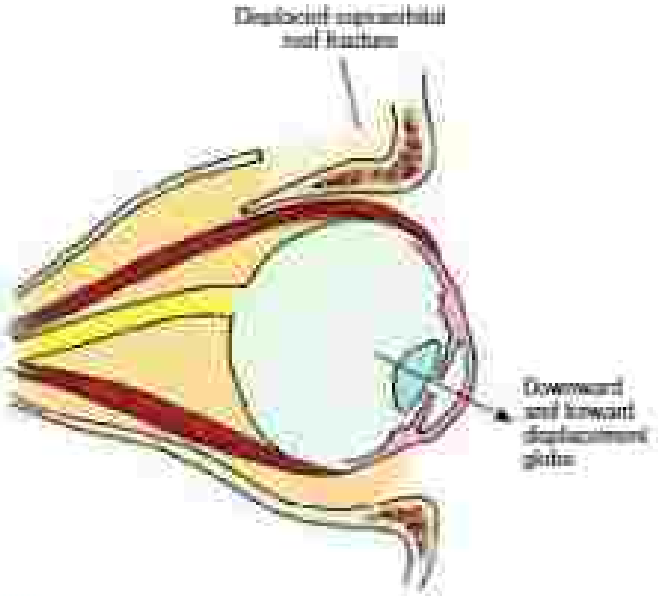


FIG. 8 Displaced supraorbital fractures produce a downward deformity of the superior orbital rim and orbital roof. The globe is dislocated downward and forward, producing exophthalmos; reduction of the fracture corrects the eye position.

or anterior posterior malposition of the globe. Anesthesia of the infraorbital nerve usually resolves without treatment. If significant destruction of an orbital floor is seen on CT scan in the absence of globe malposition, reconstruction of the orbit is indicated to prevent late globe malposition.

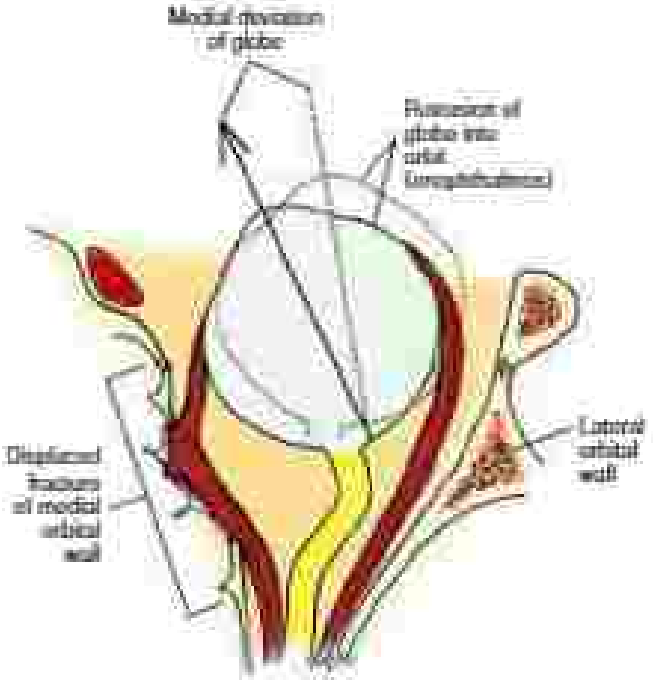


FIG. 9 Displaced fractures of the medial orbital wall crush the ethmoid sinus and expand the orbital volume. The surgical treatment consists of inserting bone grafts to narrow the volume of the orbit. The soft tissue is removed from its prolapsed position in the fracture site and replaced into the orbit and held in position by a bone graft or an orbital implant.

Treatment

Surgical treatment consists of an exposure of the defect through a lower eyelid incision (subciliary, subtarsal, or transconjunctival) with dissection of the orbital floor and removal of any incarcerated tissue from the fracture site or the maxillary sinus. The orbital floor is then reconstituted with alloplastic material (Supramid, Medpor) or carved bone grafts harvested from the calvarium, rib, or iliac region; the calvarium is often preferred, because the head is a self-contained reconstructive unit (after Tessier).

Medial Orbital Wall Fractures

Medial orbital wall fractures are suggested by the presence of periorbital and subconjunctival hematoma, diplopia when looking laterally or medially, orbital emphysema, epistaxis, enophthalmos, and medial displacement of the globe. The radiographic examination consists of axial and coronal CT scans with both bone and soft tissue windows.

The indications for surgery are radiographic entrapment of the medial rectus muscle with positive forced duction (impaired medial to lateral rotation of the globe) and the presence of enophthalmos, either on physical examination or the prediction of such an occurrence on the basis of radiographic evidence of an extensive volume-increasing medial orbital wall fracture displacement (Fig. 9).

Treatment

Surgical treatment is accomplished by a medial conjunctival or cutaneous incision with removal of incarcerated tissue from the crushed ethmoid sinuses and reconstruction of the medial orbital wall with alloplastic material or bone grafts. Patients with orbital fractures should refrain from forcefully blowing their noses for 1 month.

Le Fort's (Maxillary) Fractures

Le Fort's or maxillary fractures are classified according to a pattern described by Rene Le Fort in 1901 (Fig. 10A). A Le Fort I fracture is a horizontal or transverse maxillary fracture separating the maxillary

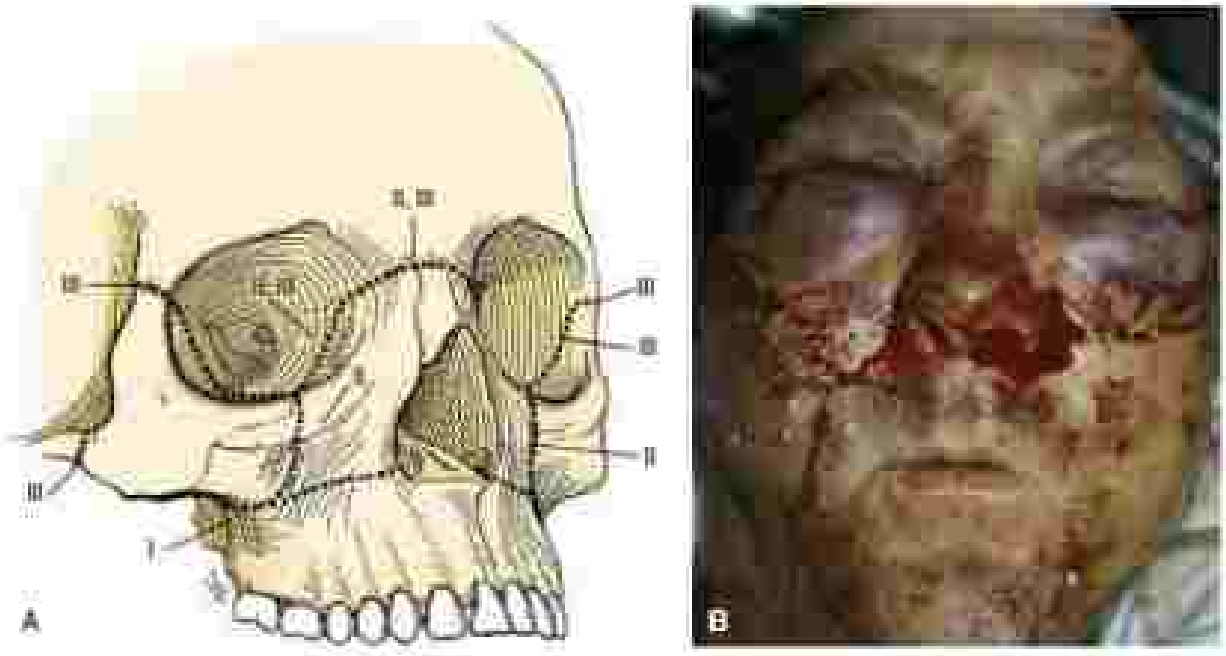


FIG. 10 (A) The Le Fort's maxillary fracture classification. A Le Fort I fracture is a horizontal fracture separating the maxillary alveolus from the upper midfacial skeleton. The *Le Fort II, or pyramidal fracture*, separates a central, pyramid-shaped nasomaxillary segment from the upper midfacial skeleton. The Le Fort III fracture is a craniofacial disjunction in which the midface is fractured *through the upper portion of the orbits*. Generally, Le Fort's II and III fractures do not exist as single segments but display combination. (B) Clinical appearance of a patient with a Le Fort's II–III fracture. The face is flattened and elongated and there are bilateral periorbital hematomas.

alveolus from the upper midfacial skeleton. A Le Fort II (pyramidal fracture) separates a central, pyramid-shaped nasomaxillary segment from the zygomatic and orbital portions of the facial skeleton. A Le Fort III fracture is a craniofacial disjunction separating the facial bones from the cranial skeleton through the upper portion of the nose and the lateral, floor and medial orbits.

Most Le Fort's II and III fractures are comminuted and consist of combinations of lesser Le Fort's fragments, such as simultaneous fractures at the Le Fort's I, II, and III levels. The injury is usually severe (many columns with multiple levels) on the side of the impact; commonly, a Le Fort III superior level fracture is seen on the donor side with a Le Fort II superior level fracture on the other. Single pure Le Fort's III fractures are unusual and frequently are accompanied by bilateral eyelid hematomas, no maxillary mobility, and a slight malocclusion (half cusp), reflecting the minimal displacement and incomplete character of the fracture. They are thus easily missed on physical examination. The *presence of bilateral eyelid hematomas* should always support the possibility of a Le Fort fracture. Also, if fluid is seen in both maxillary sinuses on CT scan, a Le Fort fracture should be suspected.

The physical diagnosis of a Le Fort fracture rests on the demonstration of malocclusion and mobility or displacement of the maxillary alveolus. This mobility is confirmed by grasping the maxillary alveolus and testing for its movement, holding the cranium stable with the contralateral hand. Crossbite (incomplete or impacted fractures that have no mobility). Upper Le Fort's fractures possess signs of zygomatic, orbital, nasal, and nasoethmoid fractures, depending on the level and extent of the injury (Fig. 10B). When Le Fort's fractures are not treated, midfacial proportions change, and midfacial elongation and retrusion generally follow. Profuse nasopharyngeal bleeding initially accompanies Le Fort's fractures; marked facial and eyelid swelling also occur. CSF leak, pneumocephalus, and orbital emphysema occur in Le Fort's II and III fractures, and 10% to 15% of Le Fort's fractures are accompanied by palatal alveolar fractures that divide the maxillary alveolus in an anteroposterior plane (sagittal fracture of the maxilla), making treatment more complicated. The radiographic examination consists of axial and coronal CT scans with bone and soft tissue windows.

Treatment

Treatment is accomplished by first placing the maxilla in IMF to occlusion with the mandible. Sagittal fractures of the maxilla are managed by plate and screw fixation to make a single one piece unit of the maxillary alveolus to the *roof of the mouth* and at the piriform aperture. The Le Fort I fracture is treated by plate and screw fixation at the four anterior buttresses of the maxilla (Fig. 11) through an intraoral gingival buccal sulcus incision. IMF may then be released preoperatively if rigid fixation has been used. Otherwise, the patient is kept in IMF for 4–6 weeks period to ensure bone healing.

The treatment of a Le Fort II fracture involves exposure through a lower eyelid incision (subciliary, subtarsal, or lower orbital rim), with a reduction of the orbital rim and floor or medial orbital wall components of these fractures and open reduction of the central midface and nasoethmoid area. A coronal incision may be required to upper Le Fort's II fractures for an open reduction and internal fixation of the nasofrontal area. Upper Le Fort's fractures are often accompanied by simultaneous fractures in the frontoethmoidal region.

Complex or Panfacial fractures

Panfacial fractures consist of combinations of frontal, midface, and mandibular fractures. The treatment consists of reconstructing the lower face as one unit and reconstructing the upper face as a separate unit, relating both units to the cranial base in their proper relationship. The upper face is then reconstructed to the lower face at Le Fort's I level, and both the horizontal and vertical portions of the mandible are stabilized with open reduction. The upper midface, the orbits and nasoethmoid area are stabilized to the frontal bone and cranial base and then linked to the stabilized lower face (mandible and Le Fort's I segment) at the Le Fort's I level. Previously,

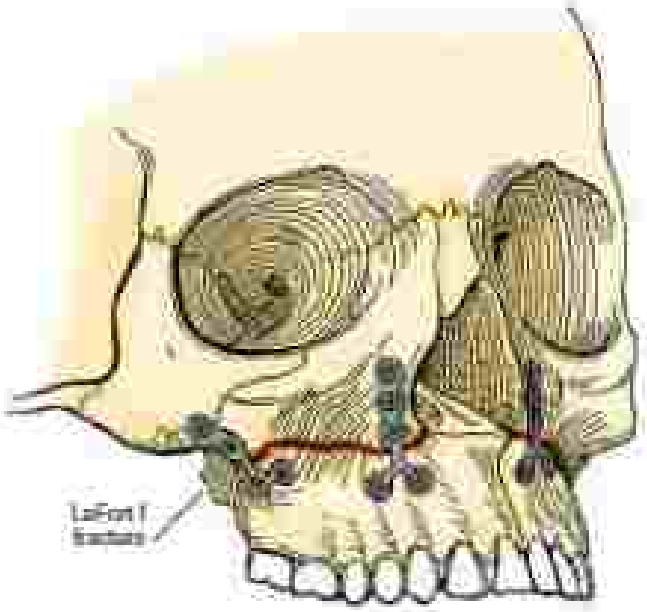


FIG. 11 A Le Fort I fracture has been treated by plate-and-screw fixation at the four anterior buttresses of the maxilla at the Le Fort's I level. The patient is initially placed in intermaxillary fixation. The fracture fragments are aligned, and fixation is applied to stabilize the reduction. Postoperatively, the intermaxillary fixation can be released because of the stability of plate and screw fixation.

as an initial step, the maxilla is aligned with the mandible and the dental arches through IMF.

Mandibular Fractures

Mandibular fractures are one of the most common facial injuries. In the horizontal mandible and the tooth bearing area, they are usually compounded into the mouth; less commonly, they are compounded through the skin. Fractured, loose, or broken teeth, bleeding from a tooth socket, and intraoral lacerations imply the presence of a mandible fracture. One third of mandible fractures occur in the condylar-subcondylar area, one third occur in the region of the angle, and the other third occur in the body, symphysis, and parasymphysis areas (Fig. 12A), which represent weaker areas of the mandible. The angle is weakened by the presence of the third molar tooth and, anteriorly, the parasymphysis by the long root of the canine tooth and the mental foramen.

The subcondylar area represents a thin region in the ramus. More than 50% of mandibular fractures are comminuted and multiple; therefore, the presence of a single mandibular fracture prompts a thorough search for a second or third fracture, often present contralaterally. Known combinations such as parasymphysis and contralateral subcondylar, parasymphysis and contralateral angle, or symphysis with unilateral or bilateral subcondylar fractures are frequent. The diagnosis of a mandibular fracture is suggested by pain, swelling, abnormal occlusion, numbness in the distribution of the mental nerve (lower lip), swelling, bruises, external or intraoral lacerations, bleeding from a tooth socket, fractured or missing teeth, trismus, or pain on moving the jaw (Fig. 13B). Inability to bring the teeth into occlusion, which may occur anteriorly, laterally, or bilaterally; abnormality or irregularity in dental arch form; malocclusion of the teeth; steps or level discrepancies in teeth or bone height or position; or gaps detected either in the dentition or by palpating the mandible are all indications of possible fracture. Bleeding from the ear canal implies the possibility of a condylar fracture/dislocation. In some cases, segments of the dental alveolus are separated from the lower portion of the mandible and constitute an alveolar fracture, which is defined by separation of the dental alveolus from the rest of the basal mandible. Dental (alveolar) fractures may occur as isolated fractures alone or in the presence of more extensive mandibular fractures by comminution. An unpleasant odor in the mouth is present soon after mandibular fractures occur.

The plain radiographic examination includes posteroanterior, lateral oblique, and Towne films of the mandible. Seldom now are plain radiographs taken, but a CT scan (Fig. 13D) for the condylar, coronoid, and ramus areas and horizontal portion of the mandible is routine. The Panorex examination is the one helpful plain film radiograph, but it requires a cooperative patient who is able to stand, and often it cannot be obtained urgently because they are available in dental departments. Occlusal and apical dental films are sometimes required to visualize specific areas of the teeth to examine for root fracture and apical or tooth root pathology which complicates mandibular fracture treatment and predisposes to infection.

Treatment

The treatment of mandibular fractures includes the application of arch bars to the teeth, placing the teeth of the mandible in IMF to occlusion with the maxilla. IMF is continued for 4 to 8 weeks depending on the fracture type. If plate and screw (rigid internal fixation) is used, the jaws are not wired together postoperatively, and immediate mobilization is permitted with a light diet. Closed reduction is appropriate for many condylar, coronoid, and ramus fractures and those stable fractures in the angle, body, or symphysis that are not displaced. Displaced fractures in the horizontal mandible require open reduction with plate and screw fixation. Exposure is obtained intraorally, the preferred exposure for the anterior portion of the horizontal segment of the mandible. Angle fractures may be treated intraorally if simple and extraorally if comminuted. Condylar and subcondylar fractures that require open reduction are those that would result in mechanical interference with mandibular motion or a loss of ramus height such as a dislocated condylar head, are exposed with a preauricular, retromandibular, or intraoral ramus incision for fixation.

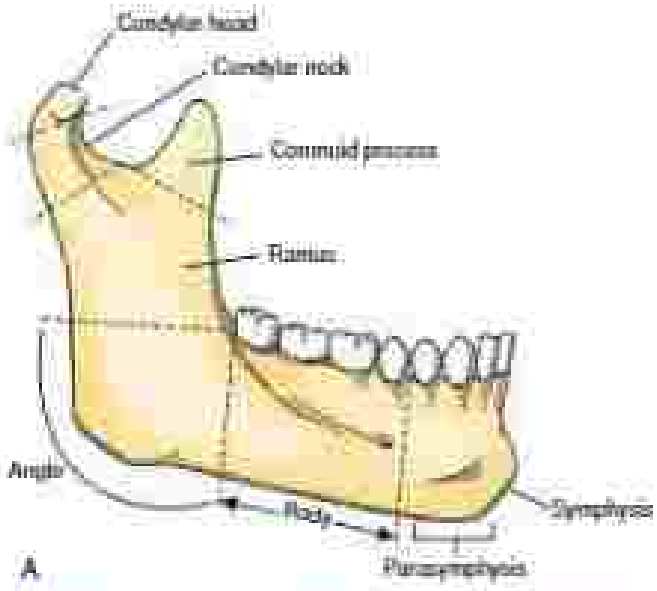
Patients who require IMF are given a soft, blenderized diet, and the average patient with IMF loses 15 to 20 pounds in 4 to 6 weeks. The use of rigid internal fixation (plate and screw fixation) allows many patients to immediately move the mandible, to have better oral hygiene, and to take a soft diet. Occlusion must be observed at least weekly in all patients to detect any displacement.

Gunshot and Shotgun Wounds

Gunshot wounds of low velocity may be managed as facial fractures with overlying lacerations. The soft tissue injury is carefully excised and closed. Fractures are repaired as in fractures with overlying lacerations.

High velocity gunshot or close range shotgun wounds produce extensive damage to, and loss of, soft tissue and bone. Zones of soft tissue and bone loss and separate zones of soft tissue and bone injury are identified and characterized. The bones are immediately stabilized in anatomic position in all regions where present by rigid internal fixation. Areas of bone loss are stabilized, preserving the length of bone defects with rigid fixation to achieve anatomic reconstruction of the bone architecture to normal dimensions. Soft tissue closure is obtained either by advancement or skin to mucosa closure after conservative debridement, with replacement procedures performed early for missing soft tissue replacement.

Serial second look procedures are required at 48 hour intervals until no further devitalized tissue is seen. Soft tissue reconstruction may then be completed, and distant flap transfer is usually required for intraoral lining defects and dead space or sinus obliteration and mucosal or cutaneous replacement. At the time of flap transfer, composite replacements of bone and soft tissue may be considered, or soft tissue reconstruction may be accomplished first and then bone reconstruction secondarily. The bone gaps resulting from missing bone are maintained by rigid internal fixation until bone grafting/replacement can be performed.



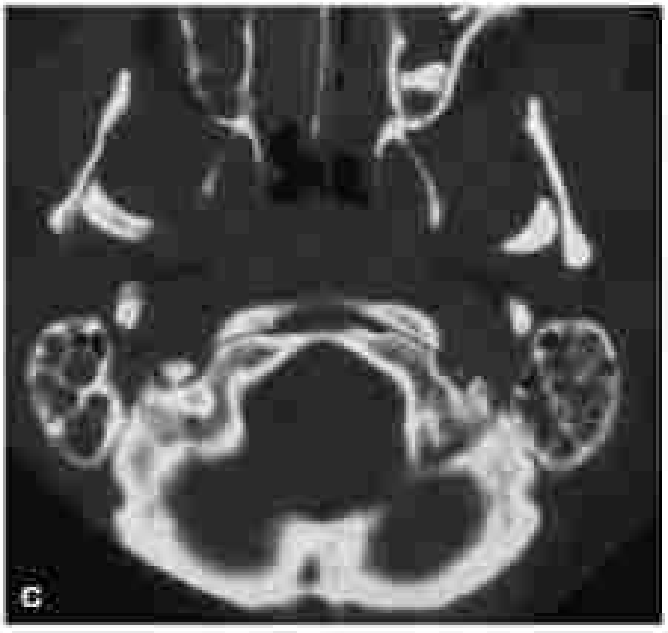


FIG. 11 (A) The anatomic regions of the mandible include the condylar and subcondylar areas and ramus posteriorly, the angle and the body laterally, and the symphysis and parasymphysis areas anteriorly. Weak areas are the subcondylar region, the angle, weakened by the third molar tooth, and the parasymphysis area, weakened by the long roots of the canine teeth. (B) A patient with anterior mandible, hemipalatal fractures, and a Le Fort I maxillary fracture. Computed tomography scan of (C) bilateral subcondylar and symphysis fractures of the mandible.

Late Scarring From Wounds

Generally, it takes 1 to 2 years for a cutaneous scar to fully mature. A red, raised scar that is initially quite prominent and shows some soft tissue contracture may resolve satisfactorily with time. Patients who understand the course of scar maturation can be encouraged to be accepting through the healing process. Early scar revisions are generally not indicated; in fact, they are discouraged except in the cases of obvious malalignment of tissues or contractures of the type that cause functional problems, such as ectropion and corneal exposure or oral incompetence.

SUMMARY

The face is of supreme importance in communication, nutrition, perception, and interpersonal relationships. The aesthetic attractiveness of an individual's facial features influences his or her personality and success. Although there are few facial emergencies, the literature has consistently underemphasized the advantage of prompt, definitive reconstruction of facial injuries and the contribution of early anatomic skeletal reconstruction to superior aesthetic results. It is not unusual for a victim of a multiple injuries to be principally concerned about residual facial deformity after other more life-threatening injuries have been resolved. The early definitive care of maxillofacial injuries is safe and possible and will repay the surgeon with superior results and grateful patients. A coordinated reconstruction is accomplished by interspecialty communication. All patients require counseling and rehabilitation, and psychological dividends result from these efforts.

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Penetrating Neck Trauma

Cory R. Evans, MD, Katherine Santor, MD, and Timothy C. Hollier, MD

Penetrating neck trauma is a common presenting injury to civilian trauma centers. These injuries are usually the result of either stab wounds or gunshot wounds (GSWs). GSWs are much more likely to cause significant injuries requiring surgical repair. Recent data from the conflicts in Iraq and Afghanistan report injuries to the head, face, and neck accounting for 21% to 39% of all injuries, with 18.8% of these involving the neck. Mortality from penetrating neck trauma has been reported to be around 3% to 4% from recent military data. Civilian mortality ranges from 1% to 5%.

ANATOMY

Although the neck is divided into several triangles by the classic anatomist, in trauma, the neck is divided into three zones. Zone I spans the thoracic inlet (the clavicles) up to the level of the cricothyroid membrane. Zone II is the area between the cricoid and the angle of the mandible, and zone III is the angle of the mandible and above. The division of the neck in this manner assists the surgeon in thinking about what and where vital structures could be injured. More important, it helps guide what approach must be taken to repair them. With this in mind, these three incisions allow access to the neck: the anterior sternocleidomastoid, the collar incision, and the median sternotomy. These incisions are very versatile (in particular, the anterior sternocleidomastoid and the median sternotomy incisions) and can be extended into one another to assist with operative exposure. This is very important because missile tracts often cross zones, necessitating better exposure, not only for proximal or distal vascular control, but also for facilitating high-quality repair, and decreasing the rate of iatrogenic or missed injuries.

Initial Management

Initial management of a patient with a penetrating neck wound should begin with a standard trauma evaluation using the ABCDE format (Fig. 1). The airway is especially important given that injuries in this region are more likely to cause airway compromise, and the injury could also be to the airway itself. A low threshold for endotracheal intubation exists in these circumstances. Stridor, respiratory distress, or an expanding hematoma should trigger early intubation. For patients with difficult-appearing airways who are able to protect their airway with upright positioning, consider proceeding to the operating room for intubation in a more controlled setting.

As with all trauma patients, the major branch in the decision-making tree is whether the patient should go immediately to the operating room versus proceeding with further imaging. Historically, violation of the platysma was an indication for surgical exploration. This policy of mandatory exploration led to a number of nontherapeutic operations, upwards of 80% to 90%. Now the decision to operate immediately is based on the presence of hard signs of vascular or aerodigestive tract injury. Although there exists debate as to the definition of hard signs, we use hemodynamic instability, severe active bleeding, expanding or pulsatile neck hematoma, massive subcutaneous air, bubbling from the wound, neurologic deficits, and hematemesis. Although zone of injury will be important when deciding your surgical exposure, it should not influence your decision to operate. This no zone approach oversimplifies decision making and can lead to a lower rate of negative explorations. For GSWs, preoperative x-ray imaging is a useful adjunct to locate missiles. We have seen entrance wounds in the neck with bullets that have travelled to thorax and even abdominal locations. It is better to know this before ending up in the operating room with unexplained hypotension after a negative neck exploration.

As imaging technology has advanced, in particular the development of high-resolution computed technology, selective neck exploration has become the standard of care. For patients without hard signs, further diagnostic testing is indicated. Angiography used to be considered the gold standard for diagnosing vascular injury. However, this has been surpassed by computed tomography angiography (CTA) as initial imaging modality of choice. It has high sensitivity and specificity for detecting vascular injuries. Intravenous access should be opposite the side of suspected injury and contrast bolus should be given from the side opposite suspected injury. Doing this will decrease artifact from the venous contrast bolus and improve imaging quality. Ultrasound is growing in popularity as a diagnostic modality for vascular injury; however, it is limited in trauma patients because of overlying or surrounding soft tissue injury and has a lower sensitivity and specificity than CTA. If the CTA demonstrates a trajectory that is remote from vital structures, the need for additional studies may be eliminated. A limitation of CTA is streak artifact from retained bullets or metallic fragments. This may necessitate fine-cut axial angiography of the neck to completely rule out injury.

CTA also has the advantage of a high sensitivity to rule out aerodigestive tract injury. When emphysema exists in deep fascial planes or around aerodigestive structures, continued suspicion of esophageal injury should be maintained. Further diagnostic testing includes esophagogram, esophagoscopy, or both. Esophagram done with water soluble contrast will miss injuries, so should be repeated with barium if initially negative. Esophagoscopy is more practical for detecting injury in patients who are intubated, or intraoperatively if there is high suspicion of injury, but one cannot be located. It is also better at identifying hypopharyngeal injuries. For these reasons, esophagoscopy has largely replaced esophagram in many centers. For suspicion of laryngeal or airway injuries, consult with

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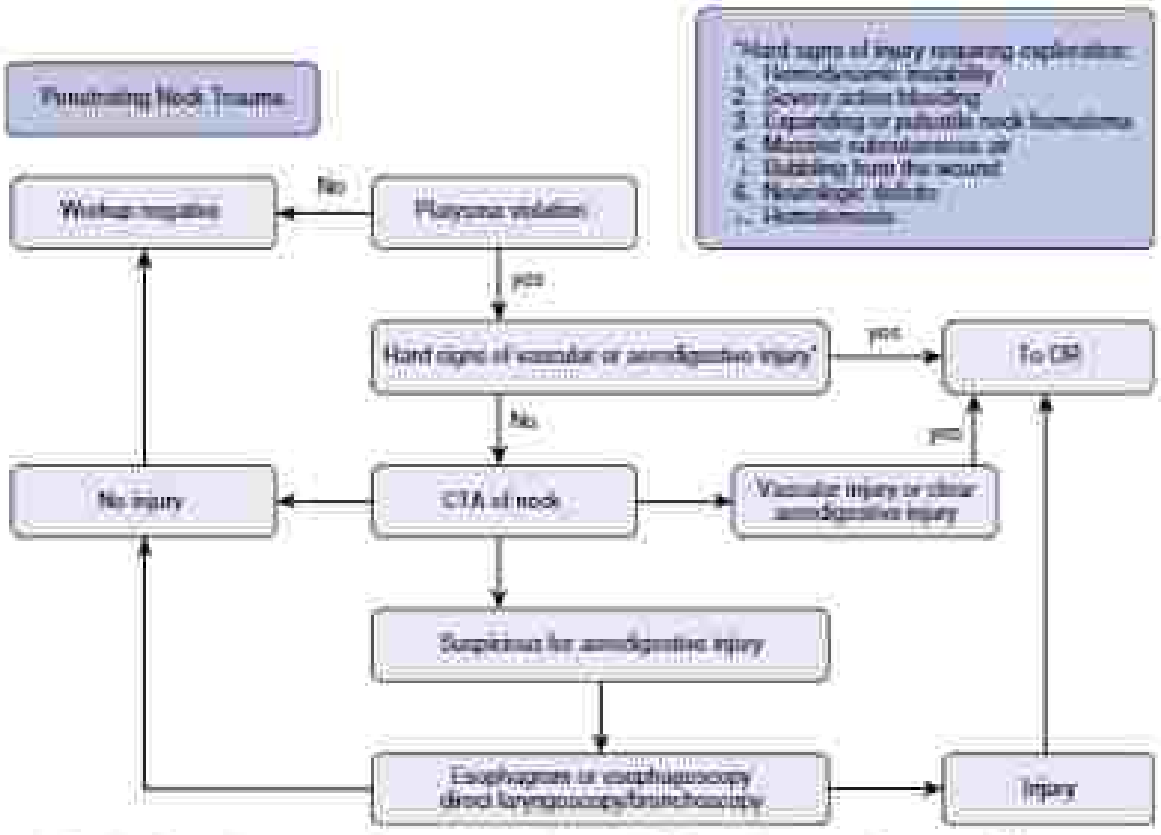

FIG. 1 Algorithm for initial management of penetrating neck trauma. CTA, Computed tomography angiogram; OR, operating room.

otolaryngology for direct laryngoscopy is the gold standard study. The American College of Radiology recommends direct visualization techniques for diagnosing aerodigestive injuries.

Operative Exposure

The patient is placed supine with a shoulder roll and the neck extended if there is no concern for cervical spine injury. The head can be rotated away from the side of injury, however, keeping the head straight can facilitate a bilateral exploration if needed. The patient should be prepped from the earlobe to the umbilicus. This allows extension to the chest if needed. Prep a groin and thigh in case vein graft is required. The initial incision runs along the anterior border of the sternocleidomastoid muscle. For a bilateral exploration, consider a collar incision two fingerbreadths above the sternal notch. Alternatively, bilateral sternocleidomastoid incisions can be connected inferiorly. Sternocleidomastoid incisions can be extended into a sternotomy for additional exposure. For exposure superiorly, such as a high carotid injury, subluxation of the mandible anteriorly and division of the digastric muscle can allow for better exposure.

The incision will be carried through the platysma with cautery. Next, find the anterior border of the sternocleidomastoid and define it along the length of the incision. Continue the dissection through the connective tissue here until the internal jugular vein is encountered. The next step will be to dissect out the anterior border of the internal jugular vein. Along its course, you will encounter the facial vein. A key step in neck exploration is ligating and dividing the facial vein. Immediately underneath should be the bifurcation of the carotid artery. The major pitfall of this step is dividing and ligating the internal jugular vein at a branch point running posteriorly. Once the facial vein has been divided and the internal jugular vein is dissected free, locate the carotid artery by palpation. Sharply enter the carotid sheath immediately on top of the artery and continue dissection into the pretracheostomial plane. Staying directly on top of the vessel and in the pretracheostomial plane will help avoid injury to other structures. Identify and preserve the vagus nerve which usually runs lateral to the artery. The ansa cervicalis will be anterior to the carotid sheath. If possible, identify and preserve this as well.

To explore the esophagus, continue medially and deep to the carotid artery. Bluntly develop the filmy flow plane behind the esophagus and anterior to the vertebral bodies. Having no serosal layer, the esophagus may be hard to distinguish from the overlying strap muscles, especially in the austere environment of a trauma case. Placement of an esophagus tube and palpation of the tube can help identify the esophagus. Beware of the recurrent laryngeal nerve running in the tracheoesophageal groove. Instillation of air or methylene blue into a withdrawn nasogastric tube can help identify or locate esophageal injuries.

Operating in the neck of a trauma patient is not usually a painless environment. If a hematoma is present, begin your dissection proximally and distally. Try to obtain vascular control before entering the hematoma. If there is already active hemorrhage into the operative field, it is very important to follow your landmarks to avoid iatrogenic injury during your dissection.

Management of Specific Injuries

Veins

Isolated venous injuries will likely not require exploration and will frequently self-tamponade. However, when encountered intraoperatively, these can easily be controlled with finger pressure. Ligate pesky bleeding anterior and external jugular veins with impunity. Injuries to the internal jugular vein can be repaired or ligated. Repair the internal jugular vein with transverse venorrhaphy if possible. Complex repairs should be avoided, especially if the contralateral jugular is uninjured.

Arteries

Carotid arterial injuries should be managed with primary repair when possible. Repair with a patch can be used if the repair would

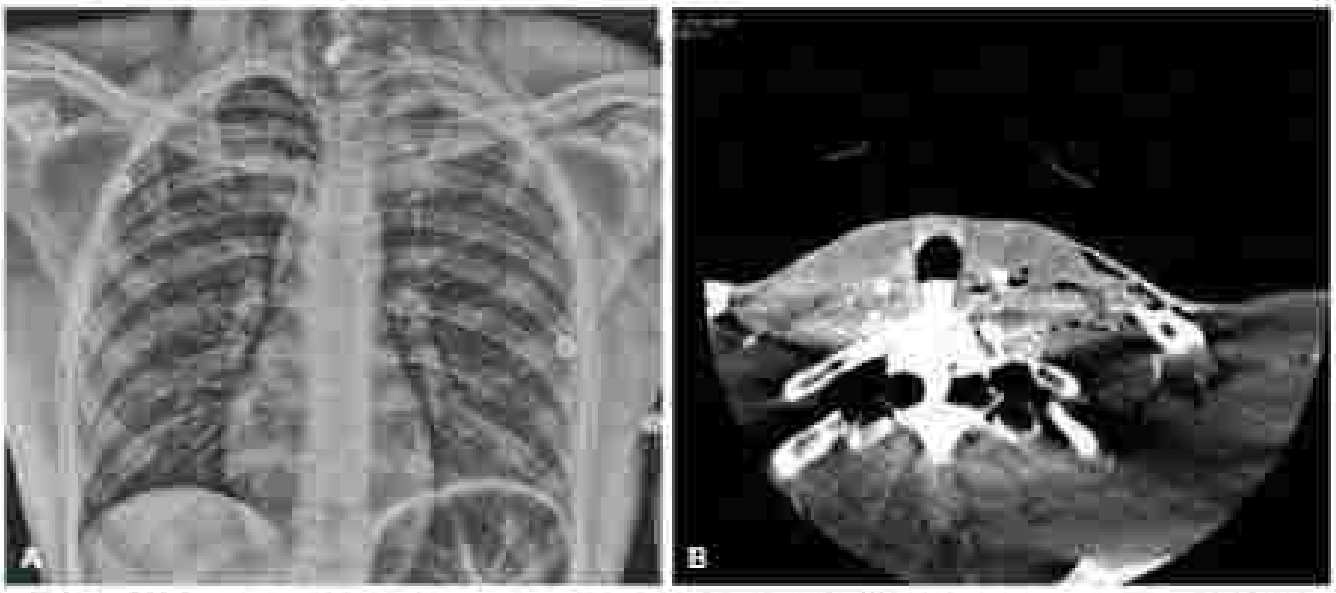

FIG. 2. A 24-year-old man presented with a single gunshot wound to the angle of his right jaw. He was hemodynamically normal, with no hard signs of vascular injury. However, he had sensory and motor deficits in his bilateral lower extremities. A, a chest radiograph, the bullet was seen in the proximity of C7–T1 vertebral bodies in the midline. He was electively intubated for airway protection because he was to be kept mostly flat for further studies. Computed tomography angiogram revealed a bullet lodged in the T1 vertebral canal, possible thyrocervical trunk injury and possible right vertebral artery injury. He underwent angiography that demonstrated traumatic occlusion of his thyrocervical trunk. Because of suspicion of aerodigestive injury, he underwent further investigation with both esophagoscopy and bronchoscopy. He was found to have a hypopharyngeal injury that was treated with a short course of antibiotics and nasogastric tube decompression. He was extubated on hospital day 2 after a cuff leak was detectable. A diet was started on hospital day 3, and the patient was discharged to a rehabilitation facility on hospital day 4.

result in narrowing of the vessel. Additional length can be gained by dividing the superior thyroid artery. Grafting seems to lead to more complications and there is an additional nature that to worry about; however, grafting is likely the best option if the defect is greater than 2 cm. If grafting is necessary, one of the saphenous vein is preferred to polytetrafluoroethylene or Dacron. A completion angiogram should be performed if grafts are used. Division and transposition of the proximal external carotid artery to the distal internal carotid artery may be an option for repair to avoid using a graft. The patient should be heparinized as soon as vascular control is obtained to prevent thrombus formation. Shunts may be a useful adjunct to maintain cerebral perfusion if a vein graft is to be obtained. Patients presenting with neurologic deficits should be repaired as this has been shown to lead to less morbidity and mortality. Comatose patients should likely be repaired as well because outcomes seem to be dismal regardless of approach.

Zone I carotid injuries may require median sternotomy for exposure with extension to an anterior SCM incision. Additionally, distal carotid artery injuries (zone 3) may require anterior mandible subluxation to reach the injury as well as division of the omohyoid and digastric muscles. The glossopharyngeal nerve lies inferior to these structures. If the distal portion of the injury is within the skull base the only option remaining is ligation. Intravascular techniques may be useful for zone 1 and zone 3 injuries that would be difficult to access surgically.

Vertebral artery injuries are difficult to manage. The vessels are either buried in bone or in direct contact with bone making ligation a technically demanding exercise. Initial vascular control may be maintained by inserting a Foley catheter into the wound and inflating the balloon. Some advocate for bone wax placement into the injury and compression. Vascular control could be obtained at the takeoff of the vessel from the subclavian artery; however, this necessitates an infraclavicular incision and a median sternotomy to expose the vessel at this point. Removal of the medial portion of the clavicle may facilitate this exposure. Temporary packing and referral to interventional radiology for embolization could be a more reasonable option.

Esophageal Injury

When an esophageal injury is identified, exposure of the entire injury is paramount. Debride injured esophageal tissue and expose the entire mucosal defect. Repair the injury primarily in two layers, with absorbable suture on the mucosa. Reapproximate the muscular injury with interrupted nonabsorbable sutures. Hypopharyngeal injuries can be repaired in a similar fashion. Beware the recurrent laryngeal nerve during exposure. A second esophageal injury is likely to be encountered, as completely mobilizing the esophagus or exploration from the contralateral side to surround unless clinical suspicion of a second injury is very low. The repair can be buttressed by mobilizing a strap muscle, or by mobilizing the sternal head of the sternocleidomastoid. This is especially important with concomitant tracheal injury. Strap muscles must be mobilized distally to preserve the blood supply. We do not advocate drainage following primary repair; however, if injuries are discovered in a delayed fashion, surgical debridement and drainage is the cluster of treatment. The tissue at this point will friable and repairs are likely to fail. A cervical esophagostomy can be created for large defects with gross contamination as a bailout option. Esophagram should be performed prior to resuming an oral diet.

Tracheal Injury

Tracheal injuries require exposure and debridement of injured tissue before repair. The repair can be done with interrupted absorbable sutures with the knots on the outside. Large injuries with extensive tissue damage may necessitate resection and primary reconstruction of the trachea. The endotracheal tube should be in place below the level of the injury. Early tracheostomy can be done if it is suspected the patient will require prolonged intubation. This predisposes the patient to increased risk of surgical site infection but does decrease mortality compared with prolonged intubation. Patients tend to fare

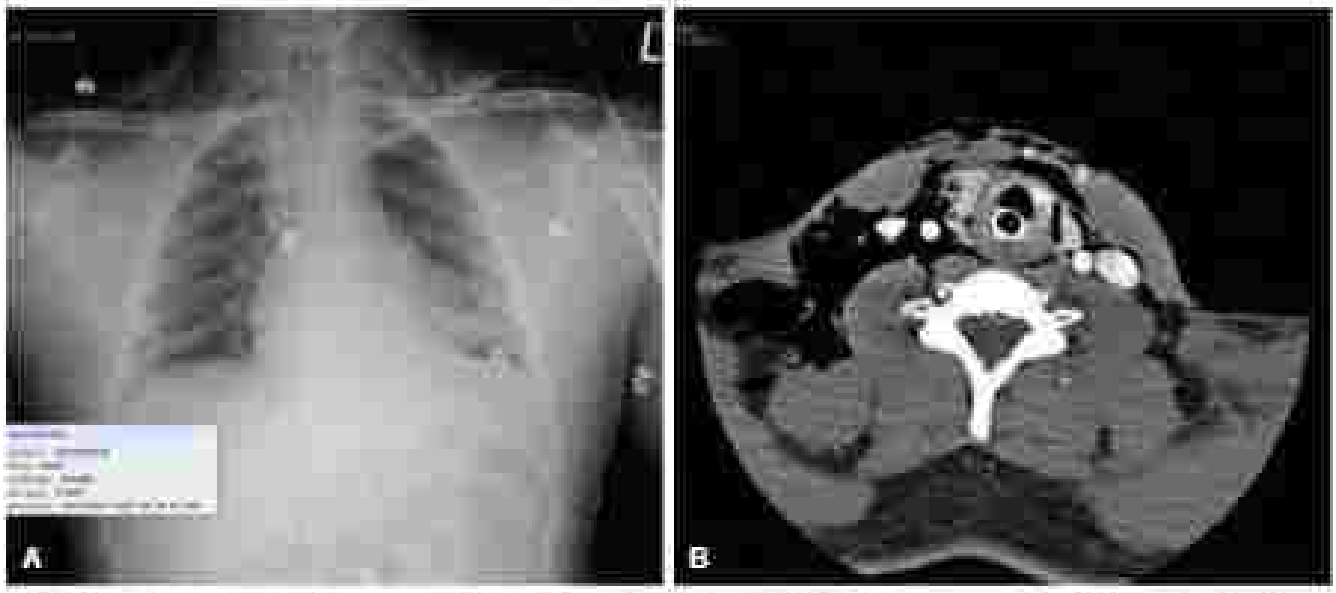

FIG. 1 A 29-year-old man sustained a gunshot wound to the anterior neck. He was noted to have air emanating from the wound with forceful coughing and talking. On chest radiograph, the bullet was seen to lie somewhere in the right mediastinum. He was electively intubated in the operating room in case an emergent surgical airway was necessary. Imaging revealed massive subcutaneous emphysema and mediastinal air. He was taken back to the operating room for bronchoscopy and esophagogastroduodenoscopy, which revealed injuries to both his trachea and his esophagus. His esophageal injury was approached via anterolateralmost incision and repaired with 3-0 PDS and buttressed with a portion of strap muscle. The tracheal injury was small and was not repaired. The patient was extubated and underwent an unremarkable upper gastrointestinal swallow study before initiation of a diet.

better with early intubation; however, this is largely dependent on concomitant injuries. It is wise to involve otolaryngology in the operative decision making to help manage postoperative complications should they arise. Otolaryngology can also help manage complex laryngeal injuries. Make sure to evaluate for combined esophageal injury. The esophagus is quite mobile compared with the trachea and associated esophageal injuries may not be immediately adjacent to the tracheal injury, especially if the head is turned to the side for operative exposure. In the instance of combined tracheoesophageal injury, it is especially important to buttress between the repairs with a muscle flap.

Suggested Readings

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Blunt Cardiac Injury

Anna M. Ledgerwood, MD, and Charles E. Lucas, MD

Blunt cardiac injury (BCI) can occur in any patient who sustains a significant impact to the chest. Clinical manifestations may encompass a wide spectrum of injury patterns ranging from simple myocardial bruise to rupture of a ventricle and death. The myriad injuries include minor electrocardiogram (ECG) abnormalities, complex arrhythmias, cardiac failure, septal rupture, valve rupture, coronary artery thrombosis, pericardial rupture, and chamber wall rupture.

INCIDENCE

The incidence of BCI varies widely (0%–19%) due, primarily, to the lack of a gold standard for diagnosing BCI after major thoracic injury. The diagnosis of myocardial contusion was often suggested in patients who had blunt thoracic injury with sternal fracture and elevated cardiac enzymes. Most likely this was over diagnosing BCI in patients who had no cardiac symptoms. Autopsy series of injured patients who die at the scene, however, show a relatively high incidence of BCI from a ruptured heart and pericardial tamponade.

MECHANISM OF INJURY AND PATHOPHYSIOLOGY

BCI should be considered in any patient with a high speed impact to the thorax from a motor vehicle collision, bicycle, or motorcycle crash, falls greater than 10 feet, blast injuries, assaults, and crush injury to the chest. Any mechanism such as a direct precordial impact, a compression or crush between the sternum and spine, or a deceleration/tension force causing a cardiac tear at a fixed point such as between the right atrium and vena cava can cause BCI. Even an abrupt compression of the abdomen causing a significant and sudden rise in venous pressure that is transmitted to the right heart can result in cardiac rupture. This hydrostatic pressure can also produce rupture of the pericardium or its diaphragmatic attachments. Most patients with blunt thoracic injury, however, have no BCI. In contrast, most patients with cardiac chamber rupture die at the scene and seldom present alive to the emergency department.

CLINICAL DIAGNOSIS OF BCI

There are no signs or symptoms specific for BCI. The most common complaint is chest pain, which could be due to the associated thoracic injuries including rib fractures, sternal fractures, or chest wall contusions. The presence of associated thoracic trauma, however, should raise suspicion for BCI. Likewise, auscultatory findings of a thrill, murmur, or rub should raise suspicion for BCI, but they usually are not present. Hypotension may accompany BCI but is usually from other causes such as a tension pneumothorax, spinal cord injury, or hemorrhagic shock.

The use of ECG and cardiac enzymes to diagnose BCI in the emergency department has been extensively studied. Velmahos and coworkers determined that the combination of a normal ECG and troponin I level on admission and eight hours later rule out the diagnosis of significant BCI. They prospectively evaluated 333 consecutive patients with major blunt trauma and defined significant BCI as the presence of cardiogenic shock, arrhythmias requiring treatment, or posttraumatic structural deficits. They noted that all 131 patients with normal serial ECG and troponin I levels had no significant BCI. Only 48 patients (14%) had significant BCI and, of these, 94% had both abnormal ECG and troponin levels. They reported that 22% of their patients with only an abnormal ECG and 7% of their patients with only an abnormal troponin level developed a significant BCI. However, 43 of their 48 patients with significant BCI had an abnormal ECG on admission.

Testing for creatinine kinase-MB isoenzyme and the use of radionuclide angiography have not been helpful in diagnosing BCI. The initial chest radiograph is helpful in ruling out a tension pneumothorax and/or a hemothorax that may be a source of blood loss and hypotension. A careful physical examination confirming movement of the lower extremities and the presence of rectal tone prior to giving drugs for intubation rules out spinal cord injury as a cause of hypotension. The FAST examination helps determine whether there is any cardiac activity in the patient who presents without vital signs and identifies if there is fluid in the pericardial sac in patients who present with vital signs. A transthoracic echocardiogram or a transesophageal echogram is recommended on those patients who have abnormal ECGs on admission. These studies provide information regarding the cardiac function.

BCI INJURY SEVERITY

The American Association for the Surgery of Trauma has identified an organ injury scale for BCI. A grade I BCI is identified by ECG abnormalities, such as nonspecific ST or T wave changes, premature atrial or ventricular contractions, or persistent sinus tachycardia. Grade II BCI includes patients with heart block or ischemic changes without cardiac failure. Grade III injury includes patients with sustained arrhythmias, septal rupture, valvular incompetence, papillary muscle dysfunction, distal coronary artery occlusion without heart failure, or blunt pericardial laceration without cardiac herniation. Grade IV BCI includes patients with septal rupture, pulmonary or tricuspid incompetence, papillary muscle dysfunction, distal coronary artery occlusion with cardiac failure, rupture of the right or left atrium or the right ventricle, or aorta, or mitral valvular incompetence. Grade V BCI includes patients with proximal coronary artery occlusion, left ventricular perforation, or rupture of more than one chamber.

TREATMENT OF BCI

Grade I Injury

Patients with a grade I BCI will have only ECG abnormalities and should be observed by continual monitoring until the ECG abnormalities have corrected. This typically occurs within 24 hours. The treatment of associated injuries resulting from the blunt force has a higher priority.

Grade II Injury

Patients with grade II BCI have heart block and/or ischemic changes and need to be monitored until ischemic changes resolve and the ECG pattern returns to normal. Arrhythmias should be anticipated and treated promptly. Close monitoring and serial assessment of troponin levels should continue while associated injuries are treated. Resolution often occurs within 48 hours. Inotropic support is not needed unless the patient worsens and develops evidence of heart failure.

Grade III Injury

Patients who have BCI associated with ventricular arrhythmias with or without an anatomic defect such as septal rupture, papillary muscle dysfunction, or distal coronary artery blockade without heart failure need to be monitored closely for progression to cardiac

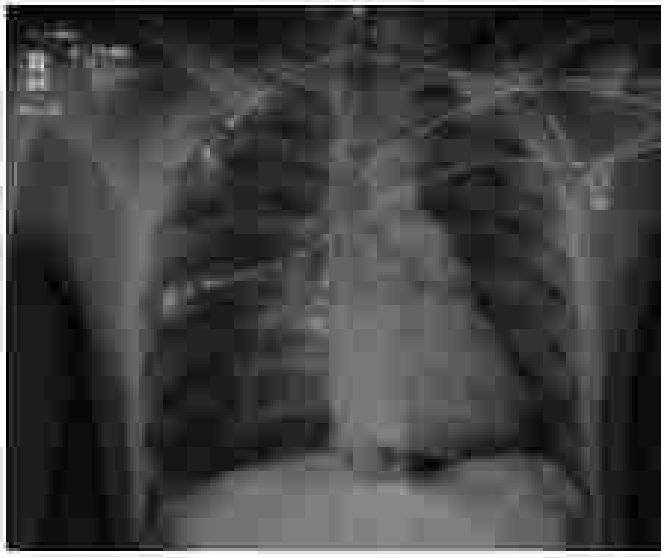

FIG. 1. Initial chest radiograph in a patient with grade 3 blunt cardiac injury demonstrated a small left pulmonary contusion but did not show significant hemothorax to explain his hypotension after arrival in the emergency department.

failure. Even patients who have a blunt pericardial rupture can be followed nonoperatively as long as this does not interfere with cardiac output and total body perfusion. If the patient with grade III injury has evidence of pericardial fluid, be careful to look for any evidence of pericardial tamponade and treat promptly with pericardiocentesis or, if necessary, open pericardiotomy. This type of nonpenetrating injury in patients with grade III BCI is potentially life-threatening and requires careful observation and seldom requires operative intervention.

This type of a grade III BCI was recently treated in a 23-year-old man who was found on the embankment of the freeway after ejection from the back seat of an SUV that struck a semi truck at high speed. He was awake and could answer questions but had a Glasgow Coma Score (GCS) of 12. His palpable systolic pressure was 100 mm. He had multiple abrasions and contusions but, on arrival to the emergency department, was moving all extremities. Shortly after arrival, he became hypotensive (80/57 mm Hg), tachycardic (145 beats/min), and tachypneic (22 breaths/min) with a GCS of 8. He was resuscitated, and his FAST examination of the chest and abdomen was negative. Initial chest radiograph suggested left lung contusion (Fig. 1). Subsequent computed tomography (CT) of the chest confirmed bilateral hemothoraces with small pneumothoraces, left pulmonary contusion, bilateral rib fractures, and nondisplaced sternal fracture (Fig. 2). He also had fractures of thoracic T12 vertebra, fracture of the transverse processes of L1–L3, and nondisplaced fracture at the base of the sacrum. The abdominal CT scan demonstrated a grade III liver injury and a grade II splenic injury (Fig. 3). Blood studies showed an arterial pH of 7.16, a lactate of 5.9 mmol/L, an alcohol of 165 mg/dL, and a troponin of 1.67 ng/mL. Bilateral tube thoracostomies yielded 750 mL of blood on the right and 150 mL on the left. The EKG showed sinus tachycardia with ST elevation.

Repeated episodes of hypotension in the intensive care unit were treated with blood and crystalloid solution, to which he responded. He gradually improved over the next 12 hours when his pH was 7.3, the troponin was 2.50 ng/mL, and the elevated liver enzymes began to normalize. The transthoracic echo examination showed "normal left ventricular size with slight increase in left ventricular wall thickness with mildly decreased left ventricular systolic function. He had global hypokinesis, and the left ventricular ejection fraction was 45%

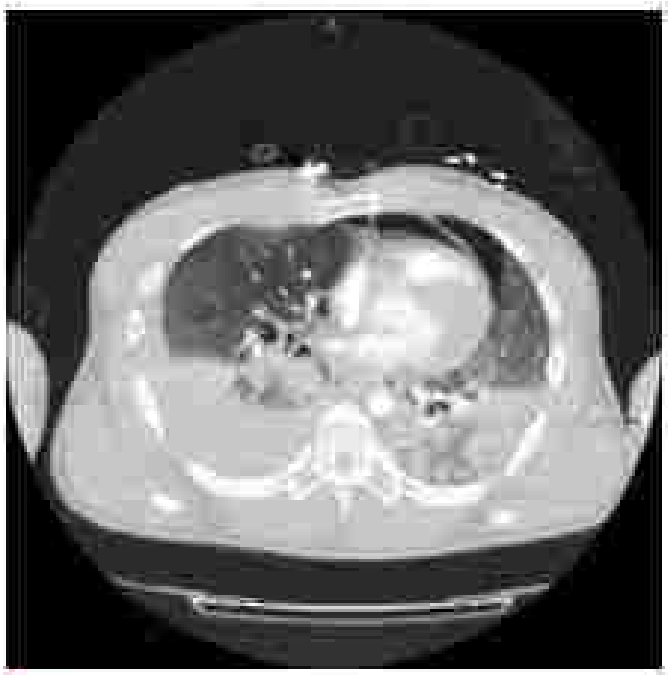

FIG. 2. Chest computed tomography scan in a patient with grade 3 blunt cardiac injury demonstrated a left pneumothorax, bilateral hemothorax and showed the pulmonary contusion.

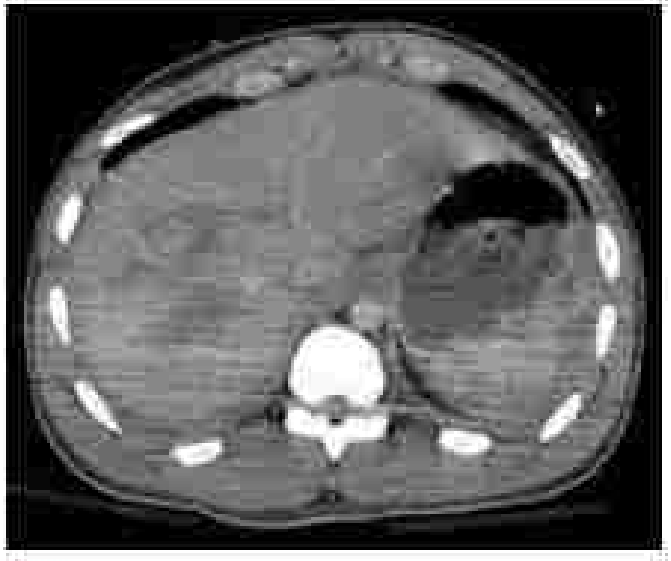

FIG. 3. Abdominal computed tomography scan in a patient with grade 3 blunt cardiac injury showed a grade 3 liver injury and a grade 2 splenic injury but no obvious reason for the patient's hypotension.

to 50%. Throughout day 1 and on to day 2, he had a fever (39.2°C), remained tachycardic (135 beats/min), and required continued resuscitation with crystalloid, packed red cells, and fresh frozen plasma. By day 2, his troponin had risen to 2.53 ng/mL, and his abdomen was full and difficult to evaluate.

Laparotomy at this time revealed 9 .0 mL of blood. He underwent gastrostomy tube placement, tracheostomy, and bronchial alveolar lavage, which returned a gram-positive cocci and gram-negative coccobacilli, for which he was appropriately treated. He progressed to severe respiratory distress (partial pressure of oxygen/fraction of

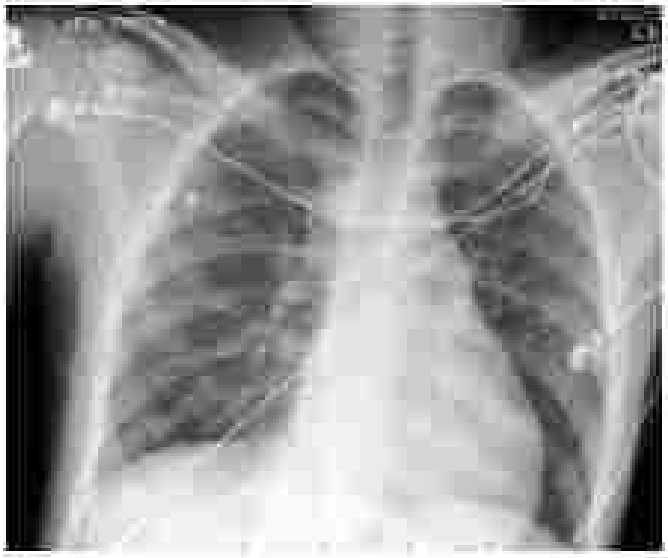

FIG. 4 Admission chest radiograph in a young man who developed a grade 4 blunt cardiac injury following a motor vehicle collision showed a globular heart.

required oxygen (100%) even though his troponins and liver enzymes normalized. He remained tachycardic for the next 10 days but, by day 14, his pH and blood gases normalized. Repeat transthoracic ECG (TTE) at this time showed normal left ventricular function with an ejection fraction of 60% to 65%; the right ventricular size and function were normal. He slowly improved, so that by day 30, his chest tubes, tracheostomy tube, and percutaneous endoscopic gastrostomy tube had been removed, and he was able to tolerate oral diet and he was transferred to the rehabilitation center. The long-term result was good. This example of grade III BCI, sometimes referred to as severe myocardial contusion, may produce prolonged tachycardia, ST segment changes, elevated troponin, and impaired cardiac function, but usually responds to supportive care while the associated injuries are treated.

Grade IV Injury

Grade IV BCI associated with septal rupture, valvular incompetence, or chamber rupture of the right ventricle, either atrium or the right atrial appendage often die at the scene; when arriving at the hospital alive, prompt diagnosis and therapy are needed. The diagnosis of valvular incompetence or papillary muscle dysfunction shows a reduced ejection fraction or dyskinesis. Likewise, patients with distal coronary artery occlusion will have evidence of cardiac ischemia and inotropic compromise, which can be documented by TTE. These patients tend to have myocardial support but usually do not require operative intervention unless there is chamber rupture. An example of a patient requiring operative intervention follows.

This young man was found outside his vehicle after an MVC. He was confused, drowsy, tachycardic (115 beats/min), and hypotensive (systolic blood pressure, 80 mm Hg). He was given Narcan with little immediate improvement in his drowsiness, but when he arrived in the emergency department, his pressure rose (140/100 mm Hg), but the tachycardia (120 beats/min) persisted. His GCS was 10. He moved all four extremities, thus ruling out spinal cord injury. His blood alcohol was 76 mg/dL, and he had a positive drug screen for benzodiazepine and cannabinoids. Chest radiograph demonstrated normal lungs, but a globular heart (Fig. 4). A CT of the chest showed pericardial effusion (Fig. 5), and CT of the abdomen showed hepatic inotropy with edema around the liver and gallbladder (Fig. 6). The troponin level on arrival was 0.052 ng/mL. Shortly after admission to the surgical intensive care unit, he became hypotensive (BP 60/40 mm Hg) and did not respond to a 1-L bolus. The arterial pH was 7.19. He was taken to the operating room for laparotomy and was found to have yellow, cloudy ascites with a very large, edematous, purple-looking liver of undetermined etiology. No specific treatment was done, and he returned to the intensive care unit, where a repeat troponin level was 1.56 ng/mL; the liver enzymes including bilirubin were normal. TTE demonstrated a large pericardial effusion, thus explaining his recurrent hypotension. A difficult transthoracic pericardial window was performed with return of a large amount of bloody exudate, which led to a sternotomy, pericardiotomy, and primary repair of a 4-mm hole in the right atrial appendage. Postoperatively, his troponin level was 3.97 ng/mL, but his vital signs stabilized, and the transient rise in his liver enzymes returned to normal. He had an uneventful recovery.

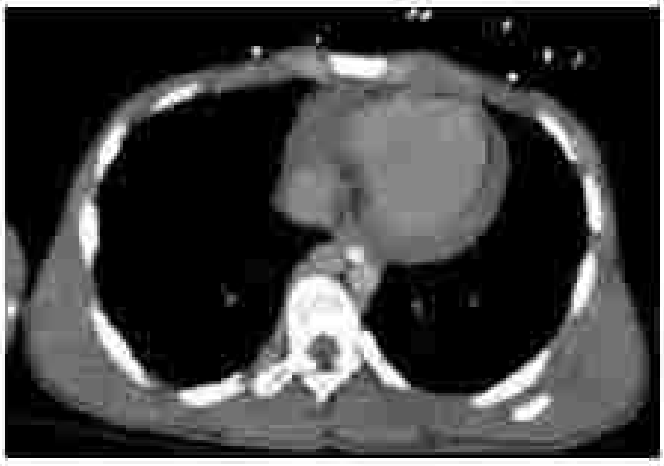

FIG. 5 Computed tomography scan of the chest in a young man with a grade 4 blunt cardiac injury demonstrated a pericardial effusion.

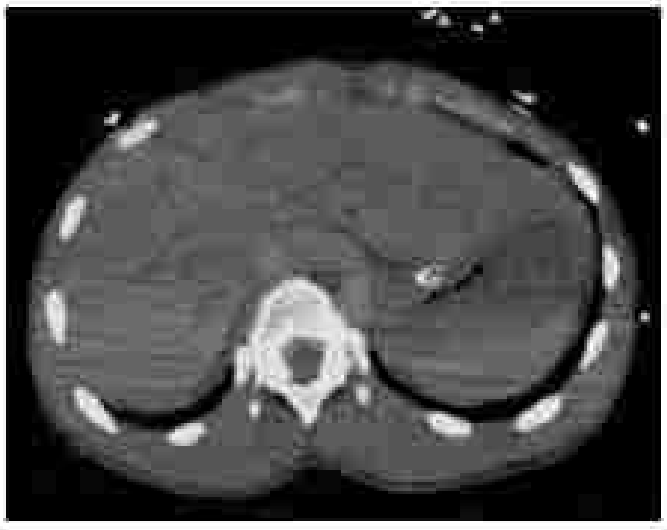

FIG. 6 Abdominal computed tomography in a patient with grade 4 blunt cardiac injury demonstrated significant hepatomegaly and edema around the liver.

The rarity of this type of BCI led to the delay in recognizing pericardial tamponade, which should have been detected on an initial FAST examination and confirmed on the CT scan. Definitive care should have included a transthoracic pericardiocentesis followed by

a prompt left anterior thoracotomy. The engorged purple liver in this patient was caused by impaired hepatic venous return because of the pericardial tamponade.

Grade V BCI

BCI associated with rupture of the left ventricle or more than one heart chamber is highly lethal. The vast majority of these patients (>80%) have been injured in motor vehicle collisions, hitting vehicles, motorcycle crashes, or pedestrian/vehicular mishaps; less common causes would include thoracic crush injury, falls from major heights, and other events that exert a great force on the chest. Chamber rupture is more likely to occur in the right atrium or ventricle (60%) followed by the left ventricle with few patients having rupture of more than one chamber. The lethality of this syndrome is reflected by the fact that most patients die at the scene or receive cardiopulmonary resuscitation at the scene only to be declared dead at the time of arrival in the emergency department. The force of the impact is so great that almost all such patients have major associated injuries and very high injury severity scores.

The typical scenario of BCI with chamber rupture was seen in a 21 year old restrained front seat passenger in a vehicle that struck a tree at 80 mph. She was unresponsive at the scene, was intubated, and had cardiopulmonary resuscitation during her 20 minute trip to the hospital. Upon arrival, she had pulseless electrical activity with no cardiac movement per ultrasound and was declared dead. Injuries identified at autopsy included fractures to the right humerus, left femur, 10 right ribs, six left ribs, in addition to atlanto occipital separation, bilateral pulmonary contusions, and rupture of the right hemidiaphragm, liver, and spleen. She had a 6.3 cm laceration of the apical portion of the right ventricle and numerous lacerations of the right atrium with bilateral hemothorax. This patient's mechanism of injury, attempted resuscitation by emergency medical services, and subsequent death are typical for patients with ventricular rupture, or rupture of more than one chamber.

COMMOTIO CORDIS

Commotio cordis is sudden death from cardiac arrest associated with no anatomic structural damage to the heart identified at autopsy. This condition occurs in young people typically after a blunt blow to the chest inflicted during competitive sporting activity. Direct impacts from a baseball or hockey puck have caused this sudden death. These patients have no underlying congenital cardiac disease, cardiomyopathy, or other preexisting abnormalities. This condition appears to be caused by the impact transmitted to the heart inducing ventricular fibrillation during a phase of ventricular excitability such as cardiac repolarization. This untoward event is most often refractory to cardiopulmonary resuscitation and defibrillation. These patients present to the hospital in cardiac arrest and the FAST examination will show no cardiac activity and no pericardial fluid.

LONG-TERM FUNCTION AFTER BCI

There have been few studies that have evaluated the long-term effects of BCI. The studies that have been done show that most of these patients do well and require no further treatment.

ALGORITHM FOR DIAGNOSIS AND MANAGEMENT OF BCI

Any patient who presents with blunt thoracic trauma should be suspected of having BCI despite its rarity (Fig. 7). The patient who presents without vital signs should have a FAST examination done to determine if there is cardiac activity. In the absence of cardiac activity nothing further should be done and the patient should be pronounced dead. The patient who presents unresponsive after blunt thoracic trauma should have a FAST examination done as part of the secondary survey. If the heart is beating and there is no pericardial fluid, the patient should have an ECG and troponin measurements. If both ECG and troponin are normal, no further tests or monitoring for BCI is indicated. However, if the ECG, and/or troponin is abnormal with findings such as tachycardia, arrhythmia, and/or ST elevation, the patient should be admitted to the intensive care unit and the ECG and troponin levels repeated in 6 hours. An echocardiogram should be done within that first 24 hours. These patients will usually remain stable and will have correction of their abnormal ECG and troponins within the first 24 to 48 hours. If the echocardiogram is abnormal, it should be repeated in 48 to 72 hours. Treatment of the BCI in this setting is supportive. The tachycardia is best treated with a β-blocker and any pulmonary injury is treated with ventilatory support.

The patient who presents with blunt thoracic trauma and is hypotensive presents a real challenge. The initial examination and chest radiograph should exclude spinal cord injury, a tension pneumothorax, or other sites of hemorrhage including the chest or fractures. The FAST examination is most helpful in determining whether there is fluid in the pericardial sac. If there is pericardial fluid and the patient is stable, a CT of the chest is recommended to determine whether the fluid resembles a serous pericardial effusion from an underlying medical condition or blood. Some patients may have a comorbid condition leading to pericardial fluid which is typically serous as occurs in renal failure. If the pericardial fluid has the appearance of blood, and the patient is stable, immediate operation is indicated. If the patient is unstable and has pericardial fluid, the patient should have pericardiocentesis on the way to the operating room. Recommended operation is a left anterolateral thoracotomy, which provides rapid access for pericardiotomy and repair of most BCI. We do not recommend a transabdominal pericardial window that, in the presence of BCI, leads to rather sudden blood loss and does not facilitate expedient repair. We recommend either a definitive median sternotomy or a left thoracotomy. The pericardium is then opened parallel to the phrenic nerve. The blood is evacuated and the heart examined for injury. Most of these patients will have a small injury involving the atrium or the atrial appendage. A simple primary repair including clamping of the atrial appendage followed by ligation, and control of the bleeding. Repair of the atrium and/or the ventricle can be done with a 3-0 silk suture on a noncutting needle. Bleeding is controlled with digital pressure while the sutures are being placed. Some surgeons prefer pledgeted sutures. The main objective is to control bleeding. If a left thoracotomy is done which limits access to the heart, the incision could be carried across the sternum into the right chest as a clamshell thoracotomy. Occasionally, there may be bleeding from the pericardial sac itself so that there is blood in the pericardial sac but no rupture of the heart. The pericardium should be approximated leaving the anterior part of the pericardial sac open for about 3 to 4 cm to permit egress of any postoperative pericardial blood. Successful therapy of BCI requires definitive management of the other injuries including the pulmonary injuries which are usually severe.

Injuries to the coronary vessels are very unusual and include coronary artery contusion or rupture. Rupture of a valve or papillary muscle may also occur. These injuries would probably be detected on an echocardiogram and would require cardiopulmonary bypass for repair. Cardiopulmonary bypass should be available for repair of any chamber ruptures but has not been found to be useful for cardiac support alone.

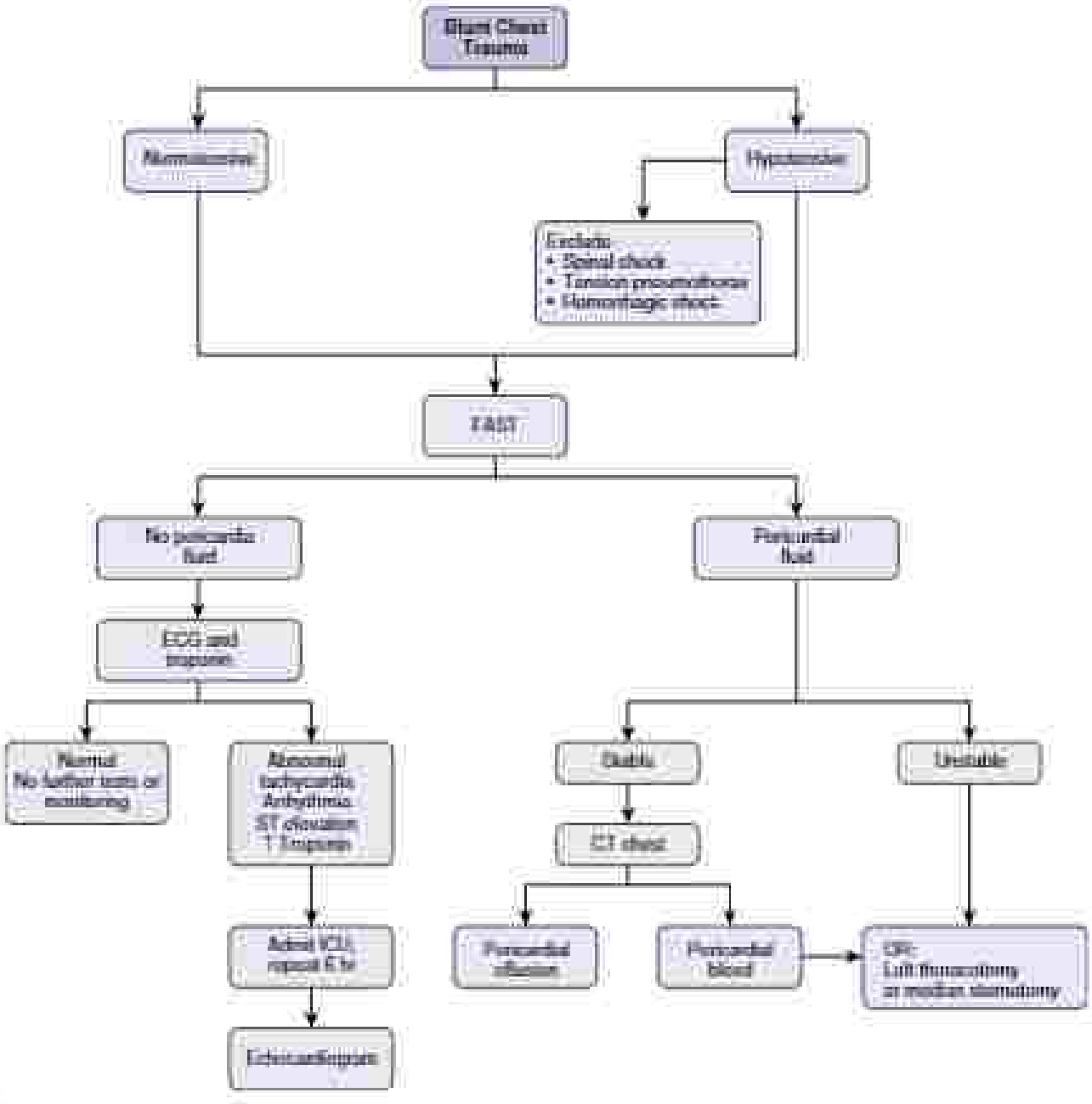

FIG. 1. Algorithm for diagnosis and management of blunt cardiac injury. CT, Computed tomography; ECG, electrocardiogram; ICU, intensive care unit; OR, operating room.

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Abdominal Compartment Syndrome and Management of the Open Abdomen

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Abdominal compartment syndrome (ACS) is the end stage of a progression from a mild increase in intraabdominal pressure (IAP) to the development of intraabdominal hypertension (IAH). Once IAH occurs, there are negative effects on multiple organ systems. Intraabdominal hypertension occurs when the accumulation of bowel wall edema, retroperitoneal swelling from blood or edema, intraluminal gas, or a combination of these factors outstrips the compliance of the abdominal wall and diaphragm. Primary IAH occurs as a result of an intraabdominal injury or process. The classic presentation of primary IAH and subsequent ACS is a patient with an intraabdominal injury that results in hemorrhagic shock and large volume resuscitation with blood and crystalloid. The abdomen is closed at the index operation and the patient develops IAH and then ACS. Intraabdominal injury is not the only reason IAH and ACS occur. Primary IAH has been described in patients with gastrointestinal bleeding, liver transplantation, superior mesenteric vein thrombosis, pelvic fractures, and ruptured abdominal aortic aneurysm to name a few.

Secondary IAH occurs as a result of the need for a massive resuscitation from a cause other than a primary intraperitoneal injury or process. This form of IAH is a consequence of capillary leak leading to the accumulation of fluid in the bowel wall and retroperitoneum. The mechanisms behind the development of capillary leak are multifactorial, but the commonality is a systemic inflammatory response. Septic shock, burn wounds, and large volume soft tissue injury can all result in the need for high paced resuscitation with crystalloid, putting patients at risk for secondary IAH and ACS.

DIAGNOSIS

Clinically, ACS is diagnosed in the intensive care unit (ICU) in a patient who has required massive resuscitation and who develops worsening renal function, increased peak airway pressures (PAWPs) on the ventilator, worsening abdominal distention, and persistent hypotension. These signs occur in the end stage after the patient is suffering from the full effects of ACS. These particular signs occur as a result of the complex pathophysiology of IAH. Increased IAP causes decreased venous return resulting from compression of the intraabdominal portion of the vena cava. Cardiac output subsequently drops because of lower preload pressures. Additionally, the increased pressure in the abdomen causes collapse of the microvasculature supplying the intestines and abdominal organs leading to ischemia. Initially, blood pressure is maintained by increasing systemic vascular resistance until vasoconstriction can no longer keep pace with the reduction in preload. Renal function is impaired from the lower systemic blood pressure. Renal function is further compromised by direct pressure and compression of the kidneys because of their intraabdominal location. Increased intrathoracic pressure occurs from limitation on the excursion of diaphragm. As a consequence, pulmonary compliance is reduced and PAWP begins to rise. Intraabdominal hypertension can have effects on organs distant from the abdomen as well. Intracranial pressure is thought to increase in patients with a combination of a head injury and IAH to the point that decompressive laparotomy might be considered to reduce dangerously high intracranial pressures.

Recognition of rising IAH and impending ACS is important to prevent these potentially harmful complications from occurring. Risk factors for the development of IAH on arrival to the intensive care unit include a history of transfusion of more than 10 units of packed red blood cells, infusion of more than 7500 mL of crystalloid, the presence of a coagulopathy, or a pH of less than 7.2. In patients at risk for IAH, the physical examination is often unreliable to detect IAH; therefore, frequent monitoring of IAP is required. The World Society of Abdominal Compartment Syndrome developed guidelines for the diagnosis, management, and classification of IAH. Intraabdominal pressure should be measured using a trans-bladder approach with the patient in the supine position and at end expiration. Every effort should be made to ensure that the abdominal muscles are not contracting at the time of the IAP measurement, including the administration of short-acting neuromuscular blocking agents, if necessary. Manometry or continuous measurement can be used to determine IAP after instilling 25 mL of sterile saline through a catheter to the bladder. The World Society of Abdominal Compartment Syndrome defines normal IAP as 5 to 7 mm Hg in critically ill adults and IAH begins at 10 mm Hg. Intraabdominal hypertension is graded from I to IV (Table 1). It is important to be aware that continuous bedside monitors in use in the ICU often measure pressures in cm H_2O instead of mm Hg. The corresponding cm H_2O are also given in Table 1. Abdominal compartment syndrome is defined as a sustained IAP of greater than 20 mm Hg that is associated with new organ dysfunction or failure.

THERAPY

Management of Intraabdominal Hypertension

Once IAP begins to climb in a patient at risk for the development of ACS, it is important to aggressively treat IAH. In patients with grade I and grade II IAH, medical management strategies are used as primary treatment modalities. Treatments for IAH are aimed at improving abdominal wall compliance, reducing intraluminal volume, removing intraabdominal fluid, maintaining sedation, and supporting at-risk organs, including the pulmonary system. These strategies are used in a multimodal manner to maximize reductions in IAP. Once IAH is identified and treatments started, IAP should be measured at least every 4 hours to determine the effectiveness of the treatments used to reduce IAP.

To improve abdominal wall compliance, it is important to ensure adequate sedation and analgesia. Although easy to overlook, removal or loosening of abdominal dressings or release of abdominal eschars in the setting of a burn can also help to increase abdominal wall compliance. The reverse Trendelenburg position can be helpful if the patient can tolerate a change in position. If these maneuvers do not result in adequate reduction of IAH, consider the use of neuromuscular blockade as a last resort.

There is sufficient evidence to suggest that after the IAP reaches 15 mm Hg that there is a logarithmic rise in IAP. Thus, small changes in intraabdominal volume may have profound effects on IAP once above this threshold. Placing a nasogastric or nasoenteric tube and use of a rectal tube can reduce intraluminal pressure and subsequently IAP. The use of prokinetic agents can also help to reduce IAP. Minimizing enteral nutrition, colonoscopy, decompression, and enema administration to evacuate a large stool burden can be considered in cases where there is persistent IAH. Reducing space occupying lesions in the abdominal cavity may also be an option. This is particularly helpful if the patient has ascites that can be easily identified with ultrasound and drained at the bedside.

The use of a balanced resuscitation strategy in patients with hemorrhagic shock with a near 1:1 plasma to packed red blood cell ratio is associated with fewer episodes of IAH and ACS. Once the initial resuscitation is complete, maintaining euvolemia with goal directed fluid resuscitation strategies are important in the setting of IAH. In

TABLE 1 Grade of Intraabdominal Hypertension and Corresponding Pressure Measurements

Grade	Bladder Pressure	
	mm Hg	cm H_2O
I	10–15	13–20
II	16–25	21–35
III	26–35	36–47
IV	>35	>48

the critically ill patient, it is easy to allow fluids to begin to accumulate at a rapid rate because of the need for drips for sedation and blood pressure maintenance, antibiotics, and maintenance fluids. Once the initial resuscitation is complete, which is usually after the first 48 hours, one should attempt to achieve a zero fluid balance. If the patient's situation allows, diuresis and negative fluid balance should be continued. In severe cases, hemodialysis or ultrafiltration should be considered to achieve zero balance. Another way to reduce IAP is to reduce intrathoracic pressure. Use of lower than normal tidal volumes and the use of ventilator strategies that allow for lower mean airway pressures can also lead to reductions in IAP.

Intervention for ACS

Once a patient has sustained IAP of greater than 20 mm Hg and evidence of at least one organ system dysfunction or failure, then abdominal decompression is the treatment of choice. Decompression is achieved via a generous midline laparotomy from the xiphoid to the pubis. A large incision allows for the abdominal viscera to extrude from the abdominal cavity and for any intraabdominal fluid to escape. If the ACS is severe or has been prolonged, there is a chance that the patient will suffer from the effects of rapid reperfusion and washout of accumulated lactic acid and potassium. To reduce the chance of catastrophic cardiac collapse, we protect patients with bicarbonate prior to or at the time of abdominal decompression. Subcostal and paramedian incisions should be avoided because they do not allow for adequate decompression of the abdominal cavity and these incisions are much more difficult to manage in the open abdomen stage.

Initial Management of the Open Abdomen with Temporary Closure

The ideal temporary closure technique should protect the intraabdominal viscera, allow egress of intraabdominal fluid, minimize damage to the abdominal wall tissues, be easy to apply, and be loose enough to prevent ACS from developing again. Techniques that are now mostly of historical interest do not meet all of these criteria. The Bogota bag, first described by surgeons in Colombia, repurposes a 3 L urologic irrigation bag or an x-ray contrast cover. The bag or cover is cut to size and sutured to the patient's skin with a running heavy nylon stitch. Closed suction drains are placed around the open abdominal wound and an adhesive dressing can be placed over the drains and the bag to control fluid egress from the abdominal cavity. Although effective, this technique damages the skin, takes time to complete, and risks injury to the bowel while suturing the bag in place. Perforating towel clips can be placed approximately 2 cm apart to bring the skin of the abdominal wall together. The main disadvantages of this technique are that the towel clips can damage the skin and that the towel clips are radiopaque, which can complicate subsequent radiographic studies of the abdomen. Another disadvantage is that the closure is sometimes too tight and IAH can redevelop. One scenario to which a higher pressure might be helpful, however, is when the liver is packed in the upper abdomen. Towel clip closure of the upper one third of the abdomen may help with achieving tamponade of packed liver injuries.

FIG. 1 Open abdomen managed with Barker Vac Pac dressing.

In the modern era, there are two widely used strategies that meet the ideal temporary abdominal closure criteria. In 2000, Barker and colleagues published the results of their vacuum pack technique of temporary abdominal closure. In the originally described technique, a 10–10 polyethylene sheet is perforated with scissors or a scalpel. The sheet is placed under the abdominal fascia. A moist surgical towel is placed under the fascia but above the polyethylene sheet. Two No. 10 flat Jackson Pratt drains are placed on the bowel and connected to wall suction via a T-connector. Alternatively, two nasogastric tubes can be used for the same purpose. The entire wound is then covered with a plastic polyester adhesive drape, also known as an Ioban drape. The suction must be on and the skin should be as dry as possible before placing the Ioban. The use of benzoin can aid in the adherence of the Ioban to the skin. A modification of this technique is to avoid use of the surgical towel and to ensure that the holes in the polyethylene drape are not large enough to allow the Ioban to stick to the underlying bowel. Using a scalpel to perforate the 10–10 drape is the best way to ensure the holes are small enough to protect the underlying bowel (Fig. 1). More recently, commercially available products have been developed that are similar to the Barker vacuum pack technique; these products can also be effective at temporary abdominal closure. Commercially available negative pressure wound therapy systems are rapid to apply and aid in the removal and quantification of fluid from the peritoneal cavity.

Management of the Patient with an Open Abdomen in the ICU

Patients who develop abdominal compartment syndrome are often in extremis from overwhelming trauma or shock and require ongoing aggressive resuscitation. However, after the initial resuscitation phase has passed, attention should rapidly be turned to other management priorities such as administration of nutrition, antimicrobial management, and ventilator weaning strategies.

Nutrition

Patients with an open abdomen will require repeated operations for a second look, washout, and attempts at definitive closure. With every surgery, the question should be asked, "Is it appropriate to feed this patient enterally? If so, through what access?" Contraindications to early enteral nutrition (EN) include bowel discontinuity, ongoing massive resuscitation, and high dose vasopressor requirements. Consideration should be given to placing temporary feeding access, such

as a small bore nasogastric, or more preferably, a nasojejunal feeding tube while in the operating room because direct palpation of the tube passing through the stomach and into the small bowel ensures accurate placement and mitigates the need for this procedure to be done blindly in the ICU setting. Once access has been established, tube feedings can safely be started if the patient no longer requires massive blood product transfusion or large volumes of fluid, bearing in mind that tube feeding formulations are not appropriate to be used for resuscitation. Although it may cause some apprehension on behalf of the surgeon, early EN in patients with open abdomens has not only been demonstrated to be safe, but also to provide significant benefit for the patient. A recent multiinstitutional trial sponsored by the Western Trauma Association determined that early EN is associated with earlier fascial closure, decreased complications, and decreased mortality. The choice of enteral tube feeding formula should be discussed with the dietitian, taking into consideration the volume of the feedings, the patients' existing medical conditions (such as renal or hepatic failure), and protein needs. Patients with an open abdomen have large insensible volume losses and an increased protein sink while serous fluid is being sequestered from the peritoneal cavity. As such, patients with an open abdomen routinely require 2 to 2.5 g/kg per day of protein to meet nutritional goals. Recent data from our institution in a retrospective review of 217 critically injured trauma patients revealed that those who meet their protein goals within 4 days of admission have fewer complications, such as infections and delayed wound healing, than patients who do not achieve protein goals, further emphasizing the benefit of early protein rich nutrition.

At the definitive operation for either primary fascial closure or definitive closure with a mesh product, consideration should be given to placement of durable enteral access such as a gastric tube or jejunal tube. These translocal feeding tubes should not be placed before the definitive operation because their ultimate abdominal wall location will migrate with gradual reduction of bowel edema and reclamation of abdominal domain when initial resuscitation is over.

Medications

Patients managed with an open abdomen require no specific antibiotic prophylaxis. Routine perioperative antibiotic dosing per institutional guidelines is sufficient. The routine use of chemical deep vein thrombosis prophylaxis is encouraged if not otherwise contraindicated by ongoing bleeding or injuries such as intracranial hemorrhage. Standard protocols for gastrointestinal bleeding prophylaxis are appropriate but no additional gastrointestinal medications are indicated in the patient with an open abdomen.

Fluid Management

Strict measurement of all fluid intake and output is essential in the management of patients with an open abdomen. Large volume serosanguinous drainage from the abdomen must be measured. The fluid balance should be monitored daily and day over day accumulated balance should be calculated. Patients can rapidly fall behind in their fluid balance, with large volume losses from the peritoneum and other sources such as nasogastric tube, ileostomy, urine output (especially diabetic insipidus in a head injured patient), or chest tube drainage. Occasionally, replacement of large volume losses to a 1:1 or 1.5:1 mixture with crystalloid will be required to maintain euvolemia. Judicious use of fluids during the resuscitation phase may help minimize massive bowel edema and promote efforts toward fascial closure. Ultimately, the goal is for the patient to maintain euvolemia and evidence of adequate end organ function.

Additional methods used to support adequate perfusion of the intestine may also be used. One such technique is direct peritoneal resuscitation as described by Weaver and Smith. This technique involves the instillation of hypotonic fluid into the abdomen while ongoing intravenous resuscitation is occurring, which promotes dilution of the electrolytes supplying the bowel and reducing ischemia. Animal studies using this technique are promising and reveal improvements in bowel edema, increased organ blood flow, and a reduction in inflammatory serum markers. Direct peritoneal resuscitation used in the clinical setting has shown encouraging results in terms of earlier fascial closure and a reduction in abdominal complications.

Ventilator Management

It is not mandatory that patients with an open abdomen remain ventilated. Patients who otherwise meet criteria for extubation and have a contained, well dressed abdominal covering, such as a commercial negative pressure vacuum device, can safely be extubated between abdominal washout procedures. It is, however, important to consider each patient's individual risk factors for complications if extubated and no longer sedated. Combative or head injured patients may not be able to comply with dressing changes or may increase their abdominal pressure to the point of disrupting the abdominal dressing with coughing or pulling at tubing connected to a vacuum device. Ventilated patients have the benefit of continuous monitoring of PAWP as a signal of the degree of intraabdominal pressure. During sequential tightening of temporary closure devices, as described in the following section, PAWP can provide guidance as to the tolerance of advancements toward closure. Rapid and large increases in PAWP during attempts at closure are indicative of a high risk for ACS and ultimate failure of the closure.

Wound Care

Regardless of the choice of technique chosen to manage the open abdomen, general wound care principles apply. The wound is not considered sterile and once the bowel is covered with mesh or a sponge and direct access to the peritoneum is eliminated, dressing changes do not need to take place in the operating room or under strict sterile conditions. Routine barrier precautions are all that is required of the personnel caring for the patient.

Closure of the Open Abdomen

Definitive fascial closure is the goal for any patient with an open abdomen to avoid early and late complications. For patients who rapidly resolve the injury or derangement necessitating an open abdomen and are able to tolerate primary fascial closure at a subsequent operation, we recommend a tension free closure of the fascia and forgoing staged skin closure to mitigate the risk of infection. The open skin can be treated with wet to dry dressings in the traditional manner or a commercial vacuum closure device can be placed. In many patients, however, this straightforward closure is not possible. The presence of multiple descriptions of techniques to achieve definitive fascial closure in the literature indicates that this goal may remain elusive in some patients. However, several important concepts in the management of patients with an open abdomen that may help to improve rates of definitive fascial closure include: (1) controlling the underlying physiology and aggressively managing fluid balance; (2) preventing the adherence of the abdominal viscera to the abdominal wall; (3) preventing the loss of abdominal domain by using dynamic tension on the abdominal wall; and (4) attempting to cycle the fascia at regular intervals and at least every 48 hours.

We have experience with two techniques for closure of the abdomen that adhere to these stated principles. The group at Denver General Hospital described a technique in which white sponges are placed on the bowel and mated under the fascia. If more than one white sponge is required, the sponges are cut to fit and stapled together. Once the white sponges are in place, single interrupted heavy nonabsorbable sutures are placed approximately 5 cm apart to pull continuous traction on the fascia and to prevent the fascia from laterally retracting. A black VAC sponge is placed on top and the wound is covered with adhesive dressing and vacuum applied. The

patient returns to the operating room at least every 48 hours. If the abdomen can be closed, then the fascia is closed with a running heavy monofilament absorbable suture. If the fascia cannot be completely closed, interrupted figure of 8 fascial sutures are placed inferiorly and superiorly in a sequential fashion until fiery tension precludes the placement of further interrupted sutures. The white sponges are replaced and the interrupted fascial bridging sutures are replaced and tightened. The rest of the dressing is replaced as previously described.

Two potential disadvantages to using the technique described are that the fascia is violated by repeated suture placement and there is the potential that the bridging fascial sutures will put pressure on the underlying bowel, even though there is a white sponge between the bridging sutures and the bowel. Miller and colleagues at Wake Forest described a technique that avoids these two potential disadvantages. In this technique, a perforated 10–18 polyethylene drape is placed over the abdominal viscera but below the fascia, preferably to the parietal gutters on both sides. Next, the black sponge is placed over the top of the covered abdominal contents. A heavy nylon suture is used to approximate the skin to the sponge. The suture is placed using full thickness bites of skin from inside out on both sides and in a running fashion taking 3- to 4 cm bites along the length of the wound. This helps to preserve abdominal domain and to limit additional injury to the fascia.

Other techniques to achieve fascial closure that have been described include the use of commercially available Velcro closure devices that can be used to close the abdomen by serially tightening the Velcro closure until the fascia is reapproximated. Another option is to perform an early definitive repair using a component separation technique or by bridging a fascial defect with a biosynthetic mesh. The use of prosthetic mesh in the acute setting is not recommended due to the high risk for infection. Enthusiasm for early definitive repair, although potentially appealing, should be tempered by the fact that many patients with an open abdomen remain catabolic and in a poor nutritional state. Thus, these patients are at significant risk of wound healing issues and dehiscence. If the patient's metabolic state is not conducive to early definitive repair, other techniques should be used to manage the abdominal wound until such time that the patient is metabolically optimized for a definitive repair.

There is no definitive time frame in which attempts at fascial closure become futile. There are reports of successful closure out to more than 40 days. However, if fascial closure is not achieved within 2 weeks, it is unlikely that definitive closure will be possible and other techniques for wound coverage should be considered. It is our practice that once the decision is made that further attempts at fascial closure are futile, a piece of polyglycolic acid (Vicryl) mesh is placed over the abdominal contents and sutured to the fascial edge if possible or the skin edge if the fascial edge is not able to be safely used. The wound is allowed to granulate and then a split thickness skin graft (STSG) is placed. The polyglycolic mesh does not need to be removed to place the STSG as long as there is adequate granulation tissue. It is important to cover the granulation tissue as soon as practical. The large abdominal wound acts as a metabolic sink and prevents the patient from converting from a catabolic state to an anabolic one. The longer the abdominal viscera remain uncovered, the higher the likelihood of formation of an entero-atmospheric fistula. Once the bowel is covered with an STSG, a white sponge can be placed over the graft and then covered by a black sponge and an adhesive dressing and suction can be applied. We leave this dressing in place for 5 days and then remove it to examine the underlying STSG. If the STSG has taken, we use Xeroform or petroleum jelly gauze to cover the graft and then change the dressing every 48 hours until it is healed (Fig. 2).

The patient can then return in 6 to 12 months for definitive repair. Typically, it takes 6 months for the STSG to separate from the underlying abdominal viscera. We have found that waiting much past 9 months does not usually result in further loosening of the STSG and there can be an additional loss of abdominal domain with added waiting time. For definitive repair, we use the Memphis modification of the standard 'component' separation technique described by Ramirez. Using standard components separation, it is possible to obtain approximately 5 cm of length for fascial closure on each side. The Memphis modification allows for up to 10 cm of length on both sides if the fascia is fully intact. The steps of the operation are outlined in Table 2.

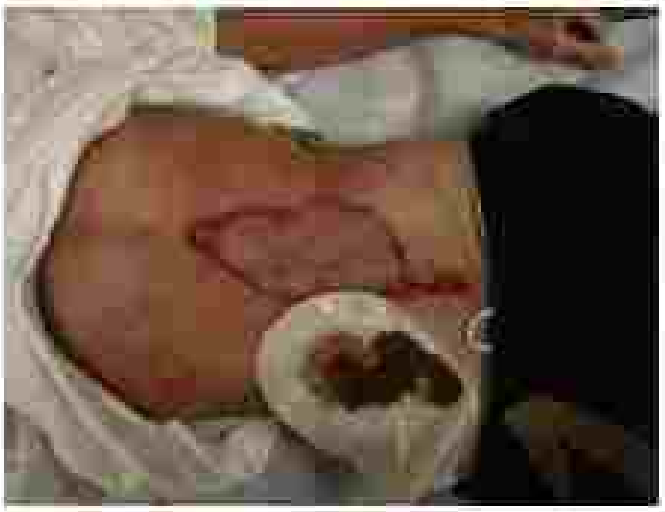

FIG. 2. Partial fascial closure with granulating wound managed with split thickness skin graft. Note the lateral placement of an ostomy in the left lower quadrant to facilitate dressing changes and delayed fascial closure.

There are two factors that may influence preoperative decision making at the time of definitive repair. The presence of an ostomy complicates the acute and delayed management of an open abdomen. Placing the ostomy in a more lateral position and outside of the rectus sheath, while increasing the potential for a parastomal hernia, preserves the tissue planes needed for definitive repair. Another factor to consider is the amount of skin available for coverage once the fascia is approximated. For large defects or in cases where there has been loss of skin resulting from the original injury, it may be necessary to place tissue expanders in the weeks before definitive repair to have adequate skin for closure (Fig. 3).

Complications

The most feared complication from an open abdomen is an entero-atmospheric fistula. The American Association for the Surgery of Trauma Open Abdomen Study Group published the results from their accumulated experience with entero-atmospheric fistula formation in the setting of an open abdomen. They found that cryocolloid administration of more than 5 L in the first 24 hours, the number of reoperations, and the presence of a bowel anastomosis were all associated with entero-atmospheric fistula formation. Interestingly, the type of temporary closure that was used was not related to fistula formation. Once a fistula forms, it can be devastating for the patient, so prevention is paramount. Early definitive closure, using the measures to protect the underlying bowel, meticulous wound care and limiting reoperations can all help to reduce the risk of fistula formation. If a fistula does occur, it is unlikely that the fistula will close on its own, and operative repair will be needed; however, it is often not possible to operatively repair the fistula in the acute setting. It is important to determine the location of the fistula if possible. More distal fistulas are easier to manage and may allow enteral nutrition to continue and avoid the need for total parenteral nutrition for prolonged periods. One of the most difficult issues when confronted with a fistula in the setting of an open abdomen is controlling the output from the fistula. There is no perfect strategy and creativity is paramount. If possible, performing an STSG as early as practical can aid in the ability to manage the fistula. If the output from the fistula can be temporarily reduced or controlled by suturing the fistula closed, placing a Malecot tube, or by some other means, it is possible to place

TABLE 2 Delayed Repair of the Abdominal Wall Using the Memphis Modification of the Components Separation Technique

Step	Description
1. Remove split-thickness skin graft	It is easiest to start the operation over the liver in the right upper quadrant. Once access to the peritoneal cavity is gained, the STSG can be removed from the underlying bowel.
2. Raise full-thickness skin flaps on either side of the defect	The correct anatomic plane is avascular and just above the abdominal wall fascia. Flaps should be raised to just beyond the insertion of the external oblique fascia into the lateral rectus sheath.
3. Release of the external oblique component of the anterior rectus fascia	The release is started by incising the anterior fascia approximately 3 cm lateral to the rectus. The release extends from the costal margin to the pubic symphysis. The serratus anterior can be divided to obtain more length at the midline.
4. Dissection of the posterior sheath	After incising the medial portion of the rectus sheath the posterior sheath is dissected free from the rectus muscle.
5. Release of the internal oblique component of the anterior fascia	After identifying the lateral border of the rectus muscle by placing the hand under the muscle but above the posterior rectus sheath, the anterior fascia is incised and the internal oblique is the medial from the arcuate line superiorly to the costal margin. Be careful to preserve the integrity of the posterior rectus sheath.
6. Translocation of anterior fascia and muscle	At this point, the medial border of the posterior rectus sheath can be sutured to the lateral border of the anterior fascia using interrupted figure-of-8 nonresorbable heavy absorbable suture.
7. Close the midline	The midline is closed with a running heavy nonresorbable absorbable suture. If there is tension in the midline, it is preferable to place a bridging piece of biologic mesh.

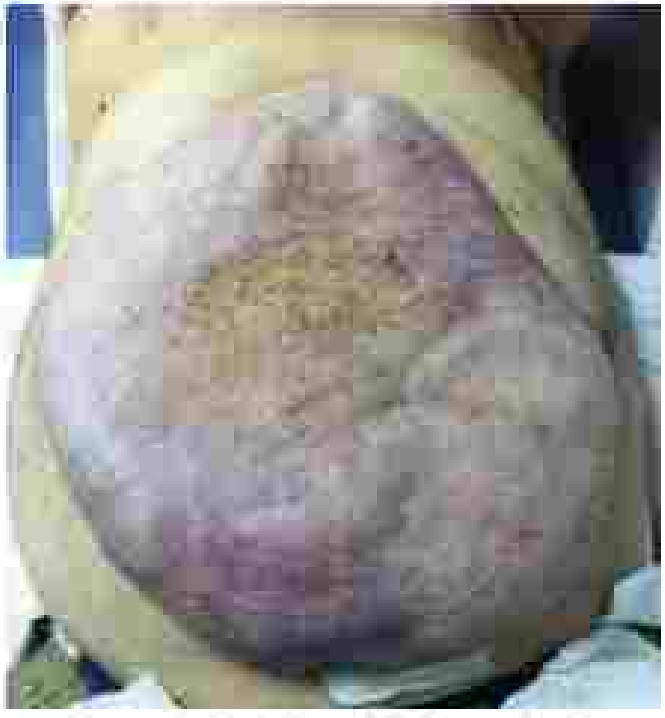

FIG. 3 In cases with a large abdominal wall defect, consider placement of tissue expanders before definitive fascial closure to ensure there is adequate skin to cover the repair.

an STSG in this setting. By stopping or controlling output for 5 to 10 days, it may be possible to get enough of an STSG to take that placement of an ostomy appliance becomes much simpler. If an STSG does not take or if it is not possible to place one, then using a combination of white sponges, black sponges, adhesive dressings, negative pressure therapy, and an ostomy appliance may make it possible to control fistula output. However, the dressing must be changed every 48 hours to prevent wound-related complications.

SUMMARY

Early detection and treatment of rising IAP using multimodal treatment strategies may help to prevent ACS and the need for a decompressive laparotomy and subsequent open abdomen. If an open abdomen is required, meticulous attention to detail is needed at every stage in management. Although knowledge of several management options is helpful in achieving fascial approximation, it is more important to become proficient with one or two strategies and to learn the benefits and pitfalls associated with these strategies. Ultimately, one must develop an algorithm for the management of these complicated patients to have the best outcome possible.

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Coagulation Issues and the Trauma Patient

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Even with dramatic advances over the last 2 decades, trauma continues to be the leading cause of death in individuals aged 0 to 44 years. Although traumatic brain injury persists as a leading cause of death from injury, hemorrhage is still considered to be responsible for more than 40% of trauma deaths and the number one *potentially* stable cause. The purpose of this chapter is to review the current understanding of hemorrhage owing to trauma and identify evidence-based therapies for treating the hemorrhaging trauma patient.

NORMAL COAGULATION

Hemostasis is a complex process designed to limit bleeding and hemorrhage following injury. Although the main physiologic parts of the cascade (local vasoconstriction, platelet plug formation, fibrin deposition, and fibrinolysis) occur in a sequential manner, there is extensive redundancy with the system (Fig. 1). Without vascular injury or trauma to the system, blood remains in a steady state system in which its purpose is to deliver oxygen to and remove carbon dioxide from tissues. Once normal coagulation is exposed to trauma and endothelial injury, the coagulation system begins the process of cessation of hemorrhage.

Hemostasis starts with constriction of injured vessels and is most pronounced in those with smooth muscle within their media layer. The release of arachidonic acid leads to thromboxane A2 (a potent constrictor of smooth muscle). The subsequent release of serotonin and endothelin from injured vessels and platelets results in further vasoconstriction and platelet aggregation. Platelet aggregation leads to formation of a hemostatic plug and the generation of thrombin. Platelet degranulation follows with a release of adenosine diphosphate, calcium, thromboxane, and other substances, and formation of fibrinogen (cleaved into fibrin strands) that helps to serve as a bridge for platelets and the injured endothelium (via glycoprotein receptors IIb/IIIa). Initiation of coagulation occurs from exposure of tissue factor following endothelial injury. Clot propagation begins with tissue factor binding to an activated factor VII, and following through a sequence of enzymatic reactions, resulting in activation of factor X. Thrombin is then formed, converting fibrinogen to fibrin, with the redundancy of the system resulting in further activation of factors V, VII, VIII, XI, and XIII.

Balance in the hemostatic system is maintained by the actions of endogenous anticoagulants (such as antithrombin, protein C, and protein S), whose role is to downregulate fibrin formation and thrombin generation. This balance is also maintained by the actions of prostacyclin and nitric oxide that function to inhibit platelet aggregation. Finally, the fibrinolytic system works to breakdown clot that is made after injury. In the uninjured patient, the coagulation system works in a delicate balance to maintain homeostasis; major trauma, however, throws this balance off. Trauma-induced coagulopathy (TIC) is the byproduct of severe tissue injury, hypoperfusion, and the profound inflammatory and hemostatic processes that can lead to death if not addressed in a timely fashion.

TRAUMA-INDUCED COAGULOPATHY

TIC is an overall failure of the coagulation system to maintain adequate hemostasis after major trauma and hemorrhage as a result of endothelial level injury, shock, and poor resuscitation support. TIC progresses rapidly in response to tissue injury and hemorrhagic shock resulting in hypocoagulation and hyperfibrinolysis. This process will continue unabated and will be exacerbated by ongoing bleeding, hemodilution, acidemia, and hypothermia. Brohi and colleagues have elucidated some of the mechanisms behind TIC, demonstrating that endothelial injury (mediated through shock and hypoperfusion), along with anatomic injury (mediated through actual tissue trauma) activates the protein C pathway. Activation occurs as a result of thrombomodulin exposure to thrombin (via endothelial injury and glycocalyx disruption), with thrombin then binding, thereby preventing cleavage of fibrinogen (and formation of fibrin). This thrombomodulin–thrombin complex activates protein C, which then inhibits factors V and VIII, thus preventing further thrombin generation. This reduction in fibrin formation leads to decreased clot strength and, as a result, increased bleeding. Endothelial injury lead activation of protein C also consumes plasminogen activator inhibitor-1 (PAI-1). PAI-1 serves as the major antagonist of tissue plasminogen activator, when considered as a whole, the activation of protein C leads to decreased clot formation by direct factor inhibition and promotion of clot breakdown (fibrinolysis).

Hypothermia

The presence of hypothermia will potentiate the effects of TIC. The creation of clot occurs during a series of enzymatic reactions that are temperature sensitive. For every drop in the body temperature by 1°C, there is a 10% reduction in coagulation factor activity. Hypothermia is categorized as mild (temperatures <32°C to 36°C), moderate (28°C to 32°C), or severe (20°C to 28°C). Studies have shown that temperatures less than 33°C will reduce the coagulation factor activity below 33%, and will also alter the fibrin kinetics. Hypothermia also functions to directly inhibit the interaction of platelet surface proteins with von Willebrand factor, as well as reducing the rate of thromboxane B2 production. It is paramount that all traumatically injured patients are warmed to normal temperature in a timely fashion. Expedited removal of wet clothing, prophylactic placement of warming blankets, and maintaining a warm trauma bay/resuscitation room will help to mitigate the influence of hypothermia on TIC.

Acidosis

Acidosis is another factor that will accelerate the negative effects of TIC. Metabolic acidosis is the result of tissue hypoperfusion (shock) and the subsequent oxygen debt in tissues. Therefore the mechanisms and pathways responsible for coagulopathy after injury are also responsible for acidosis, which markedly worsens the coagulation insult. At a pH of 7.2, the activation of thrombin is reduced by 50%, and at a pH of 6.8, it is reduced by 90%. Because of changes to the platelet structure at a pH of less than 7.1, platelet aggregation is impaired by 50%. Restoration of pH to normal or near normal levels allows the patient's own homeostatic mechanisms of acid base regulation to again assume their vital function.

In situations of severe acidosis, some authors have advocated the use of acid buffers such as tris(hydroxymethyl)aminomethane (THAM) and sodium bicarbonate. THAM is a weak base providing a temporary buffer to the extracellular fluid through the acceptance of hydrogen ions. Unlike sodium bicarbonate, its effects are observed even when carbon dioxide elimination is impaired. THAM rapidly restores pH and acid base regulation, resulting in reversal of acidosis-related coagulopathy and cardiac dysfunction. Sodium bicarbonate, whereas also effective in rapidly changing a patient's pH, generates free CO_2 and paradoxically aggravates acidosis when CO_2 elimination from tissues or lungs is hindered (e.g., hemorrhagic shock). Although administration of bicarbonate or THAM will both increase the pH in the traumatically injured patient, neither addresses the underlying cause of acidosis. Given these limitations and knowing that early correction of the underlying cause of the acidosis is paramount to slow

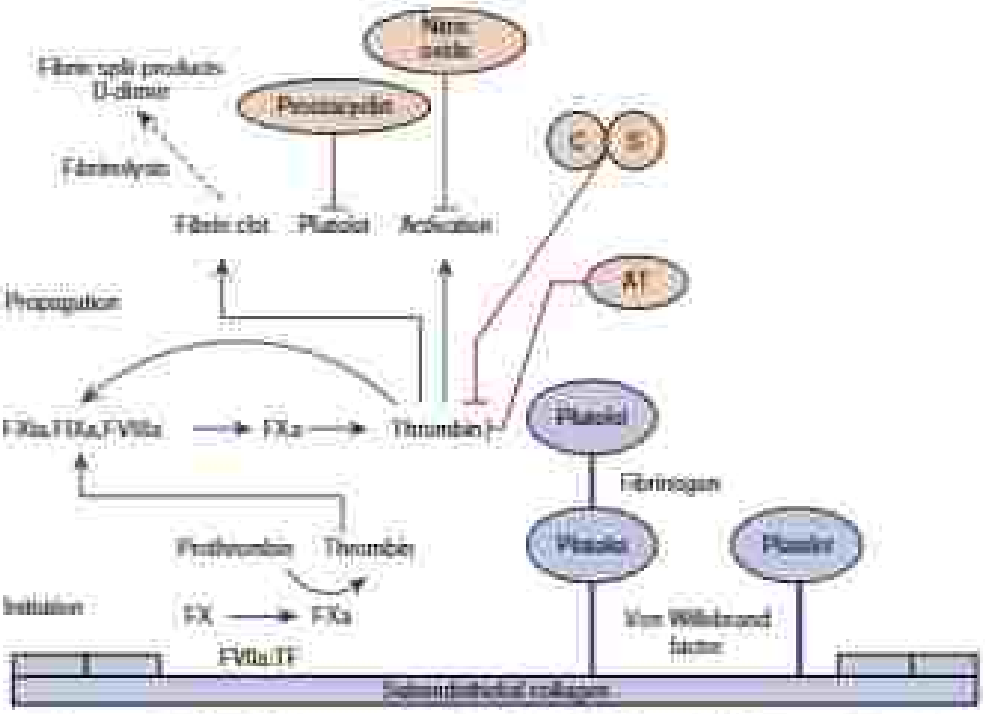

FIG. 1 Normal hemostasis. Hemostasis is initiated by the exposure of subendothelial collagen, which initiates activation of the coagulation cascade through tissue factor (TF) and factor VIIa (FVIIa). Subsequent production of small amounts of thrombin results in propagation and amplification of the coagulation response, leading to fibrin clot formation and platelet activation. Collagen exposure also triggers platelet adhesion and aggregation through interactions with von Willebrand factor (adhesion) and fibrinogen (aggregation). The endogenous anticoagulants protein antithrombin (AT) and the protein C (C)/protein S (S) complex, inhibit thrombin activity and generation, and prostacyclin and nitric oxide inhibit platelet function. The fibrinolytic system degrades fibrin clot, into fibrin degradation products such as D-dimers. FVIIa, Activated factor IX; FVIIIa, activated factor VIII; FIX, factor IX; FIXa, activated factor X; FXa, activated factor Xa.

the progression of TIC owing to acidosis, plasma is the ideal resuscitation fluid to correct both acidosis and coagulopathy. Plasma is an excellent buffer solution with a fivefold higher buffering capacity than crystalloids. In addition to its high citrate content (which makes it ideal for the resuscitation of severe acidosis from shock), plasma contains all necessary clotting factors and countless microparticles, and has been shown to protect and reestablish endothelial vascular integrity by stabilizing the endothelial glycocalyx, limiting coagulopathy progression (Fig. 2).

Hypocalcemia

Calcium functions as a cofactor in the enzymatic regulation of coagulation factors II (prothrombin), VII, IX, and X, facilitating the binding of these factors to the membranes of activated platelets. Calcium also plays a direct role in the stabilization of clots, the polymerization of fibrin, and platelet aggregation and activity. A lack of calcium will lead to impaired clot formation and propagation of TIC. The goal ionized calcium for resuscitating trauma patients is greater than 0.9 mmol/L. The presence of citrate in both fresh frozen plasma (FFP) and packed red blood cells (PRBCs) will also deplete calcium stores. To adequately resuscitate traumatically injured patients, one must maintain normal levels of calcium to facilitate hemostasis.

DIAGNOSIS OF TRAUMA-INDUCED COAGULOPATHY

Conventional Coagulation Tests

Classically, there were five plasma-based conventional coagulation tests (CCTs) that were utilized to identify TIC: international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen levels. PT and partial thromboplastin time (PTT) were originally developed and validated to evaluate and treat patients with hemophilia and those who were on anticoagulant therapy. PT directly reflects the extrinsic pathway, specifically the activity of factor VII, whereas PTT assesses the intrinsic pathway, analyzing the activity of factors XI, IX, and VIII. The activity of factors X, V, and II, otherwise known as the common final pathway, is reflected by both the PT and PTT. Classically, an INR greater than 1.2 and/or an aPTT longer than 30 seconds was associated with TIC. The group out of Denver has shown that for patients requiring massive transfusion (>10 RBCs/first 6 hours), 2% had a prolonged INR (>1.3), 13% had an elevated aPTT (>30 sec onds), and 72% had combined abnormalities of INR and aPTT. Interestingly, 13% of these patients had normal INR and aPTT.

The benefit to CCTs is that physicians are familiar with ordering them and are comfortable interpreting their results. However, there are countless flaws when evaluating and treating TIC. First, these tests were never developed with TIC in mind; they were developed to guide therapy for patients with hemophilia and those anticoagulated with heparin or warfarin. Guidelines that were developed for resuscitation based on CCTs were targeted toward management of elective general surgery patients, rather than severely injured trauma patients. Timely intervention for TIC is necessary to prevent further complications, and the turnaround time to get results from CCTs is prolonged. One can only resuscitate based on clinical evaluation when waiting for the results from CCTs, flying blindly until the labs are run. Moreover, as these tests are typically run on a machine remote from the patient, the results reflect where the coagulation status was some time ago, rather than where the patient's coagulation is now. With respect to platelet count and fibrinogen count, these tests simply provide a quantitative assessment of each component, and do not tell the surgeon about the functional status (which is what determines performance of each in clot formation) of the patient's platelets and fibrinogen. Finally, these

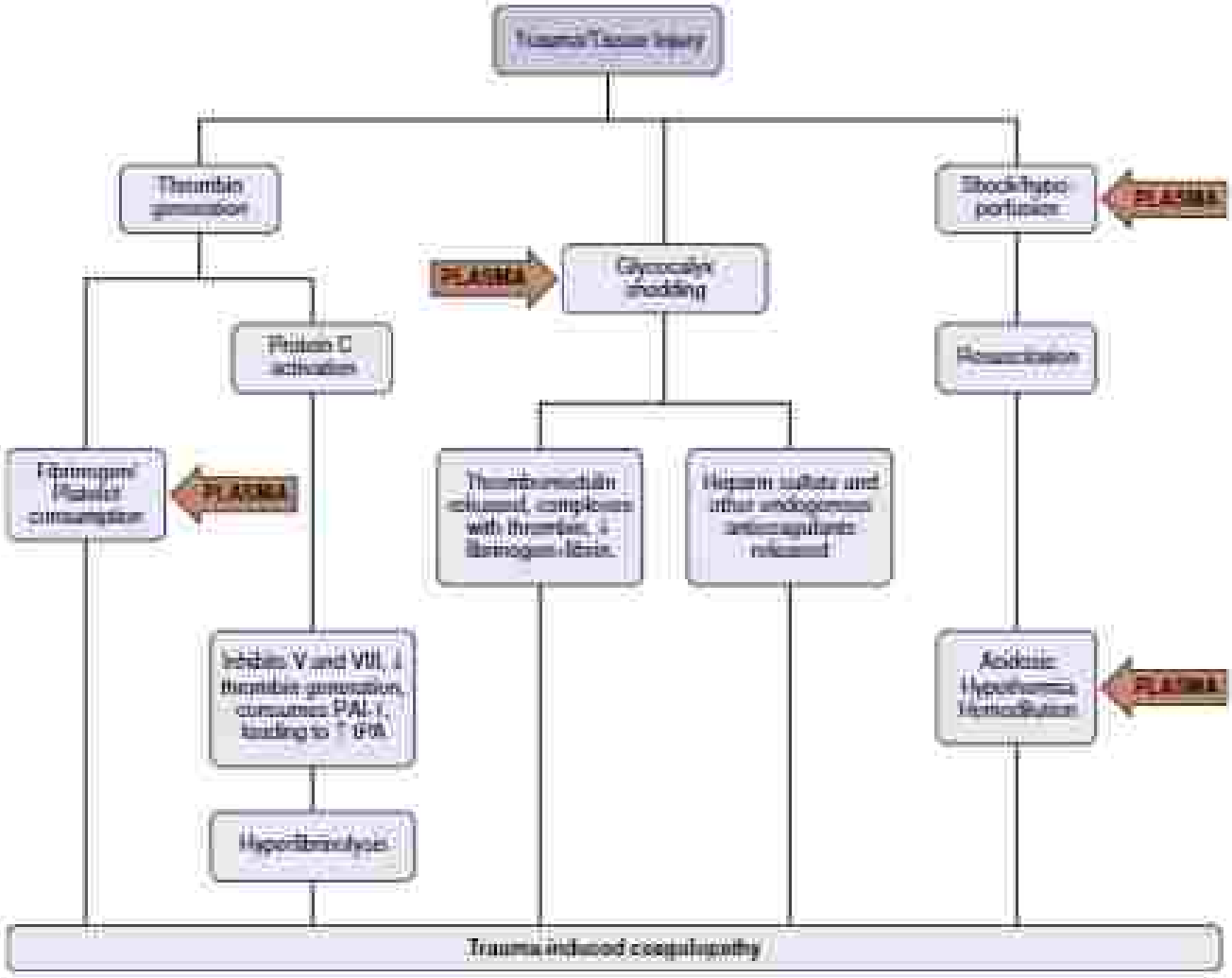

FIG. 2 Development of trauma-induced coagulopathy (TIC) through initial tissue insult, hypoperfusion, consumption, and activation of endogenous anticoagulants. The red arrows demonstrate points along the pathway where early transfusion of plasma can resuscitate the patient from shock, reinstitute the endothelial glycocalyx, prevent consumptive coagulopathy, and address severe acidosis, all of which may improve/reverse TIC. PAI-1, Plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

test are run down on specimens that have been spun down, generating a plasma only sample for which to assess clotting function. Given the contribution of the other blood components (RBCs, platelets, etc.), these plasma only specimens fail to account for the true hemostatic potential and deficits of the patient's blood in a bleeding scenario. Although moderate prolongations to the INR and aPTT are associated with TIC, there are better qualitative and quantitative evaluations of the coagulation system of the traumatically injured patient.

Thromboelastography

Thromboelastography (TEG) was initially conceived in Germany in 1948 and was applied in Europe during the 1950s to evaluate the coagulation system during liver transplantation. The first article published in the United States using TEG was from 1958 by Henry Swan at the University of Colorado characterizing the effects of hypothermia and cardiopulmonary bypass during cardiac surgery. TEG functions by taking a whole blood (WB) sample, approximately 360 µL, placing it in a cylindrical plastic cup and having the cup oscillate while a pin on a torsion wire is suspended in the sample. As the fibrin strands of the clot develop, the resistance built up couples the pin to the motion of the cup. As clot strength increases, more rotation energy is transmitted to the wire and detected by the electromagnetic transducer. The signal from the transducer is then interpreted by the TEG software, which then characterizes the development of the clot. The strength of the clot is reflected by the distance to the limit on the tracing, reflecting the firmness with which the cup is bound to the pin. Once the clot is broken down, or undergoes lysis, the tracing reflects the subsequent decrease in amplitude as the binding of the cup to the pin. TEG software allows for real time interpretation of clot dynamics as the clot develops and subsequently breaks down (Fig. 3).

Conventional (standard) TEGs are run with the addition of kaolin to start the clotting process (calcium is also added to recalcified samples). Rapid TEGs (rTEG) are an accelerated version that uses both kaolin and tissue factor to activate the clotting process. The inclusion of tissue factor accelerates the development of the clot and allows for earlier analysis of clot formation, and mimics the exposure of the clotting system to injured endothelium and tissue factor. For standard TEG, the traditional reaction time (R time) is the time to clot initiation, representing the status of clotting factors and/or the effects of anticoagulants. Normal values for the R time with standard TEG are 4 to 8 minutes. TEG ACT is the activated clotting time (CT) for the rTEG, with normal values ranging from 88 to 120 seconds. The K time (normal range, 1 to 2 minutes with rTEG and 1 to 3 minutes with standard TEG) is the time needed to reach 20 mm clot strength; this is generally increased in states of

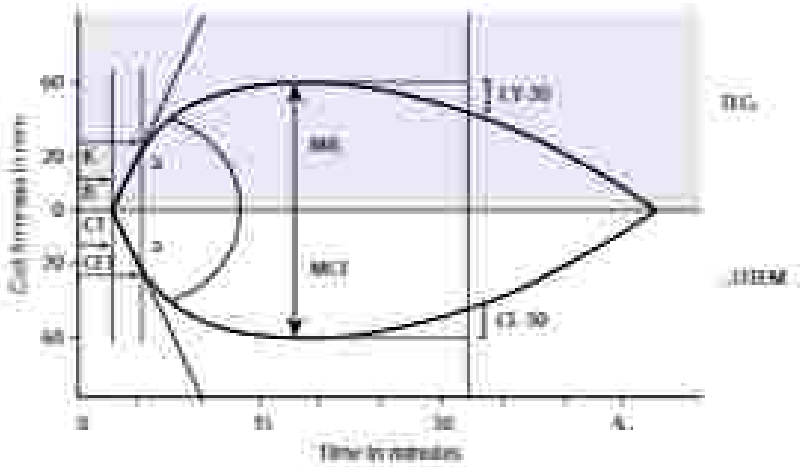

FIG. 3 A side-by-side comparison of the overlapping features of thrombelastography (TEG) and rotational thromboelastometry (ROTEM). Although nearly all values are describing the same coagulation defect, their names differ with respect to some variables. The initial clot formation is represented as R time for kaolin TEG, activated clotting time for rapid TEG (rTEG), and clotting time (CT) for ROTEM. Clot kinetics assessed as time to clot firmness of 20 mm are represented as K time for TEG and rTEG and clot formation time (CFT) for ROTEM. Acceleration of clot formation and fibrinogen contribution are expressed as α angle for all three tests. The maximal firmness of the clot and assessment of platelet function (and fibrinogen to a lesser degree) are represented as maximal amplitude (MA) for TEG and rTEG and maximal clot firmness for ROTEM. The lysis of the clot assessed as percent reduction 30 minutes after achieving MA or maximum clot firmness is expressed as lysis at 30 (LY30) and clot lysis at 30 (CL30).

hypofibrinogenemia. The α angle (normal range 53 to 78 degrees) is the slope of the tracing that represents the rate of clot formation. The α angle is decreased with hypofibrinogenemia or platelet dysfunction. The maximal amplitude (MA; normal range, 54 to 69 degrees) is the greatest amplitude of the tracing and reflects platelet contribution to clot strength. Low MA values correspond with states of platelet dysfunction or hypofibrinogenemia. The G value (normal range, 5kIII to 10,900 dynes/cm^2) is a global measure of the absolute clot strength (both enzymatic and platelet contributions) and is decreased in hypocoagulable states. Lysis index 30 (LY 30) (normal range, 0 [0%–2.5% to rTEG and 0%–15% to standard] is the percent amplitude reduction at 30 minutes after MA, and when elevated reflects a state of hyperfibrinolysis. CCT are unable to assess fibrinolysis and this aspect is one of the keys to the superiority of TEG over CCT for diagnosis and treatment of TIC.

The superiority of TEG over CCT was documented by Cotton and colleagues starting in 2011, in which they showed that over a 5-month period evaluating 272 trauma activations that when comparing CCT to TEG, TEG provided real time results available in minutes, was able to predict who was going to need massive transfusion and was predictive of who would need blood product transfusion. The same group then showed that the change for rTEG was similar to the five CCTs ($317 vs $786) but gave faster, more accurate results. They concluded that admission CCTs can be replaced with rTEG.

Rotational Thromboelastometry

Rotational thromboelastometry (ROTEM) provides similar information to TEG when used to diagnose and treat TIC, yet the mechanism and graphs of ROTEM differ in those from TEG (Fig. 3). ROTEM, like TEG, provides information on the time to clot initiation, the kinetics of clot growth, clot strength, and breakdown of the clot. Similar to TEG, a timed sample is placed in a cup into which a pin is introduced. ROTEM differs from TEG in that the pin rotates through an angle of 4.75 degrees, whereas with TEG the cup rotates. The rotating pin then initiates the clot formation process, and the ROTEM software produces the functional clotting graphs. The TEG produces just one tracing for the clot; ROTEM, however, produces five: intrinsic activation (INTEM), extrinsic activation (EXTEM), fibrin component of the clot (FIBTEM), aprotinin addition (a fibrinolysis inhibitor used with EXTEM) (APTEM), and the HEPTEM (includes the addition of heparinase to remove the influence of heparin on the clot). Each of these four graphs provides an insight into the development of the clot. The INTEM corresponds to the activation of the intrinsic clotting pathway, utilizing ellagic acid addition as the activator for clot formation. EXTEM corresponds to the activation of the extrinsic clotting pathway utilizing tissue factor as the activator to activate clot formation. Both tests by default evaluate the common final pathway too. The purpose of the FIBTEM is to isolate fibrinogen function via the addition of cytochalasin D, a potent platelet inhibitor. This leaves only the clotting proteins to identify the contribution of functional fibrinogen to clot formation. APTEM excludes the influence of fibrinolytic proactivity via the addition of aprotinin. The addition of heparinase to the HEPTEM allows for identification of coagulopathy when a patient is fully heparinized. The utility of the HEPTEM for trauma is minimal, unless the patient is actively being heparinized.

CT corresponds to the patient's ability to generate thrombin resulting in the onset of clot formation, normal if less than 80 seconds. Clot formation time reflects the time from initiation of clotting until a clot firmness of 20 mm is detected. This represents the fibrin polymerization and stabilization of the clot, normal if 30 to 110 seconds. The α angle is the angle at which the clotting curve achieves 2 mm off of its baseline, representing the initial development of clot. Normal value for the α angle is 70 to 83 on INTEM, and 63 to 83 on EXTEM. Amplitude 10 (A10), amplitude 20 (A20), and maximum clot firmness (MCF) reflect the firmness and stability of a clot owing to the interaction of platelets, fibrin, and factor XIIIa. Normal A10 and A20 is 44 to 71 mm. Normal MCF is 50 to 72 mm. LY 30 is a representation of clot lysis after 30 minutes from CT. More useful is the maximum lysis (ML), which is the percentage of maximum breakdown of clot. ML less than 15% is considered to be normal fibrinolysis. ML greater than 15% reflects hyperfibrinolysis.

The majority of the literature supporting the use for ROTEM in the treatment and diagnosis of trauma is from Europe. Multicenter studies have been undertaken showing the ability of diagnosing and treating TIC using ROTEM; however, they suffer from lack of patients enrolled. The superiority of TEG versus ROTEM has not specifically been studied; however, the volume of literature with TEG is large and founds greater than ROTEM.

Treatment of Trauma-Induced Coagulopathy

Thrombelastography-Guided

Paramount to the identification of and treatment of TIC is obtaining a TEG at the time of admission. The rTEG allows for identification of coagulopathy in less than 5 minutes, however, standard TEG will also do this but in 10 minutes. Either way, a prolonged ACT longer than 120 seconds or R time longer than 9 minutes reflects prolonged factor deficiency or severe hemodilution (Table 1). Do treatment for this is resuscitation with FFP. A prolonged K time greater than 2.5 minutes reflects the lack of fibrinogen or platelet dysfunction, requiring resuscitation with plasma and/or cryoprecipitate. A depressed α angle (<50) is associated with lack of fibrinogen and/or platelet dysfunction. Correction of this requires transfusion of cryoprecipitate. A decreased MA less than 55 mm is associated with platelet dysfunction and is an indication for transfusion of platelets. Hyperfibrinolysis is suggested by an LY 30 greater than 3%, which is treated with tranexamic acid (TXA) if identified in less than 3 hours from the time of injury. Standard kaolin TEG value thresholds are similar to those of rTEG, yet do require some modification (Table 1). Once abnormalities are identified, they should be corrected and repeat rTEG or TEG needs to be undertaken after resuscitation to ensure correction of coagulopathy.

Rotational Thromboelastometry-Guided

When using ROTEM to guide the identification of and treatment of TIC, specific aspects of the graphs that are produced are useful. Prolongation of the CT, more than 240 INTEM and more than 100 EXTEM, is an indication for transfusion of FFP. As with the ACT or R time, this is a reflection of prolonged factor deficiency or severe hemodilution. A depressed α angle is associated with lack of fibrinogen and/or

TABLE 1 Recommended Thresholds for Treatment of Thrombelastography Values in the Injured Patient Among Different Institutions and Different Thrombelastography Formats

Value	Interpretation	Treatment
rTEG PARAMETERS AT THE RED DUKE TRAUMA INSTITUTE		
ACT >120 seconds	Prolonged with factor deficiency, severe hemodilution	Plasma
K time >2.5 minutes	Prolonged in hypofibrinogenemia + platelet dysfunction	Plasma + cryoprecipitate
α angle <65 degrees	Decreased in hypofibrinogenemia or platelet dysfunction	Cryoprecipitate/fibrinogen concentrate
Maximal amplitude <55 mm	Decreased with platelet dysfunction + hypofibrinogenemia	Platelets + cryoprecipitate
LY 30 >3%	Increased with accelerated fibrinolysis	Tranexamic acid
nTEG PARAMETERS AT DENVER GENERAL/DENVER HEALTH		
ACT >120 seconds	Prolonged with factor deficiency, severe hemodilution	Plasma
α angle <65 degrees	Decreased in hypofibrinogenemia or platelet dysfunction	Cryoprecipitate
Maximal amplitude <55 mm	Decreased with platelet dysfunction + hypofibrinogenemia	Platelets
LY 30 >3%	Increased with accelerated fibrinolysis	Tranexamic acid
STANDARD KAOLINTEG PARAMETERS AT THE RED DUKE TRAUMA INSTITUTE		
R time >9 minutes	Prolonged with factor deficiency, severe hemodilution	Plasma
K time >2 minutes	Prolonged in hypofibrinogenemia + platelet dysfunction	Plasma + cryoprecipitate
α angle <60 degrees	Decreased in hypofibrinogenemia or platelet dysfunction	Cryoprecipitate/fibrinogen concentrate
Maximal amplitude <52 mm	Decreased with platelet dysfunction + hypofibrinogenemia	Platelets + cryoprecipitate
LY 30 >8%	Increased with hyperfibrinolysis	Tranexamic acid
ROTEM PARAMETERS AT THE UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES		
INTEM CT ≥240 or EXTEM CT ≥100 seconds	Prolonged with factor deficiency, severe hemodilution	Plasma
FIBTEM A10 <10 mm	Decreased in hypofibrinogenemia or platelet dysfunction	Cryoprecipitate/fibrinogen concentrate
FIBTEM A10 >10 mm and EXTEM A10 <46 mm	Platelet dysfunction	Platelets
EXTEM ML >15%	Increased with hyperfibrinolysis	Tranexamic acid

ACT, activated clotting time; CT, clotting time; EXTEM, extrinsic activation, FIBTEM, fibrin component of the clot; INTEM, intrinsic activation; LY 30, lysis index 30; ML, maximum lysis; rTEG, rapid TEG; ROTEM, rotational thromboelastometry; TEG, thrombelastography.

or platelet dysfunction. Correction of this requires transfusion of cryoprecipitate and platelets. A depressed A10, A20, or MCF identified on INTEM, EXTEM, or FIBTEM reflects dysfunctional platelets. A20 less than 40 on INTEM or EXTEM requires the transfusion of platelets. If the corresponding FIBTEM A10 less than 7, that equates to dysfunctional platelets as well as fibrinogen, requiring transfusion of platelets and cryoprecipitate. Hyperfibrinolysis is reflected by an ML greater than 15% on INTEM, EXTEM, or FIBTEM. If identified in less than 3 hours from the time of injury, the use of TXA is indicated. As with TEG-based resuscitation, repeat ROTEM is necessary to ensure correction of coagulation abnormalities.

Conventional Coagulation Test–Guided

Resuscitation of TIC based on CCTs, while still done today, is less precise, takes more time, and is unable to identify hyperfibrinolysis. Clinically, the threshold of INR greater than 1.2 was an indication for resuscitation with plasma, as was an aPTT longer than 30 seconds. Based on complete blood count evaluation, platelet count less than 100,000 for diffuse bleeding and less than 50,000 for microvascular bleeding were indications for platelet transfusion. Hypofibrinogenemia (< 229 mg/dL) was identified as the threshold at which to transfuse cryoprecipitate. Cryoprecipitate contains 150 to 250 mg of fibrinogen in a 15- to 20-mL unit. Each unit of cryoprecipitate should raise the fibrinogen level by 10 mg/dL. There is no CCT for the evaluation of hyperfibrinolysis, but some centers use D-dimer as a surrogate and/or give antifibrinolytics empirically when TEG or ROTEM are not available. Conventional wisdom would suggest that continued bleeding in light of adequate resuscitation and bleeding control may be owing to hyperfibrinolysis. If less than 3 hours from the time of injury, TXA could be used to potentiate the hyperfibrinolysis. However, extreme caution should be used in the early care of coagulopathic trauma patients as TXA has been shown to be harmful when administered more than 3 hours from the time of injury.

PRODUCTS AND ADJUNCTS FOR TREATING TRAUMA-INDUCED COAGULOPATHY

Whole Blood

WB was first implemented successfully during World War I, with over 1 million units of WB transfused when factoring in all the conflicts since then, including the Global War on Terror. Similarly, WB was the go-to product for civilian hemorrhagic shock resuscitation until the mid-1970s, when, alongside dramatic advances in blood component separation, blood centers were able to supply hospitals with individual components and the availability of WB decreased rapidly. Unfortunately, this occurred without any data supporting downgrading resuscitation products from WB to component-based therapy in hemorrhagic shock. In recent military conflicts, the transfusion of fresh, warm WB was associated with increased 24-hour and 30-day survival when compared with balanced component therapy. As well, a randomized trial from Cotton and colleagues demonstrated that civilian trauma patients resuscitated with WB achieved better hemostasis and required less blood products than those resuscitated with even 1:1:1 component therapy (plasma/platelets/RBCs). When patients are bleeding, they are bleeding WB, not just random ratios of components. Resuscitation with WB is superior in light of the fact that each 500 mL unit has a hematocrit of 38% to 50%, 150,000 to 400,000 platelets per microliter with full activity, and 100% activity of clotting factors (Table 2).

With the development and implementation of cold-stored WB programs in the military at several United States centers, the safety and efficacy of low-titer group O (LTO) WB is being demonstrated. With this new universal product alternative, an increasing number of trauma centers and aeromedical programs have adopted LTO-WB into their early resuscitation of hemorrhagic shock. Given our previous evidence of clinical utility, hemostatic benefit, and safety, our institution implemented a cold-stored LTO-WB program in 2017. We currently keep WB on our trauma bay and on our aeromedical transport services.

TABLE 2 Comparison of Component Therapy and a Single Cold-Stored Whole Blood Unit With Respect to Content and Volume

	Component Therapy (1:1:1)*	Whole Blood
Hematocrit (%)	29%	39%
Platelet count	80,000 to 96,000 per μL	150,000 to 250,000 μL
Coagulation factor activity (%)	≤30% to ≤35%	85% to 100%
Fibrinogen	240 to 400 mg	1000 mg
Total volume	625 mL	450 mL

*1 unit plasma, 1 unit platelets, 1 unit red blood cells.

We limit the transfusion of LTO-WB to 4 units, unless we are able to demonstrate the blood type and Rh status of the individual. Following these units, non-group O patients are transitioned to type-specific component therapy. Any patient who receives LTO-WB has a daily hemoglobin panel obtained for the first 48 hours postadmission. If this panel suggests hemolysis or clinical transfusion reaction is identified, a direct antiglobulin test is ordered and performed by the blood bank.

With respect to whether to administer Rh− or Rh+ product to patients initially, much of this has to do with concern of the rare but potentially fatal isoimmunization risk in women of childbearing age. The current practice of most centers and the recommendations of the AABB are for the use of Rh− in women younger than 50 years (and often male children as well) and Rh+ in men. However, as with RBC transfusions, the risk of hemolytic transfusion reaction and Rh-related complications are likely overstated and much less common than that observed in the nontrauma, nonbleeding setting. First, approximately 85% of patients are Rh+, and 70% of trauma patients are male (and many female trauma patients are older than 50 years). In addition, the 10% to 40% immunization reported from Rh isoimmunization in the nontrauma setting is only 20% to 30% risk in the severely immunosuppressed setting of trauma and hemorrhagic shock. Moreover, the conversion rate (development of anti-D antibodies from Rh incompatibility) varies in the literature from 3% to 30%, and options exist for lowering this even further in women of childbearing age (Rh immunoglobulin therapy and/or exchange transfusion therapy). Therefore the risk/benefit ratio appears to favor using Rh+ products in all patients, regardless of age or sex.

Red Blood Cells

RBCs are generally considered the initial product of choice in the bleeding trauma patient (as with gastrointestinal bleeds, obstetrical hemorrhage, etc.). However, the majority of trauma patients are not extremely anemic on presentation and the oxygen-carrying capacity of most individuals is initially adequate. Therefore in centers without WB immediately available, we would recommend beginning resuscitation with plasma, then adding RBCs to the regimen after the first 2 to 3 units are transfused (or simultaneously with RBCs when using a rapid infuser). That said, RBCs do improve tissue perfusion and oxygenation and do actively contribute to the coagulation cascade. The surface of RBCs expresses phosphatidyl serine that assists in the process of thrombin generation. In addition, through elongation, RBCs displace platelets to the periphery of the vessel, increasing contact with the injured vessel and exposed tissue, thereby facilitating adhesion and the subsequent interactions of platelets, glycoproteins, and endothelium.

With respect to anemia, transfusion of RBCs is necessary, and although lower hemoglobin values are recommended in the nonbleeding patient, most would transfuse RBCs to keep the patient's hemoglobin at 10 g/dL while actively bleeding. This transfusion of RBCs is usually begun with universal, uncrossmatched product to

the form of group O blood. Current guidelines recommend using Rh– in women younger than 50 years (and male children as well) and Rh+ in men. As soon as the patient arrives, a type and screen should be sent along with the activation of the massive transfusion protocol. Type specific blood can be made available in 10 minutes, whereas fully crossmatched blood may take 40 minutes or more to prepare.

Plasma

As stated earlier, plasma may be the ideal resuscitative agent in the absence of WB. Plasma is a strong acid–base buffer (fivefold higher capacity than crystalloids, fivefold higher than albumin), an excellent volume expander (smooth, quiet, and contains all necessary clotting factors and numerous involved immunoparticles. In addition, it has the potential to reverse or attenuate endothelial injury from shock.

There are two critical logistical considerations to making this nearly ideal transfusion product more immediately available. First, many centers do not keep this product ready for immediate transfusion. It is often kept frozen until requested, and then thawed. This process can take between 20 and 40 minutes to be made available for transfusion. Understanding that time is critical to saving the lives of bleeding patients, many centers have begun to keep thawed plasma available in their emergency departments or blood banks. However, once thawed, the product only has a 5 day shelf life. To address this, some centers have transitioned to liquid (never frozen) plasma. In addition, to the absence of temperature injury to plasma proteins, this product has a 21- to 24-day shelf life. Second, although blood group AB plasma is the universal donor for emergency settings, several investigators have demonstrated that plasma with low anti-B titers can be safely used as a universal product while awaiting delivery of type specific plasma. As such, both of our centers currently employ low titer group A liquid plasma as our emergency release, universal plasma option.

Platelets

Although they are usually a late transfusion consideration, platelets are critical to hemostasis and to nearly every component of the coagulation cascade. In the setting of noncranial coagulopathy, absolute platelet counts less than 100,000/μL have been identified as thresholds below which diffuse or "medical" bleeding occurs. However, from a quantitative rather than qualitative standpoint, it is usually at much lower counts (<50,000 to 40,000/μL) that one sees such diffuse bleeding in the trauma setting. However, as with hemoglobin thresholds in the actively bleeding patient, we would recommend maintaining platelet counts in the hemorrhagic shock patient at or near 100,000/μL, especially in those with concurrent traumatic brain injury. Platelet transfusions should be part of a center's massive transfusion protocol and should be employed early, alongside that of plasma and RBCs. In fact, some have argued that the immediate transfusion of platelets in both arms of the PROPPR (Prospective, Randomized Optimal Platelet and Plasma Ratios) trial resulted in the nonstatistically significant findings. A standard dose of apheresis platelets contains ≥ 6 to 8×10^{11} platelets and will typically increase the platelet count by 30,000 to 60,000/μL. However, our centers primarily utilize viscoelastic testing (MA in TEG and MCF in ROTEM) to guide platelet transfusions.

Fibrinogen/Cryoprecipitate

Historically, hypofibrinogenemia has been common in patients with massive blood loss, regardless of trauma, obstetrical, or gastrointestinal origin. Although much of this may have been related to poor resuscitation techniques (large volume crystalloid and RBCs early, with plasma late), some of this is because of the consumption of fibrinogen in patients with severe hemorrhage. Also, as with platelets, the function of available fibrinogen is likely more important to hemostasis than the actual fibrinogen value. That said, fibrinogen values less than 200 in the bleeding patient are associated with significant increases in mortality. The qualitative state, or fibrinogen function, can be monitored using conventional laboratory assays such as the Clauss fibrinogen assay or with viscoelastic testing (TEG or ROTEM). Fibrinogen as a product is available in plasma (approximately 800 mg per unit dose), in cryoprecipitate (1500 mg or more per dose), or in fibrinogen concentrate. Cost has made cryoprecipitate the product of choice in the United States, whereas transfusion related complications have made fibrinogen concentrate (virally inactivated human fibrinogen) more common in Europe. Cryoprecipitate is usually delivered in a 10 unit dose, delivering 1500 mg per bag. Many recommendations suggest 10 to 20 units in standard sized adults to increase the fibrinogen level by 100 to 200 mg/dl.

Tranexamic Acid

TXA is a synthetic antifibrinolytic that blocks plasminogen from binding fibrin, and thus inhibits dissolution of the fibrin clot. The initial data from the CRASH 2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) trial showed that implementation of 1 g of TXA over 10 minutes, followed by 1 g TXA infused over 8 hours, was associated with increased survival when administered to traumatically injured patients or those with suspected hemorrhage. However, a more in-depth look at this trial shows the following: (1) the difference in bleeding related mortality was less than 1%, however, in a study with 20,000 patients, this was statistically significant (but perhaps not clinically meaningful; (2) the patients who most benefitted from TXA were with penetrating trauma, with severe hypotension (<75 mm Hg), and who received the drug within 1 hour of injury; and (3) patients receiving the drug after 3 hours were harmed by administration of TXA.

In the absence of empiric administration of TXA, identification of hyperfibrinolysis requires the implementation of ROTEM or TEG. Centers with experience with these viscoelastic tests generally use lysis of 3% to 5% as a trigger to administer TXA to their patients. The implementation of TEG and ROTEM, and deeper study into its use and measurements, has provided insight into the three distinct phenotypes of fibrinolysis: (1) hyperfibrinolysis (LY 30: >3%); (2) physiologic (LY 30: 0.08%–3.0%); and (3) shutdown (LY 30: <0.8). The majority of these data come from the work of groups in Denver, Miami, and Houston. Their works have shown that although the highest mortality rates are associated with hyperfibrinolysis, the shutdown group was associated with delayed death due to organ failure due to proinflammatory mechanisms.

When considering the use of TXA, it is important to take pause prior to empiric dosing. Given the three distinct fibrinolysis phenotypes, and specifically that the shutdown groups mortality was due to prothrombotic events, one can surmise that empiric use of a medication that will enhance thrombosis may lead to more deaths in the shutdown group. Mature trauma systems in which hemorrhage control can be achieved in a timely manner, and implementation of TEG or ROTEM to identify TIC and specifically the fibrinolysis phenotype, are the ideal places to optimize the use of TXA based on fibrinolysis status. Further research is necessary to identify whether or not empiric use of TXA is associated with worse outcomes. In light of all this, for the traumatically injured patient who is far from a center where hemorrhage control can be achieved, the empiric use of TXA, when given less than 3 hours from injury, may lead to improved outcomes.

Massive Transfusion Protocols

Protocolization of an institution's massive transfusion policy and delivery system has been shown to be as critical to improving survival as is the contents of that protocol. In fact, the PROPPR trial demonstrated that every 60 second delay in delivery of the initial massive transfusion cooler (from time of activation) was associated with a 3% increase in mortality, regardless of the ratio of products delivered. Therefore the ability to predict, early, who will require a massive transfusion is key to successful resuscitation and prevention of TIC. Current military casualty management utilizes the presence of *hostile* mental status, in the absence of head injury, and a normal radial pulse as two factors that are most predictive of need for transfusion and lifesaving intervention. The ABC (assessment of blood consumption) score was developed in a civilian trauma center, and

utilizes immediate vital signs and ultrasound to predict who will need massive transfusion. One point is given for the presence of each of the following: (1) positive FAST, (2) penetrating mechanism, (3) systolic blood pressure less than 90 mm Hg, and (4) heart rate greater than 120 beats/min. When considered, a score of 2 or greater, although having a tendency to overactivate the massive transfusion protocols (MTP), misses less than 5% of massive transfusion or substantial bleeding scenarios. This score has been validated in a multicenter trial and is a key component to identification of who will need MTP when ultrasound is available. The ABC score is used by our prehospital aeromedical personnel to trigger transfusion en route, by our hospital-based team to activate our institutional MTP, and has been used in multiple randomized trials as inclusion into those studies of hemorrhagic shock patients. Other centers utilize the shock index, which is calculated by dividing the heart rate by the systolic blood pressure. This is another useful tool to help facilitate early prediction of who will need MTP. For those patients with a shock index greater than 1, there is a high likelihood that they will need MTP. The key difference is that the shock index does not require the individual calculating the score to need an ultrasound. Anyone in the care team, be it prehospital or in the resuscitation bay, can calculate the shock index. A recent analysis by Dutton and colleagues showed that although the sensitivity of the ABC score for predicting the need for MTP was greater, both were successful at identifying patients who were at risk for needing MTP.

The breakdown of product allocation for massive transfusion continues to be a source of variation, although the PROPPR trial would suggest that 1:1:1 (plasma, platelet, RBC) is most likely to achieve hemostasis and have lower bleeding-related mortality. The PROPPR trial compared 1:1:1 versus 1:1:2 for patients predicted to need MTP. Although there was no overall difference in mortality, bleeding-related mortality (death from exsanguination) was less in the 1:1:1 group. As with previous studies, the majority of deaths owing to hemorrhage in either arm occurred in the first 3 hours from arrival. As such, the authors believe that en route resuscitation and early care should mimic the transfusion of WB and include products in a 1:1:1 ratio. Moreover, these products (WB, plasma, RBCs) should be immediately available in the emergency department and should be utilized and transfused as the hospital's MTP is being rushed for delivery to the patient.

Damage Control Resuscitation

Damage control resuscitation (DCR) is a strategy that focuses on three tenets: limiting crystalloids, delivering WB or high ratios of plasma and platelets, and maintaining permissive hypotension. This concept was first described in 2006, by a multidisciplinary team who endeavored to reduce morbidity and mortality from hemorrhage among injured soldiers. They set out to achieve this by replicating WB with higher ratios (and later using fresh, warm WB), avoiding "popping the clot," and minimizing the harm associated with crystalloid-based resuscitation. Recent research has shown that large volume crystalloid resuscitation is associated with worsening hypoxia, acidosis, and hypothermia. Crystalloid exacerbates the effects of TIC by diluting out the clotting factors and creating acidosis. The protective effect of permissive hypotension is the byproduct of randomized control trials that confirmed that delaying resuscitation to a normal blood pressure until after operative control of bleeding in both blunt and penetrating trauma was associated with improved mortality. A strict no prehospital fluid practice was also shown to increase survival in patients with penetrating trauma presenting with a systolic blood pressure less than 90 mm Hg. Those patients treated with permissive hypotension by delaying resuscitation had improved survival compared with those with immediate fluid resuscitation. The positive outcomes shown in both military and civilian trials of MTP using 1:1:1 in the final tenet of DCR.

The implementation of DCR has been associated with an almost 50% reduction in crystalloid use in certain centers. Other studies have shown a profound decrease in the morbidity from abdominal compartment syndrome, infection, organ failure, and death from hemorrhage in centers where DCR is practiced. The implementation of the three tenets of DCR is necessary to prevent the development of TIC and prevent mortality from hemorrhage.

Antiplatelet and Anticoagulant Management

The use of antiplatelet and anticoagulant agents continues to become increasingly common throughout the United States and around the globe. Moreover, their use is made even more apparent as the surgeon as the aging trauma population continues to grow rapidly. Although the bleeding associated with these agents do not technically result in TIC, their use in a patient who sustains injury may make the life-threatening bleeding unstoppable and quickly fatal. Available

TABLE 3 Agents to Restore/Improve Hemostatic Function in Patients Taking Antiplatelet and Anticoagulant Drugs

Reversal agent	Drug Indication	Mechanism of Reversal	Dosing
Platelet transfusion	Aspirin, clopidogrel, prasugrel	Provides unbound platelets to potentially restore function	Aspirin: 1 to 2 aphaeresis platelets Clopidogrel: 2 to 4 aphaeresis platelets
Desmopressin	Aspirin, clopidogrel, prasugrel	Improves platelet binding by stimulating release of vWF/FVIII from endothelium	One-time dose of 0.3 μg/kg
Vitamin K	Warfarin	Bypass warfarin's inhibition of vitamin K dependent coagulation factors	10 mg of vitamin K IV (infuse no faster than 1 mg/min)
Prothrombin complex concentrates	Warfarin	Replacement of vitamin K dependent coagulation factors	INR <4: 25 IU/kg INR 4 to 6: 35 IU/kg INR >6: 50 IU/kg
Prothrombin complex concentrates	Rivaroxaban, apixaban	Replacement of unbound factors II, VII, IX, and X	35–50 IU/kg
Idarucizumab	Dabigatran	Antibody binds, inactivates dabigatran	5 g IV (dosed in two 2.5 g infusions, 5 to 15 minutes apart)
Andexanet	Rivaroxaban, apixaban	Antibody binds, inactivates rivaroxaban, apixaban	Apixaban: 400 mg bolus, then 480 mg infusion/2 hours Rivaroxaban: 800 mg bolus, then 960 mg infusion/2 hours

INR, international normalized ratio; vWF, von Willebrand factor.

treatment (possible several agents) for bleeding issues in this patient population is illustrated in Table 1.

RECOMMENDED APPROACH TO TRAUMA-INDUCED COAGULOPATHY

Traumatically injured patients should be expedited to the nearest trauma center. Early evaluation for those at risk for needing MTP by either the ABC score or shock index is critical to stay ahead of and prevent or attenuate TIC. Adoption of and implementation of MTP that mimics WB in a 1:1:1 ratio is key to reducing filtered translusion and minimizing TIC. Utilization of the principles of DCR by limiting the use of crystalloid, allowing permissive hypotension, and balanced resuscitation of blood products will lead to a greater chance of survival. Warming fluids, warming resuscitation bays, and liberal use of warm blankets will go far to limit the influence of hypothermia on the development of TIC. Early identification of coagulation abnormalities within minutes of arrival via ROTEM or TEG is key to resuscitating and preventing the development of TIC. Serial evaluations of the coagulation via ROTEM or TEG for ongoing bleeding will tailor the resuscitation of blood products and/or cryoprecipitate to the treatment of TIC. Early hemorrhage control in either the operating or interventional radiology suite will prevent the development of further coagulopathy and minimize unnecessary transfusions.

Suggested Readings

Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127–1130.

Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017;82(3):605–617.

Cotton BA, Guy JS, Morris JA Jr, et al. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26(2):115–121.

Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg. 2013;74(2):523–530.

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The Abdomen That Will Not Close

Heidi N. Overton, MD, and Kent A. Stevens, MD, MPH

The principle of damage control has changed the practice of surgery dramatically over the past 2 decades and has become one of the central and dominant practices in trauma and acute care surgery. As a result, the morbidity and mortality associated with abdominal compartment syndrome (ACS), abdominal coagulopathy, hypothermia, acidosis, and a myriad of other resuscitative complications have been reduced dramatically. However, with all significant advances come new challenges. With the widespread practice of damage control surgery (DCS) and abbreviated laparotomy, surgeons must be prepared to manage an open abdomen with a temporary abdominal closure (TAC) as well as the abdomen that will not close.

This chapter reviews TAC techniques, management of patients with an open abdomen (OA), subsequent definitive closure of the abdomen, and long-term reconstruction options in patients who develop hernias resulting from OA management.

INDICATIONS FOR LEAVING THE ABDOMEN OPEN

Initially described by trauma surgeons, DCS is among the most common reasons for leaving an abdomen open. It was originally reserved for a traumatically injured subset of patients, defined as those with (1) at least one major vessel injury (e.g., inferior vena cava), (2) at least two visceral injuries, and (3) profound shock. Early results from DCS were very impressive, survival for such traumatically injured patients jumped from 11% to 77%, and use of DCS subsequently spread to less severely injured patients. However, many now believe that the pendulum has swung too far and, in some cases, the risks associated with leaving the abdomen open outweigh the benefits. Thus, patient selection is vital. In general, there are five distinct groups of patients in whom the abdomen should be acutely left open.

1. **Patients with or at risk of intraabdominal hypertension (IAH) and subsequent ACS.** This group includes patients undergoing major elective operations as those who will require massive resuscitation are at risk for primary ACS. Similarly, patients who require substantial resuscitation because of severe medical illness or trauma that requires abdominal decompression are at risk for secondary ACS and are included in this group.
2. **Patients after non-DCS.** This group includes patients undergoing DCS for massive abdominal trauma, such as a patient with a gunshot wound through a major vessel (e.g., renal artery), a solid organ (e.g., kidney), and multiple segments of bowel. Once the major vessel injury and solid organ injury have been controlled and spillage from the bowel injury contained, the patient may be too unstable for reconstruction of the bowel and closure of the fascia. In this case, DCS allows rapid truncation of laparotomy before the patient enters the "lethal triad" of hypothermia, acidosis, and coagulopathy. Once the damage has been controlled, the patient can be taken to the intensive care unit (ICU) for resuscitation and stabilization. It is important to decide on the need to perform DCS early on in the operation. Predictors of a patient's need for DCS include: temperature below 34°C, pH less than 7.2, estimated blood loss greater than 4 L, transfusion requirement of more than 10 units of packed red blood cells, systolic blood pressure less than 70 mm Hg, lactate levels greater than 5 mmol/L, base deficit greater than −6 in patients older than 55 years or greater than −15 in patients younger than 55 years, and/or prothrombin time greater than 1.6. DCS may also be required in patients undergoing elective general surgery with overwhelming blood loss or unexpected intraoperative findings that require further stabilization/resuscitation.
3. **Patients whose fascia cannot be closed.** This category includes patients who may be physiologically stable but have swollen abdominal contents from an ongoing resuscitation (e.g., DCS) or loss of fascial domain such that they cannot be closed primarily. Fig. 1 depicts a patient who required TAC while waiting for bowel edema to resolve. The latter example must be kept open until the patient is ready for a definitive closure with mesh or other modalities.
4. **Patients with severe intraabdominal infections or necrotizing fasciitis of the abdominal wall.** This includes patients with necrotizing pancreatitis, a soft tissue infection, or a large amount of purulent material in the abdomen requiring repeated washouts.
5. **Patients having a planned repeat exploration or second look surgery.** These are patients with intraabdominal pathology that require another laparotomy in the next 48 to 72 hours. For example, a vascular surgery patient with mesenteric ischemia who undergoes a small bowel resection, and 48 hours later needs to be reexplored to check for additional bowel ischemia.

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FIG. 1 AbThera VAC system (Kinetic Concepts, Inc.) features a foam that controls exudate laterally to assist in volume removal. (Courtesy KCI, an Acelity Company.)

Once the decision has been made to leave the patient open, a TAC is performed and the patient transported to the ICU for further management. In some situations, such as with massive liver injury, the abdominal viscera may be packed with laparotomy pads for direct pressure to control bleeding prior to a TAC. As stressed previously, the practice of closing the fascia under tension must be avoided to prevent IAH and ACS and to prevent wound complications that arise from ischemia and pressure such as infection and dehiscence. For hemodynamically stable patients who present challenges to primary abdominal closure during the index case, several options to achieve a tension-free abdominal closure exist, some of which are highlighted later in this chapter.

TEMPORARY ABDOMINAL CLOSURE

Once the decision to leave the abdomen open has been made, the most optimal TAC technique as allowed by local resources should be used. The ideal method for TAC should prevent loss of domain, limit contamination, allow egress of peritoneal fluid, and avoid adhesion formation. Many TAC techniques have been described in the 20 plus years since Bjorcke and Schwab coined the term *damage control surgery*, and all share the following attributes:

- Easily encompasses the bowel and abdominal viscera
- Allows enlargement of the abdominal cavity in situations of massive bowel, tissue, or retroperitoneal edema without inducing IAH and while preventing ACS
- Is expansible but also sturdy enough to permit the tamponade effect of packing the liver or other bleeding surfaces
- Does not damage the fascia and prevents fascial retraction
- Contains and quantifies fluid loss
- Prevents adhesions formation between viscera and abdominal fascia
- Promotes removal of infectious materials
- Is quick to apply and remove
- Has a good primary fascial closure rate (>50% in a systematic review of trauma-only series by van Hensbroek et al.)

Options can be divided into skin approximation techniques (towel clip closure, the Bogota bag, the slip technique), fascial closure techniques using an interposition graft material sutured to the abdominal fascia (e.g., the Wittmann Patch), or negative pressure wound therapy (NPWT) (Barker's vacuum pack, commercially available vacuum-assisted closure [VAC] devices). Table 1 compares the most common methods of TAC.

Although the earliest forms of TAC, the towel clip and Bogota bag closures, are mentioned in the table, these have largely been replaced with improved techniques. The 2014 International Consensus Conference on Open Abdomen in Trauma recommends NPWT whenever feasible. These devices create a negative pressure silo that contains the abdominal contents, is somewhat expansible, and enables measurable fluid removal. The negative pressure is applied medially up through the open abdomen, minimizing fascial retraction and loss of abdominal domain. These dressings are also very quick and easy to apply and they can be used in situations of massive bowel swelling. Although several variations of the negative pressure TACs exist, most include the following key features:

1. Semipermeable (fenestrated), nonadherent inner membrane: The innermost layer of fenestrated plastic or plastic-coated sponge acts to protect the viscera from the overlying suction device and simultaneously permit evacuation of intraabdominal fluid.
2. Sponge inlay: The middle layer of the VAC device consists of a porous sponge, often made of polyurethane, placed in an inlay position between the fascial edges and flush with the level of the skin. This layer transmits the suction effect onto the inner viscera to remove intraabdominal fluid. Suction effect on the inlay sponge also produces wound contraction and gentle fascial edge approximation over time.
3. Adhesive impermeable outer layer: The outer layer of the VAC dressing is an adhesive, impermeable layer used to create a seal around the edges of the wound and to anchor the dressing to the periwound skin and allow gentle tension or wound contraction.
4. Suction device or machine: Finally, the suction device or machine typically connects to the dressing via an adaptor placed overtop an intentionally created defect in the impermeable outer layer to allow transmission of negative pressure directly onto the middle sponge layer.

Figs. 1–3 illustrate the AbThera VAC device (Kinetic Concepts Inc.). Fig. 4 illustrates the Barker dressing, which uses materials readily available in the operating room to create a vacuum pack dressing. The World Society of Emergency Surgery also recommends NPWT with continuous fascial traction as the preferred method for TAC but acknowledges that TAC without negative pressure (e.g., Bogota bag) can be applied in low-resource settings accepting a lower delayed fascial closure rate and higher intestinal fistula rate.

Practical Tips for Use of VAC Closure Dressing as Temporary Abdominal Closure

Maximally Lateralize the Inner, Visceral Protective Layer

To prevent viscera from sucking out at the edges of the inlay sponge, it is important to maximally lateralize the inner, visceral protective layer. This also prevents adhesions of the viscera to the undersurface of the abdominal wall, which could make eventual abdominal closure more difficult. It can be helpful to take down the falciform ligament as well as any secondary adhesions to the anterior abdominal wall. One technique is to use an abdominal wall retractor to facilitate adequate placement.

Place Intestinal Anastomoses Deep in Abdominal Cavity

The previously mentioned 2014 International Consensus Conference on Open Abdomen in Trauma found that GIA and NPWT do not harm intestinal anastomoses as long as they are buried deep within the pelvis or central abdomen under multiple loops of bowel or tucked laterally under the abdominal wall.

Avoid Leaks

Air leaks, typically at the edges of the wound or at skin creases and ostomy sites, are the Achilles heel of VAC therapy. Using an appropriate overlap of adhesive is important, as is intraoperative leak testing before leaving the operating room. The use of ancillary liquid

TABLE 1 Various Methods of Temporary Abdominal Closure

Closure Technique	Description	Advantages	Disadvantages
SKIN APPROXIMATION			
Towel clip closure	Serial application of towel clips or sutures	Rapid	Does not prevent IAH, may interfere with radiography or angiography
Bogota bag	IV bag, Steri-Drape, Silastic bag, plastic bag attached to skin	Inexpensive, quick, semiadherent	Risk of evisceration, loss of abdominal domain, risk for IAH, fluid losses difficult to quantify
FASCIAL CLOSURE			
Absorbable mesh	Suturing of absorbable mesh to fascial edges	Can be applied directly over bowel, allows for drainage of peritoneal fluid	Rapid loss of tensile strength (in the setting of infection), potentially large volume late ventral hernia, risk for bowel fistula, damage to fascial edges limits repeated suturing
Wittmann patch (Star Surgical)	Suturing of artificial burr (e.g., Velcro) to fascia, staged abdominal closure by application of controlled tension	Good tensile strength, allows for easy reexploration and eventual fascial closure	Poor control of third space fluid, adherence of bowel to abdominal wall, potential for fistulae
NEGATIVE-PRESSURE WOUND THERAPY			
Barker's vacuum pack	Bowel covered with plastic sheet and towel or laparotomy pads, that drains attached to wall suction and outer adhesive layer	Inexpensive, uses available materials, moderate control of fluid, suction provides constant medial traction, preventing loss of domain, high success in fascial closure	Difficult to quantify suction, unknown whether full benefits of negative-pressure therapy are realized
VAC Abdominal Dressing System	Reticulated polyurethane foam dressing over the plastic covering of the bowel; negative pressure is controlled with a computer-controlled vacuum pump that applies a constant, regulated pressure to the wound surface and a sensing device to prevent uncontrolled fluid (e.g., blood) drainage	Increase in blood flow, a reduction in abdominal wall tension, reduction in size of the abdominal wall defect, decreased bowel wall edema, and potential removal of inflammatory substances that accumulate in the abdomen during inflammatory states; edema and third space losses are controlled	Expensive, not available in all institutions or in all low-resource settings; mechanisms of action not fully understood, but also lead to hypersensitization; full relationship to fistula needs further study

IAH, intra-abdominal hypertension; IV, intravenous; VAC, vacuum abdominal closure.

FIG. 2 Placement of foam pad layer for the ABThera VAC (Kinetic Concepts, Inc.), which combines with an embedded foam that lies on laterally making it easier to apply and also assists in bowel parietal fluid and effluent removal.

FIG. 3 Vacuum-assisted closure dressing on patient in the surgical intensive care unit. This dressing was easily applied despite an enormous bowel and massive retroperitoneal bulging.

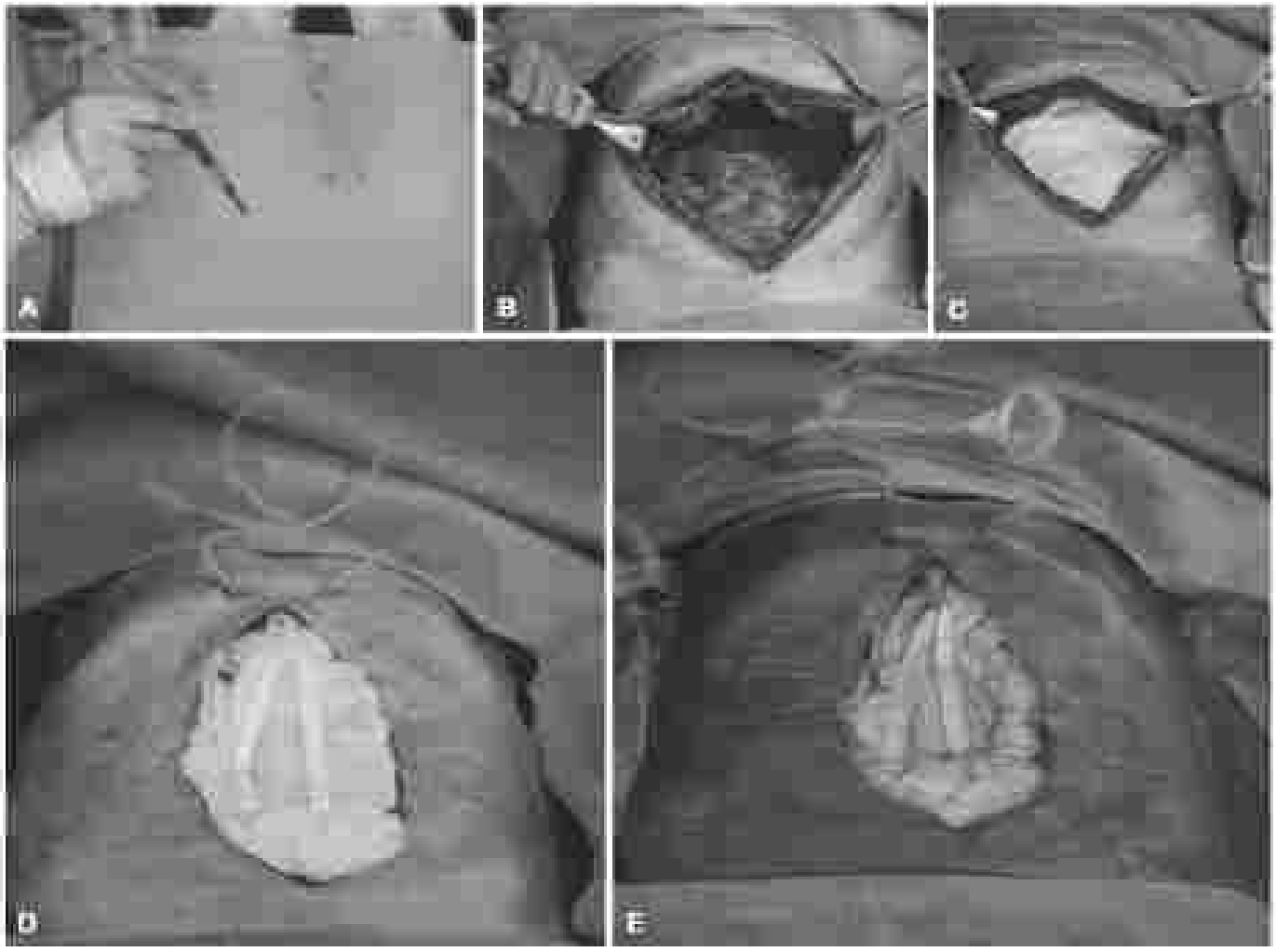

FIG. 8 Barker vacuum pack technique. (A) The polyethylene sheet is perforated multiple times with a scalpel blade. (B) The sheet is placed over viscera and beneath the parietoumbilical wall. (C) A moist towel is placed over the polyurethane and positioned below the skin edges. (D) Suction drains are placed. (E) An outer adhesive dressing is applied and the drains are hooked up to wall suction. (Courtesy Donald H. Barker, MD, Department of Surgery, University of Tennessee, Chattanooga.)

adhesives, such as tincture of benzoin or Mastisol can facilitate a good seal, especially in difficult areas for adhesion. Pulling and placing the outer dressing under tension should be avoided as it can lead to epidermal blistering leading to long-term skin problems.

Staples for Skin-Sponge Approximation

Polyurethane sponge damages the epidermis when direct contact is made under negative pressure; however, the inlay sponge must come to a flush approximation with the skin edge to maximize the effectiveness of the dressing. One solution is to use skin staples to temporarily affix the inlay sponge to the edges of the wound during dressing application and initial suction, although this is not a necessary step. These staples then are removed at the next VAC dressing change.

Overlap Outcomes With Adhesive Outer Layer

VAC therapy in the presence of an ostomy creates a very difficult problem for wound management. If the ostomy is close to the wound or if the patient has an enteric atmospheric fistula in the middle of the wound, there are other possible solutions to ensure a good seal of the VAC dressing. With the ostomy appliance off, a sheet of adhesive outer layer can be placed over the stoma site, with a small hole cut to allow the stoma to pass through. The ostomy appliance then is reapplied on top of the adhesive layer and simply changed every 48 hours with the dressing.

Appropriate Hole for Vacuum Device

Although simple, the use of an appropriately sized hole in the outer adhesive layer is a critical step. At least a 3 × 3 cm hole is appropriate and allows efficient transmission of negative pressure.

Amount of Negative Pressure Depends on Clinical Condition

The optimal therapeutic amount of negative pressure that maximizes tissue growth is approximately 125 mm Hg, with some flexibility based on clinical conditions and time of management. If active bleeding caused by coagulopathy is suspected, the pressure level should be lower, approximately negative 75 mm Hg, to decrease risk of hemorrhage.

OA POSTOPERATIVE CARE

After DCS, patients require management in a critical care unit with aggressive hemodynamic monitoring. The immediate postoperative period should consist of rewarming, correction of coagulopathy,

acidosis, and metabolic derangements, and likely ongoing resuscitation. During this early "fluid seeking" phase, patients should not be restricted in terms of fluid administration because of concerns about bowel edema or ultimate fascial closure. Hypertonic crystalloid solutions for both infusion and bolus therapy during the resuscitative phase may provide durable volume expansion while restricting edema to a certain degree. All patients who sustain penetrating abdominal wounds should receive a preoperative dose of prophylactic, broad-spectrum antibiotics. In the presence of a hollow viscus injury, the literature supports use of prophylactic antibiotics for not more than 24 hours. However, there is a lack of evidence regarding the need to continue antibiotics solely in patients with an OA. If the patient is thought to have sepsis, however, broad-spectrum antibiotics should be initiated and narrowed as appropriate based on culture results and clinical course. It should be recognized that OA patients are in a hypermetabolic condition and adequate nutritional support is mandatory. Early enteral nutrition is preferred if the gastrointestinal tract is intact and viable. Further goals for resuscitation are well delineated in the DCS literature as well as in the chapter on damage control in this text. In brief, we believe patients should receive judicious sedation and return to the operating room every 24 to 72 hours for abdominal washout and evaluation for abdominal closure.

Subsequent Take-Backs to the Operating Room

At 1- to 3-day intervals, the patient should be returned to the operating room to irrigate the abdomen, change the abdominal VAC dressing, and perform the necessary therapeutic maneuvers (e.g., bowel anastomosis, drainage of purulent collections) and to evaluate for abdominal closure. At our institution, abdominal VAC dressing changes are only done at the bedside if the patient is unstable and cannot tolerate a trip to the operating room. Close collaboration between the critical care team and the surgical team will allow for early closure of eligible patients, and in turn, earlier abdominal closure. Data suggest that patients who remain open at day 8 are unlikely to have a primary closure and are at increased risk for serious complications, including wound infections and fistulas. Alternative closure techniques should be undertaken in these patients unless there is some compelling reason to keep the abdomen open, such as the continued need for fascial debridement.

Definitive Closure of the Abdomen

Once the patient is ready for abdominal closure, the best-case scenario is primary fascial closure. We generally place heavy, interrupted, absorbable sutures in figure-of-8 fashion. In a setting of colonic perforation or heavy contamination, the skin should be left open. Some authors suggest the use of retention sutures, but we do not routinely place them. Retention sutures do not prevent fascial dehiscence but can help prevent bowel evisceration should dehiscence occur. Additionally, they can be placed when wound infection and subsequent dehiscence is a concern. It must be reiterated that the fascia must not be closed under tension as this may lead to IAH and ACS.

Research on OA management has found that direct closure is usually possible when the fascial edges are approximately 3 to 7 cm apart. When this cannot be achieved, different surgical techniques must be considered. Skin flaps can be raised to gain some medial length to the fascia. The fascia can also be advanced by releasing the lateral obliques; however, a full component separation is not recommended for the acute closure of an open abdomen. For patients who need mesh to bridge a gap between fascial edges, the options include biologics such as human acellular dermal matrix (HADM), absorbable mesh such as Vicryl (Ethicon), and composite meshes. Two possible techniques for management at this stage are outlined in the following section.

If the fascia cannot be closed but the skin of the abdominal wall is lax enough to close at the midline, an underlay biologic mesh can be placed to bridge the fascial defect. The overlying skin can then be closed to provide coverage for the mesh. In this situation, the method of skin closure or reapproximation can be assisted by VAC therapy. The underlay of biologic mesh typically is placed in an intraperitoneal position and affixed to the abdominal wall using transfascial suture techniques.

Where neither fascia nor skin has the capacity for midline closure, we routinely default to a temporary Vicryl (polyglactin) mesh closure with delayed placement of a split thickness skin graft. This temporary absorbable mesh then is placed in an underlay, intraperitoneal position. Standard saline moist to dry dressings are placed twice daily for about 2 to 4 weeks until satisfactory granulation tissue has appeared in the wound bed. At this time, a split thickness skin graft can be placed to cover the wound. The patient should be advised to avoid strenuous activity and heavy lifting during the several months of convalescence, and an abdominal binder can be considered for external support. Although this technique is neither novel nor aesthetically or functionally appealing, it is a time tested strategy to avoid OA catastrophes. With the advent of modern abdominal wall reconstruction techniques, these patients now can be offered a genuine and fairly reliable opportunity for restoration of abdominal wall continuity, albeit at a later date once they have completed convalescence for their acute illness. Usually this is accomplished after a minimum of 6 to 12 months, allowing for softening of intraabdominal adhesions and recovery from what is likely an extended stay in the ICU, hospital, and rehabilitation center. The benefit of this approach is that the native abdominal wall musculature is not violated and remains intact, allowing a number of possible internal definitive closure techniques. Fig. 1 describes an algorithm for managing an open abdomen.

Transfascial Tension-Bearing Closure Techniques

A distinct alternative to standard closure for management of the OA is a group of techniques collectively referred to as transfascial tension bearing closure techniques. Typical examples of such closures include the standard Wittmann Patch of hook and loop (Velcro) sheets and the Canica ABRA system. The guiding principle in all such techniques is to redistribute abdominal wall tension to a position lateral to the rectus sheath rather than to the medial portion of the abdominal wound, where the tension is highest in a standard closure. In doing so, these techniques are postulated to produce myofascial release by gradually lengthening the retracted oblique and transversus abdominis myofascial groups to regain abdominal domain.

The most recently described application of this technique has been popularized by the trauma and acute care surgical group at Cook County Hospital in Chicago and is known as the transabdominal wall traction (TAWT) method (http://www.stanmorepal.com). The TAWT technique takes advantage of a variation on the original Wittmann Patch whereby the same hook and loop (Velcro) sheets are used but are affixed lateral to the rectus sheath using heavy sutures passed through all layers of the abdominal wall and tied externally by a multicolored layer. The excess beneath the hook and loop sheets are protected by a semipermeable plastic adhesive barrier. The sutures then can be tightened gradually during serial abdominal washouts and adhesion barrier changes every 48 hours. The group at Cook County Hospital reports great success with this technique and has a near 100% rate of eventual abdominal closure, with only a relatively small number on average of tightening and washout procedures. A standard vacuum suction dressing is applied on top of the wound between tightening procedures. Once a midline tension-free closure can be obtained with the TAWT system, a layered closure can be performed either primarily or via a retromuscular approach. The retromuscular space is developed and the posterior sheath is closed primarily. Then a mesh can be placed in the retromuscular position before closure of the anterior sheath and vacuum assisted management of the open cutaneous portion of the wound (Figs. 6 through 8).

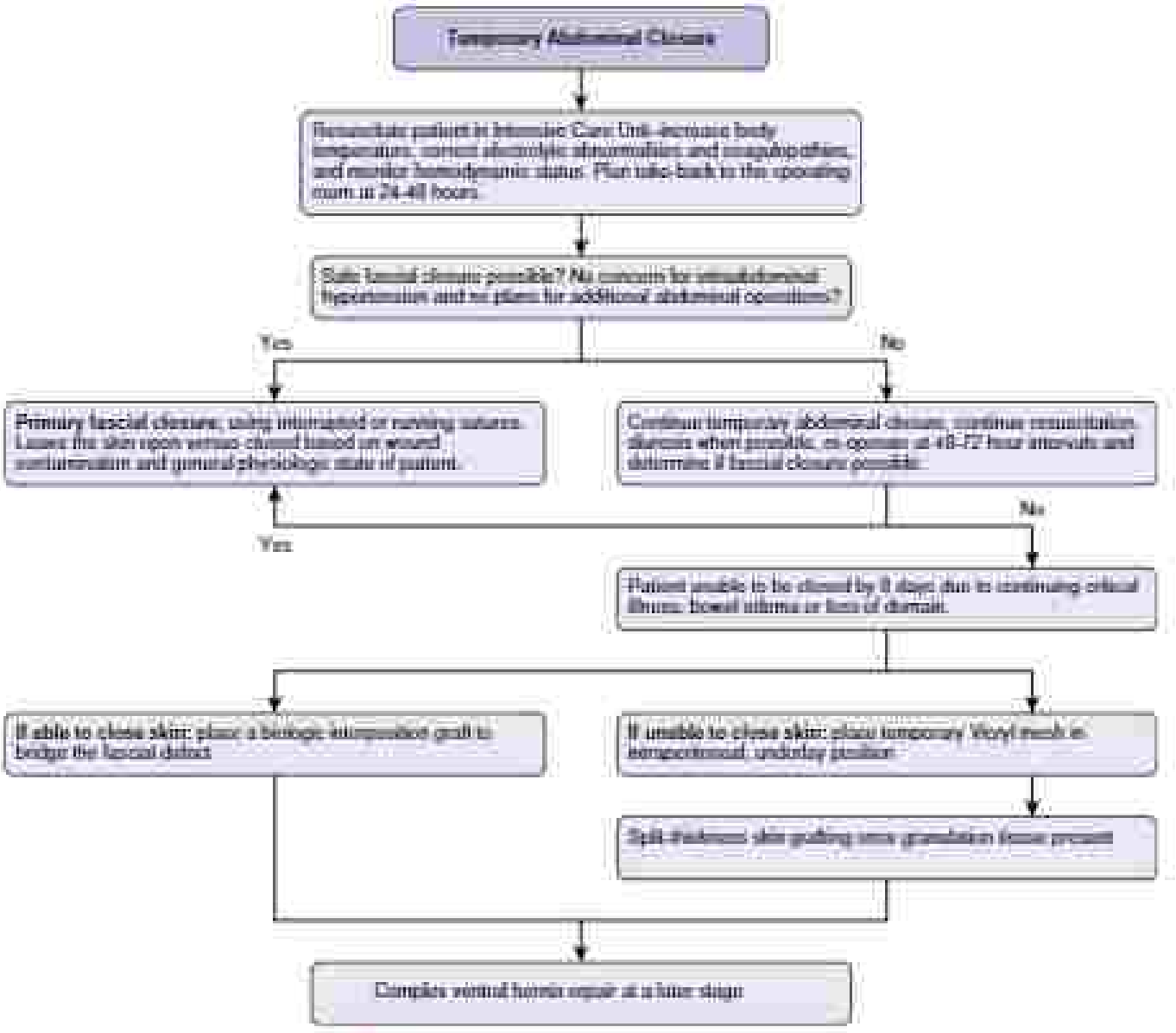

FIG. 3 Algorithm for management of an open abdomen.

FIG. 4 Human acellular dermal matrix (AlloDerm) used as an interposition graft where the fascia could not be primarily closed. Note that the human acellular dermal matrix is placed stretched and sutured in as tautly as possible. (Courtesy Richard Nichols, MD, John Lipkin, Rock, and the Innovative Surgery, Littleton, MD.)

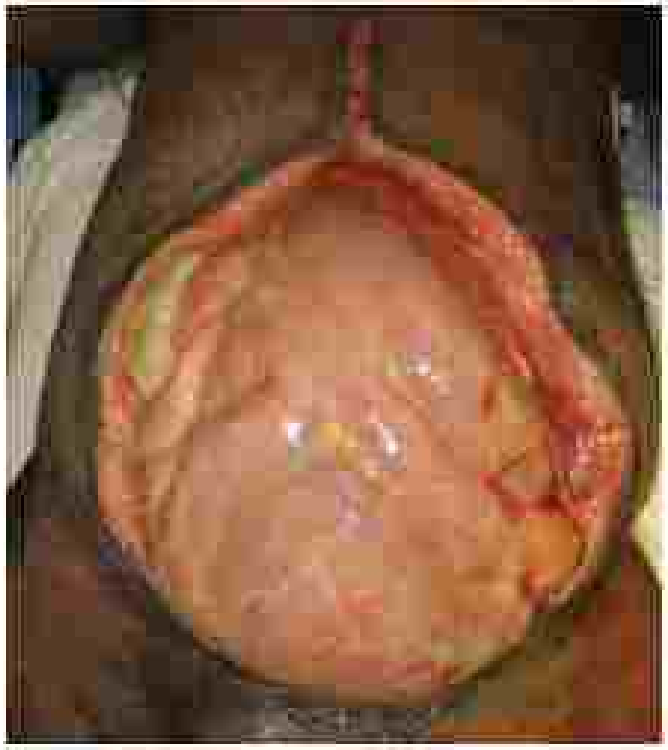

FIG. 7 Open abdomen after several dips of a temporary abdominal closure, where the fascia cannot be primarily closed and a mesh closure is required. (Courtesy Dr Elliott Haut, Johns Hopkins Acute Care Surgery Baltimore, MD.)

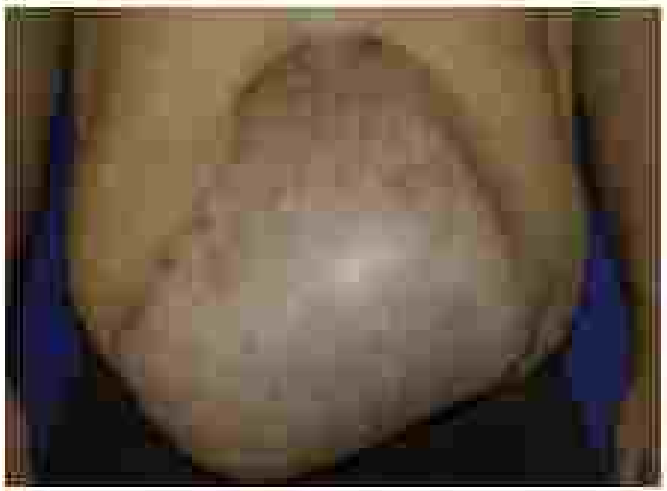

FIG. 8 Large ventral hernia after closure of the fascia with Vicryl mesh (Ethicon) and placement of split-thickness skin graft. (Courtesy Dr Richard Redett, Johns Hopkins Plastic and Reconstructive Surgery Baltimore, MD.)

LONG-TERM MANAGEMENT AND DEFINITIVE ABDOMINAL WALL RECONSTRUCTION

The development of a significant ventral hernia is common in long-term survivors of OA management. Although hernia development is a risk factor regardless of the closure technique chosen for acute management of an OA, a hernia is expected in patients closed with an absorbable mesh and overlying skin graft. Careful planning is required before attempting to repair these hernias, and the patient must be completely recovered from the initial illness. The patient should also be well nourished and physiologically optimized.

Another important aspect is to allow sufficient time for remodeling of any adhesions that may have occurred between the mesh or fascia and viscera. In the case of Vicryl mesh and subsequent skin graft, one indicator of remodeling is the ability to pinch the mesh/skin graft structure away from the underlying abdominal contents. This separation indicates that the patient is ready for repair of the ventral hernia. Many general surgeons will request assistance from plastic surgeons, especially if tissue expanders or complex tissue rearrangement is required. The steps to reconstruction are:

1. Assess overlying skin and place tissue expanders, if necessary, before surgery.
2. Excise the skin graft and any previously placed mesh.
3. Perform extensive lysis of adhesions to release viscera from underlying fascia.
4. Reapproximate fascia, which may require one or all of the following:
   a. Raise large skin flaps and dissect skin and subcutaneous tissue from anterior fascia.
   b. Perform component separation, in which the aponeurosis of the external oblique muscle is transected longitudinally bilaterally, allowing the fascia to be pulled medially; the posterior sheath of the rectus may be similarly transected to gain further length.
   c. Use of mesh: if the fascia does not come together, mesh can be placed as an underlay (retrorectus position, above the posterior rectus fascia or intraperitoneally with fascia overlay) or as an interposition (bridging the fascial defect) graft; most authors suggest the use of ITALOM or other biologics for this purpose.
5. Onlay mesh on top of the fascia for reinforcement. If a ITALOM underlay or interposition has been placed, we may also apply a polypropylene mesh as an overlay. If no underlay was required, a polypropylene may be placed as an onlay mesh to reinforce the fascia.
6. Before skin closure drains can be placed in the subcutaneous space to draw off accumulated fluid.
7. Standard primary skin closure with staples or a hybrid skin VAC system as described by Soares and colleagues.

SUMMARY

In the appropriately selected patient, an OA can serve as a lifesaving component of an overall damage control strategy. Techniques to achieve eventual closure of the OA should include balanced resuscitation with crystalloid minimization, regular returns to the operating room, and a carefully selected approach to closure based on patient, surgeon, and institutional factors. Ongoing improvement in abdominal wall reconstructive techniques will continue to improve mortality and quality of life for patients who require damage control surgery or for those with ACS.

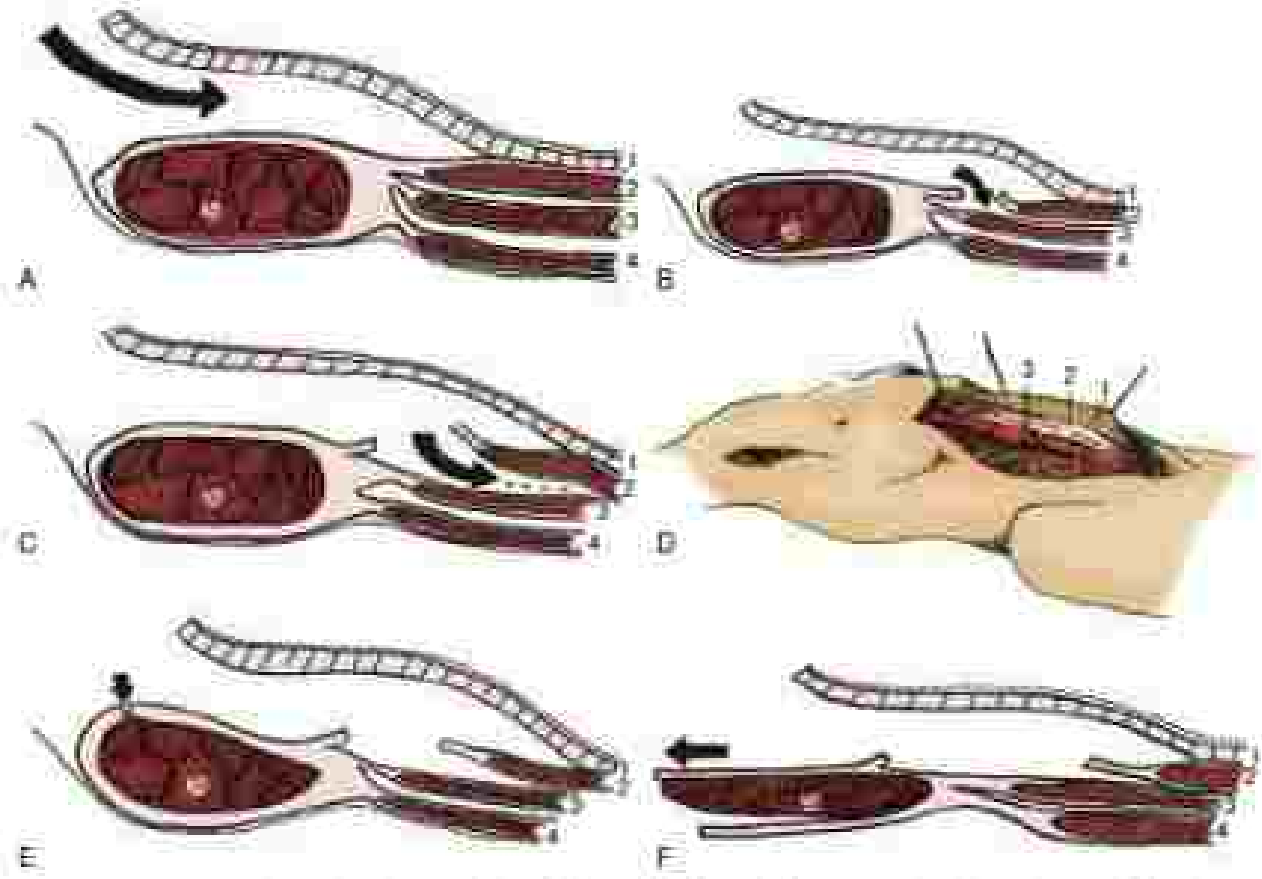

FIG. 1 Component separation technique for the repair of large abdominal wall hernias. After entering the abdominal cavity, the bowels are dissected free from the ventral abdominal wall. (A) The skin and subcutaneous fat (1) are dissected free from the anterior sheath of the rectus abdominis muscle (3) and the aponeurosis of the external oblique muscle (2). (B–C) The aponeurosis of the external oblique muscle (2) is transected longitudinally about 2 cm lateral from the rectus sheath, including the muscular part on the thoracic wall, which extends at least 5 to 10 cm cranially of the costal margin. (D) The external oblique muscle (2) is separated from the internal oblique muscle (3) as far laterally as possible. (E–F) If primary closure is impossible with undue tension, a further gain of 2 to 4 cm can be reached by separation of the posterior rectal sheath from the rectus abdominis muscle (5). Care must be taken not to damage the blood supply and the nerves that run between the internal oblique and transverse muscles (6) and enter the rectus abdominis muscle in the posterior side. (From Ibrahim MM, Maloney S, Ren C, et al. Component separation technique for the repair of large abdominal wall hernias. J Am Coll Surg. 2010;210(5):658–663.)

Suggested Readings

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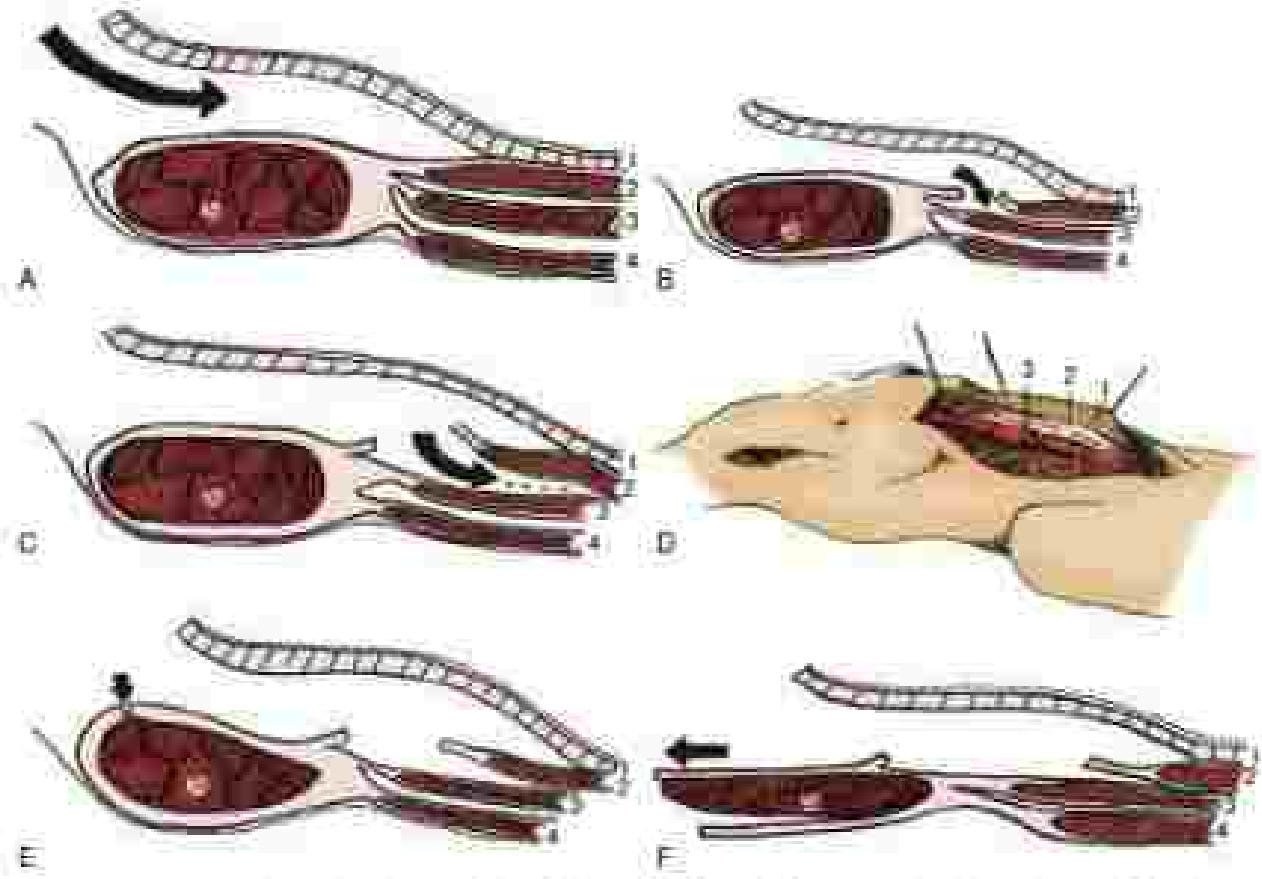
Management of Vascular Injuries

Andrew Schulick, MD, MBA, FACS

The management of vascular injuries is determined by both the location and the nature of damage as well as the presence of associated trauma. Despite advances in care, major vascular injuries remain associated with significant morbidity and mortality. The general principles of trauma resuscitation are addressed elsewhere in this book. This chapter will focus on evaluation and management issues specific to injuries of major blood vessels of the neck, chest, abdomen, pelvis, and extremities.

INITIAL EVALUATION

Hard signs of vascular injury include (1) pulsatile bleeding, (2) expanding hematoma, (3) the presence of a bruit or thrill, and (4) evidence of ischemia, including the six P's (pain, pallor, paresthesias,



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BOX 1 Signs of Vascular Injury

Hard Signs

Pulsatile bleeding
Expanding hematoma
Presence of a thrill or bruit
Evidence of ischemia including (for a PI) (pain, pallor, paresthesia, poikilothermia, paralysis, pulselessness)

Soft Signs

History of significant hemorrhage
Injury in proximity to a major vessel
Nonexpanding hematoma
Diminished or asymmetric pulses
Unexplained hypotension or tachycardia

poikilothermia, paralysis, pulselessness). These hard signs are present; however, in the minority of patients with vascular injury limited, evidence of injury may present more subtly, as soft signs, which include (1) a history of hemorrhage in the field, (2) injury in proximity to a major vessel, (3) nonexpanding hematoma, (4) diminished or asymmetric pulses, and (5) unexplained hypotension or tachycardia. Failure to recognize these signs can result in delays to diagnosis, so a high index of suspicion, based on history and the mechanism of injury, is warranted (Box 1).

Vascular injuries often occur in association with musculoskeletal injuries. Common patterns are listed in Table 1, and the presence of associated injuries should prompt a thorough vascular evaluation. Many vascular injuries, especially penetrating wounds of the extremities, can be diagnosed and managed based on physical examination alone. Because computed tomography angiography (CTA) can be obtained rapidly and allows diagnosis of associated injuries, it has become the first line test in the investigation of vascular trauma and has largely supplanted conventional angiography for this purpose. Other useful diagnostic tests include segmental pressure measurements and duplex ultrasonography, neither of which require intravenous contrast, and both of which can be performed at the bedside without the need for patient transport. The utility of these tests, however, is highly operator dependent.

Before definitive treatment of injury to specific blood vessels, resuscitation is continued and is based on the principles of damage control. The goal is not necessarily to restore normotension, which may actually promote increased bleeding, but to maintain adequate organ perfusion while averting the deadly triad of hypothermia, coagulopathy, and acidosis. As a rule of thumb, this means maintaining systolic blood pressure in the 80 to 90 mm Hg systolic range, and liberally transfusing warmed blood products in preference to crystalloid, both to maintain oxygen carrying capacity (red blood cells) and to combat coagulopathy (fresh frozen plasma and platelets). Associated brain trauma, in which increased cerebral perfusion pressure is required, is an exception to the strategy of permissive hypotension. Refractory bleeding resulting from coagulopathy may be improved by the administration of factor VIIa and can be considered in extreme circumstances of refractory bleeding. Use of tourniquets, topical hemostatic agents, as well as pressure bandages and garments may all have a role in the initial management of vascular trauma, and should be familiar to and available for providers.

BASIC PRINCIPLES OF MANAGEMENT

After initial assessment and resuscitation of the trauma victim, the most important decision is to determine, based on the patient's condition, the type of intervention required. In the setting of a normal examination and physiologic stability, minor vascular injuries identified on physical examination and imaging studies can be followed serially, with intervention reserved for deterioration. Vascular injuries that may be safely followed include noncircumferential intimal flaps, nonflow limiting stenoses, small false aneurysms, and arteriovenous fistulae. The minority of these injuries will produce complications that require intervention, and most interventions, when necessary, can be safely deferred until more pressing, associated injuries are addressed.

In the severely injured patient, operative intervention often requires the coordination of multiple medical and surgical specialists, as well as early involvement of the blood bank. In the setting of damage control, which prioritizes physiologic stability over all else, definitive repair of extremity injuries may not be possible, especially if concomitant severe head, abdominal, or thoracic injuries are present. In these circumstances, temporary shunting or ligation of extremity injuries may be required for the sake of patient survival. In extreme cases, initial primary amputation may be necessary.

Operating rooms are ideally outfitted for both endovascular and open surgical procedures (hybrid operating room). Endovascular intervention has evolved into a robust complement to conventional surgery in the treatment of vascular injuries. Catheter-based interventions have highest utility to torso and proximal extremity injuries, as well as zone 1 and 3 injuries of the neck (see the following section). Endovascular techniques can also be used as an adjunct to open surgery to help control bleeding from vessels that are difficult to expose. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a high profile example. As is usual in all vascular surgical operations, wide preparation of the patient is mandatory, with an emphasis on access to autologous conduit for reconstruction. Polytetrafluoroethylene (PTFE) may be used if vein is not available or is not indicated. An operative approach with extensile exposure is preferred. Systemic heparin should be avoided if severe multiple injuries are present, including head, spinal cord, and torso. In these circumstances, local heparin can be administered to avoid operative thrombosis. Finally, decompression fasciotomy should be considered in extremity trauma to avoid the sequelae of compartment syndrome.

OPERATIVE TREATMENT

Neck

For management of penetrating trauma, the neck is classically divided into three anatomic zones (Fig. 1). Zone 1 is located below the clavicles and encompasses the thoracic outlet. Zone 2 is the region between the clavicles and the angle of the mandible. Zone 3 lies between the angle of the mandible and the base of the skull. Zone 2 is the most common zone for vascular injury. Because of the high density of critical structures in the neck, associated injuries are common. Management of vascular neck injuries is determined by presentation. Overtly symptomatic patients who present with major hemorrhage or asphyxiation require urgent airway control followed by immediate exploration for bleeding in the operating room. Asphyxiation in these patients may be due to airway or lung injury or tracheobronchial compression related to hematoma. Initial control of bleeding in zone 2 is often effectively achieved with manual pressure. For zone 3 injuries uncontrolled with manual pressure, an occlusive balloon can be gently advanced into the bleeding tract and inflated to give temporary control; alternatively, the opening and tract can be tightly packed with sterile gauze on the way to the operating room. Victims with less acute presentations undergo diagnostic evaluation referable to the suspected injury. The vascular system is most expeditiously evaluated with CTA. Evaluation of the aerodigestive system may include endoscopy and swallowing studies. For penetrating injuries of zone 1, echocardiography should be strongly considered to evaluate for pericardial effusion, suggestive of cardiac injury.

In terms of operative approach, penetrating zone 1 injuries may require either a median sternotomy for right sided or medial left sided injuries or a high anterolateral thoracotomy for left sided injuries. Incisions can be extended or combined into "clamshell" or "trap door" combinations for more extensile exposure. Exposure of zone 3 generally requires mandibular subluxation and division of the digastric muscle. In a bloody field, the exposure can be hazardous. Zone 2

TABLE 1 Patterns of Associated Musculoskeletal and Other Structures With Specific Vessel Injury

Vessel	Musculoskeletal	Other
Carotid artery	Cervical spine Mandible, Le Fort II/III facial fracture Skull base	Vertebral vein Carotid artery Trachea, esophagus
Vertebral artery	Cervical spine (vertebral foramina) Skull base	Jugular vein Carotid artery
Subclavian artery or vein	Clavicle Sternum, manubrium	Thoracic duct (left) Brachial plexus, recurrent laryngeal nerve
Axillary artery or vein	Shoulder, proximal humerus	Brachial plexus, axillary nerve
Brachial artery or vein	Midhumerus Biceps, triceps	Ulnar nerve Median nerve
Radial or ulnar artery	Elbow fracture or dislocation Radius, ulna, wrist Forearm and hand flexor tendons	Distal radial nerve (sensation) Ulnar nerve
Thoracic great vessels	Sternum, manubrium	Innominate vein Recurrent laryngeal nerve
Descending aorta	Thoracic spine Posterior rib fracture or dislocation Diaphragm	Esophagus Lung Left subclavian vein (blunt)
Abdominal aorta or vena cava Suprarenal Infrarenal	Thoracic or lumbar spine T12, L2 (with or without spinal cord) L2, sacral fractures	Zone 3 retroperitoneal hematoma Stomach, transverse colon, pancreas Duodenum, small bowel
Portal vein or Superior mesenteric vein	Lumbar spine fracture or ligament injury Rib fractures	Zone 1 retroperitoneal hematoma Duodenum (second or third portion), head of pancreas Portal triad (hepatic artery, common bile duct)
Renal artery or vein	Lumbar spine Posterior rib fracture or dislocation	Zone 2 retroperitoneal hematoma Kidney, proximal ureter, adrenal or gonadal vessels
Iliac vessels	Pelvic fracture Sacral fracture Sacroiliac joint disruption	Zone 3 retroperitoneal hematoma Cecum (right), sigmoid colon (left) Bladder, ureters
Femoral artery or vein	Pelvic fracture Acetabulum Proximal to mid-femur	Femoral nerve, sciatic nerve (rare) Inguinal ligament Spermatic cord
Popliteal artery or vein	Dislocated or "floating" knee Distal femur, proximal tibia	Tibial nerve Calf compartment syndrome
Tibioperoneal trunk	Tibia, fibula Ankle fracture or dislocation	Tibial nerve, peroneal nerve (foot drop) Calf compartment syndrome

From Cronenwett JL, Johnston KW, Rutherford's vascular surgery, 8th ed. Philadelphia: Saunders; 2014:2622.

injuries are generally explored via incisions along the anterior border of the sternocleidomastoid muscle, but transverse incisions may also be indicated.

Once control and exposure have been achieved, and the extent of injury determined, a decision is made regarding the mode of repair. Clean arterial lacerations may be primarily repaired. Jagged disruptions may require interposition grafting. In general, autogenous saphenous vein is the preferred conduit. Because of the difficulty of exposure in zones 1 and 3, hybrid endovascular techniques can be extremely helpful to control, and in some cases are the preferred approach to management. Covered stent graft placement is especially useful for internal carotid artery injuries high in zone 3 and for the treatment of subclavian artery injuries.

Blunt cervical injuries may be a result of a direct cervical blow, basilar skull fracture, flexion extension or rotational forces, or clothesline type trauma. Screening should be performed for all patients with signs and symptoms of injury, and for those who present following high-energy mechanisms. CTA has largely supplanted contrast angiography as the diagnostic test of choice in a patient sustaining blunt cervical trauma and has proven to be highly accurate in detection of clinically significant vascular injuries. Blunt carotid injuries are most commonly classified using the grading scale developed in Denver by Biffl: grade 1, luminal irregularity or dissection with less than 25% narrowing; grade 2, dissection or intraluminal hematoma with 25% or greater narrowing, intraluminal thrombus or raised intimal flap; grade 3, pseudoaneurysm; grade 4, occlusion; and grade 5, transection with free extravasation (Box 2).

To prevent stroke, grade 1 to 4 injuries are treated with anticoagulation or antiplatelet agents. Recent reports have demonstrated equivalence between the two classes of drugs in stroke prevention. Since

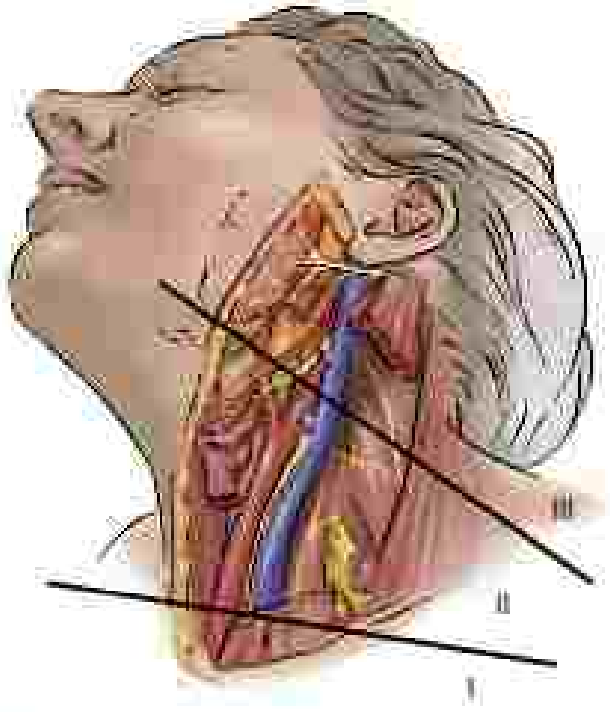


FIG. 1. Anatomic zones of the neck. Zone I is the thoracic outlet from the sternal notch to the cricoid cartilage. Zone II extends from the cricoid cartilage to the angle of the mandible. Zone III extends from the angle of the mandible to the skull base. *(From Rutherford, R., ed. Vascular trauma. In: Vascular surgery. 5th ed. Philadelphia: Saunders; 1996.)*

BOX 1 Grading Scale for Blunt Carotid Artery Injuries

- Grade 1: Intimal irregularity with <25% narrowing
- Grade 2: Dissection or intramural hematoma with >25% narrowing
- Grade 3: Pseudoaneurysm
- Grade 4: Occlusion
- Grade 5: Transection and extravasation

grade 3 lesions and progressing grade 2 lesions should be considered for treatment with endovascular stents, especially if associated with new neurologic events. Grade 1 lesions in poorly accessible locations are treated with endovascular stents if feasible, otherwise, open surgical repair is indicated.

Vertebral artery injuries are uncommon and are generally the result of penetrating trauma. The V1 segment (origin through the transverse foramen of C6) is surgically accessible, and injuries can be directly addressed either with reconstruction or ligation. The second (V2, in the bony foramina of the cervical spine) and third (V3, C2 to dural) vertebral artery segments are surgically hazardous and are best treated *either* by endovascular means (stent or embolization) *or* via open ligation of the V1 segment.

Chest

Thoracic great vessel injuries may occur after either penetrating or blunt trauma. The majority of injuries resulting from penetrating trauma result from gunshots and stabbings. Blunt vascular trauma is often associated with multisystem injury. Most victims with severe chest injuries die in the field. Those who are successfully transported generally arrive in the emergency department in hemorrhagic or cardiogenic shock. In selected cases, emergency resuscitative thoracotomy is indicated and is performed through a left anterolateral thoracotomy positioned at the fourth interspace. For right-sided injuries, the incision is extended across the sternum in a clamshell fashion. Evaluation entails inspection of the left lung and cross-clamping the hilum if necessary. Alternatively, after mobilization of the inferior pulmonary ligament, the lung can be torqued 180 degrees around the hilum to gain temporary control of bleeding. The pericardium is entered anteriorly to avoid the phrenic nerve. Cardiac injuries are controlled with mattressed nonabsorbable sutures such as 3-0 prolene; large needles are preferred. The descending aorta can then be cross-clamped to augment cerebral and coronary perfusion, and bimanual cardiac massage initiated. Absence of an intrinsic rhythm may warrant intracardiac administration of epinephrine as well as direct defibrillation. Mortality remains high.

For stable patients with penetrating trauma, physical examination and plain radiographs may provide evidence of major vascular injury and may aid in localizing missile fragments and their likely trajectories. CTA has rapidly become the first line test for screening for major injuries after chest trauma. Penetrating injuries revealed on screening evaluations generally require operative repair, with the surgical approach determined by the location of the injury. The ascending and transverse aorta, as well as the innominate artery and left common carotid artery are approached via a median sternotomy. The descending aorta and left subclavian artery are best approached via a left anterolateral thoracotomy. Endovascular approaches are increasingly used for definitive treatment. Utility of these less invasive approaches is determined by the location injury, the presence of associated trauma, and patient stability.

Following blunt chest trauma, the likelihood of major vascular injury is determined by the mechanism of injury, and the nature of damage is diagnosed with a combination of physical examination and imaging studies, typically chest radiography and CT scanning. The most common vessel injured in the aorta at the isthmus and is usually the result of rapid deceleration. The majority (80%) of victims of blunt aortic injury die at the scene. The majority of patients who arrive at the hospital have contained injuries, either intramural hematomas or false aneurysms at risk for free rupture. The risk of free rupture and exsanguination is decreased by prompt control of blood pressure and heart rate. Definitive repair in stable patients can be deferred up to 24 hours to allow adequate evaluation, resuscitation, and treatment of other life-threatening injuries. The exception is with concomitant major brain injury in which higher blood pressure is warranted. In these patients, aortic repair should proceed immediately.

Thoracic endovascular aortic repair (TEVAR) is the preferred approach for blunt aortic injury in anatomically suitable candidates (Fig. 2). Conventional open thoracotomy is associated with higher mortality and increased morbidity, including paraplegia, stroke, nephropathy, and pulmonary dysfunction. To increase the proximal seal zone with TEVAR, the left subclavian artery can be covered, if necessary, in the acute setting. Revascularization of the left subclavian (and vertebral), if required, can generally be deferred until the patient is more stable. A significant problem with TEVAR in young trauma victims is inadvertently undersizing of the stent graft in a hypotensive aorta, which can result in prior seal and graft migration. Use of intravascular ultrasound, which allows assessment of dynamic aortic diameter, has been useful to more accurately assess. Major thoracic venous injuries are generally treated with lateral venorrhaphy or, if necessary, ligation. Treatment of intrathoracic inferior vena cava (IVC) injuries may require cardiopulmonary bypass.

Abdomen and Pelvis

Abdominal vascular injury refers to trauma of large intraperitoneal or retroperitoneal vessels of the abdomen or pelvis. Most abdominal vascular injuries are penetrating in nature, either from gunshots or stab wounds, but major blood vessel can suffer damage after blunt trauma as well. The majority of patients with significant injuries

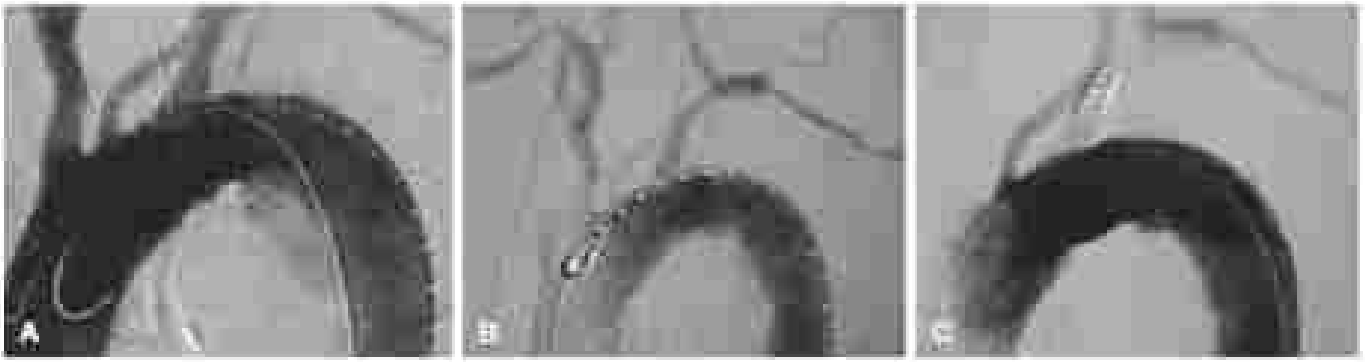


FIG. 2 Summit thoracic aortic rupture resulting from blunt trauma. (A) Contained pseudoaneurysm caused electively. (B) Intentional coverage of the subclavian artery after carotid-subclavian bypass to gain additional proximal landing zone. (C) Coil embolization to prevent endoleak from the proximal landing zone. (From Moore WS, Ahn SS: Endovascular Surgery. 4th ed. Philadelphia: Elsevier, 2013.)

arrive in the emergency room in profound hemorrhagic shock. Approximal patients may require resuscitative thoracotomy for survival. Use of REBOA as an endoluminal aortic cross-clamp to treat infradiaphragmatic exsanguination, has demonstrated utility, and has been used with success in some trauma centers (Fig. 3). In both stable and unstable patients, a rapid, surgeon performed ultrasound is useful in detecting tamponade or hemothorax.

Anatomically, abdominal vasculature is divided into three zones (Fig. 4). Zone 1 is central, zone 2 is lateral, and zone 3 is pelvic. Some authors distinguish a zone 4 encompassing the porta hepatis and the retrohepatic IVC. Most of the large vessels subject to injury are located in the retroperitoneum, making them difficult to quickly assess during exploration. As such, an organized approach based on mechanism of injury and location is required to optimize outcomes.

Abdominal vascular injury may present in one of three ways, including hemorrhage, as a contained hematoma, or with distal thrombosis. Patients present with either evidence of ongoing hemorrhage, or as physiologically stable. Unstable patients and those with injuries due to penetrating trauma generally require urgent operative exploration. In stable patients, CTA continues to prove its utility in localizing bleeding. This may be especially useful in stable blunt trauma victims in which CT findings may warrant further evaluation with angiography or operative exploration.

At exploration, active bleeding is controlled with direct compression or packing; compression of the aorta at the diaphragmatic hiatus is also an option. For proximal aortic injuries, control via a left thoracotomy may be required. The abdomen is explored systematically, and intraabdominal injuries are addressed or temporized for later repair. The approach to exploration of retroperitoneal hematomas depends on the mechanism of damage, hematoma location, and suspected vascular injury. Injuries resulting from penetrating trauma require exploration, an exception to the lateral zone 2 injury that has been adequately evaluated and characterized on preoperative imaging. Blunt injuries to zones 2 and 3 should be explored if the hematoma is pulsatile or expanding. Another indication for exploration of zone 3 hematomas are those associated with absent femoral pulses.

Injuries to the aorta, celiac artery, superior mesenteric artery, or left-sided zone 2 injuries are best exposed via a left medial visceral rotation (Fig. 5). The disadvantage is the time it takes to perform the maneuver. Infrarenal aortic injuries may be more quickly exposed akin to elective infrarenal AAA repairs. Limited aortic injuries are amenable to lateral repair. Larger injuries may require patch repair or grafting. The celiac axis and inferior mesenteric artery may be ligated if necessary. The superior mesenteric artery should be either repaired, bypassed, or shunted because ligation is not tolerated. Bleeding from the IVC or right-sided zone 2 injuries are best approached via a right medial visceral rotation (Fig. 6). Most IVC injuries can be repaired primarily. IVC ligation can be considered as a last resort, but results in significant morbidity. For zone 2 renal artery injuries not amenable to lateral repair, stable patients may require interposition grafting. The magnitude of the renovascular injury, warm ischemia time, and the patient's physiologic state will dictate if nephrectomy is the best option. Confirmation of a functioning contralateral kidney is required before nephrectomy. For zone 3 vascular injuries in which the bleeding vessels cannot be easily identified, the technique of total pelvic vascular isolation can be used by cross-clamping the abdominal aorta, IVC, and the external iliac vessels. Repair or bypass can then be performed as indicated. The common and external iliac arteries should be preserved to maintain limb viability; maintenance of perfusion is especially important in the hypovolemic patient to avoid limb ischemia. The hypogastric artery can be ligated with little consequence. Iliac vein injuries are often amenable to lateral repair. Analogous reconstruction can be considered in stable patients. For large injuries or in the unstable patient, the iliac veins can be ligated.

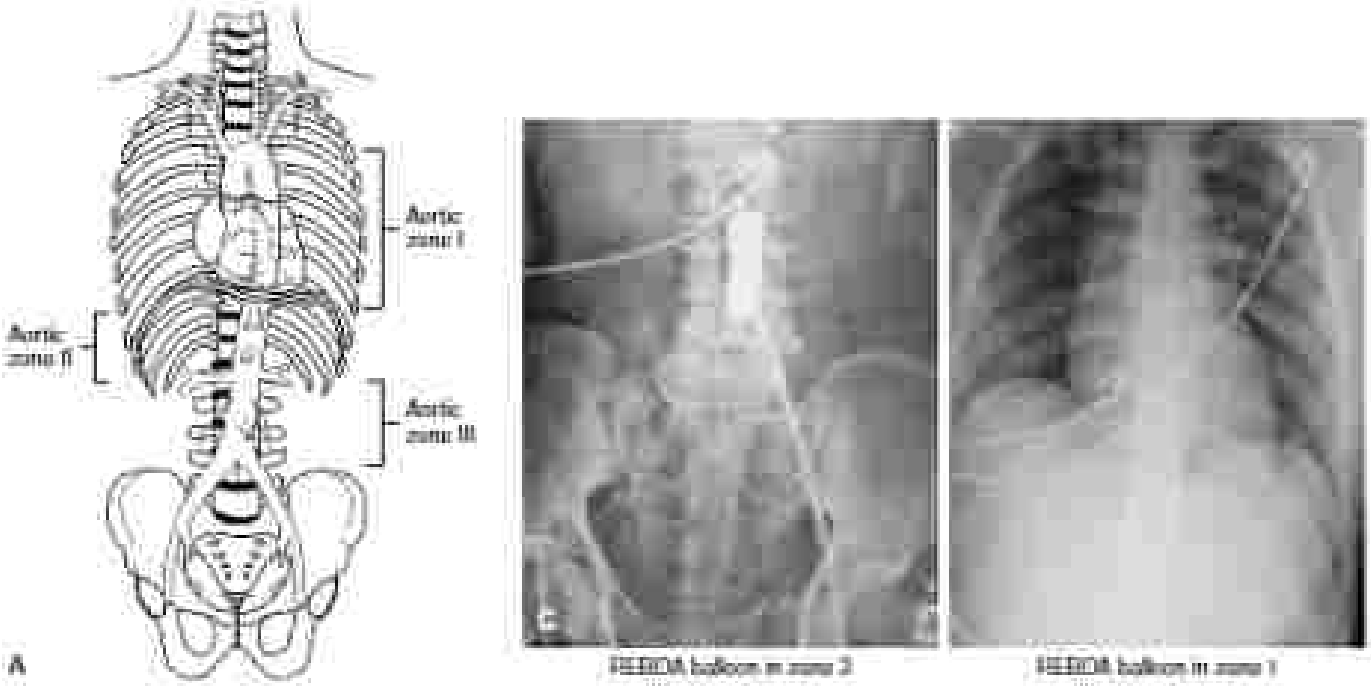
In damage control situations, the aorta can be shunted with an intraluminal large bore chest tube or equivalent; other bleeding is either controlled with gauze packing or with selective vessel ligation and shunting. When reasonable hemostasis is achieved, the abdomen may be closed temporarily for tamponade effect or may be covered with a wound VAC. The patient is brought back to the intensive care unit for further resuscitation before definitive intervention. When vascular reconstruction is required in a contaminated field, autologous vein is preferred although use of PTFE is acceptable. With severe enteric contamination, extraanatomic bypass such as axillofemoral or femoral-femoral bypass grafting is preferred.

Although most abdominal vascular injuries are managed surgically, indications for endovascular interventions continue to expand. In stable patients with localized, anatomically suitable, vascular injuries, the endoluminal approach avoids the morbidity of open surgery and minimizes potential exposure to contaminants. The techniques are particularly useful in major aortic branch vessels such as the renal arteries, especially when the injury involves flow limiting intimal flaps, false aneurysms, or fistulae (Fig. 7).

Bleeding associated with pelvic fractures deserves special consideration. Hemorrhage is due primarily to vascular shear injury, and is often primarily venous. Optimal treatment involves orthopedic stabilization of the pelvic ring, followed by angioembolization to treat arterial bleeding, and allowing venous bleeding to tamponade in the retroperitoneum (Fig. 8). Surgical exploration of these hematomas is not advised. In damage control situations or where bleeding persists, the pelvis can be packed. The technique of preperitoneal packing with or without laparotomy has also been described to augment hemostasis, and is performed via an extraperitoneal lower midline incision (Fig. 9).

Extremities

Most extremity vascular injuries can be diagnosed with a combination of physical examination and arterial pressure index measurement.



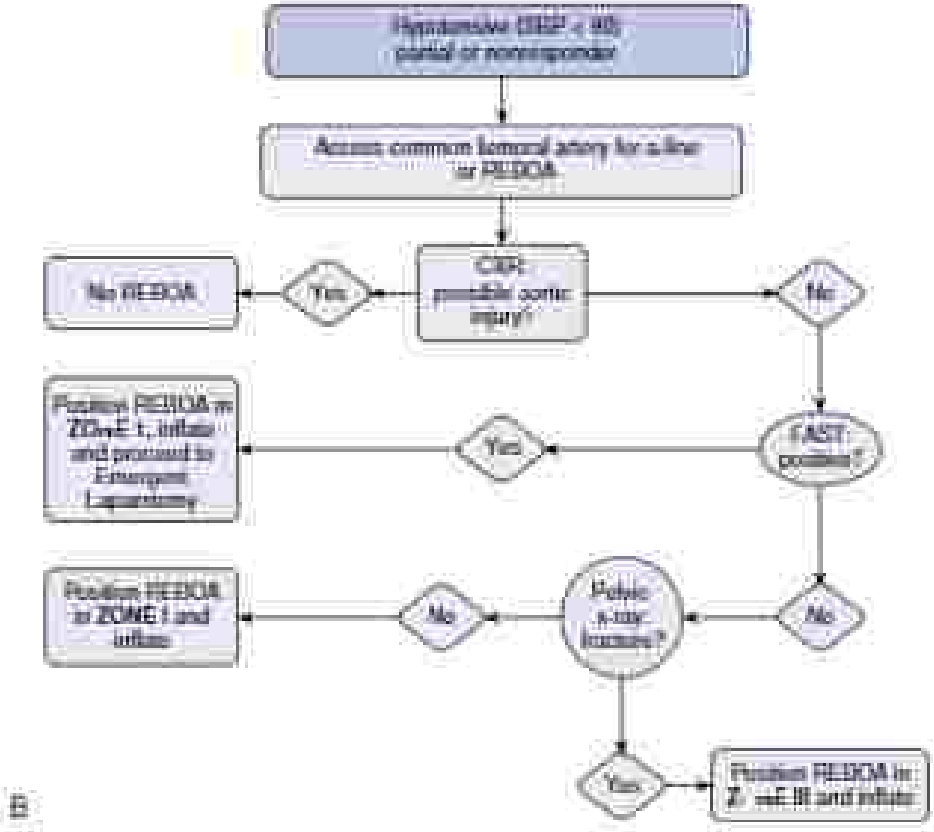


FIG. 3 Resuscitative endovascular balloon occlusion of the aorta (REBOA). (A) Occlusion zones of the aorta. (B) Algorithm for use of REBOA in abdominal and pelvic trauma. (C) REBOA balloon inflated in zone 3 (with contrast in the balloon) versus zone 1 (saline filling balloon). SBP, Systolic blood pressure. (A and B from Moore LJ, Moran CJ, Harvin JA, et al. Resuscitative endovascular balloon occlusion of the aorta for control of non-compressible truncal hemorrhage in the abdomen and pelvis. Am J Surg. 2016;212(6):1227-1235.e1. From Napolitano LM. Resuscitative endovascular balloon occlusion of the aorta: indications, outcomes, training. Crit Care Clin. 2016;32(3):435.)

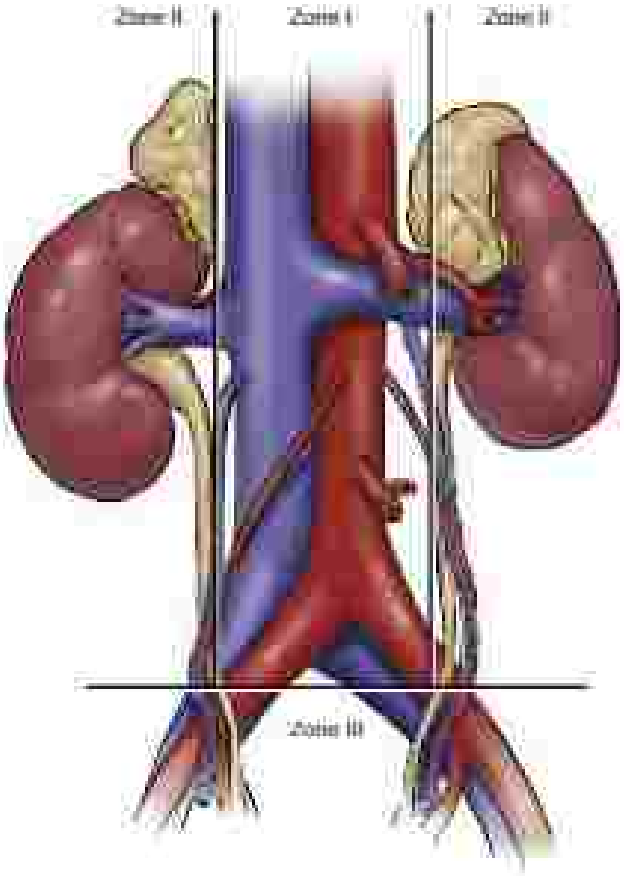


FIG. 4 Retroperitoneal zones. Zone I is central, zone II is lateral, zone III is pelvic. (From Asensio JA, Ka NR. Ed's Vascular Trauma. 3rd ed. Philadelphia: Saunders; 2014.)

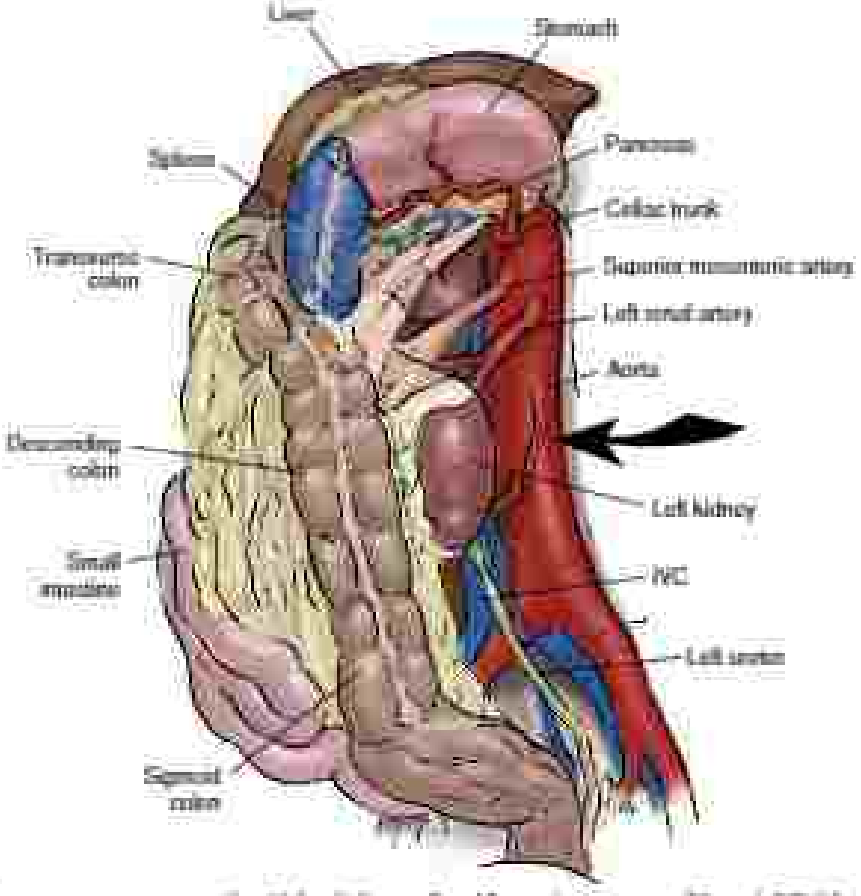


FIG. 5 Left medial visceral rotation to expose zone I and left retroperitoneal zones II and III vascular structures (Pfannes). IVC, Inferior vena cava. (From Asensio JA, Ka NR. Ed's Vascular Trauma. 3rd ed. Philadelphia: Saunders; 2014.)

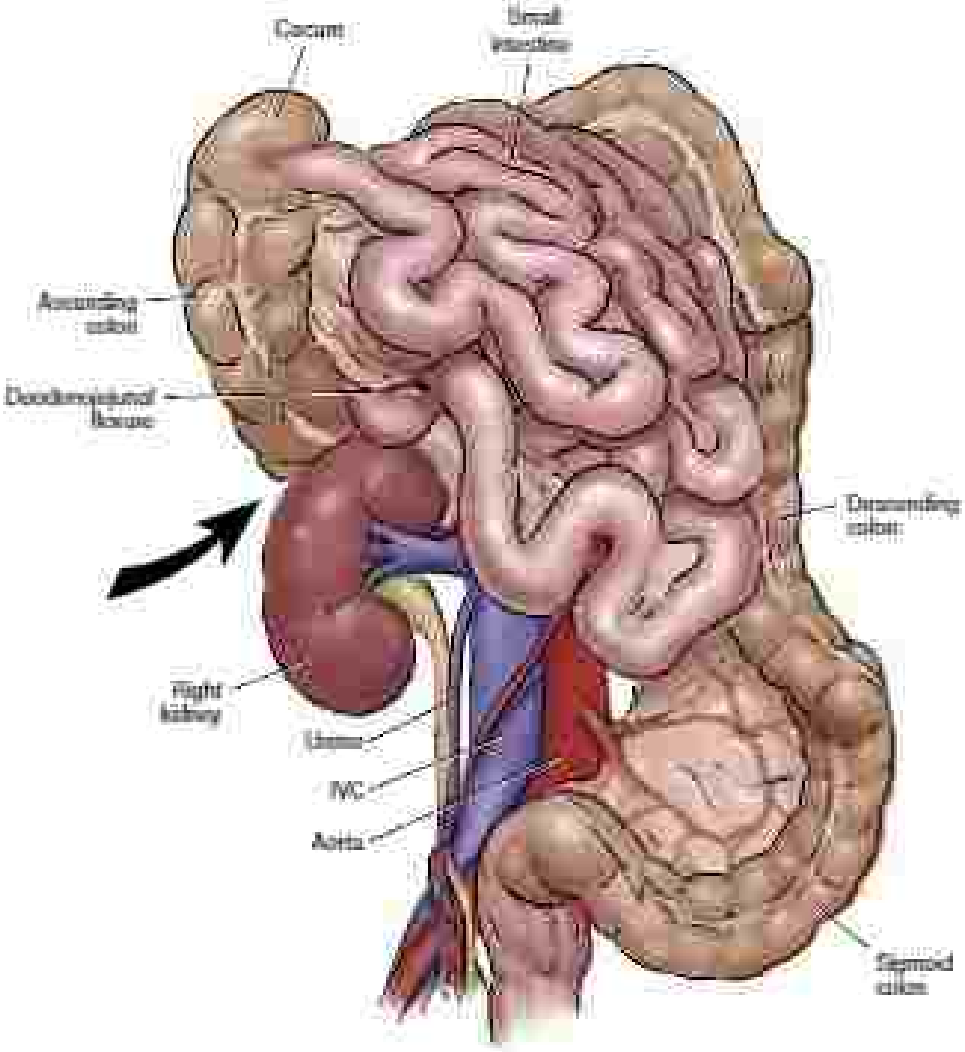


FIG. 6 Right medial visceral rotation to expose right-sided zone 2 and zone 3 vascular structures. Includes the Kocher and Cattell-Braasch maneuvers. IVC, inferior vena cava. (From Rasmussen TE, Tai NRM, Vascular Trauma, 1st ed. Philadelphia: Elsevier; 2015.)

The presence of hard signs of vascular injury, except arteriovenous fistula, mandates urgent operative intervention. Presentation with an ischemic limb should prompt consideration for systemic heparinization, which should be given in the absence of contraindications. The presence of an arteriovenous fistula itself, soft signs of arterial injury, or an arterial pressure index lower than 0.9 should prompt further investigation with CTA.

If possible, surgery should be performed in hybrid operating rooms, allowing endovascular interventions to be performed if needed. Temporary shunting may be indicated in some circumstances, to allow initial orthopedic stabilization of the badly fractured limb, to allow distal perfusion of an ischemic limb during reconstruction, and in the damage control situation to allow time for physiologic recovery prior to definitive repair (Fig. 10). Shunts may also be used as a bridge to replantation.

As a general rule, easily accessible arterial injuries should be addressed surgically. Once proximal and distal control is obtained, the injury can be assessed. If the injury results in little or no loss of vessel length, the defect can be closed in a transverse fashion with prolene sutures. For more substantial lesions, patch angioplasty or segmental interposition grafting may be required. In the heavily contaminated field, ligation and extra-anatomic bypass grafting may be indicated. In general, saphenous vein from an amputated extremity is the preferred conduit. PTFE is an acceptable alternative. Repairs and reconstructions should be covered with viable soft tissue to prevent anastomotic blowout.

Endovascular interventions are generally reserved for treatment of arterial injuries that are difficult to expose. Stent grafts are particularly useful in treating subclavian artery injuries, as well as some iliofemoral injuries. Angioembolization has become a useful adjunct in the treatment of some tidal vessel injuries when other central vessels are shown to be patent. Extremity venous injuries can be treatment with ligation, however vein preservation is preferred when possible. Compromised venous outflow will predispose to shunt thrombosis and the development of compartment syndrome.

Brachial Artery

The brachial artery is the most commonly injured upper extremity artery, and damage is most frequently the result of penetrating trauma. Supracondylar fracture of the humerus is the most common associated orthopedic injury. The brachial artery is explored through a medial longitudinal incision positioned in the groove between the biceps and triceps muscles. Through the antecubital fossa, a gentle S-shaped incision is used. For more distal brachial artery injuries, proximal control can be quickly obtained with a temporary upper arm tourniquet. Lateral repair or saphenous vein interposition grafting is performed as required. Venous injuries are ligated. Forearm fasciotomy may be required for prolonged ischemia.

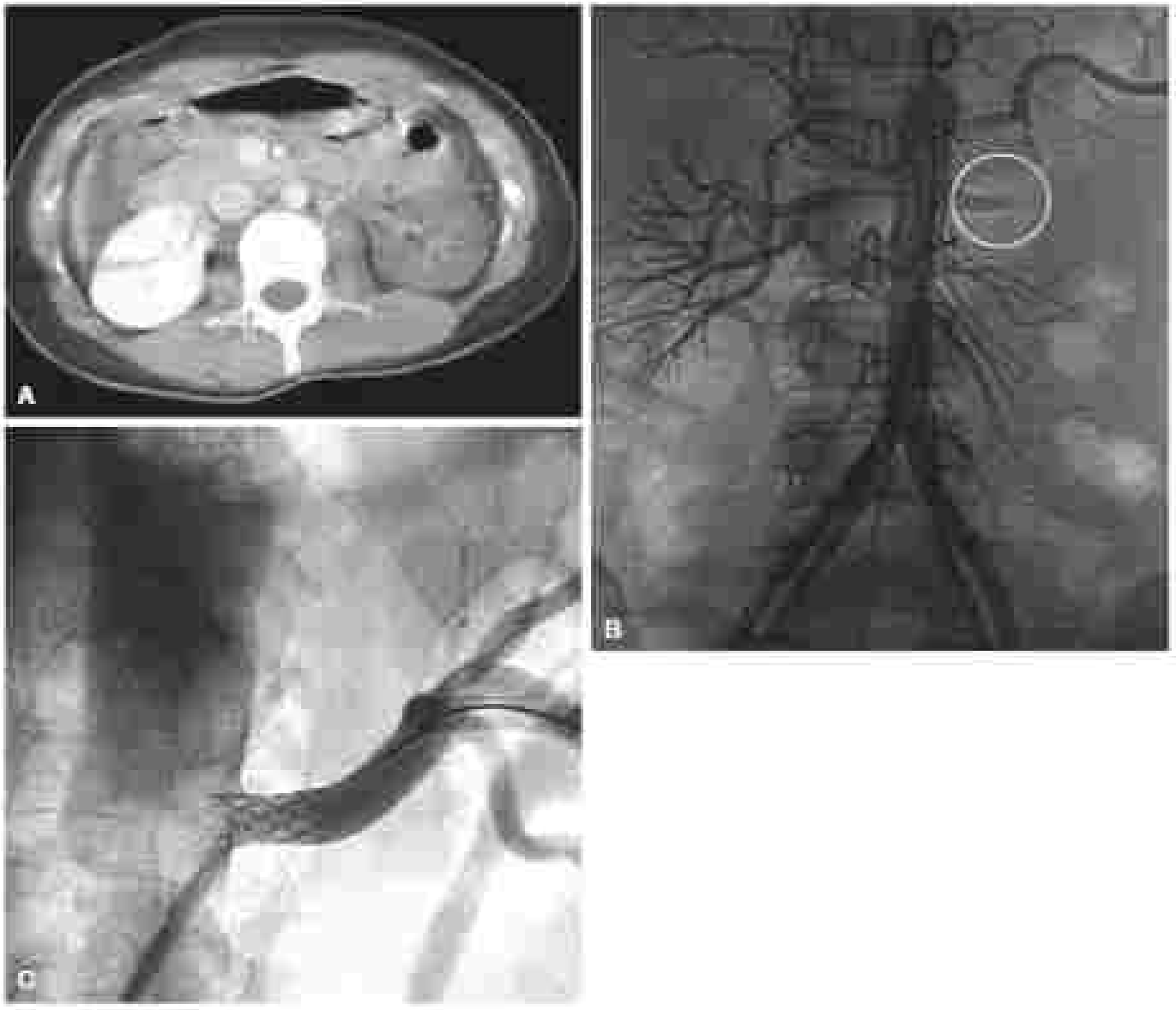


FIG. 1 Blunt injury to the left renal artery. (A) Computed tomography scan showing a nonfunctioning left kidney after a traffic injury. (B) Angiography shows complete occlusion of the renal artery (*circle*). (C) Revascularization with an endovascular stent. (From Salim AM, Perry RA. Endovascular surgery and percutaneous therapy. In: *Trauma*. 8th ed. Philadelphia: Elsevier; 2017.)

Forearm Arteries

Penetrating injuries are most common. An isolated radial or ulnar artery injury can be ligated before sacrifice, adequate collateral flow through the remaining vessel must be verified, usually by physical examination or pencil Doppler probe. Combined injuries of the radial and ulnar artery mandates repair of at least one of the vessels. The ulnar artery is generally larger and is the dominant vessel in the majority of individuals. The size difference is less pronounced in the distal forearm, so with distal injuries, repair should be performed on whichever vessels is less injured.

Femoral Arteries

The superficial femoral artery is the most commonly injured lower extremity artery, with the vast majority of injuries demonstrating hard signs of arterial damage. Common femoral artery injuries may require supra-inguinal retroperitoneal exposure of the external iliac artery for control. Exposure is accomplished via a transverse lower quadrant incision located just above the inguinal ligament. Common femoral vein injuries should be repaired when possible. The superficial femoral artery is exposed in a plane in front of the anterior edge of the sartorius muscle. In obese individuals, where landmarks are obscured, exposure is accomplished along a line extending from the anterior superior iliac spine to the tibial tuberosity. Most injuries require interposition grafting. The superficial femoral vein can be ligated if necessary but should be repaired if feasible. Consideration should be given to calf fasciotomy when ischemia is prolonged, especially in the circumstance of major venous ligation.

Popliteal and Tibial Arteries

The relatively fixed position of the popliteal artery, from the adductor canal to the gastrocnemius distally, make it prone to injury after posterior knee dislocation. In hyperextension, the popliteal artery is splayed across the tibial plateau, resulting in traction injury or vessel disruption. Pulse examination is often misleading and benign, and a

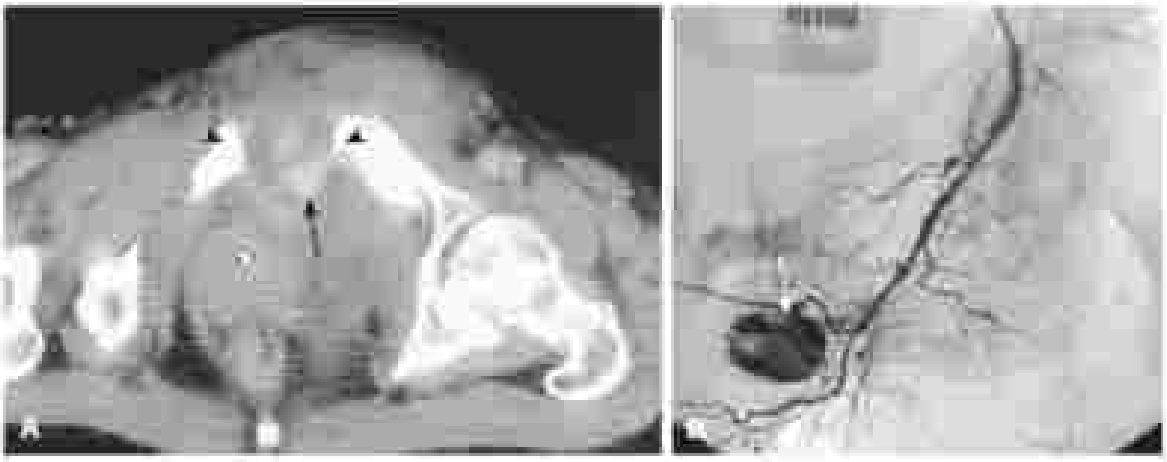


FIG. 8. "Open book" pelvic fracture with arterial bleeding treated with orthopedic stabilization and embolization. (A) Axial CTA demonstrating diastasis of the pubic symphysis (*arrowheads*) and extravasation (*arrow*) of contrast into a pelvic hematoma. (B) Selective left internal pudendal artery angiogram demonstrating extravasation (*arrow*). The bleeding was subsequently embolized. (*From Saadiyan JA, Lee MJ, eds. Vascular and Interventional Radiology. Oxford: Philadelphia; 2004.*)

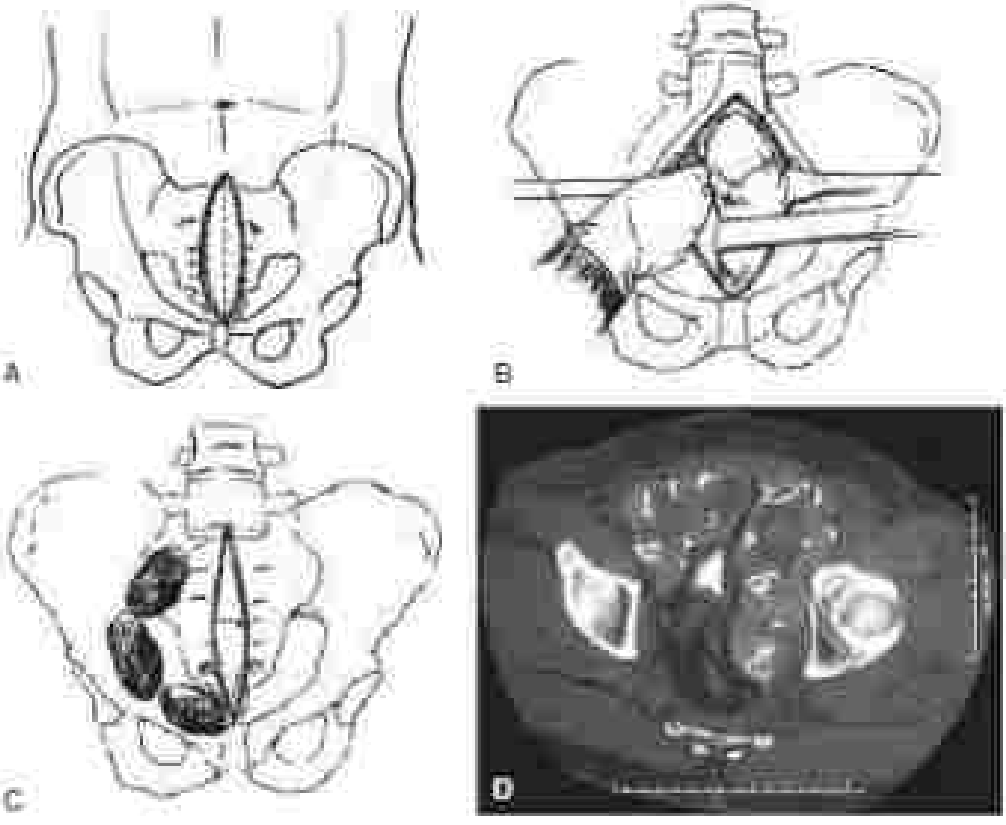


FIG. 9. Preperitoneal pelvic packing technique. (A) Lower midline incision; (B) blunt dissection of preperitoneal space; (C), packing the preperitoneal space; (D), postprocedure computed tomography scan demonstrating packs in situ. (*A–C, from Cothren CC, Osborn PM, Moore EE, et al. J Trauma. 2007;62:834–839; D, from Saadiyan A, Madura J, Skupa NL, et al. Extraperitoneal pelvic packing as salvage procedure to control massive traumatic pelvic hemorrhage. J Trauma. 2007;62:1004–1005.*)

high index of suspicion is required to avoid missing an injury. CTA is reasonable in a patient suspected of having sustained a traumatic knee dislocation. Bypass grafting is generally required for arterial reconstruction. Contralateral vein is generally preferred, but for a short interposition graft across the knee, PTFE is acceptable. Fasciotomy should be considered, especially when associated venous injury is present.

An individual tibial artery can be sacrificed if the remaining vessels are proven to be patent. Evaluation is aided with Doppler interrogation or angiography. If multiple tibial arteries are injured, vein interposition grafting is performed to the one best supplying the foot, as long as it is also amenable to soft tissue coverage at the site of the anastomosis.

Fasciotomy

Victims of vascular extremity trauma are at risk for developing compartment syndrome. If not diagnosed promptly, compartment syndrome results in significant morbidity and potentially in limb loss. History and examination features suggestive of compartment syndrome include: (1) hypotension in the field or continued hypotension with resuscitation, (2) delay in extremity reperfusion of

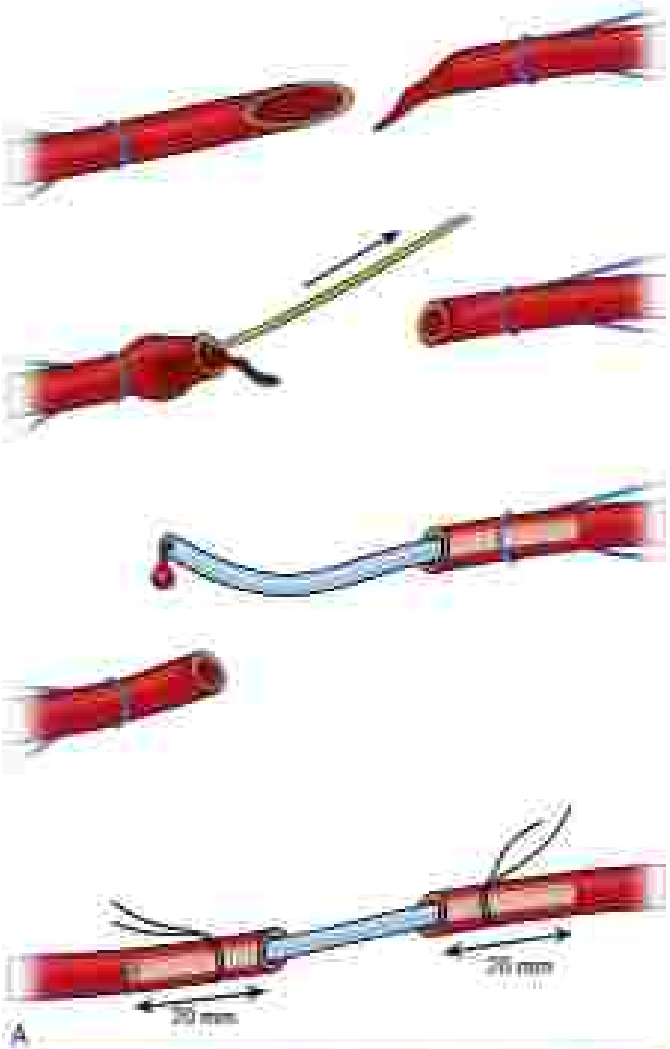


FIG. 10 (A) Sequential steps in management of a temporary vascular shunt. (1) proximal and distal control of the artery; (2) sharp debridement of injured vessel to healthy tissue; (3) shunt insertion; (4) secure tight fit after shunt placement. (B) Shunt in situ in a humeral vascular injury. (From Stannard A, Eliason JL, Rasmussen TE. Endovascular and open management of vascular injuries. Surg Clin North Am 2010;90:1211–1230.)

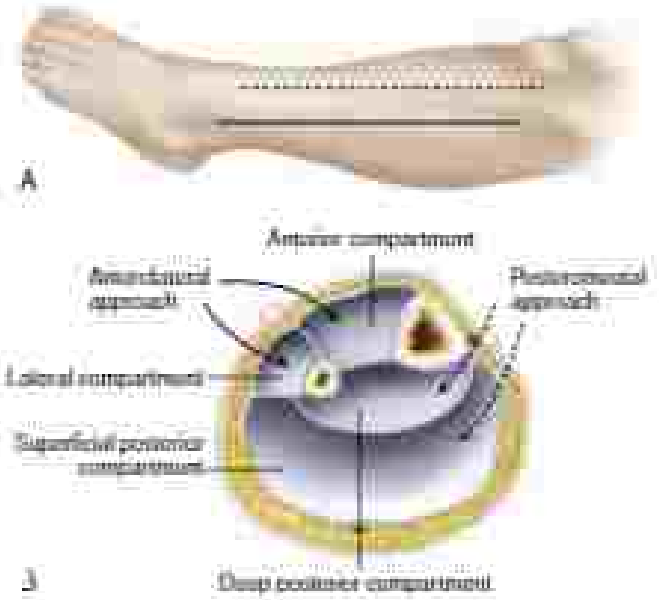


FIG. 11 Two incision approach to four compartment calf fasciotomy. A long anterolateral incision is made over the septum separating the anterior and lateral compartments. A separate but parallel posteromedial incision is made behind the tibia allowing access to the superficial and deep posterior compartments. (A) Bar axis view. (B) Cross sectional view. (From Schreiber MA, Aarabi S, Beekley AC, Operative Techniques: Orthopaedic Trauma Surgery. Philadelphia: Saunders; 2010.)

more than 3 to 4 hours, (3) limb pain out of proportion to the apparent injury; and (4) extremity swelling without significant injury. Extremity crush injuries and injuries involving both the artery and vein, especially in instances in which the vein requires ligation, are especially prone to developing compartment syndrome. There is an argument for performing fasciotomy in response to any of the high risk scenarios, the adage "if you think about doing a fasciotomy, do it" generally applies. When clinical context and examination are not clear cut, compartment pressure can be measured using a modified arterial line set up or using commercially available manometers. In general, compartment pressure greater than 30 mm Hg, or a difference between compartment pressure and diastolic blood pressure less than 30 mm Hg warrants decompression fasciotomy. Calf compartments require fasciotomy most commonly (Fig. 11).

SUMMARY

Because of the varied ways that vascular injuries can present, management can be complex, especially in the context of concomitant severe orthopedic, organ, or soft tissue injury. When presentation is subtle and the examination relatively benign, accurate management requires a high index of suspicion, with signs, mechanism of injury, and suggestive history should prompt further investigation, usually with CTA. The presence of hemorrhagic shock or hard signs of arterial injury (except intermittent bruits) are usual indications for prompt surgical intervention.

Patients in shock should be treated using the principles of damage control, permissive hypotension and liberal use of blood products are cornerstones of management and use of shunts are an important operative adjunct. For all vascular trauma patients, surgery should be performed in hybrid suites when possible. The patient should be prepped and draped for extensile exposure, with access to autogenous conduit if needed. Fasciotomy should be liberally used to prevent complications of unrecognized compartment syndrome.

The use of endovascular procedures in trauma has grown. [illegible] an adjunct for hemorrhage control [illegible] endovascular [illegible]

SUGGESTED READINGS

[illegible]

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ENDOVASCULAR MANAGEMENT OF VASCULAR INJURIES

Joseph A. Lee [illegible], DO; Sabina Fakhoury, DO

With a rise in the use of endovascular techniques, both in surgical training and in practice, the extension of this technique to the treatment of traumatic vascular injuries is not surprising. Endovascular techniques are now being used to treat some of the most dangerous traumatic vascular injuries encountered. This newer technology can assist with quick control of difficult injuries and lead to improved outcomes in trauma patients, especially when combined with traditional open techniques.

Endovascular options provide a less invasive approach to injuries that otherwise may require large, morbid exposures. In addition, the prospect of using a familiar endovascular approach to an arterial tree avoiding a difficult or rarely encountered open exposure is attractive to many surgeons, especially those with limited trauma experience. While it may be enticing to utilize a familiar elective approach to a trauma situation, it is important to remember that trauma alters normal anatomy in unpredictable ways. Often the best approach to a traumatic vascular injury is a combination of endovascular and open techniques, and any surgeon treating these complex injuries should be prepared to use a combination tool best suits each patient.

PRE-PARE PROCESS

The first step to a successful endovascular repair of a traumatic injury happens long before the injury itself occurs, with the creation and stocking of a hybrid suite. As previously stated, the best approach to most vascular trauma includes a combination of open and endovascular techniques. Although some of the following techniques can be performed in any operating suite with a traditional C-arm, a true hybrid operating suite, capable of both endovascular and open repairs, is invaluable.

Inventory including a wide variety of wires and catheters, stents and stent grafts provides necessary options in challenging cases with variable anatomy. As many trauma patients are younger than the average vascular patient, injury due to often smaller as well. This creates a need for stents and stent grafts in smaller diameter sizes. A well-stocked endovascular trauma suite may have a much different inventory than that which we use for the average vascular patient.

In addition to a hybrid suite and a well-stocked trauma inventory, having properly trained staff available at all times is important for any program that wishes to successfully treat traumatic vascular injuries in a hybrid manner. Nurses and technicians familiar with endovascular products and techniques are an essential part of any vascular trauma team. With a combination of the appropriate staff, inventory, and operating suite, all manners of vascular injuries can be treated successfully.

MANAGEMENT OF BLUNT THORACIC AORTIC INJURIES

Blunt thoracic aortic injury (BTAI) is one of the most common and most deadly injuries encountered in trauma patients. Identification requires a high grade of clinical suspicion, as many patients with BTAI present without [illegible] dynamic instability, and films of the chest are used to assess for gross aortic abnormalities during the initial trauma evaluation. Traditionally, abnormalities, including changes in the contour of the aortic knob or widening of the mediastinum, prompted further investigation with invasive aortography. Today, however, computed tomographic angiography (CTA) is used to evaluate any patients with a high suspicion for injury.

Grading of injuries is one of the guiding principles of management. The most widely used classification scheme, first proposed by Azizzadeh et al, includes four grades of BTAI: grade I (intimal tear), grade II (intramural hematoma), grade III (pseudoaneurysm), and grade IV (rupture) (Fig. 1). These grades can help make decisions regarding treatment strategies and timing in order to optimize results.

Most grade I injuries heal spontaneously. Serial imaging with repeated control is, therefore, a reasonable treatment plan. Imaging on or near the third post-trauma day confirms stability or regression of the lesion in the majority of patients. Nonoperative management is supported by the Society for Vascular Surgery (SVS) guidelines. Grade IV injuries, which rarely survive initial injury and transport to the hospital, have a similarly simple treatment algorithm. These patients should all proceed immediately for repair.

Grade II and III patients, however, present more challenging management decisions. For each patient, two main questions must be answered: (1) Is repair required? and (2) If so, what is the optimal timing of intervention? Although the 2010 SVS guidelines recommend

The use of endovascular procedures in trauma has grown. Translational interventions, such as REBOA, are being used enthusiastically as an adjunct in trauma resuscitation. Stent grafts have demonstrated utility in the definitive treatment of injuries that would otherwise be difficult or morbid to approach surgically. It is likely that indications for endovascular therapy will continue to expand.

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Endovascular Management of Vascular Injuries

Joseph V. Lombardi, MD, and Marissa Farmakes, DO

With a rise in the use of endovascular techniques, both in surgical training and in practice, the extension of this technology to the treatment of traumatic vascular injuries is not surprising. Endovascular techniques are now being used to treat some of the most dangerous traumatic vascular injuries encountered. This newer technology can assist with quick control of difficult injuries and lead to improved outcomes in trauma patients, especially when combined with traditional open techniques.

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Grading of injuries is useful to guide future management. The most widely used classification scheme, first proposed by Azarbal et. al., includes four grades of BTAI, grade I (intimal tear), grade II (intramural hematoma), grade III (pseudoaneurysm), and grade IV (rupture) (Fig. 1). These grades can help make decisions regarding treatment strategies and timing in order to optimize results.

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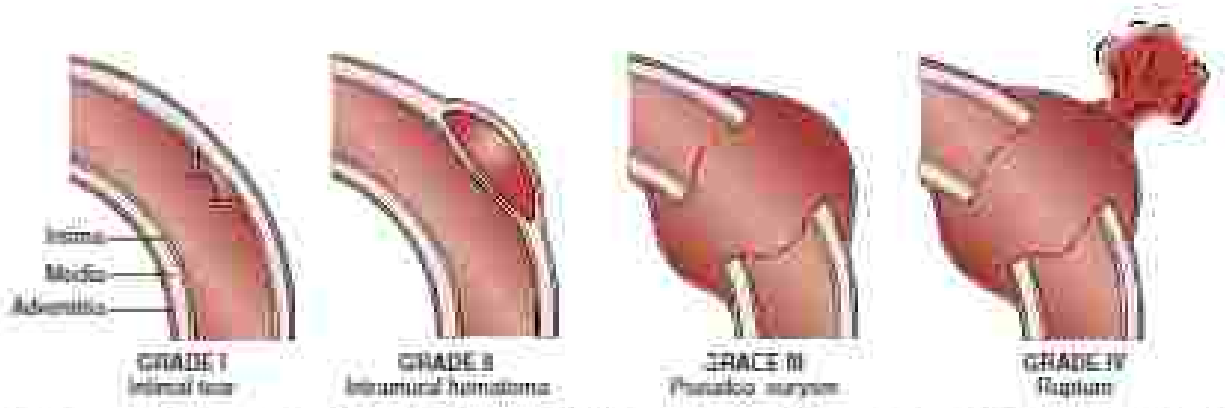

FIG. 1. Classification of traumatic aortic injury (from Cowan AR, Gleason TG, Eskandari MK, et al. Endovascular repair of traumatic thoracic aortic injuries: clinical experience and follow-up outcomes from the first multicenter registry. J Vasc Surg 2008;47:1008–13; discussion 1013–4).

intervention for all grade II and III patients, recent evidence is challenging this recommendation and deserves special review.

Several studies have reported the relative safety of nonoperative management in patients with grade II injuries. The infrequency of a true grade II injury has led several authors to group these patients together with grade I patients, reporting combined outcomes and further complicating the data. Other proposed classification schemes even group these two grades together initially. The true nature of disease of these intramural hematomas, however, remains unclear. Although it is likely that observing grade II injuries is safe, it is unclear and currently unsupported by official societal guidelines. Any observation mandates close follow up and careful impulse control.

Nonoperative management of aortic pseudoaneurysms (grade III BTAI) is also controversial. One review of 8 patients with grade III BTAI reported a 0% early aortic related mortality in patients treated with nonoperative management. A large systematic review of published reports revealed a less than 3% aortic specific mortality in patients treated nonoperatively but follow up was poor and results reporting was not standardized. All reports suggesting feasibility of nonoperative management document the need to perform this strategy only in "select patients." Unfortunately, predictors of failure have not been identified, and therefore choosing the correct patients, at this time, is impossible. In addition, continued follow up, an absolute necessity in patients with higher grade injuries managed nonoperatively, is famously impossible to achieve routinely, especially in trauma patients. A 1–3% risk of need for surgical repair in grade III patients has been reported, proving the importance of continued, reliable follow up. With an early risk of potentially preventable fatality, and a high risk of failure to follow up, the danger in observing grade III injuries is unacceptably high.

The above data suggest, however, that delaying intervention on grade II and III injuries while polytrauma patients are optimized is likely a safe option. A delay before thoracic endovascular aortic repair (TEVAR) has become increasingly common nationwide and is associated with improving national outcomes for BTAI patients. Close observation with impulse control and serial imaging is necessary, as an important caveat is that of the traumatic brain–injured patient. When purposeful hypertension is necessary to maximize cerebral perfusion, the principles of care are often at odds with the impulse control necessary to safely observe a BTAI. In these specific and not infrequent cases, we often elect to proceed with early TEVAR, allowing for permissive hypertension and the optimal treatment of any concomitant neurologic injuries.

Once intervention is deemed necessary, a surgical approach must be chosen. Traditional open repair has been compared with endovascular repair in several studies. TEVAR has been shown to decrease both mortality and morbidity, including spinal cord ischemia and renal failure, in patients with BTAI. For these reasons, endovascular repair is recommended over open repair whenever anatomically feasible, including in pediatric patients. National trends reflect these recommendations, with a sharp decrease in the number of patients with BTAI treated with open surgery being reported over time.

Several devices have been proven to be safe and effective in the endovascular treatment of BTAI. Percutaneous femoral access is the preferred method of access when suitable, although femoral cutdown or iliac conduit may be required in patients with diseased access vessels. Obtaining wire access across an injury can be challenging, especially in cases of transection. In these cases, careful use of a glidewire is often the best way to cross a lesion. Access into the true lumen of the healthy, proximal aorta can be confirmed with intravascular ultrasound or transesophageal echocardiogram, although in practice often a good angiogram is sufficient.

Landing in healthy aorta with at least 20 mm of neck proximal and distal to the aortic injury is an important tenet of endovascular repair. This often requires coverage of the left subclavian artery (LSA). In most patients, routine revascularization of the LSA is unnecessary and not recommended. However, in patients with stenotic or absent right vertebral artery or prior left internal mammary artery cardiac bypass, early revascularization should be performed. As the risk of spinal cord ischemia in BTAI patients is low, routine use of spinal fluid drainage is not recommended, although close postoperative evaluation of neurologic exam is important.

The ideal timing of surveillance after TEVAR for BTAI is unclear. Multiple studies have reported extremely low rates of reintervention following TEVAR for BTAI, suggesting low utility in frequent imaging. Problems leading to re-intervention predominantly occur early, usually within 3 months, for these reasons, several authors have suggested a decreased frequency of surveillance after stable scans at 1 year. Patient noncompliance is historically low in all trauma patients, and clear discussions with the patient and family are necessary to ensure any surveillance program is followed.

PENETRATING AXILLOSUBCLAVIAN INJURIES

Penetrating injuries to the axillary or subclavian artery are rare, but carry a high mortality. Open surgical repair is difficult and exposure is often time consuming. Endovascular therapy is gaining popularity as a first therapeutic treatment option for these unstable patients. Small studies have demonstrated superiority of endovascular repair to penetrating axillosubclavian injuries, with lower mortality and morbidity when compared with open surgical repair. A larger review of contemporary data from 11 large centers, however, points out the importance of patient selection, as in real-life experience endovascular repair is often used in more stable patients with less severe injuries. Endovascular repair is certainly an important tool that can assist in both control and repair of these challenging injuries.

brachial access to offer the quickest way to cross an innominate injury. This method can be performed percutaneously, although in practice a brachial cutdown is often the preferred method of choice. Brachial access avoids traversing the aortic arch prior to crossing the injury, a step that can be time consuming in patients with difficult arch anatomy. A combination of femoral and brachial access may be necessary for patients with difficult lesions, tortuosities, or small brachial arteries. Covered self expanding stents or balloon-expandable stents can be used, and a 10% to 20% oversizing is recommended.

Close postoperative evaluation with frequent physical exams is necessary, as this patient population is at particularly high risk for stent thrombosis. When appropriate, antiplatelet therapy should be initiated.

ENDOVASCULAR REPAIR OF TRACHEOINNOMINATE ARTERY FISTULA

tracheoinnominate fistula (TIAF) is a rare but feared complication of tracheotomy. Caused by pressure of the trachea from the tracheostomy tube tip or cuff against the overlying crossing innominate artery, TIAF is thought to be more common in patients where the cuff or edge of the tube reaches this area. This may be secondary to a low tracheostomy, a long tracheostomy tube, or patient anatomy.

The first important step in treating a TIAF is diagnosis. Although some patients initially present with overt hemorrhage, a herald bleed that stops spontaneously often precedes this event. TIAF should be suspected in any patient with a new episode of bleeding from their tracheostomy, especially if the tracheostomy was placed more than 3 days prior to the episode. Bronchoscopy remains the diagnostic test of choice, as CTA is rarely diagnostic. A lesion on the anterior tracheal wall adjacent to the pulsation of the crossing innominate artery is highly suggestive of fistula and should prompt repair. As the time between a herald bleed and overt hemorrhage is unpredictable, evaluation should be obtained emergently after any episode of bleeding.

Patients who present in extremis with active bleeding present a unique challenge. The first maneuver attempted should be to overinflate the tracheostomy balloon. If this is ineffective, digital compression of the innominate against the manubrium (the Chevy maneuver) can be attempted by placing a digit into the pretracheal plane, usually through the tracheostomy after orotracheal intubation. Throughout all attempts at control, the operating room (OR), preferably a hybrid suite, should be readied for emergent use.

The high mortality plaguing open repair of TIAF has led to many attempts at endovascular repair of these difficult lesions. Although the TIAF is considered a contaminated lesion, postoperative infectious complications occur in a minority of cases. It is therefore reasonable to attempt endovascular repair, with close postoperative follow up and lifelong antibiotic therapy. It should also be noted that the patient population experiencing TIAF is often fraught with comorbidities and the documented survival after these events, even after successful repair, is low. This has led many authors to compare endovascular TIAF repair to a palliative procedure.

Although coil embolization of the innominate has been suggested, stent graft placement across the lesion is usually considered first line therapy. Wire access across the lesion can be obtained via femoral approach, although carotid cutdown is often preferred as it allows for protection against distal embolization and easy access across the lesion without navigating the arch. The length and size of the innominate artery often makes graft selection for this area difficult, with thin grafts often being the most appropriate choice. Type II endoleak from a patent subclavian artery can be problematic (Figs. 2 and 3). In this case, a supraclavicular approach to the right subclavian allows for proximal ligation of the artery and subsequent carotid subclavian bypass (Fig. 4).

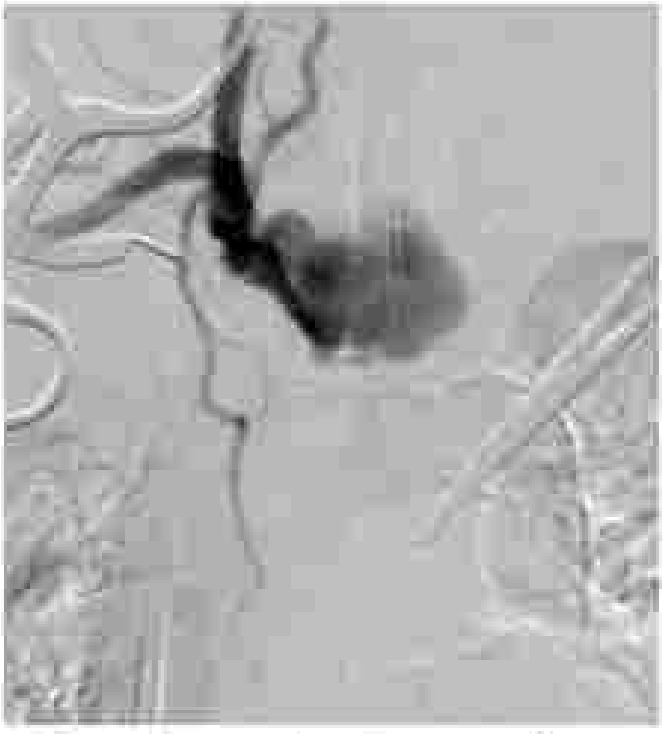

FIG. 2 Retrograde angiogram of innominate artery pseudoaneurysm. (From Hausman MA, Daugherty ME, Yu W, et al. Collagen-fill stent graft placement for a tracheoinnominate artery fistula. Ann Vasc Surg 2004;18[6]:[812-817].)

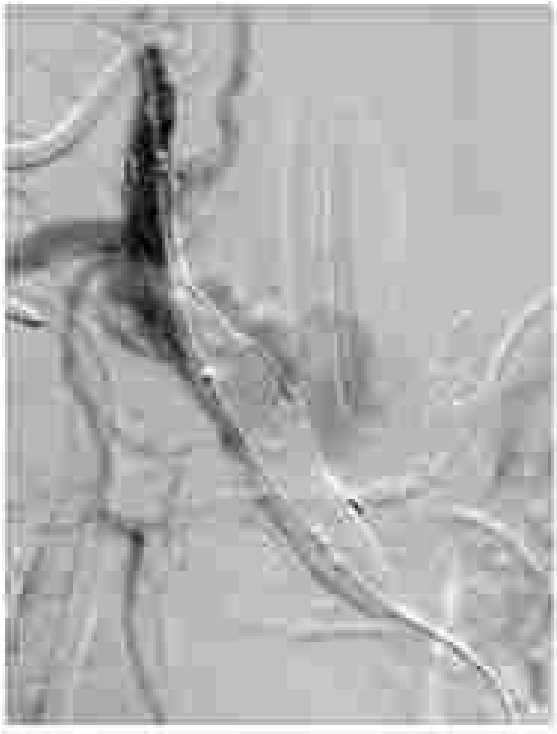

FIG. 3 Large type II endoleak from right subclavian artery after stent graft placement. (From Hausman MA, Daugherty ME, Yu W, et al. Collagen-fill stent graft placement for a tracheoinnominate artery fistula. Ann Vasc Surg 2004;18[6]:[812-817].)

FIG. 4 Computed tomographic angiography after stent graft exclusion of innominate artery pseudoaneurysm with carotid to subclavian bypass. (From Brunicardi FM, Dougherty MJ, Lyons R, Gallagher JD. Stent graft placement for a pseudoaneurysm of the innominate artery. Ann Vasc Surg. 2014;28(4):1032.e1–4.)

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

Injury causing hemorrhage from a noncompressible vessel in the abdomen or pelvis is notoriously difficult to control quickly and can lead to significant morbidity and mortality in trauma patients. In the past, noncompressible torso hemorrhage leading to hemodynamic collapse was treated with resuscitative thoracotomy (ie, ED) and cross-clamping of the descending thoracic aorta. An effort to improve upon this maximally invasive approach led to the development of resuscitative endovascular balloon occlusion of the aorta, or REBOA.

In REBOA, a balloon inserted through the common femoral artery is used to occlude the aorta either above the celiac artery or below the renal arteries, depending on the suspected location of bleeding. Aortic occlusion not only assists with control of hemorrhage, but also aims to increase cardiac and cerebral perfusion.

Insertion and use of REBOA requires several steps (Box 1). Each step has several guidelines, which, when followed, can help prevent complications. Step 1 requires accessing the common femoral artery. Traditionally, a femoral cutdown was required for safe cannulation; however, more recently, percutaneous access has been used with increasing frequency. The location of arterial access is important in the prevention of complications. A high stick can lead to retroperitoneal hemorrhage, while a low stick can lead to occlusion of the vessel by the device sheath and thrombosis. Accidental vasopuncture can cause iatrogenic arteriovenous fistula. The precise location for safe arterial access can be difficult to find, especially in a hypotensive, noncontrasted patient in the high stress environment of the trauma bay. Fortunately, ultrasound, a familiar tool readily available in the trauma bay, has been shown to significantly decrease the incidence of access complications after percutaneous arterial cannulation. In the hands of a skilled user, ultrasound decreases the time to cannulation, and should be used in all cases of REBOA placement.

BOX 1 Stepwise Approach to Implementation of Resuscitative Endovascular Balloon Occlusion of the Aorta

Step 1: Arterial access
Step 2: Positioning of the balloon
Step 3: Balloon inflation
Step 4: Management of hemorrhage
Step 5: Balloon deflation
Step 6: Device and sheath removal

Once the common femoral artery is safely accessed, the Seldinger technique is used to place an appropriately sized sheath. Although historically a number of different balloons and devices have been used, there is currently one Food and Drug Administration–approved device, the ER-REBOA (Prytime Medical). This device is inserted through a 7Fr sheath.

In step 2, the ER-REBOA device is advanced blindly into position with no fluoroscopic guidance or guidewire. This should occur without resistance. Preexisting arterial pathology or malpositioning may prevent easy safe passage of the device, and resistance should prompt abandonment of the technique. Other devices and balloons use a guidewire for positioning. Fluoroscopy or radiography is used to confirm zone positioning of the balloon, after which it is inflated. Many catastrophic complications have been documented secondary to poor balloon positioning. Therefore, it is important for practitioners to be familiar with the device they are using and the proper placement of any radio-opaque markers on that specific device.

After balloon inflation, all efforts should be made to quickly repair the patient's source of hemorrhage and subsequently deflate the balloon. Longer aortic occlusion times portend poor outcomes. There is some evidence that the hemodynamic stability provided by REBOA and the minimally invasive nature of the femoral sheath create a decreased sense of urgency, with some reports even documenting patients who have had CTAs performed during REBOA. Patients with an inflated balloon should be considered unstable and should be treated just as a patient after ED and aortic cross-clamping.

Once a patient has been stabilized, the balloon can be deflated. This maneuver should always be performed with the full awareness of the entire team, including anesthesia. Volume shifts and metabolic abnormalities can lead to hypotension after balloon deflation. Temporary partial or complete reinflation of the balloon can be helpful to augment blood pressure. If no drop in blood pressure occurs after deflation of the balloon, distal embolization or thrombosis should be suspected. After balloon deflation, the device is removed through the sheath. Again, any resistance should raise high suspicion for complications.

Finally, removal of the sheath can occur. In a patient with normal coagulation, the 7Fr sheath used for the ER-REBOA can be removed safely with manual pressure held for approximately 20 minutes. Basic postcatheterization care will assist in the prevention and identification of complications, including 4 hours of bed rest after sheath removal and close evaluation of the groin and distal pulses for at least 24 hours. Larger sheaths or any sheath in a coagulopathic patient may be unsafe for basic manual removal. In these cases, and any case when the location of initial puncture is unknown or erroneous, femoral cutdown with direct arterial repair is the safest option.

Reports in the literature regarding complications of REBOA are sparse. The Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry, a multiinstitutional database capturing REBOA use since 2013, reported only 9 complications after 83 uses. However, anecdotal reports from high-volume centers suggest

FIG. 3 Bilateral lower extremity ischemia requiring amputation and inferior mesenteric artery occlusion requiring colectomy.

that a multitude of vascular complications can, and do, occur. In our institutional experience, an IR-REBOA positioned in a dissection plane was advanced into the subrenal aorta and inflated, leading to bilateral lower extremity ischemia requiring amputation and bilateral mesenteric artery occlusion requiring colectomy (Fig. 3). Like any surgical procedure, understanding and evaluating the possible complications of REBOA are paramount to its safe and effective use. Notification of the vascular surgical team is included by some groups as an important early step in the REBOA process, helping to prevent, identify, and correct complications. This step is highly recommended.

Some small studies and the AORTA registry have documented improved outcomes after REBOA use when compared with RT. REBOA has also been shown to be an effective bridge to definitive hemostasis after severe pelvic trauma. However, questions remain regarding the safety and utility of this newly adopted technology. For example, the lack of documented complications in the literature compared with a high number of anecdotal complications is concerning, and suggests that the safety of this technique is not yet known. While in a dying patient, attempting a new or unproven technique may be justified, the literature currently does not support the safe extension of this technology to stable patients. This technique, therefore, should never be used as a replacement for traditional proximal control in open trauma or vascular cases.

ENDOVASCULAR MANAGEMENT OF INADVERTENT ARTERIAL PLACEMENT OF LARGE-BORE CATHETERS

Accidental arterial catheterization is an infrequent complication of a common procedure. Although in the femoral artery catheters can often be removed safely with manual pressure applied, accidental cannulation of the carotid or subclavian artery proves more difficult to manage. The subclavian artery is impossible to compress manually due to its anatomic location. For accidental carotid cannulation, there is an added risk of stroke due to thrombus formation on the catheter that may be dislodged upon removal. Also, as most internal jugular (IJ) venous cannulations are now performed under ultrasound guidance, accidental carotid cannulations frequently involve through and through I injuries that are not amenable to percutaneous closure.

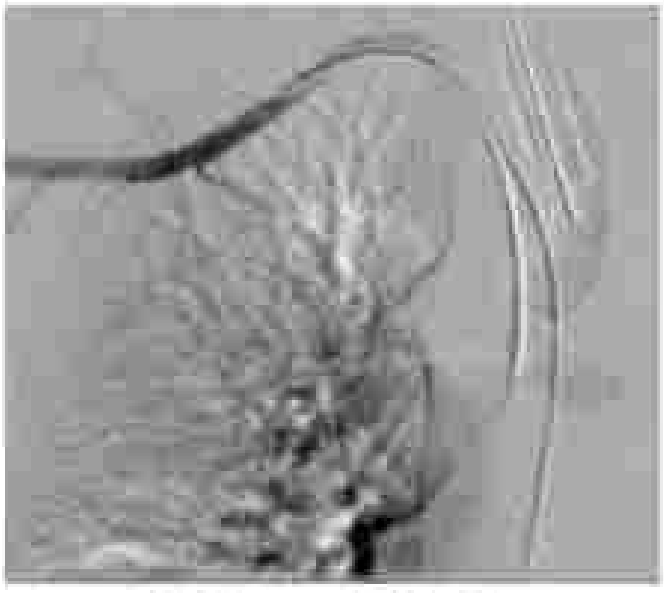

FIG. 4 Femoral approach to vessel.

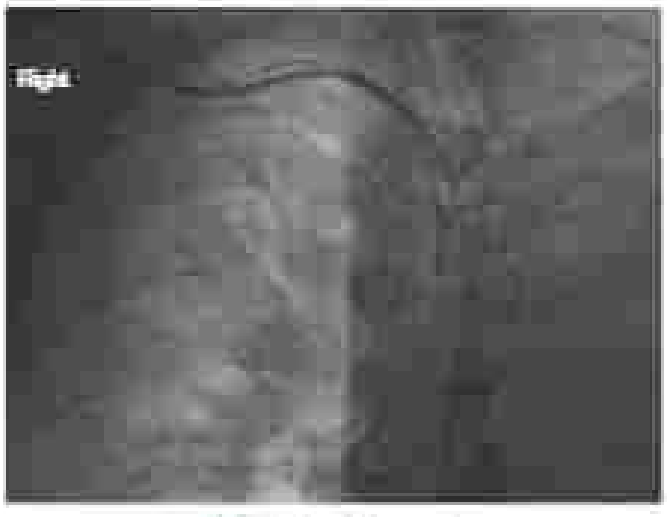

FIG. 5 Balloon placement.

Using a percutaneous closure device after accidental sheath placement has been evaluated and noted to be safe, even for carotid artery cannulations. If the accidental cannulation is identified early, before thrombus can form on the catheter tip, this is likely a reasonable approach. To prevent thrombus formation, if it were to heparinize any patient with a subclavian or carotid line as soon as it is identified. For additional safety, it is recommended that closure be performed in an OR or hybrid suite. It is our practice to obtain access to the vessel in question via a femoral approach (Fig. 4). A balloon can then be placed proximal to the injury in case proximal control is necessary (Fig. 5). The catheter is then removed and the closure device is deployed. After placement of the closure device is complete, a completion angiogram is performed to rule out any extravasation (Fig. 6). This is especially important for subclavian injuries, as manual compression is not possible in this location.

If a pseudoaneurysm or arteriovenous fistula is present at the cannulation site, placement of a covered stent over the area may be the best approach. Both self-expanding and balloon-expandable stents

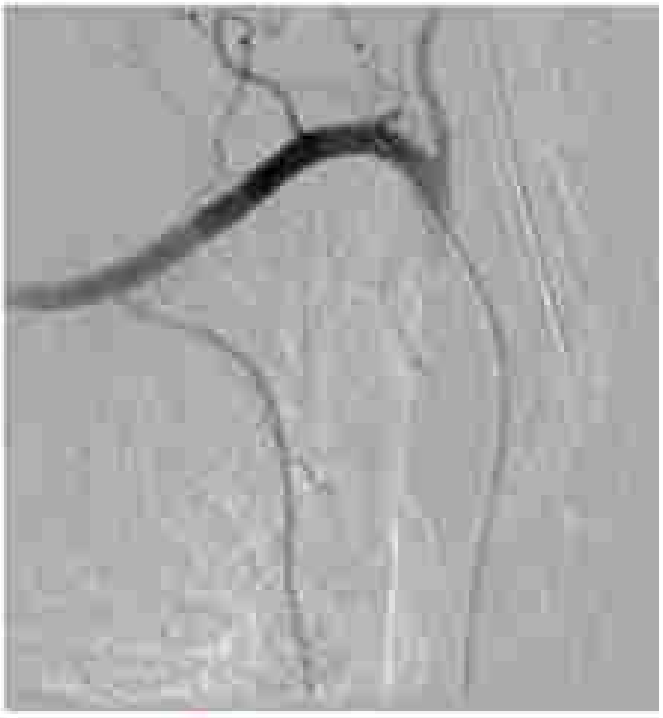

FIG. 8 Completion angiogram.

have been successfully used in this manner. In cases of accidental carotid puncture, the high likelihood of concomitant venous injury makes use of a covered stent superior to closure device as a treatment strategy. It is important to remember, however, that embolization during stent deployment to the carotid circulation is a risk. Each case must be individualized and open operative repair is often the safest approach for carotid injuries for this reason.

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Management of Extremity Compartment Syndrome

Charles E. Lucas, MD, and Anna M. [illegible]ood, PA-C

A compartment syndrome develops from excessive swelling of soft tissue within a confined space. This resultant tissue hypertension may exceed capillary hydrostatic pressure (25 mm Hg), thereby compromising oxygenation of muscle, nerve, and vessels, ultimately causing necrosis. Bywaters and Beall, in 1941, reported a lethal compartment syndrome during the World War II London Blitz. Following extrication of their neighbors with crushed limbs, the horse drawn drays transported them to nearby hospitals; those initially stable and oriented patients deteriorated that evening from extravasation of fluid into the crushed limb, tissue hypertension, muscle necrosis, rhabdomyolysis with myoglobinuria, renal failure, and death. Prevention of this fatal outcome requires an understanding of the basic pathophysiology. Elevated tissue pressure results from increased interstitial and intracellular fluid associated with ischemia/reperfusion, crush injury, or from external compression from a cast. The subsequent pathophysiology is comparable. The venous system develops outflow obstruction when tissue pressure rises. This compromises the lymphatic emptying into nearby veins, thus increasing interstitial fluid pressure, which impedes egress of intracellular fluid. This impairs nutrient flow from the capillaries, leading to cellular hypoxia and producing cellular ischemia, acidosis, muscle necrosis, myoglobinuria, renal failure, and death. Ultimately extensive debridement or amputation may be necessary.

Causes of Compartment Syndrome

Compartment syndrome may be caused by either external compression, internal tissue expansion, or a combination of both (Table 1). The classic scenario for increased external compression occurs when a tightly placed plaster cast or wrap is applied soon after long bone fracture. This external compression fails to allow for the expected soft tissue swelling, which typically follows injury. Any patient complaining of pain in this setting must have the cast bivalved or the wrap cut to relieve the pain. Masking the tissue hypertension with narcotics is potentially disastrous. This type of preventable tissue injury should never occur.

Most compartment syndromes result from an internal compartment expansion (see Table 1). The classic example is the ischemia/reperfusion injury. Artery occlusion due to injury, thrombosis, or prolonged application of a tourniquet leads to cellular ischemia with extensive tissue expansion once flow is restored. Patients with injury involving the femoral artery trifurcation or the popliteal artery are especially prone to severe distal ischemia when vascular reconstruction is delayed beyond 6 hours. The likelihood for compartment syndrome increases when the ischemic insult is combined with severe soft tissue injury typically associated with long bone fractures and/or venous injury requiring ligation. Other examples of the tissue ischemia/reperfusion syndrome occur in patients undergoing urgent abdominal aorta aneurysmectomy when there is technical difficulty reestablishing flow to one of the limbs, difficult reconstruction of the popliteal artery after severe injury (Fig. 1), and patients with arterial injury in a military setting where temporary shunting is practiced in preparation for vascular reconstruction. Prophylactic compartment decompression is routine when these soldiers have to be transferred to a higher level of care. Extensive combined injuries of bone, vessels, and soft tissues are seen after pedestrian motor vehicle collisions, high velocity rifle wounds, and close range shotgun wounds (Fig. 2).

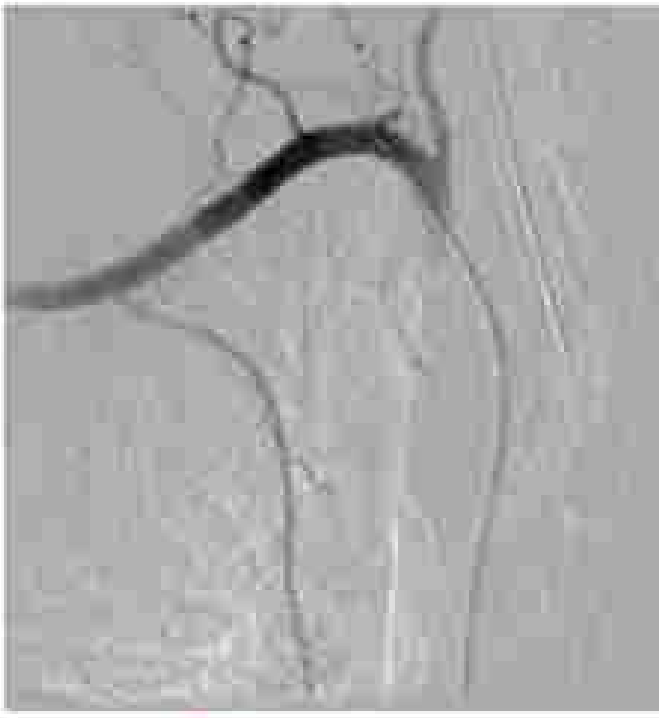

FIG. 8 Completion angiogram.

have been successfully used in this manner. In cases of accidental carotid puncture, the high likelihood of concomitant venous injury makes use of a covered stent superior to closure device as a treatment strategy. It is important to remember, however, that embolization during stent deployment to the carotid circulation is a risk. Each case must be individualized and open operative repair is often the safest approach for carotid injuries for this reason.

Suggested Readings

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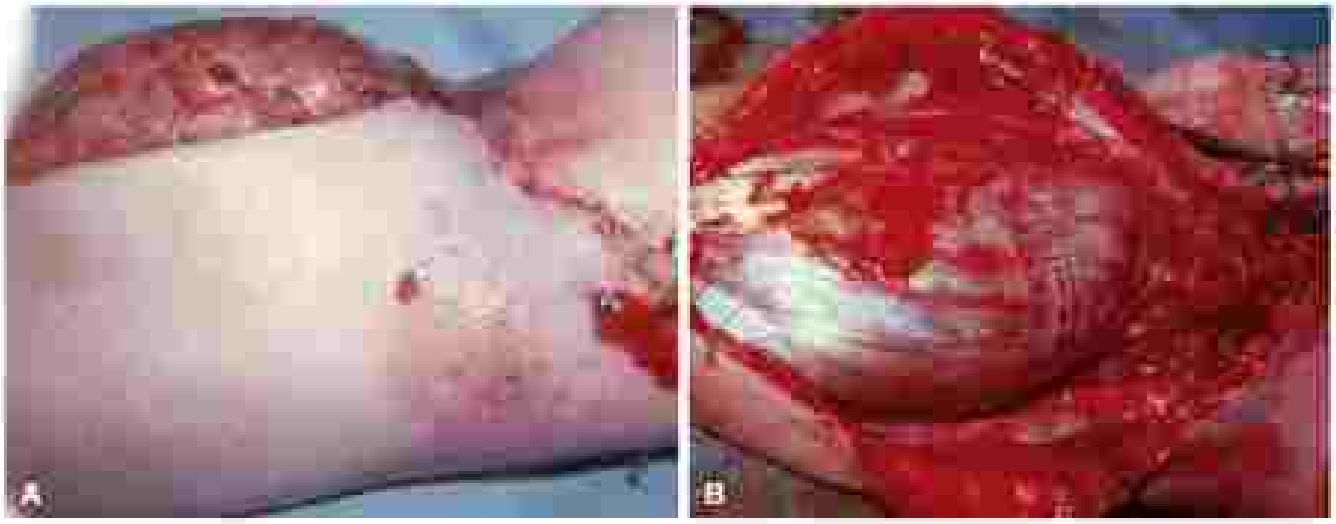

FIG. 1 (A) A delay in fasciotomy after repair of a popliteal artery injury and ligation of the adjacent vein results superficial muscle necrosis. (B) These areas of muscle ischemia and superficial death were minimally debrided and the underlying muscle gradually improved with frequent dry dressing changes over the next 3 weeks. Aggressive early debridement leads to loss of muscle fibers that would have survived.

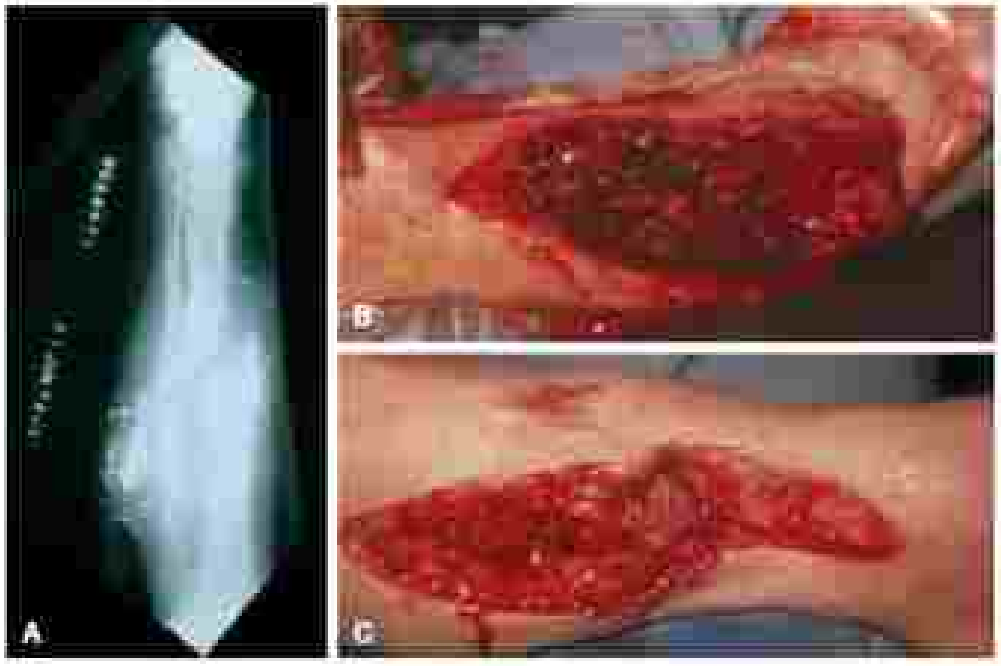

FIG. 2 (A) This 1-year-old patient had a close-range shotgun blast to the calf causing tibia and fibula fractures and extensive tissue damage with disruption of the peroneal and posterior tibial arteries. A split graft was recruited through the anterior compartment and extensions of the wounds (B) and a rent (C) wounds provided good compartment decompression. The wound was allowed to heal by second intent and by 3 weeks good granular tissue was present. He later received a skin graft and had a good long-term result.

Arterial shunting, external fixation of fractures, rapid vascular reconstruction, and extensive fascia decompression are often needed to salvage the involved limb.

Classic examples of both external compression and internal expansion include crush injury most commonly seen today in an industrial accident, a patient with circumferential burn of the extremity requiring intensive crystalloid resuscitation in association with a constrictive eschar, and vascular direct cellular insult from a high voltage electrical injury of muscle. Burns without eschar, limiting without circumferential swelling, and generalized sepsis rarely increase tissue pressure beyond hydrostatic pressure.

Venous occlusion due to thrombosis or impaired venous return from external pressure may lead to compartment syndrome (Fig. 3). The latter may occur when an intoxicated or even unconscious patient lies on the extremity for a prolonged period. Rhabdomyolysis with renal failure often accompanies this insult. Unusual causes of compartment syndrome include intramuscular or subcutaneous injection of illicit drugs causing abscess formation, extensive cellulitis, and tissue ischemia. This is commonly seen with soft tissue injection of "mixed jive" heroin, where attempted venipuncture is errant. Extensive debridement may be indicated (Fig. 4).

DIAGNOSIS

A thorough history directs the examiner to the diagnosis of compartment syndrome. The alert and cooperative patient should be assessed for the six P's, namely, pain, pressure, passive extension pain, paresis, paralysis, and pulselessness. Pain is usually described as throbbing

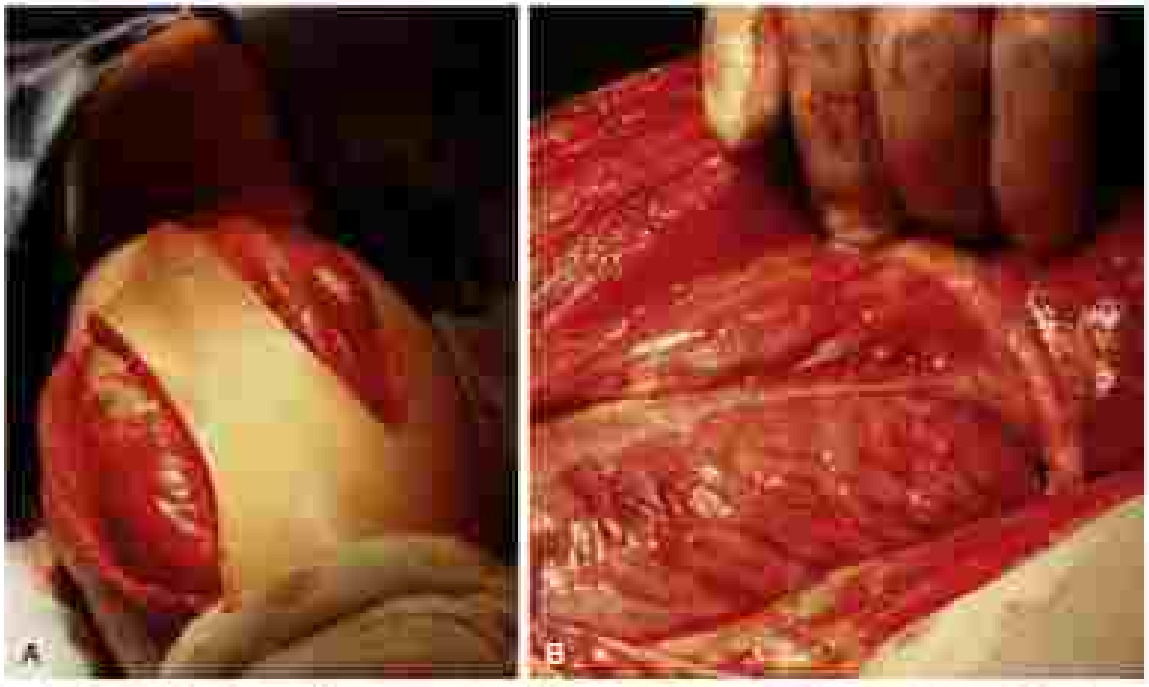

FIG. 3 This patient, admitted for a drug overdose, was seen in the critical care unit for a swollen right thigh, which was hard and tense and associated with neurapraxia. Medial and lateral thigh fasciotomies (A) revealed pale muscles, which rapidly pinked up with compartment decompression. (B) He went on to develop acute renal shutdown and required dialysis for 3 weeks, but all muscle group survived and he had good function following split thickness skin grafting.

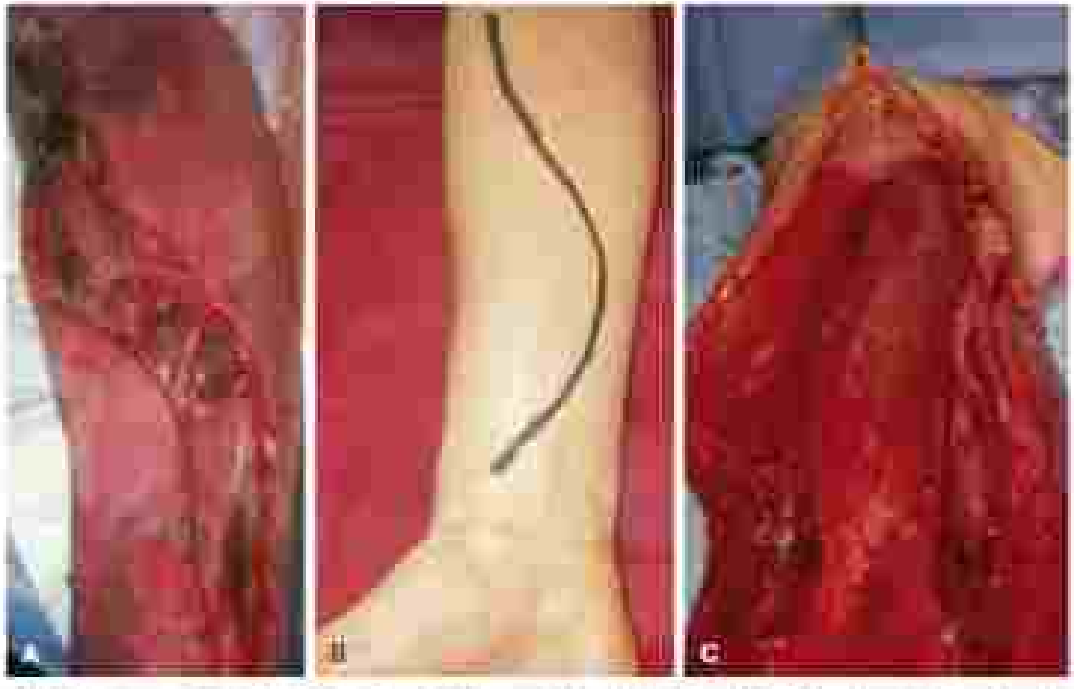

FIG. 4 (A) Injection of contaminated "mixed gas" heroin into the forearm subcutaneous tissues led to extensive soft tissue necrosis involving the forearm and distal arm with associated compartment syndrome. (B) Extensive soft tissue debridement and excision of the forearm fasciotomy incision proximal to include the anterior compartment of the arm (C) resulted in limb salvage and long-term reasonable function.

FIG. 3 The Stryker pressure monitoring system is a hand-held, solid-state transducer device that can be used to directly measure muscle tissue pressure. The syringe and manometer are contained in the special chamber and the directions for use are engraved on the back of this chamber.

and unrelenting. Pressure, the earliest objective finding, reflects the swollen, hard, and tender muscle. Passive stretch of the involved muscles increases the pain but is difficult to assess if there is an associated fracture. Paresis, or muscle weakness, is due to nerve compression and is a reliable finding with anterior compartment syndrome of the leg. The deep peroneal nerve, in the anterior compartment, innervates the web space of the great toe; paresis in this area suggests an anterior compartment syndrome. Paralysis indicates worse neural compromise. Pulselessness represents the end stage of compartment syndrome when the tissue pressure occludes a major artery, many patients with compartment syndrome still have a peripheral pulse.

Objective confirmation of a compartment syndrome in the unpaired patient requires direct tissue pressure monitoring. Compartment decompression, therefore, is usually performed on the basis of clinical examination without the need for tissue pressure manipulating. Patients under anesthesia or impaired by alcohol, street drugs, or head injury require tissue pressure monitoring. The direct needle puncture with a hand-held, solid-state transducer device (STIC catheter, Stryker Surgical) permits repeated measurements before and after decompression is provided (Fig. 3). Alternatively, a central venous pressure manometer filled with sterile saline and attached to an extension tube and an 18-gauge needle can be inserted into the muscle. The manometer is set at 40 cm H_2O and placed at the same level as the muscle when the stopcock is opened. The water column will either rise or fall. When the column rises, fasciotomy is needed; if the column falls, observation can be continued. A water column pressure of 40 cm H_2O is the same as 30 mm Hg.

COMPARTMENT DECOMPRESSION

Established compartment syndrome requires release of the constricting tissue; nonoperative therapies have no role. Release of the constricting tissue requires a long incision, which releases the skin, subcutaneous tissues, and underlying fascia. Subcutaneous fascial edges to be avoided. Debridement of ischemic muscle should be conservative since many muscle fibers that appear necrotic will survive, and the detrimental systemic effects of ischemic muscle will be avoided once the compartment is decompressed and the products of dead muscle can escape into the dressing (see Fig. 1). Nerve debridement should be avoided.

ARM COMPARTMENT DECOMPRESSION

The arm has two compartments, namely, the anterior compartment containing the deltoid and biceps brachii and the posterior compartment containing the triceps. Anterior compartment syndrome may occur after the inadvertent subcutaneous injection of heroin into

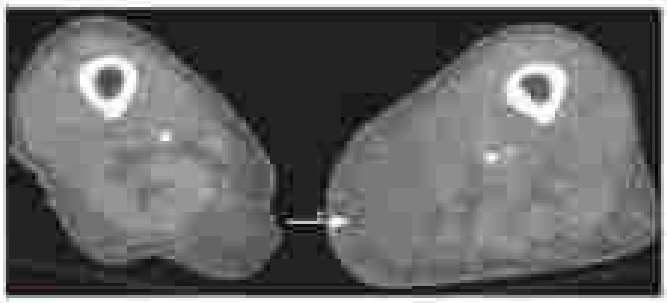

FIG. 4 This patient had severe sepsis, which was associated with myonecrosis of the gracilis and adductor muscle group. The left gracilis (right) is much smaller than the right gracilis (left). A long medial fasciotomy provided immediate relief of symptoms and allowed the underlying ischemic muscles to survive.

during attempted venipuncture. The resultant extensive cellulitis spreads rapidly, necessitating a long incision beginning just distal to the deltoid and extending over the biceps across the antecubital fossa in a curvilinear manner to the lateral portion of the forearm to the wrist. Compartment hypertension of both the anterior and posterior arm compartments more likely occurs with crush injury or long-term venous occlusion due to the patient sleeping on the arm while intoxicated. The posterior incision extends over the triceps muscle to the midline to about 3 cm proximal to the elbow. If necessary, decompression of the deltoid muscle can be achieved by extending the anterior incision proximally to the anterior cuff (see Fig. 4).

FOREARM COMPARTMENT SYNDROME

The forearm has three muscular compartments, the volar compartment contains the wrist and hand flexors, while the dorsal compartment contains the extensors; the lateral compartment contains the brachial radialis and extensor carpi radialis longus and brevis. Isolated volar compartment syndrome occurs after subcutaneous street drug injection, extravasation of intravenous infusions, or insect bites. Decompression of the volar compartment is achieved through an incision that begins at the lateral part of the elbow and descends medially in a curved manner for the proximal half of the forearm and then curves laterally down to just above the wrist (see Fig. 2). This incision also decompresses the lateral compartment. When all three forearm compartments are compromised, after severe burns or extensive trauma with long bone fracture and ischemia necessitating vascular reconstruction, a posterior decompression should be added. This incision extends from the radial head medially to the midportion of the arm and then laterally to the wrist (see Fig. 4).

THIGH COMPARTMENT SYNDROME

A thigh compartment syndrome is rare but may occur from crush injury, venous outflow occlusion, or extensive bone and soft tissue disruption from explosions or high-velocity rifle wounds (see Fig. 4). The thigh has three compartments with the anterior compartment containing the sartorius and the quadriceps femoris, the medial compartment containing the gracilis and adductor muscles, and the posterior compartment containing the biceps femoris, semimembranosus, and semitendinosus. Compartment syndrome of the thigh is likely to involve all three compartments requiring total decompression. Decompression of the anterior and posterior compartments can be achieved with an incision extending from the greater trochanter posterior laterally to just above the knee. The fascia overlying the vastus lateralis is identified so that the anterior compartment can be decompressed through an incision anterior to the intermuscular septum and the posterior compartment decompressed through another longitudinal incision posterior to the septum. Decompression of the medial compartment is achieved by a medial incision, which runs posterior to Hunter's canal and opens the fascia over the gracilis and the adductor muscles (Fig. 5).

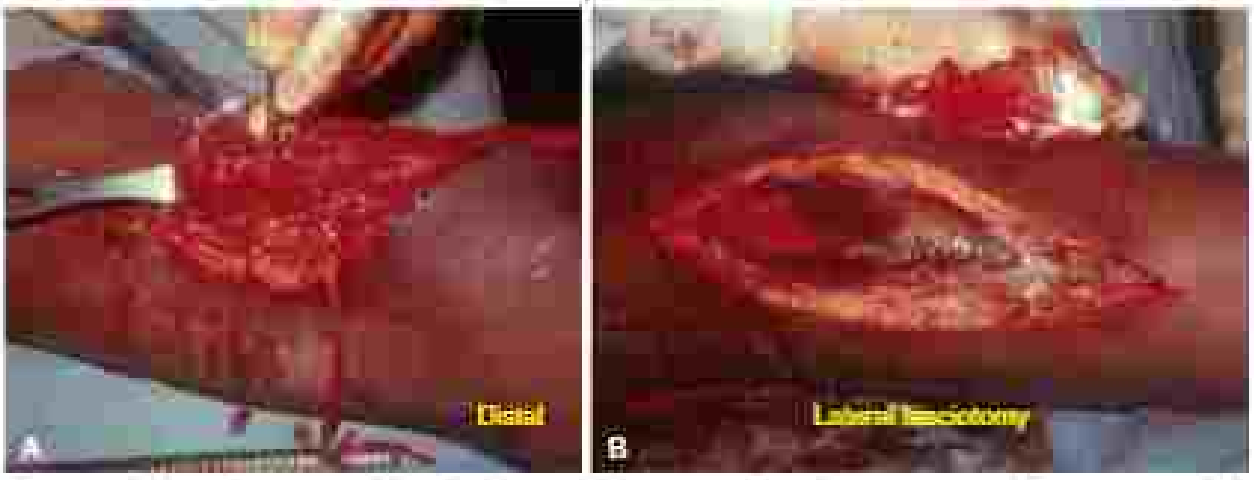

FIG. 7 The patient had a car bumper injury of the popliteal artery which was repaired through a posterior approach. Decompression of the superficial posterior compartment was achieved by extending the distal portion of the incision inferiorly (A), whereas decompression of the anterior and lateral compartments was achieved through a lateral fasciotomy (B).

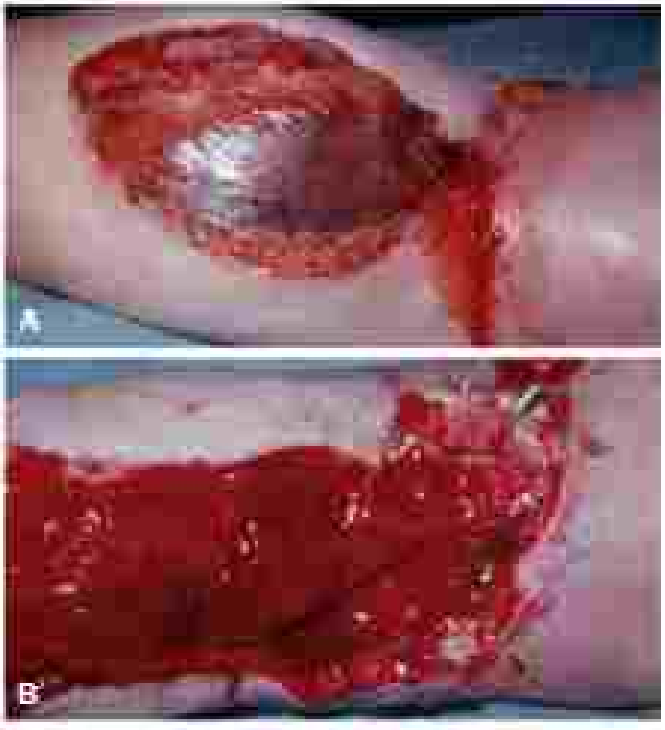

FIG. 8 The patient had primary repair of the popliteal vein and vein graft interposition of the popliteal artery following a crush injury. The skin was closed primarily leading to compartment syndrome, which shows marked bulging of the gastrocnemius (A) with superficial necrosis (B) necessitating resection or debridement of about half of the gastrocnemius. Following combined injury of the popliteal artery and vein, prophylactic compartment decompression is recommended.

CALF COMPARTMENT DECOMPRESSION

Most compartment syndromes occur in the calf and are due to ischemia/reperfusion injury associated with elective or emergency vascular reconstruction after crush injuries or combined fractures and soft tissue injury (Fig. 7). The calf has four compartments. These include the anterior compartment containing the tibialis anterior, the extensor hallucis longus, the extensor digitorum longus, and a portion of the peroneus tertius, the lateral compartment containing the peroneus longus and brevis, the superficial posterior compartment containing the soleus, gastrocnemius, and plantaris, and the deep posterior compartment containing the flexor hallucis longus, tibialis posterior, flexor digitorum longus, and popliteus. Although the lateral compartment contains the superficial peroneal nerve, the peroneal artery courses in the deep posterior compartment along with the posterior tibial artery and the deep peroneal nerve. Patients with popliteal artery injury, especially in association with popliteal venous injury, are especially prone to develop compartment syndrome. With these injuries, it is better to err on the side of being too aggressive rather than being too conservative (Fig. 8).

FOUR-COMPARTMENT DECOMPRESSION

The most common technique for decompressing the four compartments of the calf is to use bilateral incisions (Fig. 9). The medial incision is made just distal to the medial tibial condyle and extends inferiorly to about 5 cm posterior to the posterior ridge of the tibia (see Fig. 5A). The incision should divide the fascia overlying the gastrocnemius, the anterior superficial muscle fibers of the gastrocnemius and soleus are separated from the posterior periosteum of the tibia, thus giving access to the deep posterior compartment (Fig. 10). The lateral and anterior compartments are decompressed by a lateral skin incision along the anterior margin of the fibula between the muscle fibers of the lateral compartment and the lateral fibers of the anterior compartment. The skin must be retracted anteriorly to expose the fascia of the anterior compartment muscles and then posteriorly to expose the fascia overlying the lateral compartment; both fascial planes are incised the full length of the incision (Fig. 11). When there is extensive soft tissue damage with vascular disruption, the technique for fascial decompression may be modified.

SELECTIVE COMPARTMENT DECOMPRESSION

Occasionally, decompression of three of the four leg compartments will lower the pressure in the deep posterior compartment. For example, one patient with pressures of 70 cm H_2O in the anterior, lateral, and superficial posterior had three compartment decompression through medial and lateral incisions, which reduced the three compartment pressures to 5 cm H_2O. The deep posterior was then measured and was 7–8 cm H_2O. When tissue pressures can be obtained after three compartment fasciotomies and the deep posterior compartment pressure is below 20 mm Hg, no further decompression

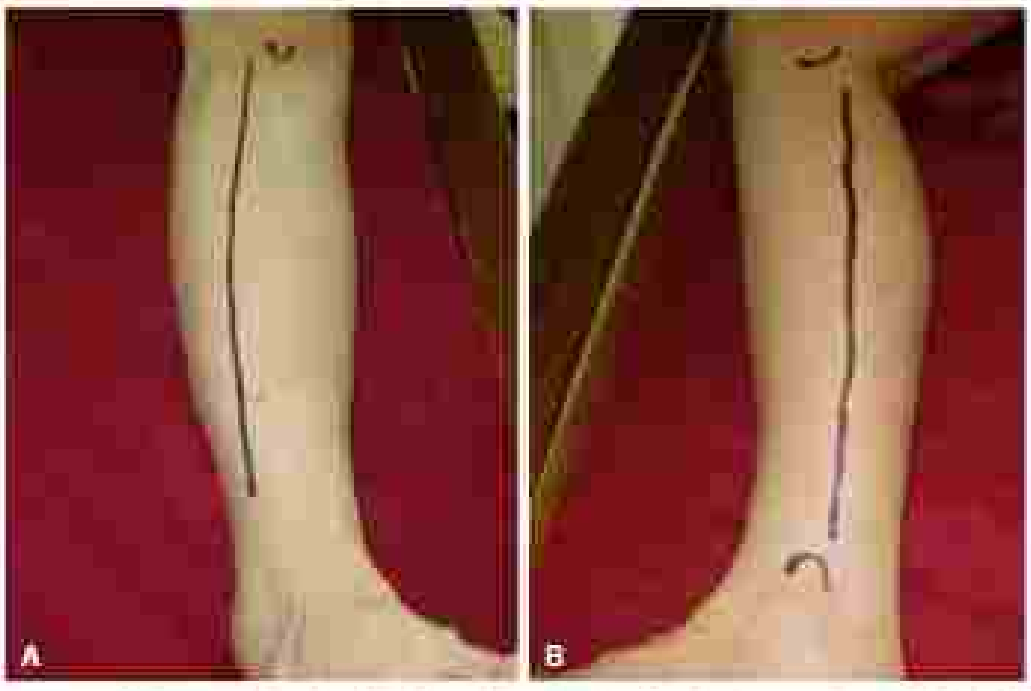

FIG. 9 (A) Four-compartment fasciotomy of the calf is achieved by making a lateral incision along the anterior margin of the fibula over the intermuscular groove separating the anterior and lateral compartments. (B) The medial incision is made just distal to the tibial condyle and extends between the superficial posterior muscle group and the tibia.

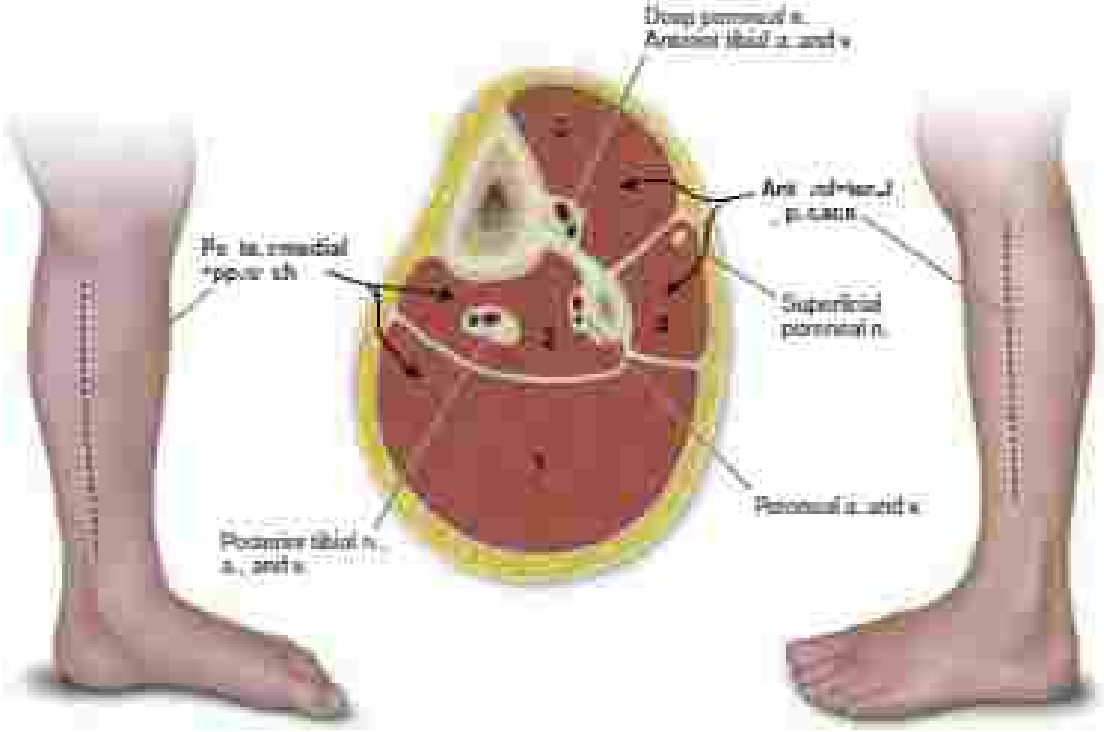

FIG. 10 Decompression of the anterior and lateral compartments through a lateral incision at the intermuscular groove exposes, with skin retraction, both the anterior compartment and lateral compartment muscles. Decompression of the deep posterior compartment through a medial incision exposes the gastrocnemius muscle, which is retracted medially along with the soleus muscle away from the tibia, providing access to the deep posterior compartment. Unless the soleus muscle is detached from the tibia, only a three-compartment fasciotomy has been performed. (From Herring JA, Tachdjian's Pediatric Orthopaedics from the Texas Scottish Rite Hospital for Children, 5th ed. Philadelphia: Elsevier; 2014.)

is needed. Selective compartment decompression is often the best approach to low-velocity injuries to arteries (Fig. 12).

ANTERIOR COMPARTMENT SYNDROME

The anterior compartment syndrome is an unusual single compartment syndrome of the calf. The patient uniformly gives a history of increased physical activity and exercise for an extended period. The patient describes how the anterior calf tightened and became extremely painful; massage did not help. The severe, constant pain is localized to the anterior compartment. The diagnosis is made clinically by noting a very hard and tender anterior compartment with excruciating pain on passive plantar flexion. This is a surgical emergency and requires immediate anterior compartment decompression by an incision from tibial tuberosity to just above the ankle in the midpoint of the anterior compartment muscle mass. Delay in operation may lead to muscle necrosis.

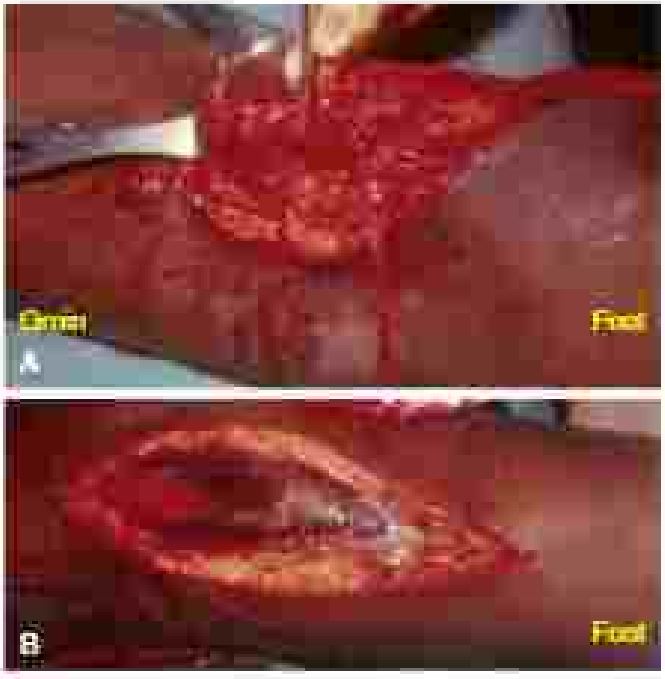

FIG. 11. This patient had a lumpectomy injury of the popliteal artery, which was repaired through a posterior approach. Decompression of the superficial posterior compartment was achieved by extending the distal portion of the operative incision inferiorly (A) whereas the lateral and anterior compartments were decompressed through a lateral fasciotomy (B).

HAND AND FOOT COMPARTMENT DECOMPRESSION

Decompression of the muscle compartments of the hands and feet is rarely needed. Such decompression may be needed with extensive burn, severe cellulitis, and industrial crush injuries. Whenever possible, incisions on the plantar surface of the foot or the volar surface of the hand should be avoided in that they impair function. Decompression of the hand compartments can be made by dorsal incisions over the second and fourth metacarpals, allowing for fasciotomy over the interosseous muscles on each side of the metacarpals (Fig. 13). Decompression of the muscle compartment of the foot, likewise, is made by dorsal incisions over the second and fourth metatarsals with a third incision made along the medial aspect of the arch muscles (see Fig. 13). When performing these dorsal incisions, one must recognize that both the dorsal and volar lymphatics of the hands and feet ascend dorsally, so that patients requiring compartment decompression will likely have extensive lymphedema, making hemostasis quite tedious.

POSTOPERATIVE MANAGEMENT

The extremities with open wounds can be dressed with dry gauze and a roll wrap and treated with elevation. A vacuum-assisted closure device can be applied if there is extensive drainage. A posterior splint of the low extremity is strongly recommended to prevent foot drop. Some fasciotomy incisions can be closed in 5 to 7 days with closure of the skin. One should avoid closing the fascial incision too soon as this may lead to recurrent compartment syndrome. If there is extensive muscle bulging precluding skin approximation, full-thickness skin grafts can be applied. Sometimes there is a delay to compartment decompression, which leads to superficial muscle necrosis. Functional

FIG. 12. The patient presented with a through-and-through gunshot wound to the proximal calf (A), as identified by the two markers (B); he had injury to the tibial peroneal trunk with a right calf necessitating bifocal fasciotomy in conjunction with resection and primary repair of the tibial peroneal trunk. Deep posterior compartment decompression was not needed.

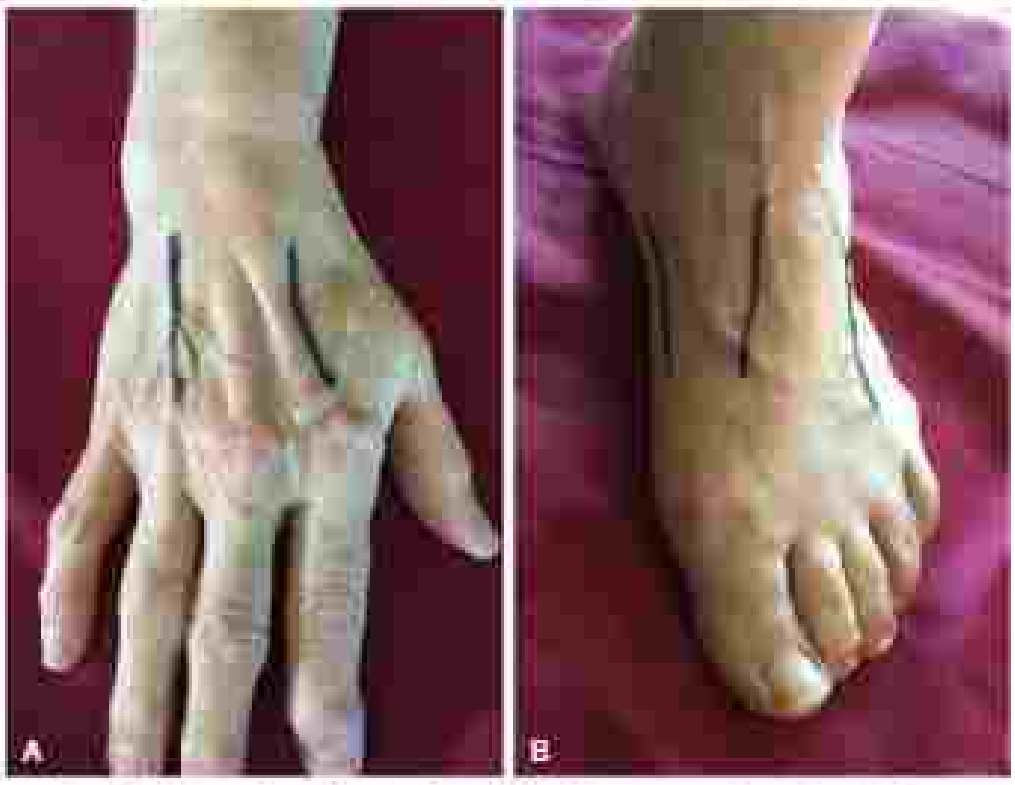

FIG. 13 (A) Decompression of the hand muscles can be achieved through dorsal incisions over the second and fourth metacarpals, thus exposing the fascia of the interosseous muscles. (B) Decompression of the foot compartments is best made by dorsal incisions made over the second and fourth metatarsals with a third incision made along the medial aspect of the arch muscles. When possible, incisions made on the plantar surface of the foot or the volar surface of the hand should be avoided since these incisions compromise function.

BOX 1 Etiology of Compartment Syndrome

External Compartmental Compression

Cast/ACE wrap
Military antishock garments
Burn eschar

Internal Compartment Expansion

Ischemia and reperfusion
Arterial injury, thrombosis, hemorrhage
Burns, frostbite
Cellular insult and swelling
...rosis injury
Fracture, contusion, anterior leg compartment
Electrical injury/high voltage
Blood accumulation and edema
...ractures
Hemophilia
Anticoagulants
Venous occlusion
Miscellaneous
Intravenous infiltration
...rug injection, soft tissue

debridement should be conservative. The underlying ischemic muscle is compromised but usually survives and regains function. A superficial layer of necrotic muscle (but pericyte can be debrided at 2 to 3 days after compartment decompression (see Fig. 1). The patient must be monitored for myoglobinuria and, if present, treated aggressively with hydration, alkalinization, and careful diuresis to prevent renal failure.

Suggested Readings

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Burn Wound Management

Guillermo Foncerrada, MD, MHS, Kara' D. Capek, MD, Celeste C. Finnerty, PhD, David N. Herndon, MD

Surgical treatment for burn injuries may involve emergency procedures such as escharotomy and fasciotomy that are limb- and life-saving. Early excision of all deep burns followed by durable wound closure is an important means to mitigate the systemic response to burn injury and has been demonstrated to offer significantly improved survival for patients under the age of 30 with burns of 30% or more of the total body surface area (TBSA). Burn surgery occurs in phases according to time post injury.

MAINTAIN PERFUSION

Burn shock can be optimized by precise resuscitation with fluids of requisite volume and composition to avoid end-organ damage or acute disturbance of the intracellular and extracellular constituents. Advanced monitoring, including central venous pressure, arterial pressure, serial echocardiography, ultrasound assessment of central venous caliber respiratory variation, pulse contour analysis, thermodilution lung water and cardiac output determination, and measurement of pulmonary arterial saturation/pressure and capillary wedge pressures, may guide therapy to select patients to optimal perfusion of jeopardized tissues. Adjunctive treatments can include cardiotonic and vasoactive medications tailored to the patient's hemodynamics and dominant clinical problem.

Compartment syndromes not infrequently complicate major burns. A compartment syndrome exists when there is sufficient increase in the tissue interstitial pressure (with respect to the capillary hydrostatic pressure—lower in systemic shock states) to critically reduce blood flow. This causes a cascade of tissue-level supply and demand mismatches, chiefly impaired tissue oxygenation. Progressive tissue death occurs, dependent on the severity of the flow decrement and the metabolic requirements of the involved tissue. Focused examination to detect the early manifestations of compartment syndromes should be performed, particularly in patients with high-voltage electrical injuries, circumferential burns, delayed resuscitation, or in the setting of high volume resuscitation. These syndromes typically evolve over 12 to 72 hours following burn and resuscitation. Indicated examination is dependent on the patient presentation, but a comprehensive examination would include palpation of the hands, feet, legs, forearms, abdomen, and eyes. This should be accompanied by an assessment of respiratory effort, oxygenation, and airway pressures. Neurologic (sensory, motor, and pupillary) examination should be carefully documented in those patients to identify acute nerve compression syndromes, including median, ulnar, tibial, peroneal, and optic nerves. When rhabdomyolysis occurs, urinary heme pigment can be seen grossly or as dipstick positive blood without red blood cells on microscopic examination. Serum creatine kinase and myoglobin levels can also assist in diagnosis, but do not supplant hands-on examination. Similarly compartment, bladder, airway, and intravascular pressure measurement may help as supportive tests to the setting of equivocal exam findings. Compartment syndromes remain clinical diagnoses, and because prompt treatment can be life-, limb-, and sight-saving, surgeons caring for burned patients need to be familiar with techniques of escharotomy and fasciotomy of the hands, including carpal tunnel and Guyon canal; the feet, including all three plantar compartments and the tarsal tunnel; forearms, including exploration of Parona space and the cubital tunnel; and legs. Additionally, chest escharotomy, peritoneal drainage/laparotomy, decompressive laparotomy, and lateral canthotomy may be indicated acutely after burn injury. These procedures are best performed in the operating room, but can be adapted to the intensive care unit, trauma room, or procedure suite if adequate equipment, preparation, lighting, and skilled staff are available. Escharotomy (Fig. 1) should be sufficient to alleviate compartment syndromes due to constricting burn eschar, but burn surgeons must maintain an adequate index of suspicion for true fascial compartment syndromes. Factors that increase the likelihood of a fascial compartment syndrome include high-voltage electrical injury, prolonged burn shock with delayed resuscitation, and high-volume resuscitation in excess of 10% of body weight.

OVERVIEW OF BURN ASSESSMENT

Burn wounds should be assessed in terms of size (percent of the TBSA involved) and depth (superficial, indeterminate-deep partial thickness, or full thickness injury). Superficial burns are expected to heal with hygiene, supportive topical treatments, and avoidance of infectious complications. Full thickness injuries benefit from prompt surgical excision and wound closure, usually with autograft. Burns that are indeterminate or deep partial thickness burns require careful assessment. In general, wounds that are expected to require more than 3 weeks for reepithelialization benefit from early surgical excision and grafting. Partial thickness scald burns, particularly in children, benefit from a trial of conservative treatment. This often results in a smaller area of excision/grafting without significantly increasing the risk of infectious complications or length of hospital stay. While the American Burn Association referral criteria (Box 1) identify patients who should be evaluated by accredited burn centers, they do not specifically identify the high mortality group that may benefit from care at a high acuity burn center. There are several calculations (see Capek et al) that provide an initial mortality estimate based on time of injury variables such as age, TBSA burned, TBSA full thickness, and the presence of inhalation injury. In the absence of prospective data, it is our consensus opinion that patients with a predicted probability of death of 20% or greater (1 in 19 odds) should ideally be stabilized and transferred to a high acuity burn center for definitive care.

OPERATIVE PLANNING AND THE LEVEL OF TISSUE REMOVAL

Except in first degree burns, there are usually necrotic tissues to be removed (excised) as part of burn wound treatment. In superficial second degree burns there is bullae (blister) formation at the intra- or subepithelial level. If either a layer of basal epithelial cells, or the basement membrane they reside upon, remains intact, rapid reepithelialization should occur within a few days, and should be complete within a week. When the basal epithelial cells are completely lost, reepithelialization is accomplished from two keratinocyte stem cell niches within the hair follicle. When the peculiar characteristics of the epithelial basement membrane are reformed (type IV collagen, laminin, integrin and other constituents), epithelial migration, proliferation, and wound closure are facilitated. Topical medications and coverage products may be employed to prevent bacterial overgrowth and facilitate the process of reepithelialization (Table 1). It is important that they do not impede epithelial proliferation/migration or exert toxic effects on the remaining proliferative cells.

Deep partial thickness burns are characterized by increasing depth of dermal necrosis. The dermis can be divided into the papillary dermis and the reticular dermis. The papillary dermis includes the rete ridges and terminal capillaries. The reticular dermis is the strength layer of skin and its components include densely packed collagen fibers and elastin fibers. At the level of burn injury associated necrosis deepens, proliferative and healing capacity is progressively

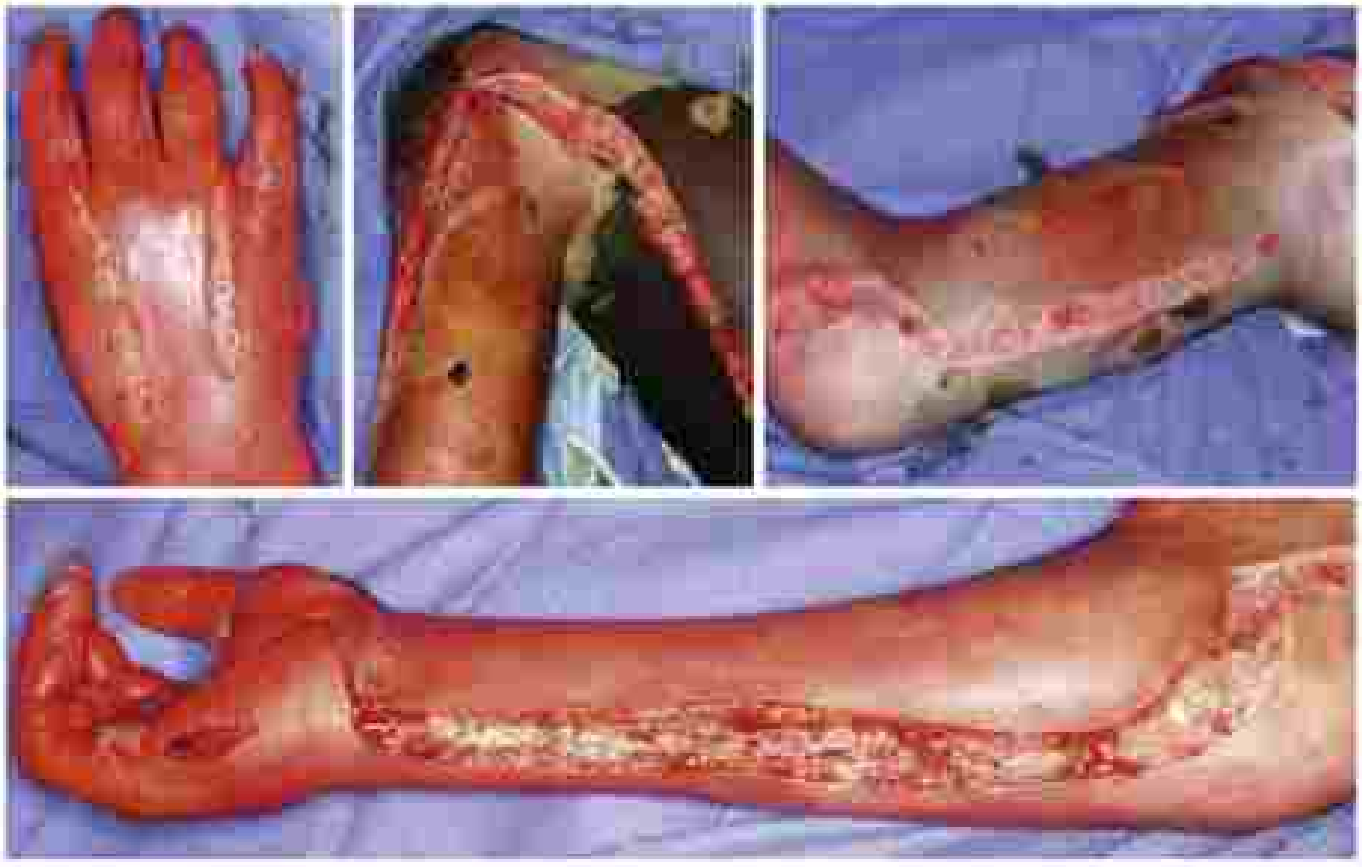

FIG. 1 Release of upper extremity burn eschar and associated compartment syndrome.

BOX 1. Criteria for Burn Center Transfer/Consultation

- Partial thickness burns greater than 10% TBSA
- Burns involving the face, hands, feet, genitalia, perineum, or major joints
- Third degree burns
- Electrical burns (including lightning)
- Chemical burns
- Inhalation injury
- Burns with preexisting medical conditions that may complicate patient management, prolong recovery, or affect mortality
- Burns with concomitant trauma, if the burn itself poses a significant risk of morbidity or mortality
- Burns in children without specialized personnel and equipment for the care of burned children
- Burns in patients with special social, emotional, or long-term rehabilitative needs
- Burns in the setting of suspected nonaccidental trauma

TBSA, Total body surface area.

but. Accordingly, as dermal necrosis approaches full thickness, the wound behaves progressively more like a full thickness ulcer and exhibits healing by deep tissue contraction and proliferation at the wound edges. Hypertrophic scarring is more frequent when the reticular dermis is involved.

Further complicating burn wound assessment and surgical treatment is the temporal evolution of the wound. Early after burn injury there is an ebb phase, characterized by high systemic vascular resistance, high catecholamines, and high endogenous thromboxane levels with relative vasoconstriction. During this phase, resuscitation is physiologically analogous to cardiac and cerebral vasospasm results in further reduction of blood flow to otherwise viable tissues. Deep partial thickness injuries may appear nonblanching (appear as full thickness) and may progress to full thickness injuries as the pressures of tissue expansion, vascular stasis dies, underlying coagulation necrosis. Adequate resuscitation, release of constricting eschar and compartment syndromes, and scrupulous avoidance of external pressure injury may help maximize the survival of at risk tissue. There are investigational pharmacologic adjuncts to mitigate the above described process.

Histologically, devitalized tissue demonstrates hemorrhagic necrosis. At excision, these same necrotic tissues can be recognized by a subtle pink hue, which represents microscopic hemorrhage into the tissues, rather than the pearl white color of intact/viable dermal collagen. Nonviable tissue also demonstrates a subtly blurred or dulled light reflection, whereas intact viable tissues typically show a sharp, crisp glistening light reflex. At excision, frankly necrotic tissues will not bleed, but often some bleeding can be observed at the level of microscopic necrosis described above.

In full thickness burns, the level of excision is below the dermis. It can be difficult to differentiate necrotic from viable subcutaneous adipose tissue, although here too the presence of microscopic hemorrhagic necrosis, seen as a subtle pink hue and dulled light reflex, may provide some guidance. However, the absence of bleeding generally identifies necrotic subcutis. In very deep burns and in the setting of burn wound infection, fascial excision may allow subsequent successful graft placement and wound healing. In the setting of true invasive burn wound infection with bacteria or mold, sometimes termed *ecthyma gangrenosum*, fascial excision is often combined with local or regional antibiotics; these cases experience a mortality rate approaching 50%. The surgical excision of compromised tissue should meet the extent to which the tissue is causing systemic

TABLE 1 Characteristics of Topical Burn Treatments

Product	Pros	Cons
Silver sulfadiazine (SSD) 1%	• Can be used on small, medium, and large surface area burns • Decreased colonization of wounds • Alleviates pain • Broad spectrum	• Limited evidence to support improved wound healing or reduction in bacterial wounds infection • May impair reepithelialization
Bacitracin ointment: 500 units/gram	• Can be used on small burns, face, ears, perineum, graft sites • Alternative agent if sulfa allergy • Ease of application and removal	• Bacterial resistance • No gram-negative coverage • May cause skin hypersensitivity
Combination antibiotic ointment (e.g., bacitracin, neomycin, and polymyxin B)	• Similar to bacitracin above, but with gram-negative coverage	• May have increased hypersensitivity or allergic reaction
Mupirocin ointment 2%	• Broad spectrum gram-positive activity • Resistant gram-positive organisms not described	• No gram-negative coverage • May cause hypersensitivity or allergic reaction
Mafenide 8.5% cream or 5% solution	• Can be used on ears and nose • Effective on dense bacterial proliferation • Excellent eschar penetration • Penetrates cartilage • Effective for gram-negative organisms including Pseudomonas	• Contraindicated in allergy to sulfonamides • Large treatment areas associated with metabolic acidosis due to carbonic anhydrase inhibitor effect
Foams (antimicrobial impregnated)	• Absorb fluid • Promote autolytic debridement • Maintain control • Conformability to wound bed • Can be used with moderate exudate • May reduce number of dressing changes	• Not effective for eschar • Not effective in the presence of high exudate • Limited opportunities for wound assessment due to extended interval between dressing changes
Honey	• Rehydrate wound bed • Promote autolytic debridement • Antimicrobial action • Can be used colonized wounds	• May cause "burning" pain (osmotic effect) • Known sensitivity • May encourage hypertrophic granulation • May cause maceration
Low adherent wound contact layer (silicone)	• Indicate to protect new tissue growth • Atraumatic to surrounding skin • Conformable to body contours	• May dry out if left in place for too long • Known sensitivity
Silver (active)	• Antimicrobial action • Useful for colonized wounds • Is available in combination dressings	• May cause discoloration • Known sensitivity • Requires maintenance of moist wound environment
Poly lactic acid sheets	• Decreased bacterial proliferation • Promotion of epithelialization • Possible decreased pain	• Increased cost, no clear benefit to reduced infections, wound complications, or faster wound healing
Hypochlorous acid	• Useful for wound rinse after local hygiene • Broad spectrum antimicrobial activity	• Limited activity (minutes) once applied to wound
0.5% Silver nitrate soaks	• Standard agent for reduction of bacterial growth in burn wounds and immediate postoperative graft dressings • Cost effective • Broad spectrum antimicrobial activity • Ease of ongoing wound assessment	• Requires q2h reapplication of soak • Discoloration of surrounding skin and materials • Known sensitivity • Higher frequency of dressing changes • May be associated with hyponatremia
Amniotic membrane	• May be associated with reduced pain, reduced scarring, and faster epithelialization, although definitive studies are lacking	• Cost • Need for donor screening, tracking, and tissue banking resources • Degrades quickly in inflammatory or infected wounds

Continued

TABLE 1 Characteristics of Topical Burn Treatments—cont'd

Product	Pros	Cons
Xenograft	• Useful in partial thickness wounds where sufficient regenerative capacity is retained, avoids autograft donor site	• Xenograft rejection possible • Incorporation and hypertrophic scarring possible • Not typically used in superficial burns
Nystatin powder (4 million units/gram strength)	• Sparingly sprinkled on wounds just before new dressing is applied • Useful to prevent fungal colonization of wounds • Useful as an adjunct in the treatment of fungal wound infections	• Hypersensitivity • Use often requires cooperation from local pharmacy • Off-label use requires physician discretion • Avoid use of lower concentration (100,000 units per gram) talc-admixed product, which creates a problematic exudate in burn wounds

dysfunction. Accordingly, invasively infected tissue with residual perfusion (analogous to wet gangrene) constitutes a threat to survival in patients with major burns.

ADJUNCTS TO DETERMINE BURN WOUND DEPTH

The search for technologies to more precisely diagnose burn depth surged when the benefits of early excision were recognized. Several noninvasive technologies have been proposed, such as thermography, nuclear imaging, pulse echo ultrasound, and photometry. Despite the higher level of technologic complexity, these techniques have not yet demonstrated superior efficacy when compared with serial assessment by a burn surgeon. Of these adjuncts, laser Doppler is best studied. Some reports suggest potential clinical benefit with the use of laser Doppler to indeterminate thickness burns. This technique provides a color perfusion map of the burn wound, and serial tests may be performed to follow up the progress of the burn. Although laser Doppler provides an objective measurement of burn perfusion, it remains an adjunct to the serial clinical assessment of the burn surgeon.

STRATEGY OF EXCISION; BLOOD LOSS AND OPERATIVE RISK

Particularly in children, optimal burn care includes early, complete excision of the burn wound. In the severely burned, this may require maximal perioperative and anesthetic resources. These include a warm, humidified operating room; several skilled assistants and often several anesthesiologists; a full-body surgical scrub and preparation; accommodation for multiple position changes including prone and side to side positioning while under anesthesia; accommodation for extremity elevation; upper and lower extremity tourniquets; wet pad electrocautery; harvest and graft preparation from all required donor sites; real time hemodynamic monitoring; rapid blood gas, electrolyte, and coagulation determinations; advanced rewarming equipment; capacity to provide rapid massive transfusion of blood and blood products; availability of sufficient skin bank resources to cover the wound; and a sufficiently staffed and experienced burn intensive care unit capable of reliably nursing patients through the postoperative period. Blood transfusion is usually needed for large burns, both due to losses from the wound as well from impaired hematopoiesis. Surgical blood loss can be estimated preoperatively based on the number of square centimeters of burned area to be excised, and the time elapsed since the burn. Within the first 72 hours after burn injury, blood loss should be less than 0.5 mL/cm^2 excised. Between days 3 and 16 postburn blood loss is expected to approximate 0.75 mL/cm^2 excised. Excision of infected wounds, while often necessary, is associated with higher blood losses (predictors range from 1–1.25 mL/cm^2). Blood volume can be estimated by 70 mL/kg (higher in infants and small children). In the setting of ideal skill, assistance, and resources, excision of burned areas predicted to incur losses of less than one blood volume (in boys, approximately 7% of adjusted body weight in kilograms for adults) may be planned. In less severe burns, or in a resource constrained setting where transfer cannot be arranged, a useful operative planning heuristic to spend no more than 2 hours operating, excise no more than 20% TBSA, and lose no more than 2 units of blood. If the wounds are clearly full thickness, we prefer to cover the posterior trunk and buttocks as rapidly as possible to better enable supine positioning later in the course of recovery. Coverage generally proceeds proximally to distally in major burn injuries where future amputation of at risk distal extremities remains a possibility. Based on the burn and patient characteristics if there is no expectation of hand or upper extremity amputation, an improved functional recovery can be achieved by autografting the dorsal surface of the hand and digits within the first 3 weeks after burn injury. Threatened sight due to ocular surface exposure, recognized by corneal epithelial defect or ulceration, may require urgent tarsorrhaphy placement and expeditious release and grafting of the eyelids to normalize eyelid function and preserve vision. The functional loss of one hand is associated with 24% whole person impairment, while loss of both hands is estimated to result in 79% whole-person impairment. Loss of sight in both eyes is associated with more than 80% whole person impairment. Prevention of functional losses and postburn disability should be individualized to each patient's needs, recognizing that hand function and sight are frequently at risk following burn injury. Timely surgical intervention can prevent or reduce resultant disability.

The postburn hematopoietic impairment is characterized as an erythropoietin resistant hypoproliferative anemia resulting from reprogramming of the common myeloid progenitors away from the erythroid lineage. It is associated with high levels of circulating erythropoietin and generally not responsive to exogenous erythropoietin.

Tangential Excision

Tangential excision is defined as the thorough removal of all burned skin by layers until reaching undurned tissue. Compared to fascial excision, tangential excision better preserves body contour. Investigators reported the procedure of tangential excision in detail, describing the procedure as the repeated excision of thin layers until reaching undurned tissue, followed by immediate application of split thickness autografts.

A variety of surgical instruments are available to accomplish the purpose of the tangential excision, including powered dermatomes, the Goulian knife, and the Watson knife. Partial thickness deep burns should be excised to uniformly viable tissue. In the case of full thickness burns, the excision should be done layer by layer, until the appearance of undurned subcutaneous tissue, which has a bright yellow color and a comparatively softer texture. If blood vessels with thrombosis, or tissue that exhibits a pink to purple discoloration or a dull yellow color are found, it should be excised because these findings are not consistent with viable tissue. Failure to excise these tissues prior to graft placement will impair graft take and impede wound healing.

Fascial Excision

Fascial excision is a procedure that entails the removal of all skin and subcutaneous tissue down to the fascia. The main indications for its use are to diminish blood loss in deep and extensive burns, and to remove invasive infection. The procedure limits excessive blood loss by avoiding the multiple capillaries located in and beneath the epidermis, while allowing for the direct control of the perforating vessels through exposure and ligation. If the subcutaneous tissue is burned or seriously infected, then fascial excision is a suitable option. Advantages may include increased graft take due to reliable perifascial blood supply and decreasing hemorrhage. Normal body contour and lymphatic function are generally lost after fascial excision, although this may be mitigated somewhat by preserving islands or a thin layer of viable deep adipose tissue superficial to the fascia.

Adjuncts to Minimize Blood Loss at Burn Excision

Adequate preparations should include blood bank requisition of autologous products, and blood products should be available to the operating room at the start of the excision proper. Strategies to decrease blood loss in the operating room include elevation, tourniquets (brief [<20 minute] inflation time) for the extremities, thrombin spray, and infiltration or topical spray with dilute epinephrine solutions and immediate compressive bandaging. The dilute epinephrine solutions can be prepared by adding 1.0 mL of 1:1000 epinephrine to 500 mL 0.45% saline solution for a final concentration 1:500,000 epinephrine. For small children, the amount of epinephrine can be reduced by half (0.8 mL). Tourniquets are particularly helpful when excising over hands and fingers. One potential pitfall is that the uniform pressure blanching that characterizes healthy tissue will not be visible. Other surrogates for tissue viability (see above) must be used in this setting.

The management of the larger blood vessels can be achieved either with ligation or electrocautery. For the smaller bleeding points, lap sponges soaked in dilute epinephrine solution can be applied topically and wrapped with elastic compressive bandages. In addition, elevation of the limb before, during, and after grafting will diminish venous bleeding and reduce hematoma formation.

The above described balanced salt solution and dilute epinephrine mixture, sometimes called Pitkin solution, works best if infiltrated before starting excision or donor site harvest. The anatomic areas that especially benefit from this subcutaneous injection are the face, the trunk, and the scalp. Epinephrine in the solution causes vasoconstriction, decreasing the amount of hemorrhage during excision. Another advantage of the infusion is that it creates an even surface that facilitates the tangential excision or donor harvest.

Reducing operating time reduces total blood loss, thus excision should be accomplished as quickly as safely possible and excised areas covered with gauze soaked in epinephrine solution, then bandaged with gauze and elastic materials. This approach uses the vasoconstrictive effects of epinephrine along with the pressure of the compressive bandage to achieve adequate hemostasis. Active hemorrhage localized to a blood vessel that persists despite the above techniques can be controlled with electrocautery.

DONOR SITE MANAGEMENT AND TECHNIQUES OF WOUND CLOSURE

Autograft donor sites are selected based on need, availability, healing characteristics, and patient preference (including ease of concealment of any donor site scar). The scalp heals rapidly and a perioperative scalp block can provide postoperative anesthesia. In general, burn wounds are closed with split thickness skin grafts (STSGs) harvested with a powered dermatome. For most body areas in large burns, a thin STSG is harvested at 0.008 to 0.01 inch. Note that most powered dermatomes have both an inch and a metric scale and the equivalent thickness is 0.1 to 0.2 mm. Slightly thicker grafts may be preferred to accomplish a specified reconstructive goal, such as increased range of motion at the hands and fingers, although the actual relationship between graft thickness and resulting contracture is often difficult to predict. As the donor site is a prototypic superficial wound, donor site dressings should be selected to facilitate reepithelialization, minimize toxicity, and prevent infection.

Skin autografts can be processed in several ways. They can be used as a sheet or meshed, and the meshing can vary from 1:1 to 6:1. Mesh ratio will be determined according to the patients' individual circumstances such as TBSA burned, area to be grafted, and availability of donor sites.

The decision of whether to mesh the graft depends on the surface to be covered. The ideal graft for small burns, and burns present on the face, neck and hands is a sheet graft. A nonmeshed graft provides the best cosmetic results. A possible complication that may arise when using sheet grafts is the occurrence of a hematoma under the graft. Making small "pie crust" incisions in the graft to allow the drainage of any remaining blood and or serum may occasionally prevent this complication and favor graft take. Postoperative assessment of the graft is important to evaluate for possible complications. If fluid (blood or serum) accumulates under the graft, this can be resolved by puncturing the graft with a needle and draining all fluid. The initial determinant for graft take is adherence between the wound bed and the graft. The optimal way to place the graft is perpendicular to the longitudinal axis of the extremity with the aim of preventing contracture. This consideration is especially important at major joints where contractures may impair flexion and extension and necessitate future surgery for scar release. On the forearm and on the dorsum of the hand it is acceptable to use longitudinal grafts.

The objective of meshing a graft is to expand it, and thus be able to cover a larger surface with viable proliferative epidermal units. Durable wound closure implies reconstitution of a stable self renewing epithelial layer, ideally with associated structures (innervation) and cells (melanocytes). Frequently used mesh ratios are 2:1 and 4:1, but these ratios can be expanded even more if the situation warrants. One advantage of the 2:1 ratio is that it is easier to handle and apply. A disadvantage of all meshed grafts is the pattern of scarring that results. If the burn is very large, the use of a 4:1 mesh ratio may be preferred to expand the coverage. 4:1 meshed autograft leaves large interstices open and the wound bed exposed in these areas. These exposed areas and the massive widely expanded autograft can be protected by placing a 2:1 meshed homograft over it. This is commonly known as sandwich or Alexander technique.

Additional methods include autograft techniques and local tissue flaps. The Meek technique, modified by Krizek, is occasionally a useful strategy to manage extensive burns. It consists of cutting the skin grafts into small squares and placing them uniformly over the wound bed. These small islands of skin promote epithelialization, although the healing process is lengthy and the cosmetic results are not favorable. The expansion ratios available for this technique vary from 3:1 to 5:1. Occasionally, local tissue flaps may be successfully incorporated in wound closure following burn excision. These acute flaps carry greater risk of failure than their reconstructive analogues and should only be employed by providers with specialized training in burn reconstruction in addition to acute burn care.

SPECIAL CONSIDERATIONS

Nonaccidental Trauma

Along with assessment and treatment of the burn wound, astute providers note the characteristics of the injury, signs of previous significant injuries, the nutritional, developmental, and psychologic state of the patient, and interactions between the patient and caregivers. These may raise suspicion for nonaccidental injury. Providers must follow state laws in addition to practice guidelines, in clinically investigating and reporting findings concerning for abuse or neglect to the appropriate authorities. It has been previously shown that abuse occurs in 10% of nonaccidental burn cases and is eventually accompanied by a 30% mortality rate. Each of these preventable deaths starkly emphasizes the importance of this aspect of burn management.

Chemical Injuries

It is important to identify and characterize the type of agent involved. A direct method for this is to obtain the Material Safety Data Sheet(s) (MSDS) on all potential agents involved in the exposure. Personal protective equipment suited to the potential agent(s) is essential for all providers. Solid particles of the burning agent should be brushed off gently. Although many chemical burns are aided by rapid and copious irrigation with water, the notable exceptions to this guideline are indicated on the agent-specific MSDS. For acid and alkali exposures, irrigation should be continued until the skin pH normalizes. It is advisable to wait 5 minutes after an initial normal reading, as additional irrigation is indicated if agent continues to leach back to the surface from deeper tissues. Chemical injuries of the eye can result in severe, irreversible vision loss and are an ophthalmologic emergency. When these are identified, immediate irrigation with water or saline should be initiated and continued until ophthalmology consultation can be obtained.

Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Blistering Skin Diseases

The skin lesions in these diseases are usually superficial partial-thickness injuries. Careful medication history may identify a potential pharmacologic trigger. Sulfa drugs, anticonvulsant drugs, and allopurinol are among the agents previously associated with development of these conditions. Care should be directed toward physiologic stabilization, avoidance of secondary infection or pharmacologic insult, and promoting reepithelialization. A number of temporary skin coverage products are available for this purpose. Maximal complications affect over half of survivors, chiefly corneal scarring, vision loss, and chronic dry eye. All of these patients require a detailed examination of the ocular surface to identify or exclude eye involvement at initial presentation, with follow-up if changes in condition are noted. Because early application of amniotic membrane grafts to the ocular surface has been shown to ameliorate these devastating complications, such patients require referral to centers capable of reliably and rapidly providing this treatment.

CONCLUSION

The phenomena of increased survival following severe burns is one of the great success stories of twentieth century surgical science, and a contemporary marker of medical progress. With increased survival, there is increased demand for prevention of disabling sequelae of burn injury. We have identified areas where prompt and indicated surgical intervention may mitigate disabling complications of the early postburn period. We want to again emphasize the importance of early excision and durable wound closure for full-thickness and near full-thickness burns. While advances in prevention, resuscitation, nutrition, care for inhalation injury, treatment of infection, and rehabilitation all benefit the burned patient, early excision of the burn wound followed by durable wound closure is the keystone. It potentiates these advances and actualizes the burn team in constructing an opportunity for increased survival following severe burn injury. Evidence also indicates that more rapid wound closure is associated with reduced hypertrophic scarring. Durable closure of burn wounds implies establishment of a stable self-renewing population of keratinocytes, thus closure of burn wounds either by native cells or autografts to be exercise in the skin organotypic culture. While short-term graft survival may reflect epithelial survival and proliferation, long-term success requires reconstitution of functional stem cell niches competent to maintain the epithelial layer indefinitely. The primary work of the burn surgeon is to optimize the conditions for this process to occur as rapidly and completely as possible.

Suggested Readings

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Medical Management of the Burn Patient

Mayur Narayan, MD, MPH, MLP, MHPE, FACS, FCCM, EICS, Aakanksha Agrawal, MD, and Phillip S. Barie, MD, MBA, FIDSA, FACS, FCCM

Nearly 500,000 burn injuries were reported in the United States in 2016. According to the Healthcare Cost and Utilization Project National Inpatient Sample (2017 data), there were an estimated 40,000 hospitalizations related to burn injury, including 30,000 at hospital-based burn centers. Mortality after burn injury has decreased over the past 20 years, largely attributable to improved physiologic support of injury and a dedicated, multidisciplinary approach to the care of the burn patient. Of the 205,000 burns in the National Burn Registry from 2016, the mortality rate for all cases was 3.2%. Despite these successes, larger total body surface area (TBSA) burns still pose a high risk of mortality and morbidity.

The pioneering research (among many others) of Charles Baxter, Henry Harkins, David Hinshaw, Lloyd McLean, Francis Moore, Carl Moyer, Basil Pruitt, C. Tom Sisters, and Douglas Wilmore and the advances by their proteges (again, among many) Peter Cameron, William Cioffi, William Curtsinger, Robert Demling, Clem Gerbasio, David Herndon, Stephen E. Lowry, Ronald Tompkins, and Roger Yurt has established that the concept of burn shock results from extensive fluid shifts in both burned and nonburned tissue. Thermal injury activates the release of inflammatory and vasoactive mediators responsible for increased transcapillary permeability, local vasoconstriction, ischemia, coagulation, and hemostatic and microcirculatory derangements that together lead to tissue hypoperfusion. Release of histamine, prostaglandins, neuropeptides, and cytokines including oxygen-derived free radicals contributes to the local and systemic inflammatory response, exacerbating the microcirculatory dysfunction. This upregulation of innate immunity, compounded by downregulated adaptive immunity, which creates such a deranged host response to injury, can have profound organ-level effects that alter cardiovascular function, endocrine, gastrointestinal, hematologic, hepatic, neurologic, renal, and pulmonary function, leading eventually to multiple organ dysfunction syndrome (MODS) and death (Fig. 1). Fortunately, both the incidence and magnitude of MODS have decreased owing to better recognition of risk, improved resuscitative, timely metabolic, nutritional, and pharmacologic support, and timely source control and wound closure.

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It is important to identify and characterize the type of agent involved. A direct method for this is to obtain the Material Safety Data Sheet(s) (MSDS) on all potential agents involved in the exposure. Personal protective equipment suited to the potential agent(s) is essential for all providers. Solid particles of the burning agent should be brushed off gently. Although many chemical burns are aided by rapid and copious irrigation with water, the notable exceptions to this guideline are indicated on the agent-specific MSDS. For acid and alkali exposures, irrigation should be continued until the skin pH normalizes. It is advisable to wait 5 minutes after an initial normal reading, as additional irrigation is indicated if agent continues to leach back to the surface from deeper tissues. Chemical injuries of the eye can result in severe, irreversible vision loss and are an ophthalmologic emergency. When these are identified, immediate irrigation with water or saline should be initiated and continued until ophthalmology consultation can be obtained.

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The skin lesions in these diseases are usually superficial partial-thickness injuries. Careful medication history may identify a potential pharmacologic trigger. Sulfa drugs, anticonvulsant drugs, and allopurinol are among the agents previously associated with development of these conditions. Care should be directed toward physiologic stabilization, avoidance of secondary infection or pharmacologic insult, and promoting reepithelialization. A number of temporary skin coverage products are available for this purpose. Mucosal complications affect over half of survivors, chiefly corneal scarring, vision loss, and chronic dry eye. All of these patients require a detailed examination of the ocular surface to identify or exclude eye involvement at initial presentation, with follow-up if changes in condition are noted. Because early application of amniotic membrane grafts to the ocular surface has been shown to ameliorate these devastating complications, such patients require referral to centers capable of reliably and rapidly providing this treatment.

CONCLUSION

The phenomena of increased survival following severe burns is one of the great success stories of twentieth century surgical science, and a contemporary marker of medical progress. With increased survival, there is increased demand for prevention of disabling sequelae of burn injury. We have identified areas where prompt and indicated surgical intervention may mitigate disabling complications of the early postburn period. We want to again emphasize the importance of early excision and durable wound closure for full thickness and near full thickness burns. While advances in prevention, resuscitation, nutrition, care for inhalation injury, treatment of infection, and rehabilitation all benefit the burned patient, early excision of the burn wound followed by durable wound closure is the keystone. It potentiates these advances and actualizes the burn team in constructing an opportunity for increased survival following severe burn injury. Evidence also indicates that more rapid wound closure is associated with reduced hypertrophic scarring. Durable closure of burn wounds implies establishment of a stable self-renewing population of keratinocytes, thus closure of burn wounds either by native cells or autografts is an exercise in the skin organotypic culture. While short-term graft survival may reflect epithelial survival and proliferation, long-term success requires reconstitution of functional stem cell niches competent to maintain the epithelial layer indefinitely. The primary work of the burn surgeon is to optimize the conditions for this process to occur as rapidly and completely as possible.

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Medical Management of the Burn Patient

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Nearly 500,000 burn injuries were reported in the United States in 2016. According to the Healthcare Cost and Utilization Project National Inpatient Sample (2017 data), there were an estimated 40,000 hospitalizations related to burn injury, including 30,000 at hospital-based burn centers. Mortality after burn injury has decreased over the past 20 years, largely attributable to improved physiologic support of injury and a dedicated, multidisciplinary approach to the care of the burn patient. Of the 205,000 burns in the National Burn Registry from 2016, the mortality rate for all cases was 3.2%. Despite these successes, larger total body surface area (TBSA) burns still pose a high risk of mortality and morbidity.

The pioneering research (among many others) of Charles Baxter, Henry Harkins, David Hinshaw, Lloyd McLean, Francis Moore, Carl Moyer, Basil Pruitt, G. Tom Shires, and Douglas Wilmore and the advances by their proteges (again, among many) Peter Cameron, William Cioffi, William Curtsinger, Robert Demling, Clem Gerbode, David Herndon, Stephen E. Lowry, Ronald Tompkins, and Roger Yurt has established that the concept of burn shock results from extensive fluid shifts in both burned and nonburned tissue. Thermal injury activates the release of inflammatory and vasoactive mediators responsible for increased transcapillary permeability, local vasoconstriction, ischemia, coagulation, and hemostasis and microcirculatory derangements that together lead to tissue hypoperfusion. Release of histamine, prostaglandins, neuropeptides, and oxidants including oxygen-derived free radicals contributes to the local and systemic inflammatory response, exacerbating the microcirculatory dysfunction. This upregulation of innate immunity, compounded by downregulated adaptive immunity, which creates such a deranged host response to injury, can have profound organ-level effects that alter cardiovascular function, endocrine, gastrointestinal, hematologic, hepatic, neurologic, renal, and pulmonary function, leading eventually to multiple organ dysfunction syndrome (MODS) and death (Fig. 1). Fortunately, both the incidence and magnitude of MODS have decreased owing to better recognition of risk, improved resuscitative, timely metabolic, nutritional, and pharmacologic support, and timely source control and wound closure.

Contemporary research inquiries in the management of the burn patient have focused largely on resuscitation to ameliorate burn shock, MODS, and the surge of inflammatory mediators to improve morbidity and mortality.

CRITERIA FOR TRANSFER TO BURN CENTER

Physicians caring for burn patients must have a working knowledge of when to transfer care of these patients to the appropriate care facility (usually, a regional burn center). The American Burn Association (ABA) has recommended that certain injuries and circumstances be considered for burn center referral after initial assessment and stabilization at an emergency department (Box 1).

Burn Classification

The physiologic impact of a burn is proportional to the extent of body surface area involved. Clinical examination remains the primary modality for burn depth estimation in the United States. The traditional classification of burns according to degree of injury (first through fourth) has been replaced by a system reflecting need for surgical intervention. Current designations of burn depth are superficial, superficial partial thickness, deep partial thickness, and full thickness (Table 1). A multitude of techniques have been developed to provide an objective estimate of burn depth and healing time. These include tissue biopsy, administration of radiopharmaceuticals, sonofluorescein and fluorescein dyes, thermography, photometry, liquid crystal (thermoindicating) film, nuclear magnetic resonance, pulse ultrasound, Doppler ultrasound, and laser doppler imaging (LDI). Outside the United States, LDI has been used increasingly to determine burn depth. In Fig. 2, the regions of interest are identified using two-dimensional clinical photos (Fig. 2, left). An outlined template is created from these regions of interest and applied to LDI and thermal imaging using anatomical and wound reference points. LDI has been shown to have several advantages: ease of use, it is noninvasive and noncontact, highly accurate (>90%) with low interoperator variability (kappa), can distinguish reliably between superficial and deep partial thickness burns, can be used as a prognostic tool to classify burns into three categories of healing time (<14 days, 14–21 days, and >21 days), and is the only modality approved currently by the US Food and Drug Administration. Cost of the device approximately $85,000 per unit, has been cited as the primary reason for the lack of more widespread adoption.

Estimation of TBSA

Accurate estimation of burn size is essential to determining when to transfer a patient and also to guide appropriate fluid resuscitation. Of note, superficial (first degree) burns are not included in percentage TBSA burn assessment. Several studies have shown underestimation of the size of large burns, especially in obese patients, and can lead to undertransfusion. Several methods have been described to estimate TBSA. These include the Rule of Nines, the Lund Browder chart, and the "palm" method. The Rule of Nines, first described by Pulaski and Tennison in the late 1940s and published by Wallace in the early 1950s, is in common usage for estimation of TBSA in adult patients. By contrast, the Lund Browder chart is considered a more accurate method for calculating TBSA in both adults and children but is cumbersome. The Lund Browder method accounts for the fact that children have proportionally larger heads and smaller lower extremities compared with adults. Finally, the single palm method, useful for patchy

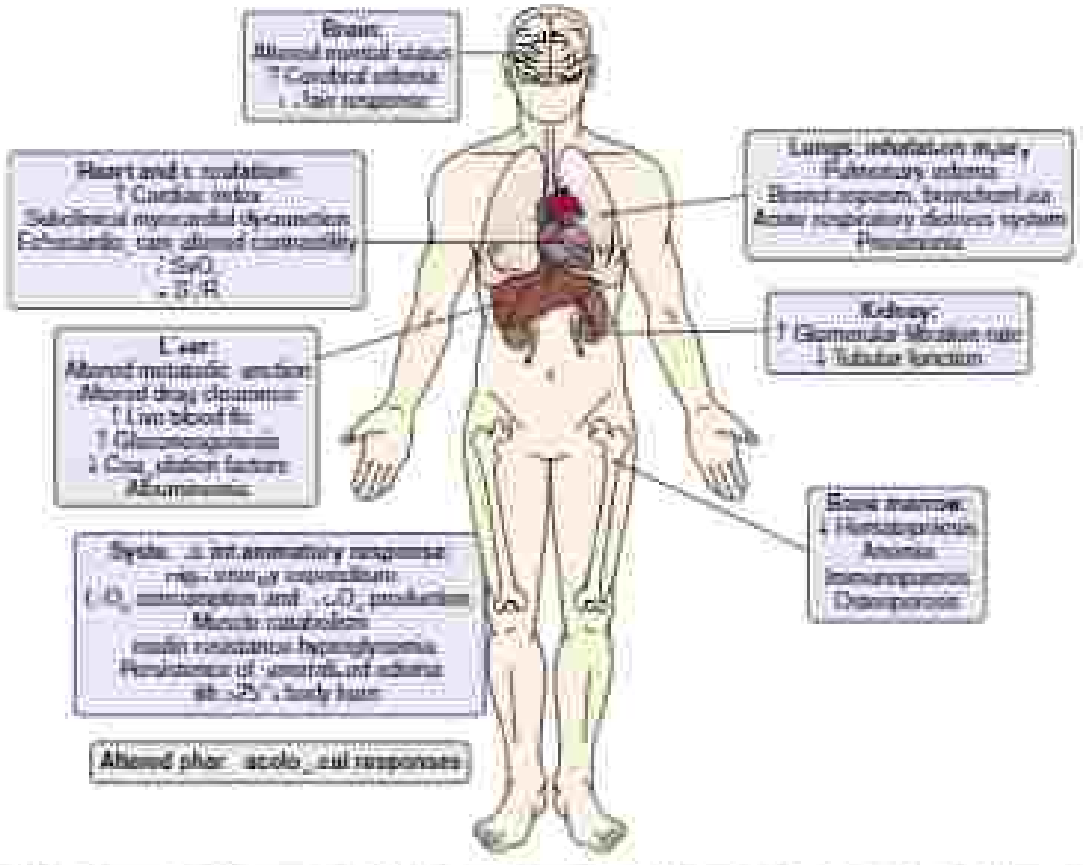


FIG. 1 . athophysiologic changes during hypermetabolic/hyperdynamic phase of burn (>48 hours). (Modified from Barret J.P., Herndon D.N., Wolfram D., et al. Acute and postacute care of the burn injured patient. In: endocrinology 2011;2720(1449-1464).

burn distribution, is calculated based on the patient's hand size. The palm of the patient's hand, excluding the fingers, is both children and adults is approximately 0.5% of TBSA, whereas the entire palmar surface including the fingers is 1% (Fig. 2).

RESUSCITATION

It is imperative to understand resuscitation tactics in the burn patient. All adult patients with burns involving more than 20% TBSA and pediatric patients with more than 10% TBSA should receive intravenous fluid resuscitation. Many formulas exist to estimate fluid requirements, some more popular than the Parkland Formula (4 mL/kg/%TBSA), with the first half of the calculated requirement given over 8 hours, starting from time of injury. It is necessary to catch up if initial resuscitation is delayed or inadequate. The remaining half is given over the next 16 hours. Resuscitation by the Parkland formula in the second 24 hours administers substantial amounts of 5% human serum albumin solution. Colloids can be given as 20% to 40% of calculated plasma volume. No crystalloids are used. Glucose in water is added to amounts required to maintain a urinary output of 0.5 to 1 mL/hr in adults and 1 mL/hr in children. Other formulas vary by fluid composition as well as rate of administration (Table 2).

A caution to providers tasked with the initial resuscitation of the burn patient. Patients with inhalation injury, delayed resuscitation, high voltage injuries, and extensive deep burns will likely require higher volumes than predicted by burn formula calculations. Resuscitation is then guided by usual parameters (e.g., sensation, urine output, cardiopulmonary function, arterial lactate clearance).

BOX 1 Considerations for Referral of a Burned Patient to a Specialized Burn Treatment Facility (American Burn Association)

I. Partial thickness burns greater than 10% total burn surface area
II. Burns involving the face, hands, feet, genitalia, perineum, or major joints
III. Full thickness burns of any location in any age group
IV. Electrical burns, including lightning injury
V. Chemical burns
VI. Inhalation injury
VII. Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
VIII. Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be stabilized by a trauma center before being transferred to a burn unit. Physician judgment, first the outset in conjunction with regional medical protocols must guide decision making.
IX. Burned children in hospitals without qualified personnel or equipment for the care of children
X. Burn injury in patients who will require special social, emotional, or long-term rehabilitative support or intervention

USE OF COLLOIDS

The problem of "fluid creep" as a result of crystalloid resuscitation was one of the early drivers of the use of colloid resuscitation. In fact, the use of plasma for burn resuscitation was described in the early 1940s by Henry Harkins, who recommended 1 L of plasma for each 10% TBSA burned for patients with burns to more than 10% TBSA. The common hypothesis for the use of colloids was based on the observation of hemoconcentration after a major burn, and the deduction that this must have resulted from a loss of plasma volume; therefore, colloid solutions containing macromolecules would theoretically increase plasma colloid osmotic pressure and act as better intravascular volume expanders than crystalloid fluid alone. Unfortunately, measurement of colloid osmotic pressure and resuscitation based on these measurements proved unsuccessful in improving outcomes of many forms of shock, including major burn injury.

During the 1970s, resuscitation tactics using balanced salt solutions arose, leading to a shift away from early provision of colloids. Moyer and others conducted resuscitation studies with Lactated Ringer's solution and concluded that burn shock likely arose from an extracellular sodium deficiency that was best treated with balanced

TABLE 1 Classification of Burns by Depth of Injury

Depth	Level of Injury	Clinical Features	Usual Treatment
Superficial (first degree)	Epidermis	Dry, red, blanches, painful	Healing time 3–6 days, no scarring
Superficial partial thickness (superficial second degree)	Papillary dermis	Blisters, moist, red, weeping, blanches, severe pain to touch	Cleaning, topical agent, sterile dressing, healing time 7–21 days, hypertrophic scar rare, return of full function
Deep partial thickness (deep second degree)	Reticular dermis, most skin appendages destroyed	Blisters, wet or waxy dry, reduced blanching, decreased pain sensation to touch, pain present to deep pressure	Cleaning, topical agent, sterile dressing, possible surgical excision and grafting, scarring common if not surgically excised and grafted, earlier return of function with surgery
Full thickness (third degree)	Epidermis and dermis, all skin appendages destroyed	Waxy white to leathery dry and inelastic, does not blanch, absent pain sensation, pain present to deep pressure, pain present in surrounding areas of second degree burn	Treatment as for deep partial thickness burns plus surgical excision and grafting at earliest possible time, scarring and functional limitations more common if not grafted
Fourth degree	Involves fascia and muscle and/or bone	Pain to deep pressure, in the area of burn, increased pain in surrounding areas of second degree burn	Healing requires surgical intervention

From Hunter SR, Shank L, Woodson L, et al. Acute and perioperative care of the burn injured patient. Anesthesiology. 2015;122(2):446–464.

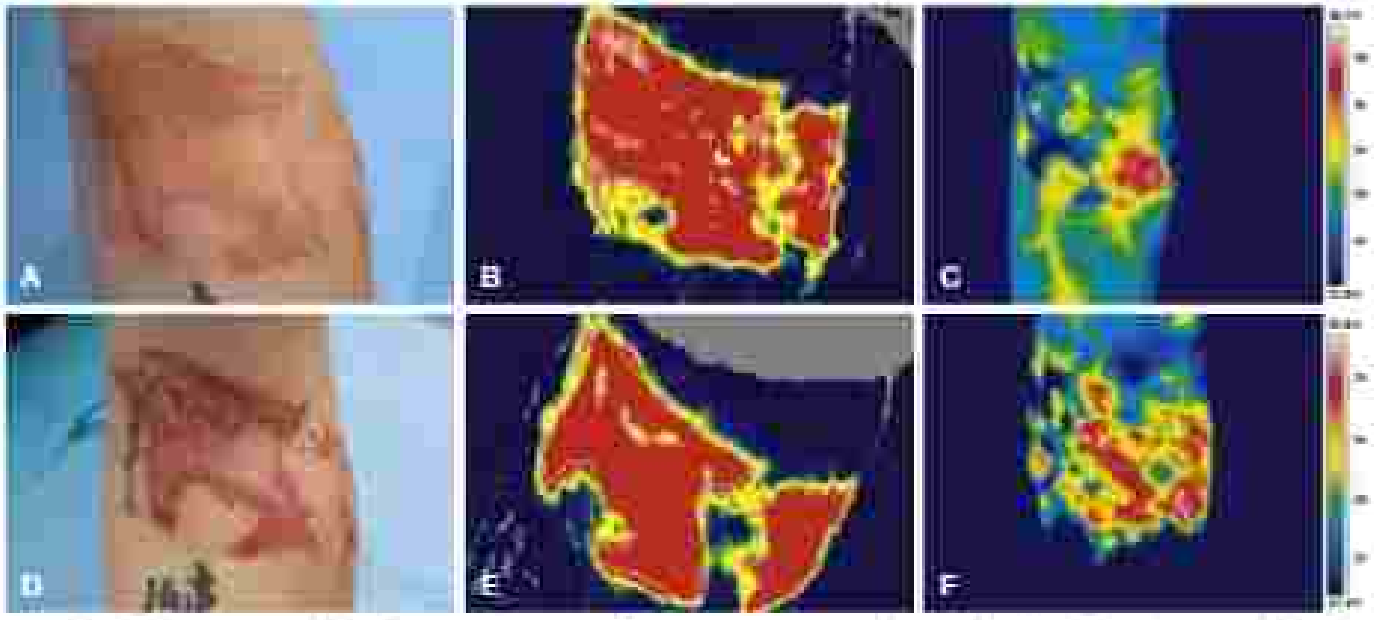


FIG. 2. Laser Doppler imaging and thermal imaging of burn injury. Prospective comparative evaluation study of laser Doppler imaging and thermal imaging in the assessment of burn depth. (A) Two-dimensional photograph of burn on anterolateral thigh (day 0). (B) LDI image of burn (day 0). (C) Thermal image of burn (day 0). (D) Two-dimensional photograph of burn (day 3). (E) Laser Doppler imaging of burn (day 3). (F) Thermal image of burn (day 3). (From Wilson L, *et al.*, Hardwicke J, *et al.* Prospective comparative evaluation study of Laser Doppler imaging and thermal imaging in the assessment of burn depth. Burns. 2013;39(8):1472–1473.)

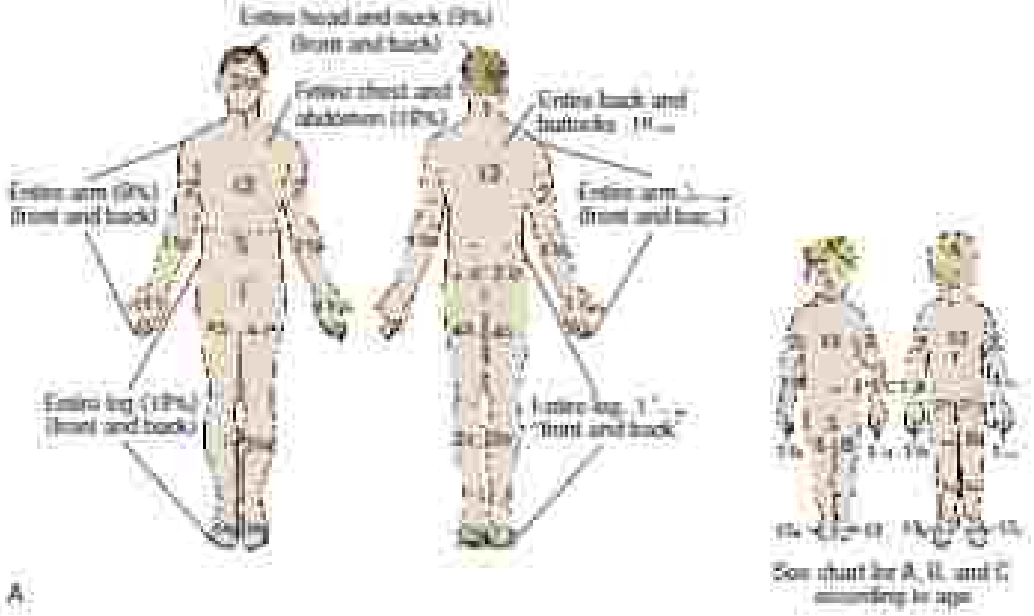
salt solution. Baxter and Shires also found that extracellular sequestration of sodium and water resulting from decreased transmembrane potential, at the expense of decreased intracellular sodium and water occurred early in burn injury. They advocated successfully for resuscitation only with balanced salt solutions in the first 24 hours. Pruitt and others found that use of colloid early in burn resuscitation did not appear to augment intravascular retention of fluid because increased extracellular osmotic pressure caused by capillary leak syndrome of sufficient magnitude results in loss of membrane integrity; the membrane becomes permeable to albumin and other macromolecules until equilibrium is reestablished along the new concentration gradient that promotes transmembrane flux of albumin. Without treatment, the clinical consequences are hypovolemia and tissue edema that may persist until microcirculatory integrity is restored and the patient begins to mobilize and excrete the fluid administered for resuscitation. As a result of these works, colloid free resuscitation in the first 24 hours post burn injury became the standard of care in burn resuscitation.

Colloid use in burn resuscitation might have become obsolete had Pruitt not described the problem of fluid creep. The phenomenon refers to the consequences of aggressive crystalloid resuscitation. Edema related complications were noted, such as massive facial and airway swelling requiring prolonged endotracheal intubation, extremity compartment syndromes (including of unburned extremities), and respiratory and cardiac failure. Other resuscitation related complications now reported as consequential to overresuscitation include abdominal compartment syndrome and rarely permanent blindness (as a result of prolonged elevated intraocular pressure).

As a result of the lessons learned from the problem of fluid creep, colloid use in burn resuscitation is regaining popularity. Considering that early colloid administration is demonstrably methodical colloid is probably administered optimally after 12 to 18 hours postinjury, either as a routine supplement or as rescue treatment of fluid creep. A 2010 international survey conducted by the International Society of Burn Injuries and the ABA found that one half of respondents initiate colloids in the first 24 hours, with nearly equal preference for fresh frozen plasma (FFP) or albumin as the chosen colloid.

Albumin is a 67 kDa protein synthesized by the liver, with 40% being distributed in the extravascular space and 60% intravascular. Total body albumin is ~3.5 to 5.0 g/kg or about 250 to 300 g for a 70 kg person. A negative acute phase reactant (albumin synthesis) is downregulated by the innate immune response to injury in favor of protein synthesis of salutary to the host response (e.g., coagulation proteins), and thus unreliable to monitor as an acute biomarker; albumin has been used as a volume expander since the 1940s. However, a late 1990s Cochrane review found that the use of albumin was associated with a pooled increased absolute risk of death of 6% (95% confidence interval [CI], 3–9). More recent trials such as the Saline versus Albumin Fluid Evaluation study, the Early Albumin Resuscitation during Septic Shock study, and the ALBumin Italian Outcome Sepsis study, found no increase in mortality associated with albumin use when compared with crystalloid fluids, albeit not explicitly after burn injury. Although hypoalbuminemia is universally present in burn patients, and its correction has been studied in numerous critically ill patient populations, more research is needed to ascertain its utility in burn resuscitation. A recent meta-analysis by Ulrich et al. found that early use of albumin based resuscitation strategies demonstrated no impact on mortality in burn patients. They concluded that more research is needed to assess the effect of albumin based solutions on mortality in burn patients, but lacking evidence of superiority, the high cost of human serum albumin as compared with crystalloids should be taken into account.

The use of plasma in early burn resuscitation (as described by Harkins) was one of the first colloid administration tactics. FFP for burn resuscitation was first described by Oser et al. As the name implies, FFP is collected ("fresh") from a single unit of donated blood or by apheresis and then cryopreserved ("frozen") at −30°C and stored for up to 1 year. FFP is an important adjunct in the management of traumatic coagulopathy as part of a balanced resuscitation strategy. Its use in burn resuscitation has gained popularity with the development of the Slater formula. The formula starts with 2 L lactated Ringer's solution given over the first 24 hours after burn, plus 75 mL/kg/% for. Importantly, FFP is titrated to achieve urine output of 0.5–1.0 mL/kg per hour. Detractors have argued that its benefits should be



AGE	Birth–1 yr	1–4 yr	5–9 yr	10–14 yr	15 yr	Adult
Head	19	17	13	11	9	7
Neck	2					
Ant. trunk	13					
Post. trunk	13					
R buttock	2½					
L buttock	2½					
Genitalia	1					
R U. arm	4					
L U. arm	4					
R L. arm	3					
L L. arm	3					
R hand	2½	3½		3½	3	3½
L hand	2½	3½		3½	3	3½
R thigh	5½	6	7½	8	8½	9
L thigh	5½	6	7½	8	8½	9
R leg	5					
L leg	5					
R foot	3½					
L foot	3½					

B BODY AREA

FIG. 3 Lund-Browder charts. (A) The Lund-Browder charts are somewhat more accurate than the rule of nines in estimating the total body surface area (TBSA) burned. (B) Proportion of TBSA of individual areas according to age. When compared with adults, children have larger heads and smaller legs. Other areas are relatively equivalent throughout life. The rule of nines is not accurate in determining the percentage of TBSA burned in children. (L, Left lower; L, left upper; R, right lower. [from Roberts et al. Roberts and Hedges' Clinical Procedures in Emergency Medicine and Acute Care, 5th ed. Philadelphia: Elsevier; 2010.])

weighed against the risk of disease transmission, transfusion-related lung injury (TRALI), and cost (double that of albumin). TRALI typically occurs within 6 hours of transfusion of blood products (usually after administration of packed red cell concentrates, but also reported after FFP administration). It is believed to occur as a result of either neutrophil priming or antibodies against recipient white blood cell antigens, activating an inflammatory cascade. Clinical presentation varies with rapid onset of dyspnea, tachypnea, and respiratory distress with noncardiogenic pulmonary edema characteristic of acute respiratory distress syndrome (ARDS). Saxe et al. conducted a retrospective review and found that whereas many patients with severe burns have preexisting acute lung injury on admission, the incidence of TRALI following FFP resuscitation from burn shock is low.

Nonprotein semisynthetic colloids, such as hydroxyethyl starch (HES) solutions, contain complex carbohydrate molecules derived from corn or potato starch. Although initial studies were promising in terms of volume expansion, larger randomized controlled trials among critically ill patients identified a significantly increased risk of renal dysfunction requiring renal replacement therapy, significantly more pruritus, and higher 90 day mortality when using HES compared with crystalloids for fluid resuscitation. Consequently, the US Food and Drug Administration has recommended against the use of HES in critically ill patients and therefore cannot be recommended for the resuscitation of burn patients at this time.

MARKERS OF RESUSCITATION

The primary goal of resuscitation is to restore and preserve tissue perfusion and metabolic homeostasis. Vital signs, including urine output, should be measured hourly. The ABA practice guidelines recommend that fluid infusion be titrated to achieve urine output of 0.5 to 1.0 mL/kg per hour. As a resuscitation endpoint, although

TABLE 2 Intravenous Fluid Burn Resuscitation Formulas

Formula	Fluid Solution	Volume in First 24 Hr	Rate of Administration
ADULT			
Parkland	Lactated Ringer's solution	2–4 mL/kg/% TBSA burn	First half over 8 hr, second half over 16 hr
Modified Brooke	Lactated Ringer's solution	2 mL/kg/% TBSA burn	First half over 8 hr, second half over 16 hr
PEDIATRIC			
Parkland	Lactated Ringer's solution	2–4 mL/kg/% TBSA burn plus maintenance fluids	First half over 8 hr, second half over 16 hr
Shriners Cincinnati	Lactated Ringer's solution plus 50 mEq sodium bicarbonate	4 mL/kg/% TBSA burn +	First 8 hr
	Lactated Ringer's solution	1500 mL/m² BSA	Second 8 hr
	Lactated Ringer's solution plus 12.5 g albumin 5%		Third 8 hr
Shriners Galveston	Lactated Ringer's solution	5000 mL/m² TBSA burn plus 2000 mL/m² BSA	First half over 8 hr, second half over 16 hr

From Warden GD: Fluid resuscitation and early management. In Herndon DN, ed: Total Burn Care, 4th ed. New York: Elsevier, 2012:115–124.
BSA, body surface area; TBSA, total body surface area.
Intravenous fluid resuscitation should be commenced in adult burns exceeding 20% TBSA and pediatric burns exceeding 10% TBSA. Pediatric patients following the Parkland formula should also receive maintenance fluids with dextrose 5% in half-normal saline at 4 mL/hr for the first 10 kg of body mass, 2 mL/hr for the second 10 kg of body mass, and 1 mL/hr for the remaining kilograms of body mass. Maintenance fluid requirements for the first 24 hours are already factored into the Shriners Cincinnati and Shriners Galveston formulas.

urine output is practical because of ease of measurement, it may be an imperfect marker, especially for patients with diabetes mellitus or those who have received a hyperosmotic medication such as mannitol or radiocontrast medium. Studies have shown that the correlation is poor between urine output and hemodynamic parameters or measures of oxygen transport or tissue perfusion. Furthermore, upon an hourly urine output in the burn patient has never been defined.

Laboratory markers of resuscitation are similar to those used in septic shock and trauma patients. They include pH, serum bicarbonate and lactate concentrations, and arterial base deficit (BD). Although not specific to burn injury, they are markers of global hypoperfusion and shock (Table 3). Multiple studies have shown that rapid correction of these indices leads to improved survival. Monitoring skin perfusion or gastric mucosal pH has not been proven to be advantageous in guidance for burn resuscitation.

Although no single laboratory parameter has been identified as perfect, serial lactate measurements early during resuscitation are an important factor in treatment for critically injured patients. Lactate, the byproduct of glycogenolysis via the lactate-pyruvate pathway, is a rapid, sensitive, and inexpensive marker of shock. Importantly, a high lactate concentration at the time of patient presentation predicts death in studies of burn, trauma, and sepsis. Dezman et al. showed that the inability to reduce lactate toward normal concentrations within the first 24 hours of hospitalization increases the risk of death.

Admission BD has long been recognized to be an excellent multifaceted predictor of mortality in trauma patients, having a good correlation with volume resuscitation. Carlson et al. found that patients with a nadir BD less than −6 mmol/L during the initial 24 hours after injury developed a more aggressive systemic inflammatory response on the first postburn day, had a higher incidence of MODS, and experienced more severe MODS. This did not appear to be related to the size of the burn, and occurred despite resuscitation to an acceptable level of urine output.

MONITORING

Initial monitoring includes standard measurements of heart rate, blood pressure, pulse oximetry, respiratory rate, and urine output (Table 1).

Central venous pressure (CVP) monitoring has served as an estimator for intravascular volume for decades because of the relative ease of data acquisition and interpretation, although invasive hemodynamic monitoring carries numerous risks. However, relationships among CVP, cardiac output (Q), and vascular resistance and capacitance are complex, making for interpretive complexity. Many factors can affect CVP measurements, including ventilation, hypervolemia, right ventricular failure, valvular heart disease, pulmonary hypertension, and mechanical ventilation. In patients ventilating spontaneously, CVP varies with the ventilatory cycle. Relative negative intrathoracic pressure in inspiration results in a decrease of measured CVP, whereas exhalation results in relatively positive intrathoracic pressure and an increase of measured CVP. These changes are considered normal respiratory variation of the CVP waveform. When patients in respiratory failure receive positive pressure ventilation from a mechanical ventilator, opposite effects are noted: delivery of a breath from a mechanical ventilator results in comparatively positive intrathoracic pressure, and elevation of measured CVP, whereas the expiratory phase leads to a decrease in measured CVP.

Use of a pulmonary artery catheter (PAC) to guide acute burn resuscitation has largely disappeared, beginning about 15 years ago. Recent studies found that this approach led to administration of excessive volumes of fluid. Invasive monitoring using a PAC provides no survival benefit and is not no longer routine. However, PACs may still be useful for carefully selected patients with underlying severe cardiac disease or acute kidney injury when renal replacement therapy is being considered.

Critically ill patients often receive extended hemodynamic monitoring with measurement or estimation of Q as an aid for guiding fluid and vasopressor therapy. With the introduction of the pulmonary artery catheter by Swan and Ganz in 1970, bedside measurement of Q by thermodilution became commonplace. However, routine use of the PAC has been questioned, owing to its invasiveness, difficulty in interpretation of results, and lack of benefit with respect to outcome.

Newer, less invasive monitoring approaches including transpulmonary thermodilution may be used to measure Q and determine volumetric measures of preload such as the global end-diastolic volume, the intrathoracic blood volume, and extravascular lung water. Arterial waveform pulse contour analysis yields real-time continuous

TABLE 3 Markers of Fluid Resuscitation

Index of Response	Normal (Target) Range
Vital signs	
HR (beats/min)	<140
BP (mm Hg)	>90/60
SaO_2 (%)	>98
Urine output (ml/kg/hr)	
Adults	0.5–1.0 (or 30–50 ml/hr)
Children	1.0
Base deficit (mM)	
Normal	−3 to 0
Target	< −6
Serum lactate (mM)	
Normal	0.5–2.2
Target	<4
Central venous pressure (mm Hg)	
Normal	2–6
Target	8–12
Mean arterial pressure (mm Hg)	>65
Bladder pressure (mm Hg)	
Normal	0–5
IAH	>12
ACS	>20
Intrathoracic blood volume index (ml/m²)	>800
Cardiac index (l/min/m²)	>3.5

From Kao KC, Mullins A, and Hedges JR: Important developments in burn care. Biol Resuscitation 2010;1:001(1):20–106.
ACS: Abdominal compartment syndrome; BP: blood pressure; HR: heart rate; IAH: intra-abdominal hypertension; Sa_{O_2}: oxygen saturation.

measures of Q, stroke volume (SV), stroke volume variation, pulse pressure, and pulse pressure variation.

Arterial pulse contour analysis measures and monitors SV on a beat-to-beat basis from the arterial pulse pressure waveform. Q is then calculated based on the pulse pressure being directly proportional to SV. Pulse pressure variability in relation to SV can be affected by positive pressure ventilation, and in hypovolemic patients whose right ventricular filling is decreased. There are several theoretical advantages of this technique when compared to the gold standard, bolus thermodilution technique. It is noninvasive, using already placed arterial catheters. In addition, the clinician can monitor changes in SV and Q on a continuous basis. A major limitation of pulse contour analysis is reduced validity in the setting of cardiac arrhythmias, aortic regurgitation, or peripheral vascular disease.

Point-of-care ultrasound has become an integral tool in management of critically ill patients, especially in determining volume status and cardiac function. Specifically, information about a patient's cardiac anatomy, assessment of cardiac function, ventricular volume, Q, ejection fraction, and inferior vena cava (IVC) diameter. IVC diameter is used to assess preload and volume responsiveness. Nevada et al. found that patients with IVC diameter <2 cm were more likely to be fluid responders (IVC diameter >2 cm after fluid bolus). Heldt et al. have described support-performed hemodynamic transesophageal echocardiography as a useful adjunct in burn resuscitation, for example, in determining whether additional fluid or vasopressors are required to treat hypotension. Potential disadvantages of point-of-care ultrasound and echocardiography are similar to any new learned technique that requires proficiency. It remains unclear how many procedures one needs to perform before proficiency is attained.

COMPLICATIONS OF BURN RESUSCITATION

Systemic complications of burn injury remain a substantial problem despite advances in burn resuscitation. Severity of complications correlates with percent TBSA, age, sex, and undertresuscitation.

ARDS is a pulmonary manifestation of the upregulation of innate immunity, resulting in systemic inflammation and clinical respiratory failure caused increased vascular permeability and impaired gas exchange and oxygen utilization. ARDS usually occurs in patients who already are critically ill from predisposing conditions such as sepsis, aspiration pneumonitis, pneumonia, burns, inhalation injury, and trauma. Burn injuries, especially those involving inhalation injuries, have the highest incidence of ARDS among all predisposing conditions. Carlson et al. found that nearly 40% of mechanically ventilated adult civilian burn patients develop ARDS. Management of the burn patient with ARDS is largely supportive with mechanical ventilation being the cornerstone of therapy. Lung protective ventilation to minimize the additive insult of volutrauma (formerly barotrauma) for example, the use of low tidal volumes of ~6 ml/kg, and the targeted achievement of lower plateau pressures (P_{plat} <30–35 cm H_2O), combined if necessary with permissive hypercapnia (allowance for a partial pressure of carbon dioxide >80 mm Hg as long as pH >7.20, absent a coexistent traumatic brain injury) has improved mortality.

ACS is a complication associated with aggressive fluid resuscitation of burns (Fig. 8). In large TBSA burns that require large volume resuscitation, measuring a baseline urinary bladder pressure on admission to the burn intensive care unit may assist in monitoring for the potential development of ACS. Burns can lead to ACS by several mechanisms. Circumferential burns of the lower torso with abdominal wall edema and eschar formation can cause reduced compliance of the abdominal wall. Large burns can lead to ischemic paralysis secondary to elevated mesenteric vascular resistance resulting from the release of vasoactive substances and inflammatory mediators from burned tissue. In addition, ascites and bowel edema secondary to massive fluid resuscitation, exacerbated by cardiovascular failure, can also lead to intraabdominal hypertension (IAH). Reed et al. showed that patients who received 12 L or more of intravenous fluid in the first 24 hours of resuscitation, or who received 200 ml/hr or intravenous fluids for more than four consecutive hours, were at risk for developing IAH and ACS, which is characterized by both respiratory and renal insufficiency. End-organ injury to the kidneys as evidenced by low urine output may be misinterpreted as requiring even more fluid resuscitation, leading to worsening of ACS. There is not consensus as to what degree of IAH should cause alarm. Intraabdominal pressure is normally 5 to 10 mm Hg. Pressure of 20 mm Hg or higher is clearly abnormal, whereas more than 30 mm Hg may require abdominal decompression to ensure homeostasis.

Severe burn injury can lead to dysfunction of the gastrointestinal system, primarily a result of loss of the gut barrier function and enteric bacterial translocation. Additionally, hypovolemia following a severe burn can result in a low-flow state of mesenchymal ischemia, further worsening gut mucosal integrity. Gut mucosal atrophy can also occur in the absence of enteral feeding, which should be instituted early after injury to promote anabolism, prevent trophic effects on gut mucosa. Early enteral nutrition, started 24 to 48 hours after burn injury, is one of the only therapies shown to decrease these complications. Moreover, abdominal wall burns or burns to the lower back can induce ileus, including the feared complication of colonic pseudo-obstruction (Ogilvie's syndrome), which usually can

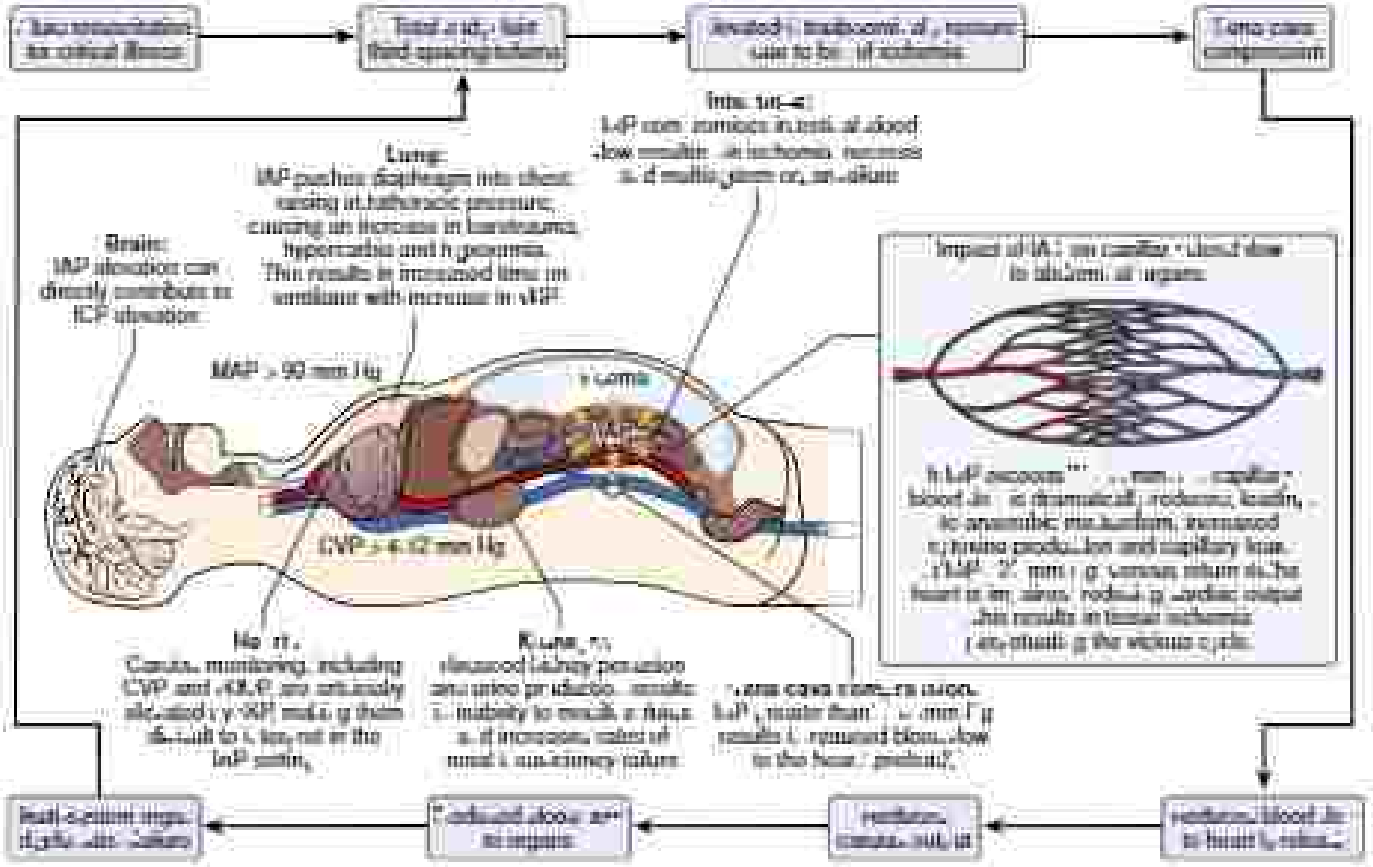


FIG. 4 Optimal use of the pathophysiologic processes leading to abdominal hypertension and abdominal compartment syndrome [illegible]

be reversed with a 2.8 mg bolus injection of neostigmine, but which may require surgical decompression in refractory cases owing to the risk of colon perforation.

Early onset acute kidney injury (AKI) results most commonly from reduced CO. Burn injury can cause hypovolemia and hypotension that stimulates a renal vasoconstrictive response via the renin-angiotensin-aldosterone axis, release of neurohormonal mediators of renal vasoconstriction, depressed myocardial contractility, a stress-related counterregulatory hormonal milieu, direct and indirect (from nephrotoxic medications) nephrotoxicity, and protein denaturation. This leads to an increase in vascular resistance and permeability and production of microthrombi in the glomeruli and renal tubules, leading to a further reduction of renal flow and tubular necrosis. The ABA has suggested avoidance of AKI using criteria such as stages of the Risk Injury Failure Loss End Stage or Acute Kidney Injury Network criteria. Early, judicious resuscitation to mitigate the innate immune response is key to preventing AKI in burn patients.

Burn wound infection and sepsis are common causes of morbidity and mortality in burn patients. Any rapid change in the burn wound appearance or the clinical condition of the burn patient may herald burn wound infection or sepsis. Categories of burn wound infection are based on clinical features and depth of invasion, which is determined through cultures and histopathology of tissue obtained by burn wound biopsy. Specific criteria that include, among other criteria, microbial invasion into adjacent normal tissue have been suggested by the ABA to define burn wound sepsis (Table 4).

Although not often discussed as part of burn resuscitation, the goals of transfusion of blood and blood products in burn management is worthy of consideration. A multicenter randomized prospective trial compared two standard transfusion tactics with hemoglobin goals of less than 10 g/dL compared with less than 7 g/dL in patients with burn injury more than 20% TBSA, and found that the restrictive protocol reduced transfusion volume without significant differences in blood stream infections, mortality, pneumonia, urinary tract infection, wound infection, hospital or intensive care unit length of stay, organ dysfunction, or wound healing. The findings of this trial confirm and extend the results of the historic Transfusion Requirements in Critical Care trial, in which restrictive transfusion was equally effective as was a liberal blood product administration protocol. These observations were confirmed subsequently in studies of hip fracture patients, cardiac surgery, and other critical care populations in addition to burn patients.

Thermal injury can occur to the upper or lower airway. Indications include singed facial hair, soot in the oropharynx, carbonaceous sputum, respiratory distress, hoarseness, persistent cough, or deep facial or circumferential neck burns. Inhalation injury of the upper airway can cause substantial swelling and subsequently complicate the securing of an artificial airway. The lower airway generates a substantial local and systemic inflammatory response mediated by the [illegible] present in smoke particles. In the lower airway, these antigens are in close proximity to large populations of airway macrophages and marginated neutrophils in the pulmonary microcirculation, and severe tissue injury can ensue, including an ARDS picture. Mucosal sloughing and carbonaceous deposits determine the grading of lower airway injury, mindful of the possibility that mucosal sloughing can lead precipitously to respiratory failure resulting from mucus plugging. Such airway debris can be managed by bronchodilators, pulmonary toilet including fiberoptic bronchoscopy, mechanical ventilation

TABLE 4 ABA 2007 Criteria of Sepsis in Burn Patients

	Children	Adults
Progressive tachycardia	≥2 SD age-specific norms (90% age-adjusted maximum heart rate)	≥110 beats/min
Progressive tachypnea	≥2 SD age-specific norms (90% age-adjusted maximum respiratory rate)	≥25 breaths/min (not ventilated) or ≥12 mm Hg (ventilated)
Thrombocytopenia (applicable only 5 days after initial resuscitation)	<2 SD age-specific norms	<100 × 10^3/μL
Hyperglycemia (without preexisting diabetes mellitus)	>200 mg/dL (without treatment) or insulin resistance >25% increase in insulin requirements in 24 hours	>200 mg/dL (without treatment) or insulin resistance >7 U/hr intravenous insulin
Inability to continue enteral feedings >24 hours	Abdominal distension, enteral feeding intolerance (residual > 50 mL/hr), uncontrollable diarrhea	Abdominal distension, enteral feeding intolerance (residual >½ feeding rate), uncontrollable diarrhea

From Greenhalgh DG, Saffle JR, Holmes JH IV, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28:776–790.
ABA, American Burn Association; SD, standard deviation.

if needed, and careful surveillance for invasive pulmonary aspergillosis, which is common in this patient population. Inhalation injury is discussed in detail elsewhere in this issue of the *Clinics*.

Burn wound sepsis is the most common cause of late mortality in burn patients. Early excision and closure of the burn wound, topical antimicrobial therapy, and systemic antibiotics when indicated have significantly reduced the incidence of burn wound sepsis. Despite these advances, burn wound sepsis remains a significant cause of morbidity and mortality in burn patients. Early diagnosis of burn wound sepsis is difficult because the signs of sepsis, such as fever, hyperglycemia, and tachycardia, are also present in patients without sepsis. Furthermore, the presence of bacteria in the burn wound is universal, and quantitative cultures of tissue biopsy specimens are the gold standard for diagnosis of burn wound sepsis. However, the use of quantitative cultures is not widespread because of the time required to perform the test and the lack of availability in many burn centers. Therefore, most burn centers rely on clinical criteria to diagnose burn wound sepsis. Unfortunately, clinical criteria are not very specific for burn wound sepsis. Recently, the American Burn Association published consensus guidelines for the diagnosis of sepsis in burn patients (Table 4). These guidelines are based on the systemic inflammatory response syndrome criteria but have been modified to account for the pathophysiologic changes that occur after burn injury. Using these criteria, the diagnosis of sepsis can be made with greater accuracy. Treatment of burn wound sepsis includes surgical debridement of infected tissue, systemic antibiotics, and topical antimicrobial therapy. Topical antimicrobials are applied directly to the burn wound and include silver sulfadiazine, mafenide acetate, and silver-containing dressings. Mafenide acetate has the advantage of penetrating eschar, but it can cause pain and metabolic acidosis. Silver sulfadiazine is painless and has a broad spectrum of antimicrobial activity, but it does not penetrate eschar. Silver-containing dressings have the advantage of providing continuous antimicrobial therapy, but they are expensive and require frequent dressing changes. Systemic antibiotics should be used only when there is clinical evidence of burn wound sepsis, because prophylactic systemic antibiotics have been shown to increase the incidence of infection with multidrug-resistant organisms.

BURN METABOLISM AND NUTRITION SUPPORT

Severe burn injury results in a massive stress response that induces profound, protracted catabolism that sometimes can persist for years after the initial insult. Typically, patients with major burns have higher caloric/metabolic requirements when compared with patients with sepsis, multiple trauma, or head injury (Fig. 3).

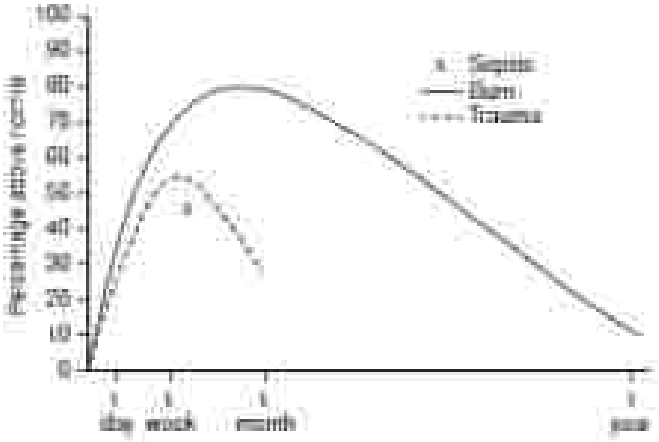


FIG. 3 Hypermetabolic response after severe burns, trauma, and sepsis. (Modified from Clowes GH Jr, Hirsch EF, Simeone FA. Nutrition and metabolism in burns. *Surg Clin North Am*. 1970;50:1251.)

The acute response to burn injury typically manifests two distinct states. The shock, or ebb phase, is typically brief in duration and is predominated by reduced cardiac function, decreased metabolism, and reduced tissue perfusion. This state can result in hypothermia, anuria and elevated lactate production.

Unlike the acute phase, the classic response to burn injury, or flow phase, is a hypermetabolic, catabolic state that may last days to months after initial burn injury. The metabolic rate and O_2 are markedly elevated, resulting in increased whole body oxygen consumption and energy expenditure (EE) above normal. The importance of adequate early nutritional support cannot be overstated in mitigating the stress response of burn injury. Failure to support full the metabolic needs of the burn patient can lead to loss of lean tissue, poor wound healing, sepsis, multiple organ failure syndrome, and death.

Early enteral nutritional support (within 24 hours of injury) attenuates the hypermetabolic/catabolic response to severe burn injury. The caloric requirements for burn patients can be estimated by a variety of formulas (Table 5). Regardless of which formula is used, the primary goal of nutritional support is to match the metabolic demand caused by the hypermetabolic state, while maintaining safety

TABLE 5 Common Formulas Used to Calculate Caloric Needs of Burn Patients

Adult Formulas	Equation	Comments
Harris Benedict	Men: 66.5 + 13.8 (weight in kg) + 5 (height in cm) − 6.76 (age in years) Women: 655 + 9.6 (weight in kg) + 1.85 (height in cm) − 4.68 (age in years)	Estimates basal energy expenditure; can be adjusted by both activity and stress factor; multiply by 1.5 for common burn stress adjustment
Toronto formula	−4943 + 10.5 (TBSA) + 0.23 (calorie intake in last 24 hr) + 0.84 (Harris Benedict estimation without adjustment) + 114 (temperature) − 4.5 (number of postburn days)	Useful in acute stage of burn care; must be adjusted with changes in monitoring parameters
Davies and Liljedahl	30 (weight in kg) + 70 (TBSA)	Overestimates caloric needs for large injuries
Curreri	Ventilated patients (208 − 11 (age in years) + 5 (weight in kg) + (244 if male) + (23 if trauma) + (804 if burn) Nonventilated patients (25 − 11 (age in years) + 25 (weight in kg) − (609 if obese)	Complex formula which integrates variables for ventilation and injury status
Cunningham	Age 1–55: 25 (weight in kg) + 40 (TBSA) Age >55: 20 (weight in kg) + 65 (TBSA)	Often overestimates caloric needs
PEDIATRIC FORMULAS		
Galveston	0–1 year: 2100 (body surface area) + 1000 (body surface area × TBSA) 1–11 years: 1800 (body surface area) + 1300 (body surface area × TBSA) 12–18 years: 1500 (body surface area) + 1500 (body surface area × TBSA)	Focuses on maintaining body weight

Source: Clark A, Imran JB, Madni TD, Wolf SE. Nutrition and metabolism in burn patients. Burns Trauma. 2017;3:11. doi: 10.1186/s41038-017-0076-0.

(principally, from either pulmonary aspiration of gastric contents/enteral feeding solution or use of a malpositioned tube) and avoiding overfeeding. The macronutrients in the formulation of burn nutrition solutions include carbohydrates, proteins, and lipids. Some research suggests that given the inhibition of lipolysis in the acute response to injury, lipids should be limited as a source of calories. Fatty acid deficiency is a rarity that takes weeks to develop even absent any intake of fat). Comparison of high carbohydrate and protein, low fat enteral formula with low carbohydrate and protein, high fat formula in a systematic way showed no clear benefit to either formula, although the risk of pneumonia may have been lower with the high carbohydrate formula. Arginine appears to be an essential macronutrient for wound healing, and protein requirements in burn patients may be 50% higher than in healthy individuals. Protein delivery should be 1.5 to 2 g/kg body weight daily.

Parenteral nutrition in burn patients is typically reserved for patients whose gastrointestinal function is impaired. Parenteral nutrition requires central venous access, is associated with higher rates of complications in critically ill patients (e.g., hepatic dysfunction, catheter-related blood stream infection), and does not support gut mucosa directly, as does enteral feeding.

Immunonutrition (use of micronutrients that modify the immune response during critical illness) has not gained popularity despite supporting evidence. Immunonutrients that have been administered to burn patients include omega-3 fatty acids (fish oil), arginine, and glutamine. Arginine is a conditionally essential amino acid that serves as a precursor to glutamine, promotes T cell proliferation, stimulates growth hormone and insulin secretion, and promotes wound healing. Glutamine is believed to be a conditionally essential amino acid that provides fuel for immune cells and enterocytes, serves as a precursor for the antioxidant glutathione, and potentially reduces insulin resistance. Whereas glutamine has shown promise as a nutritional supplement in the critical care population, a recent review of immunonutrition in the burn population found insufficient evidence to recommend its use. Evidence-based practice guidelines for the use of micronutrients in burn patients have not been developed. Intuitively, diminished gastrointestinal absorption, increased urinary losses, altered distribution, and altered carrier protein (e.g., albumin, lactoferrin) concentrations following severe burn will lead to a deficiency in many micronutrients if not supplemented. There is little evidence for pharmacologic doses of any micronutrient in burn patients. In fact, the majority of patients achieve the recommended supplemental micronutrients in sufficient amounts through standard nutritional therapy.

NEW TRENDS IN BURN INJURY MANAGEMENT

As described earlier, the burn-induced stress response stimulates secretion of catecholamines, glucocorticoids, and peptide hormone mediators that are believed to be the primary factors of hypermetabolism after severe burns. Nonspecific β-blockade with propranolol, a nonspecific beta-1, beta-2 adrenergic receptor antagonist, has shown good results in blunting the response to burn injury. Low-dose propranolol (0.5–1.0 mg/kg) in patients with severe burns reduces myocardial oxygen consumption without affecting oxygen transport adversely. Higher doses (2 mg/kg/day for 7 days) cause a 20% reduction in heart rate. Propranolol also decreases resting energy expenditure, hepatic steatosis, and sepsis. The benefit of propranolol lasts demonstrably for at least 12 months after injury.

Anabolic steroid production is decreased after severe burn injury and can remain below normal for up to 3 years postinjury. Restoring serum testosterone to severely burned patients can decrease lean tissue loss and improve protein synthesis. Oxandrolone, an analogue of testosterone, is well absorbed orally and is preferred to the authentic hormone for repletion of serum and supraphysiologic levels. In skeletal

muscle, oxandrolone binds to intracellular androgen receptors and stimulates anabolism via protein synthesis. Porro et al. demonstrated that oxandrolone 0.1 mg/kg by mouth twice a day for 1 year postburn provides benefits that persist for up to five years post injury with few deleterious side effects.

Other anticatabolic agents have also been used to improve muscle mass. Recombinant human growth hormone (rhGH) has shown promise as an agent for blunting catabolism. rhGH ameliorates the hypermetabolic response to major stress, and enhances immune function, protein synthesis, and wound healing, after burn injury. Unfortunately, Takala et al. found that rhGH increases mortality in critically ill adults. Concomitant use of rhGH and propranolol attenuated hypermetabolism, peripheral lipolysis, inflammation, and avoids the problematic effects of using rhGH alone. Insulin is a classic anabolic hormone, but stimulates weight gain primarily through increased fat stores.

Vitamin C (ascorbic acid) is an antioxidant that acts to quench oxygen free radicals that cause tissue injury via oxidation of cell membrane lipids. Much of the imbalance in predicted fluid requirements and required administration in burn patients has been attributed to lipid peroxidation and dysregulation of scavenging systems for reactive nitrogen species, altering endothelial integrity and metabolism as the result of endothelial cell injury. Several laboratory and clinical studies demonstrated that adjunctive ascorbic acid in burn resuscitation decreases the exogenous fluid volume needed to restore and maintain adequate perfusion. Tanaka et al. randomized 37 patients with more than 30% TBSA burns to receive isotonic crystalloid and colloid fluid resuscitation with or without high-dose intravenous vitamin C (66 mg/kg per hour) for the first 24 hours after admission. Patients who received ascorbic acid infusion in the first 24 hours post burn demonstrated improved partial pressure of oxygen in arterial blood/fraction of inspired oxygen with fewer ventilator days. Patients requiring escharotomies or fasciotomies were fewer in the ascorbic acid group.

Kahn et al. conducted a 3-year retrospective analysis of patients treated (2007–2009). The control group were resuscitated according to the Parkland formula, whereas the experimental group was resuscitated by the Parkland formula plus the volume required to administer an intravenous vitamin C dose of 66 mg/kg per hour. Twenty-four-hour fluid requirements were 25% less in the vitamin C–treated subjects. Although overall resuscitation volume was decreased, the study demonstrated no improvement in respiratory function or mortality.

Complications of high-dose vitamin C infusions include an increase in postburn AKI as a result of osmotic diuresis. This, in turn, leads to decreased fluid resuscitation requirements and worsening renal function without changing resuscitation endpoints. Additionally, oxalate nephropathy (obstructive uropathy secondary to crystalluria) has been described in postmortem examinations of burn patients treated with high-dose vitamin C infusion. Hyperoxaluria can worsen existing kidney injury or delay kidney recovery. More research is needed before widespread adoption.

SUMMARY

The medical management of burn resuscitation and continuing burn care has evolved over the past several decades. Judicious, balanced use of crystalloid fluid with colloid administration has resulted in minimizing "fluid creep" and its sequelae. Advances in monitoring and measurement of burn depth have also led to more precise estimation of fluid requirements. Adjuncts to care including nutrition support, prevention of complications, and the use of novel pharmacotherapies have all played a role in reducing the morbidity and mortality of burn injury.

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MANAGEMENT OF FROSTBITE, HYPOTHERMIA, AND COLD INJURIES

Paul M. [illegible]

The several types of localized cold injuries may be classified according to the temperature that produces them: (1) nonfreezing or (2) freezing temperatures. Nonfreezing, immersion foot and trench foot, are produced by cold but not freezing temperatures. Frostbite is produced by freezing temperatures. Trench foot and immersion foot and hand are seen principally in military populations, whereas chilblains and frostbite are seen more commonly in civilian populations.

Further, cold injuries may be divided into (1) localized cold injuries (i.e., frostbite) and (2) generalized cold injuries (i.e., hypothermia). Frequently, localized cold injuries such as frostbite do not co-exist with systemic hypothermia.

Localized cold injuries have in common the fact that they are produced by exposure to cold stimuli and that they occur at the extremities of circulation. Localized cold injuries may be seen in the cheeks, nose, ears, and face but are seen primarily in the hands and feet. Cold injuries to the face tend to be superficial because of the blood supply. Serious cold injuries are confined almost exclusively to the extremities, in which there is a small margin of difference between the injuries that produce superficial versus deep injury.

TRENCH FOOT

Trench foot is usually seen in military populations and occurs with exposure to above-freezing temperatures, generally over a prolonged period of time. The presence of moisture is very important to its pathogenesis. Chronic symptoms produced after recovery from the acute injury are those of pain, paresthesia, and a particular susceptibility to further cold injury.

IMMERSION FOOT AND HAND

Immersion foot and hand are seen after prolonged exposure to cold but not freezing water. After recovery from the acute episode, major nerve paralysis may be seen in addition to chronic vasospastic cold sensitivity and pain. Pain in the affected area and paresthesias are commonly seen after all types of cold injury.

CHILBLAINS

Chilblains represent the mildest form of cold injury and occur after prolonged exposure to cold and wet conditions. The symptoms consist of burning and itching and are associated with a mild dermatitis. Vesicles and hemorrhagic lesions may be seen in the acute period.

The chronic condition is characterized by cold sensitivity, itching, paresthesias, and skin eruptions, which may be reddish lesions, vesicles, or superficial ulcers. The chronic condition may be treated by protection from cold and heat to avoid production of dermatitis symptoms and pain. The role of sympathetic denervation in the management of the chronic condition has been suggested but not established. Some feel it may be helpful in chronic, well-established symptoms that require treatment. Chilblains do not produce tissue loss, and thus they require no reconstruction.

FROSTBITE

Frostbite occurs from exposure to freezing temperatures. The period of exposure required for its production may be short or long, depending on environmental conditions, wind, and protection. Frostbite has been classified into degrees of injury depending on the depth of damage. Often several degrees of injury will be seen in the same extremity, with the damage increasing as injury progresses from proximal to distal.

First-Degree Frostbite

First-degree frostbite is a superficial skin injury characterized by numbness, edema, and erythema. The injury is similar to a

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Management of Frostbite, Hypothermia, and Cold Injuries

Paul M. Hanson, MD

The several types of localized cold injuries may be classified according to the temperature that produces them: (1) nonfreezing or (2) freezing temperatures. *Trench foot, immersion hand and foot*, and *chilblains* are produced by cold but not freezing temperatures. *Frostbite* is produced by freezing temperatures. Trench foot and immersion foot and hand are seen principally in military populations, whereas chilblains and frostbite are seen more commonly in civilian populations.

Further, cold injuries may be divided into (1) localized cold injuries (i.e., frostbite) and (2) generalized cold injuries (i.e., hypothermia). Frequently, localized cold injuries such as frostbite do not co-exist with systemic hypothermia.

Localized cold injuries have in common the fact that they are produced by exposure to cold stimuli and that they occur at the extremities of circulation. Localized cold injuries may be seen in the cheeks, nose, ears, and face but are seen primarily in the hands and feet. Cold injuries to the face tend to be superficial because of the blood supply. Serious cold injuries are confined almost exclusively to the extremities, in which there is a small margin of difference between the injuries that produce superficial versus deep injury.

TRENCH FOOT

Trench foot is usually seen in military populations and occurs with exposure to above freezing temperatures, generally over a prolonged period of time. The presence of moisture is very important to its pathogenesis. Chronic symptoms produced after recovery from the acute injury are those of pain, paresthesia, and a particular susceptibility to further cold injury.

IMMERSION FOOT AND HAND

Immersion foot and hand are seen after prolonged exposure to cold but not freezing water. After recovery from the acute episode, major nerve paralysis may be seen in addition to chronic vasospastic cold sensitivity and pain. Pain in the affected area and paresthesias are commonly seen after all types of cold injury.

CHILBLAINS

Chilblains represent the mildest form of cold injury and occur after prolonged exposure to cold and wet conditions. The symptoms consist of burning and itching and are associated with a mild dermatitis. Vesicles and hemorrhagic lesions may be seen in the acute period.

The chronic condition is characterized by cold sensitivity, itching, paresthesias, and skin eruptions, which may be reddish lesions, vesicles, or superficial ulcers. The chronic condition may be treated by protection from cold and heat to avoid production of dermatitis symptoms and pain. The role of sympathetic denervation in the management of the chronic condition has been suggested but not established. Some feel it may be helpful in chronic, well-established symptoms that require treatment. Chilblains do not produce tissue loss, and thus they require no reconstruction.

FROSTBITE

Frostbite occurs from exposure to freezing temperatures. The period of exposure required for its production may be short or long, depending on environmental conditions, wind, and protection. Frostbite has been classified into degrees of injury depending on the depth of damage. Often several degrees of injury will be seen in the same extremity, with the damage increasing as injury progresses from proximal to distal.

First-Degree Frostbite

First-degree frostbite is a superficial skin injury characterized by numbness, edema, and erythema. The injury is similar to a

FIG. 1 First- and second-degree frostbite. Epidermal skin loss and peeling are seen.

first-degree burn in that it heals spontaneously (in terms of the epithelium) in 1 to 2 weeks. Superficial desquamation may occur, and regeneration is usually complete with decreased but adequate skin appendages (Fig. 1).

Second-Degree Frostbite

In second-degree frostbite, partial-thickness skin injury occurs that is characterized by numbness, edema, erythema, and vesiculation. The vesicles may be filled with either clear or bloody fluid. The partial-thickness skin injury heals in 2 to 3 weeks (Fig.). The quality of the regenerated skin depends on the depth of the injury to the dermis and parallels thermal burn injuries in that deep second-degree injuries heal with thin atrophic skin that has a reduced number of skin appendages.

Third-Degree Frostbite

Third-degree frostbite represents full-thickness skin loss. After the injury, a insensible segment of full-thickness skin loss is observed; this may be seen initially as a gray-blue patch, or death of the skin may follow an initial period of reactive hyperemia after 24 to 72 hours. Eventually, a black eschar forms that generally separates slowly in 1 to 3 months unless infection occurs (Fig.).

Fourth-Degree Frostbite

Fourth-degree frostbite signifies necrosis of all deep tissue; pain down to and sometimes including bone, black, mummified tissues are present with the initial episode. If the mummified area becomes infected, it softens and becomes swollen and macerated at the margin with viable tissue.

Pathophysiology of Frostbite

Two pathophysiologic mechanisms account for the production of frostbite injury. One is vasoconstriction and damage to the microcirculation in the zone of vascular stasis, which results in progressive vascular thrombosis. The second is direct damage to the cells or cellular fluidity from freezing. Experts disagree on the importance of these two mechanisms and the importance of each mechanism varies according to the amount of tissue freezing that occurs and the local conditions, such as circulation.

Thawing Reaction

The body responds to cold with an alternating cycle of vasoconstriction and vasodilatation (called the thawing reaction) in an attempt to conserve heat loss from the skin. As the injury becomes worse, the cycle may involve actual freezing and thawing of tissue. Circulation virtually ceases as the vasoconstriction increases, causing marked ischemia of the tissue.

[illegible] to Cold

Freezing produces extracellular and then intracellular ice crystals. Extracellular ice crystals produce direct damage to cell walls and also cause a leaching out of electrolytes and water from the intracellular compartment, resulting in intracellular dehydration followed by cell death. Intracellular ice crystals produce direct damage to important cell structures.

[illegible] Thereafter

Frostbite produces progressive dermal ischemia, similar to the process seen in thermal burns or in the no-reflow phenomenon. The role of edema and endothelial injury in the subsequent arrest of dermal blood flow has implicated various inflammatory mediators such as thromboxanes, prostaglandins, histamine, and bradykinin; these observations have led to the use of inhibitors of these mediators in an attempt to ameliorate the harmful tissue reaction and improve tissue survival.

Tissue injury occurs both from direct damage to cells and from the vasoconstriction stasis, which results in vascular stasis and thrombosis. After the state of decreased circulation, a state of reactive hyperemia occurs, which may or may not be associated with a no-reflow phenomenon, in which capillary thrombosis occurs in the zone of stasis. The pathology of tissue repair is similar to that of burn injuries in that epithelium migrates to cover the wound from the surviving remnants of sweat glands, hair follicles, and margins of the healing wound. The quality of the skin produced is intimately proportional to the depth of damage. Deep injuries have necrotic nerve, muscle, and bone and are healed by scar after the shedding of dead tissue. Frequently, autoamputation occurs after ischemic necrosis and gangrene. Left untreated, the process is generally dry and progresses to autoamputation without infection over several months.

Environmental Influences

A number of behavioral and environmental factors may influence the production of cold injuries. Two of the most significant environmental factors are the ambient temperature and the wind.

The effects of temperature may be modified by wearing protective clothing, which provides insulation proportional to its thickness and weight. The effects of temperature are modified by the presence of wind and wet conditions, which accelerate heat loss. Wet conditions increase heat conduction to the environmental air, whereas wind accelerates the loss of heat in the air. Siple has developed a "wind chill index" to reflect the magnitude of the contribution of wind to heat loss. The heat loss would be the same at 20°F with a wind of 45 miles per hour as at −40°F with a wind of 2 miles per hour.

The mean outdoor temperature recorded in frostbite injury series is −20°C. Frostbite is seen isolated to the upper extremities in 10% of cases, isolated to the lower extremities in 47% of cases, in both upper and lower extremities in 31% of cases, and with an extremity involvement in only 3% of cases.

Clothes provide insulation proportional to their thickness (one-quarter of an inch equals one clothing unit) and weight. They should be light to allow activity and may act in multiple layers to be effective. Sweating wets the clothing, reducing the insulation value. The importance of light clothing permitting work (heat production) is emphasized. The proper use of protective clothing is important. In one study, 65% of those who suffered frostbite had inadequate protective clothing, whereas 21% had adequate clothing but were wearing it improperly. Only 15% of frostbite victims had adequate clothing and were wearing it properly. Moisture accelerates heat loss.

Behavioral factors also predispose to cold injuries. Alcohol and drug intoxication; smoking; accidents such as car, plane, skiing, and vehicular failure; homelessness; high altitude; and outdoor pursuits

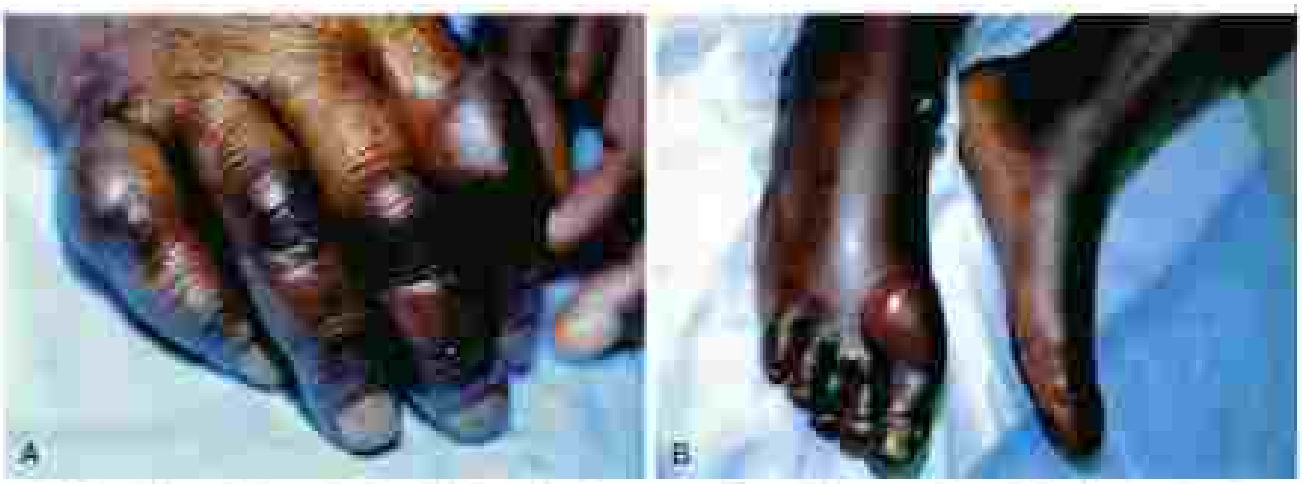

FIG. 2 (A) Second-degree frostbite to the fingers. Vesicles and swelling are seen. (B) Second-degree frostbite to the feet. Vesicles and swelling are seen.

FIG. 3 Third- and fourth-degree frostbite with tissue death and demarcation beyond the metatarsophalangeal joint.

predispose to frostbite, as does a previous cold weather injury. Medical conditions that decrease circulation (peripheral arterial disease), neuropathy, and diabetes all decrease the body's ability to adapt to colder temperatures; psychiatric illness is observed much more frequently in patients who suffer frostbite. The average age of a frostbite victim is 30 to 40 years, with men outnumbering women by 10 to 1.

Prevention of Frostbite

There are two ways to prevent cold injury: (1) by increasing heat production and (2) by decreasing heat loss. Heat loss may be decreased by avoiding wetness or contact with metal (which accelerates heat loss) and by wearing adequate protective clothing. The extremities have a large surface to mass ratio, and thus represent prime sites for heat loss. Other factors may affect the circulation to extremities, such as the presence of arterial occlusive disease. Some feel that the presence of a frostbite injury should prompt an examination for an arterial occlusive lesion or conditions such as diabetic neuropathy, which do not permit reflex vasoconstriction and vasodilatation. The importance of inactivity and immobility in reducing heat production, producing orthostatic edema, and decreasing circulation has been emphasized in studies on military frostbite. Malnutrition, hemorrhage, anemia, and the use of tobacco and alcohol all have been implicated in the increased susceptibility to frostbite injuries. Acclimatization and cold tolerance probably occur. African Americans have increased susceptibility to cold injuries, probably because of less frequent waves of cold-induced vasodilatation, and thus less effective skin warming. Military experience has emphasized the importance of working and keeping active so as to increase heat production. The importance of avoiding sweating to avoid wetness and replacing wet with dry clothing also is emphasized.

Superficial Versus Deep Frostbite

Frostbite to the head and neck area is generally superficial. The face is not subject to the same vasoconstrictive phenomena as are the extremities. The drying potential of cold in the facial area is manifested in chapped lips, nose tip, ears, and mucous membranes. Facial frostbite is generally superficial, whereas serious frostbite usually is confined to the extremities.

Mills believes that the differentiation of frostbite into first-, second-, third-, and fourth-degree injuries is cumbersome and not clinically useful. He believes that one can only classify frostbite as superficial (tissue remains soft) or deep (tissue is hard). It is initially difficult to tell the depth of the injury, and differentiation can be accomplished only after rewarming and a period of observation. Cauchy (2003) believes that the extent of the initial lesion and the result of three-phase bone scanning can predict the ultimate result of the initial lesion is confined to the distal digit, the probability of amputation is 1%; the probability increases to 31% for the middle digit, 67% for the proximal phalanx, 98% for the metacarpal and metatarsal, and 100% for the carpal and tarsal areas. In the face, a small white patch of tissue may be seen, and this clears over the course of a week.

Medically, frostbite heals with no therapy, therapy with dressings alone, or surgical debridement, amputation and dressings. Twenty-one percent of patients with frostbite are seen more than 48 hours after the injury.

In the extremities, mild frostbite is manifested by pallor, paresthesias, and a dull yellow color of the skin. Ice crystals may be observed. The area is numb, and after rewarming a prickly, itchy sensation, or aching pain occurs. After rewarming, reactive hyperemia is observed superficially; in deeper injuries, hypersensitivity and paresthesias are observed. Deep frostbite is differentiated by the absence of circulation; on rewarming, the progression (progressive vascular thrombosis) to full thickness tissue loss (eschar formation) occurs. The tissue may remain insensitive after rewarming, presenting as a blue-gray patch with absent circulation. Burning pain, paresthesias, and thick-walled blisters containing blood may follow rewarming to full thickness tissue injury.

The history of the injury is important in predicting tissue loss. Important factors include duration of the exposure, temperature, protective clothing worn, contact with metal or moisture, and the presence of previous symptoms that would indicate reduced arterial

BOX 1 Therapy for Frostbite

- Correct systemic hypothermia (temperature <35°C)
- General measures (including detection of other injuries)
- Rapid rewarming of frozen extremities (15 to 30 minutes until a digital flush is observed) in a 104°F to 108°F agitated water bath and topical antiseptic
- Tetanus immunization ± antibiotics
- Aspirin: 325 mg every 4 hours for 72 hours (Robust)
- Open or light dressings
- Clear blebs debrided
- Hemorrhagic blebs, keep intact
- Topical aloe vera (Robson) and antibacterial agents
- Selected blisters: debride, antibiotics, antiseptics
- Functional splinting, elevation
- Twice daily cleanse with antiseptics
- Avoid macerating dressings
- Surgery
- Await clear demarcation
- Allow spontaneous epithelialization
- If within the first 24 to 48 hours
  - Consider regional sympathectomy in those with troublesome, persistent symptoms; normal or low vascular response after rewarming; arteriogram of magnetic resonance imaging or magnetic resonance angiogram evidence of vascular spasm and lack of complete flow (Robson)
  - Hyperbaric oxygen
  - Intra-arterial tissue plasminogen activator, initially 0.5 mg/hr, then decreasing daily
  - Heparin therapy
  - Steroids

circulation. These include claudication, Raynaud's phenomenon, and superficial phlebitis. It is important to assess if there is any contribution of underlying vascular disease to patients with frostbite.

Diagnosis of Hypothermia

Hypothermia must be excluded, and the management of frostbite should include general and specific measures (Box 1). Management of frostbite must include restoration of core body temperature. In patients with hypothermia (temperature <37°C), the hypothermic condition must be corrected before specific treatment of frostbite begins. Death may occur at a body temperature of 28°C.

Hypothermia is defined as a core body temperature below 35°C or 95°F. It is seen principally in the military or secondary to outdoor recreation, homelessness, or substance abuse. Hypothermia has been classified as the following: (1) mild (90°F to 94°F), (2) moderate (86 °F to 89°F), and (3) severe (< 86 °F).

In mild hypothermia, the patient is shivering, complains of being cold, and has mental confusion but is communicative. In moderate hypothermia, the patient becomes more confused and is often agitated, obstinate, or combative, and the shivering ceases. There is muscle spasticity, dilated pupils, and slow respirations. At this stage, mild myocardial irritability is encountered. In severe hypothermia, the patient becomes comatose, has a flaccid paralysis, and begins to develop apnea eventually this progresses to ventricular fibrillation and death.

The body physiologically responds to lowered temperatures by increasing cardiac output with tachycardia. Hyperventilation then follows, with apnea, bradycardia, and an increase in total peripheral vascular resistance with decreased cardiac output and an increase in mean arterial pressure. Cardiac arrhythmias and sudden death occur in this sequence and follow ventricular ectopy and atrial fibrillation. Cardiac standstill occurs with temperatures decreasing below 23 °C. The blood becomes more viscous with each drop in temperature, and hemoconcentration is seen related to cold diuresis. Shivering occurs in the peripheral vessels, and respiratory depression follows. Pulmonary edema accompanies rewarming. There is a decrease in the ability to clear bronchial secretions and a diminished cough reflex resulting in cold bronchorrhea. Metabolic acidosis follows rewarming. The cold diuresis results in hypovolemia.

Treatment of Hypothermia

When the victim is identified in the prehospital setting, removal of wet clothing and replacement with dry clothing should be performed. No massage, friction rubbing, or manipulation should be performed. Patients who have sustained cardiopulmonary arrest should undergo resuscitation according to standard protocols. Patients have been salvaged following rewarming in the field, only passive warming is undertaken because active rewarming can lead to myocardial arrhythmia and hypotension and can be managed only by person in hospital monitoring.

In the hospital, accurate recording of temperature and vital signs are imperative. Complete examinations of the blood, including complete blood cell count, electrolytes, liver function tests, coagulation, and arterial blood gas analysis, are performed urgently. The workup should include toxicology screens to assess the effect of alcohol or other sedatives. A Foley catheter is inserted with a urinometer, and urine volumes are monitored. Several large bore intravenous cannulas are inserted to combat the inevitable hypotension that occurs after rewarming. Continuous electrocardiographic monitoring and a chest x-ray or appropriate extremity radiographs for trauma are obtained. The intensive care setting is mandatory, with serial blood testing. Hypoglycemia should be excluded, as should narcotic overdose. Passive rewarming at the rate of 0.1°C to 2°C hourly results in a slow increase in body temperature. Oxygen that is warm and humidified is provided.

Therapy of Frostbite After Hypothermia Has Been Resolved

There is no place for vigorous rubbing of frostbitten tissue or the application of snow (treatments mentioned in the lay literature). This merely accelerates damage to skin. There is no place for slow thawing, rubbing the area, and especially application of snow or other measures that would increase tissue damage. A frozen part should not be thawed if refreezing is likely to occur.

The management of frostbite is divided into the following phases: (1) prehospital field care, (2) acute hospital rewarming, and (3) posthospital care.

Before reaching the hospital, the frostbitten part should be protected from mechanical trauma and splinted. Warming should not be attempted if refreezing is likely.

Management of frostbite is carried out in accordance with the guidelines popularized by Mills. The patient's general condition should be assessed, and other injuries detected and managed. Shelter should be obtained, wet garments removed, and the part wrapped in warm, dry covers or blankets, being careful to avoid trauma. The benefit of antibiotics has been difficult to establish, although some prescribe them as for burn injuries, others believe that they are not appropriate. Cultures should be done so that appropriate antibiotic treatment can be instituted if infection occurs. Long term care includes physical therapy, neurologic rehabilitation, psychological support, and counseling for management of specific localized injuries.

Patients with serious frostbite (i.e., frostbite of the extremities) should be hospitalized. On admission, the frozen areas should be rewarmed properly in an agitated water bath in which temperature is controlled precisely from 104°F to 108°F (40°C to 42°C) for 15 to 30 minutes. Rewarming should be continued for 15 minutes beyond recirculation.

The rewarming may be stopped soon after the digital flush signifying a hyperemic state of perfusion is observed. Rewarming is often painful, implying that a free radical reaction is present on reperfusion.

Excessive rewarming results in further tissue damage. The temperature is critical, as excessive temperatures (>45°C) cause heat damage and lower temperatures (<38°C) are ineffective. Rewarming should be continued for 1½ minutes beyond thawing. Rewarming may be painful, and narcotic analgesics may need to be given. The pain associated with rewarming is believed to be a reperfusion injury and secondary to free radical generation.

In general, it has been recommended that open treatment or light dressings be utilized, keeping the blisters intact and bathing (hydrotherapy) the affected area once or twice daily in an antiseptic solution.

Most affected areas heal spontaneously if infection is prevented. Compression dressings are not necessary.

Hands should be splinted in a functional position, as should feet. Nonadherent (petrolatum or Xeroform) dressings assist with gentle treatment of the skin areas. It has been our experience that ointments macerate the areas and may contribute to increased infection. Dry treatment is preferred when possible. The value of prophylactic antibiotics has not been shown, and they should be used only prophylactically for short durations, such as 48 to 72 hours.

Rubkin has shown that blisters contain increased amounts of thromboxane derivatives, which can accelerate production of progressive vascular thrombosis and dermal ischemia, similar to that observed in thermal injury. Therefore therapeutic advantage may be obtained from debriding the blisters. Rubkin differentiates between white and hemorrhagic blisters, debriding only the white blisters. Rubkin recommends treatment of affected frostbite areas with topical aloe vera (Dermaide Aloe), aspirin, and antibiotics. The effectiveness of this treatment has not been shown clearly.

Daily cleaning of affected areas should be performed in a 40°C water bath, using antiseptic skin cleansers. Plantigraphic wounds of progress should be taken at 2 day intervals. Tetanus prophylaxis is recommended on admission.

It is important that the affected part be elevated and splinted in a position of function according to the usual principles of treatment of significant extremity injuries. Gentle exercise and range of motion are important, as in physical therapy. Elevation decreases edema, which is part of the vicious cycle that contributes to decreased capillary circulation.

Surgical Intervention for Frostbite

There are two options for surgical treatment of frostbite: early surgical intervention and delayed (observation) treatment. Early surgical intervention is not necessary in the typical frostbite injury but may be necessary if acute progressive infection occurs. Full demarcation of dead tissue may take several weeks or 2 to 3 months, and the general recommendation is that the process of separation of tissue be allowed to progress spontaneously. Some believe that surgery may be appropriate at 3 weeks if the demarcation is clear. Unfortunately, there may be times when circumferential extremity constriction causes impaired circulation and occurs because of an unyielding third-degree eschar.

Assessing the Circulatory System and Early Surgical Intervention

There has been considerable interest in assessing the circulation, which has been done by arteriography but mostly by technetium imaging (three-phase bone scans) done on admission. This assessment results in the ability to predict tissue loss, which accurately reflects the ultimate degree of tissue loss. These scans should be done on the first day after injury.

The accuracy of magnetic resonance imaging and magnetic resonance angiography examinations for the same purpose also have been suggested. The hope that earlier surgical intervention could lead to earlier resolution of the injury for many patients after the use of these circulatory assessments generally has not been realized. Corleth and colleagues used this to aggressively debride the soft tissue, and ultimately probably salvaged digits that otherwise would have been lost with aggressive microsurgical reconstruction of digits destined to be amputated.

Therapy to Microcirculation

The damage to the microcirculation has been treated with anticoagulation, hyperbaric oxygen, and free radical scavengers. Agents such as heparin have been shown to slightly increase tissue survival in experimental frostbite (tissue injury), as have free radical scavengers. Clinical experience has not confirmed a definite advantage of these medications, obviously because of the critical time window in which they must be administered. It has been difficult to demonstrate the clinical effectiveness of agents such as low-molecular-weight dextran in preventing sludging, and although steroids have been recommended for the vasculitis, the evidence for their beneficial effect has not been confirmed clinically. Heparin and anticoagulants have not been shown to influence the ultimate degree of tissue loss. Ultrasound treatments have been suspected of increasing tissue damage.

Rubkin recommendations have been used by some to limit the progressive vascular thrombosis and include prostacyclin and thromboxin such as recombinant tissue plasminogen activator (rtPA). Hyperbaric oxygen may be of limited value but must be begun within 24 to 48 hours to be effective. Although many questions of effectiveness, several experimental studies demonstrate improved tissue salvage when hyperbaric oxygen is begun promptly, a number of case reports since 1987 suggest some effectiveness, but a true trial has not been conducted. Hyperbaric oxygen increases tissue oxygen concentrations, stimulates angiogenesis, reduces edema, improving the microcirculation, stimulates antiinflammatory process and antioxidant enzymes, and stimulates several wound healing mediators such as basic fibroblast growth factor, transforming growth factor β1, and platelet-derived growth factor.

Tissue plasminogen activator has shown some progress in ameliorating the microcirculatory injury and in improving circulation and tissue loss (30% compared with historical controls) of lesions destined to be amputated that did not receive treatment.

rtPA must be administered intraarterially within 24 hours after the injury, the earlier the better, therapy salvaged and the clinical reports are supported by some laboratory studies. The treatment must begin within the first 24 hours to be effective and is continued for several days if effective.

Sympathectomy

Regional sympathetic blockade has been utilized to decrease the pathologic vasoconstriction and sympathetic response. Based on the theory of the importance of progressive vascular damage to severe frostbite, several authors have advocated early surgical or chemical sympathectomy. At one time, we used intraarterial reserpine to regionally block the sympathetic nervous system (chemical sympathectomy). Arteriograms have demonstrated significant proximal vasospasm a considerable distance proximal to the clinically obvious area of frostbite (Fig. 4). Recently, Rakower has attempted to define the patient populations that benefited from sympathectomy according to Doppler ultrasound and digital plethysmographic examinations after rewarming. Patients had digital plethysmograms and Doppler ultrasound mapping of digital vessels, and three degrees of vascular response to cold were found. The most common was the hyperdynamic response, implying patent digital vessels; this response was clinically apparent as warm, red digital tissue. Regional sympathectomy was troublesome in these patients. Patients with a normal or hypodynamic response had evidence of vascular compromise at the digital, palmar, or pedal arch level and benefited from regional sympathectomy with chemical mechanisms. Patients with the hyperdynamic response did not have severe pain, whereas patients with a normal or decreased vascular response had ischemic pain, stiffness, and coldness in the digital areas. It therefore seems possible that sympathectomy may be utilized for a group of patients who could most benefit from it.

Those who support regional sympathectomy claim that it provides earlier cessation of pain, more rapid decrease of tissue inflammation and edema, tissue salvage, quicker demarcation, and earlier healing. In addition, there is some evidence that regional sympathectomy

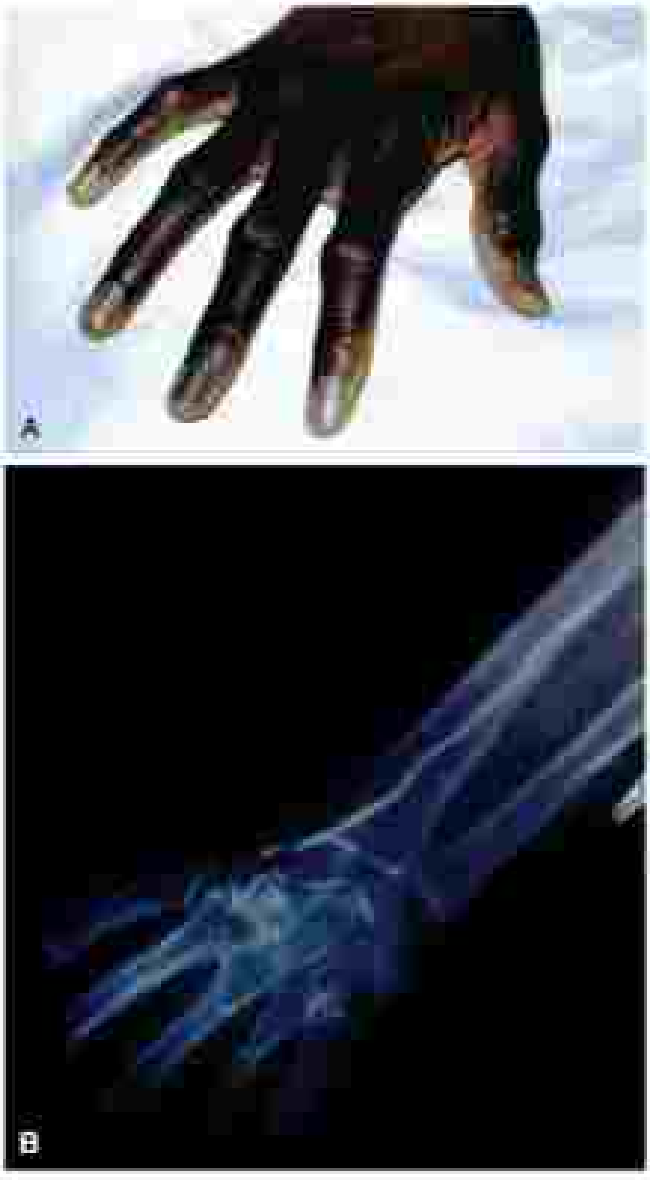

FIG. 4 (A) Second-degree frostbite. Note the poor capillary perfusion of the nail bed of the middle finger. (B) Arteriogram of the patient in part A demonstrating loss of distal circulation secondary to intense vasoconstriction. The ulnar artery flow ceases in the forearm, and the palmar arch and digital vessels are not seen.

provides significant diminution of the late sequelae of frostbite: impaired circulation, hyperhidrosis, pallor and vasospastic and pain symptoms. It is claimed that extremities that have been subjected to a cold injury are able to perceive repeated significant cold injuries more accurately than extremities without sympathectomy.

Chronic Changes

The chronic sequelae of frostbite may benefit from sympathectomy in that sympathetic overactivity (hyperhidrosis and vasomotor tone) and cold sensitivity are reduced. The symptoms represent diminished circulation and reflect pallor and vasospastic and pain symptoms. Lubrication of atrophic skin and prevention from extreme temperatures are important. It is important that the parts affected be prevented from further cold exposure, as they are unusually more susceptible to cold injury. Platt has advocated digital artery sympathectomy for patients with troublesome digital symptoms.

Radiographic and Joint Changes

Degenerative joint disease may be seen in severe cases of frostbite, and stiff, painful joints with limited may be a sequela of moderately severe frostbite.

Intrinsic Muscle Atrophy

Platt has described intrinsic muscle atrophy and fibrosis in severe frostbite. It may be possible to minimize the intrinsic muscle damage of contracture with proper physiotherapy, splinting, and appropriate exercise.

INJURIES IN CHILDREN

Injuries to epiphyseal growth centers may result from even minor cases of frostbite in children, with joint changes being radiographically demonstrable even 6 months after injury. Bone changes may result in short digits, deviation of the digits, and osteoarthritis. Parents should be advised that these sequelae are possible despite appropriate therapy of frostbite during the period of injury.

Suggested Readings

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Electrical Injury and Lightning Injuries

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Electrical injury is an unusual and devastating form of mechanical trauma. It is associated with significant mortality and a wide range of acute and long-term physical, psychological, and social disabilities. Understanding of the physics and pathophysiology of electrical injury lays the groundwork for treatment plans aiming to mitigate the morbidity and mortality caused by accidents involving electricity. This chapter aims to cover the specific aspects of this injury that are different or additive to standard trauma and critical care protocols.

There are approximately 1000 deaths per year in the United States attributed to electrical injuries, with the most frequent cause of death related to cardiac arrest. Approximately 400 electrical injury–related deaths are due to high-voltage electrical sources, whereas lightning causes an additional 50 to 300 deaths per year. There are also at least 30,000 nonfatal electrical injuries per year. In adults, these injuries occur mostly in occupational settings and are the fourth leading cause of workplace–related traumatic death, whereas, in children, electrical injuries occur most often at home. According to the National Burn Registry, patients with electrical injuries account for just less than 4% of burn center admissions. Of these, more than one half were work-related accidents, 3% of the electrical injury patients were attributed to lightning, and 11% of the electrical injuries were in children. Only percent of the electrical injuries reported to the National Burn Registry required operations.

The majority of electrical injuries in construction and utility workers are related to brief, high-voltage (>400–1000 volts) exposure. Up to 80% of serious electrical injuries are fatal. Two-thirds of these deaths occur in the workplace. Electrocution represents 5% to 6% of all work-related traumatic mortality, accounting for more than 500 deaths per year and making it the second leading cause of occupation-related deaths in the United States. Short-term and long-term morbidity in many electrical injury survivors is typically related to significant musculoskeletal and neurologic disability.

Electrical accidents can involve arc, flame, and direct current injuries as well as a variety of traumatic injuries and ordinary flame burns. In this chapter, we will focus on arc flashes and direct current injuries, as well as lightning strikes, a form of direct current injury.

An arc flash is a sudden release of energy through the air when a high-voltage gap exists and there is a breakdown between conductors. These injuries are typically seen with electricians working near an electrical box complicated by corrosion, a dropped tool, or a buildup of conductive dust. Although the arcs can be extremely hot, with temperatures up to 4000°C to 5000°C, their fleeting nature usually results in more superficial burns. They can be associated with an extremely bright light, sound pressure up to 160 dB, and a pressure wave that can hurl shrapnel and chunks of molten metal at speeds of 700 mph. Appropriate eyewear and personal protective clothing and equipment can mitigate many of the effects of this accident. Flame injuries can be caused if the arc ignites the individual's clothing. Deep contact burns can also occur from an arc heating of metal objects against the skin such as a coin or necklace.

Deep current injuries are a result of current passing through the body as the individual becomes part of the electrical circuit. Once the current passes through the body, the risk for internal burn exists as the current turns into thermal energy. In many of these cases, the current lingers in the bone, heating up the bone, and eventually cooking the muscle and tissue that invests the bone. Another destructive mechanism also becomes clinically important in electrical injury when the electrical current causes interference with coordinated electrical activity in the body such as heart rhythms or the brain respiratory center, often killing people at the scene. Finally, in the special case of lightning, the extremely short but very high-voltage electrical energy is associated with an electrical current flowing through or around the individual's entire body can produce a wide range of possible injuries via these mechanisms, blast, or other trauma mechanisms.

Any of these direct electrical injuries can be associated with indirect injury such as a fall associated with asystole or the blast from the initial trauma, severe muscle injury from tetany, or delayed complications such as multiple organ system failure from rhabdomyolysis, compartment syndrome, or infection.

PHYSICS AND PATHOPHYSIOLOGY OF DEEP CURRENT ELECTRICAL INJURY

The severity of direct electrical injury from deep current is determined by several critical factors:

1. Voltage (high or low)
2. Type of current (alternating or direct)
3. Intensity of current (amperage)
4. Pathway of the current through the body (vertical, horizontal, peripheral)
5. Duration of current exposure
6. Area of contact on the body
7. Resistance of the body tissues involved

An understanding of the physics of electricity provides insight into how electrical energy damages tissues.

ELECTRICITY BASICS

Current

Electricity is defined as the flow of electrons through a conductor. Electrical current (I) is the rate of flow of electrons in a conductor and is measured in amperes (A). Injuries result from current in several forms: alternating current (AC), direct current (DC), or pulse-type shocks such as lightning.

AC is the directional flow of current in a circuit that constantly is being reversed back and forth in a repetitive sinusoidal pattern. In general, it is a more efficient way of generating and distributing electricity than DC. Standard household current is AC at a rate of 60 (or 50) Hz (cycles per second) and is supported by 100 to 200 A. DC means that the direction of electrical current remains constant. It is found in automobile electrical systems, railway tracks, batteries, and lightning. High-voltage utility power lines may be either AC (most common, commercial) or DC.

There can be differences in the clinical presentation of an electrical injury related to the type of current exposure. DC provides unidirectionality to the current exposure, hence the classically termed entrance and exit point cutaneous wounds that identify potential current pathway. A high-voltage DC injury could produce a small cutaneous entrance wound and a small cutaneous exit wound associated with much more significant deep tissue injury in addition to the electrical current tissue effects. In contrast, the bidirectional flow of AC produces cutaneous burns known as contact points. Furthermore, DC does not produce the same contraction of muscles found with AC. The "let go" reaction occurs when the current through a hand and arm may cause the hand to involuntarily close and remain closed so that the energized conductor cannot be released. Although a 60 Hz theoretical current 0.5 mA is the threshold for a startle reaction, the let go threshold current intensity varies from 3 to 9 mA, depending on body size, and tetany occurs at 15 to 20 mA. DC shock thresholds are about three times higher than AC; however, there does not seem to be a let go phenomenon. An individual can let go of an energized circuit but there is an intense shock when the circuit is broken. Although AC is generally

lower voltage and produces less direct tissue injury, prolonged contact can alter the cardiac cycle, causing arrhythmias and cardiac arrest. Ventricular fibrillation occurs at 50 to 100 mA, and asystole occurs at more than 3 A. Finally, in lightning or pulse type shocks, shock energy and timing in relation to the cardiac cycle (particularly those that occur during a T wave) are related to the onset of ventricular fibrillation. Pulse shocks with an energy level of 50 J can be lethal while shocks below 0.25 J are annoying but not dangerous. For example, a typical shock from walking across a carpet is about 10 mJ. Again, high-current pulses cause asystole rather than ventricular fibrillation. Unlike ventricular fibrillation, a blow or fall may convert asystole to a normal heart rhythm in some cases. Keep in mind that although most providers speak about voltage, it is the current, or amperage, that kills.

Voltage and Resistance

By definition, voltage at a point must always be measured with respect to another point. The voltage difference between the two points is a factor in determining the current that will be in a given electrical path between two points. For instance, a classic example would involve a bare high voltage conductor (for example, 7200 V) with respect to the ground; a squirrel or bird running on the conductor would not be electrocuted because each of its feet would be the same voltage with respect to the ground (7200 V); however, the voltage difference across its body would be zero.

Voltage is the force that drives electrical current (I) across the potential difference and contributes critically to the intensity of the electrical injury. Historically in medicine, electrical injuries are classified as either high voltage (>1000 V) or low voltage (<1000 V). However, because the US National Electrical Code defines the difference between low voltage and high voltage/injury at 600 V, we should consider high voltage to be 600 to 1000 V. Typical voltage delivered in homes in the United States and Canada is 120/240 V, providing 240 V for appliances that require high power and 120 V for general use. Low voltage injuries tend to occur indoors and are almost exclusively AC. In the United States, the AC power system operates at 60 Hz, causing the current to reverse polarity 120 times a second. Voltage in high tension power lines tends to exceed 100,000 V and is most commonly AC in developed areas. High voltage mortality and amputation rates typically exceed low voltage rates twofold to threefold.

Resistance (R) is the hindrance to current flow and is measured in ohms. Resistance creates heat based on Joule's law. Joule heating is energy transfer that occurs when charged particles meet resistance and lose energy to tissues in the form of heat.

Joule's Law

$$\text{Power (P)} = I^2 \text{ (current) } x \text{ R (Resistance)}$$

Materials that are the best conductors (meaning that they facilitate current flow) have the least resistance. With increasing resistance, more energy is expended in the form of heat and results in thermal tissue damage.

Different tissues have notably different resistances and resistances vary under different conditions. Overall, resistance of a tissue depends on the surface area of contact, tissues in the current's pathway, pressure applied, duration of exposure, magnitude of current flow, and absence or presence of moisture. For example, dry skin has a much greater resistance (approximately 100,000 ohms) than moist skin (<2500 ohms).

The magnitude of average electrical resistance across body tissues is as follows:

Nerve<Blood Vessels<Muscle<Skin (Variable)<Tendon<Fat<Bone

The relationship between the forces discussed is described by Ohm's law:

$$I = \frac{V}{R}$$

where the current (I) is directly proportional to voltage (V) and inversely proportional to resistance (R).

PATHOPHYSIOLOGY

Injury to the affected tissue predominantly depends on the duration and intensity of electrical exposure. For example, brief exposure to current will conduct rapidly across low resistance tissues (Ohm's law), with low heat production and structural tissue damage but more electrophysiologic derailment of end organs (i.e., heart, central nervous system [CNS], and muscle).

If contact time is brief, nonthermal direct electrical damage to tissue occurs as the current disrupts the intracellular electrical gradient across cell membranes via electroporation and conformational changes in membrane proteins. Electroporation results in a significant increase in the electrical conductivity and cell plasma membrane permeability, leading to tissue edema and possible cell injury. Muscle fibers and nerves are the most susceptible. It can either induce cell necrosis or permanently, partially, or reversibly affect cell membrane function in the absence of joule heating. Damage will be relatively localized to the involved tissue cell membranes and result in functional disruption of tissue and organs dependent on coordinated electrical activity such as heart, brain, spinal cord, and muscle. These cell membrane effects may progress over time and partially explain some of the delayed clinical symptoms observed after electrical injury, such as vascular thrombosis and rupture, cognitive dysfunction, and late appearing spinal cord deficits.

When contact time is prolonged, heat damage will dominate because the entire cell is compromised. In general, the severity of the injury is inversely proportional to the cross sectional area of the body part, with the most severe injuries seen in the wrist and ankle and decreasing proximally. Deeper tissues and regions between two bones (tibia and fibula, ulna and radius) also create heat to a greater degree. Macroscopic and microscopic vascular injury can occur immediately and is often not reversible.

Identification of contact points often helps to establish the path that the current has taken. A path parallel or vertical to the axis of the body (craniocaudal) is most dangerous because it may affect all vital organs. A horizontal path (e.g., from hand to hand) may spare the brain but still be fatal because of its effect on the heart and respiratory muscles. A path with contact points confined to a single extremity may cause extensive local damage but not be lethal (Fig. 1). However, although identification of a potential pathway of current suggests that certain organs in the pathway might be more likely to be injured, it does not guarantee that injury to other organs or deep tissues has not occurred.

Immediate cardiac arrest and life threatening arrhythmias may occur with the conduction of current across the heart. AC tends to cause ventricular fibrillation, whereas DC tends to cause asystole. Actual injury to the heart or the metabolic effects from injury elsewhere in the body (e.g., hyperkalemia and rhabdomyolysis) may result in delayed cardiac arrhythmias and acute renal failure. Paralysis of the muscles of respiration can result in apnea. Effects on the spinal cord and brain can lead to immediate death or long term neurologic abnormalities. A list of potential effects of electrical injury is presented in Table 1. These do not include multitrauma injuries such as falls or blasts associated with the accident or respiratory failure resulting from inhalation injury. CNS abnormalities can be transient, permanent, or delayed based on gross and histologic anatomic structure injury.

MANAGEMENT

Patients with major electrical injury should be evaluated, treated, and followed long term in a burn center. Because of the traumatic, multisystem nature of electrical injury (including potential associated blunt or penetrating trauma injuries), these patients should be managed according to both trauma and burn guidelines for care. In the field, bystanders and first responders should establish safe access to the electrically injured patient. Be aware of victim's ongoing contact with the current source. The rapid electrical impulses produced by alternating current can provoke tetanic spasm in muscles causing the

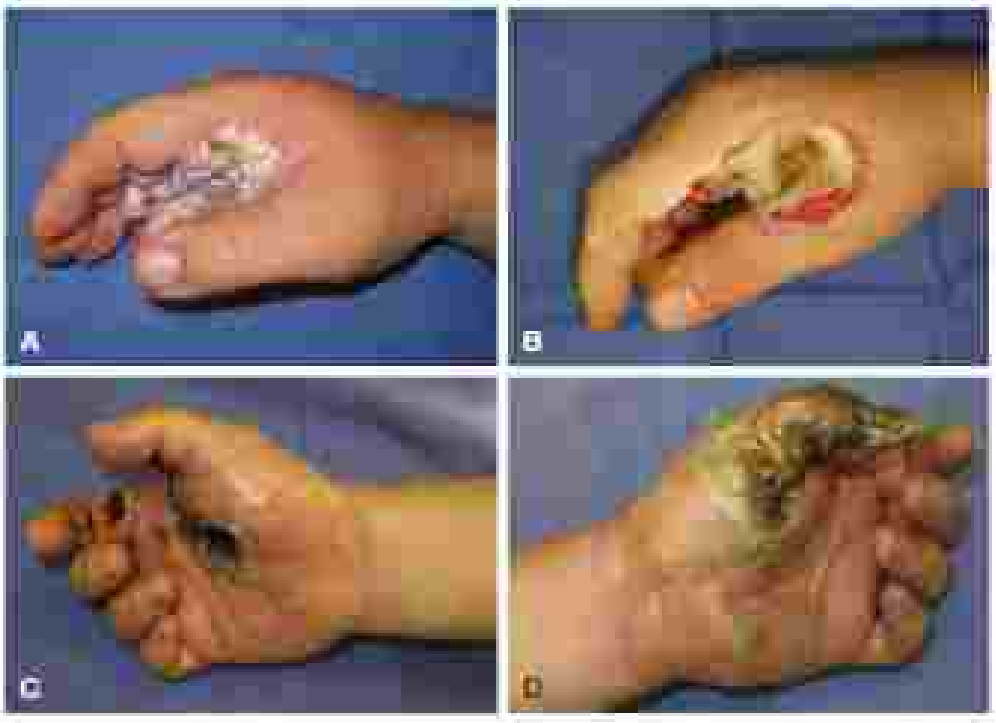

FIG. 1 (A) A farmer working in the field came in direct contact with a low-hanging wire (7000 V). (B) An electrician grabbed a cable (370 V, alternating current) overhead to avoid falling into a ditch. (C, D) A fireman touched a power line (7620 V, alternating current).

victim to close a vise-like grip on the electrodes. This phenomenon occurs because of simultaneous contraction of (stronger) forearm flexors and (weaker) forearm extensors. If still in contact, DO NOT TOUCH because specialized nonconductive equipment is necessary to safely recover these victims. Whether AC or DC, confirmation of disconnection from active, live electrical sources is needed. Avoid environmental conductors such as puddles of liquid, exposed metals, and wires. Victims of lightning injury may be treated immediately.

Rapidly assess the patient's airway, breathing, circulation, and disability (rapid neurologic assessment) and provide in-line immobilization of the entire spine (primary survey). In the event of a cardiac arrest, prolonged resuscitation is indicated if not initially responding. Treat life-threatening findings immediately: control threatened airway or ventilation, decompress tension pneumothorax or pericardial tamponade, control external hemorrhage, and manage potential core temperature heat loss (hypothermia). Establish intravenous access and continuously monitor vital signs (including temperature), neurologic examination, pulse oximetry, respiratory function, electrocardiogram (ECG), and urine output (urinary catheter). Ligature and cover thermal burn sites with clean, dry sheets or towels and then with appropriate topical dressing when at the hospital. Initiate fluid resuscitation with warmed, isotonic crystalloid intravenous fluids.

Once at the hospital, perform a complete trauma survey. In electrical injury, this includes defining the path of current through body and determining voltage of accident. Electricity usually flows from an electrical source, through the body to the ground. Although locating electricity contact points (formerly called entry and exit sites) can help suggest which organs could be damaged, this does not rule out damage to other organs or structures not in an obvious straight current path. Domestic accidents usually involve 110 V (US) or 220 V (EU). Other low voltage accidents occur related to workshops (380 V), subway third rails (600–750 V), or autos (960 V). High-voltage situations include high-tension wires (40,000 V–400,000 V), rail networks (25,000 V), and overhead lines (3500 V). If high voltage injury or if arrhythmia, ECG changes, or troponin elevation are present, check cardiac enzymes. Consider cardiac ultrasound, and possibly cardiac magnetic resonance imaging or cardiac angiogram if indicated. Pregnant females should have an obstetrical ultrasound, and patients with significant burns should be admitted to a burn center. Patients with initial loss of consciousness, cardiac anomalies, or high-voltage injury require hospital admission with continuous ECG monitoring for at least 24 hours. Otherwise, in those patients with a normal cardiac rhythm in the emergency department, a dysrhythmia is unlikely, and thus 24-hour monitoring is not needed. In those patients with cutaneous burns, calculate the total body surface area burned, assess compartment pressures, perform a complete neurologic examination including baseline vision (cataracts are long-term complications) and hearing (tympanic membrane rupture [perforation] examinations, and carefully record the history, source of the history, and all physical findings in the medical record because many of these cases will eventually find their way into the legal system.

The management of all trauma patients, including those with electrical injury (with or without external burns), is a standardized process per Advanced Trauma Life Support protocol with the addition and consideration of these additional caveats to consider: compartment syndromes and the need for decompression, cardiac arrhythmias and which patients require longer term cardiac monitoring, and the administration of fluid given the possibility of a massive injury that may or may not externally visible as well as the need for hydration to prevent acute kidney injury from rhabdomyolysis. In patients with significant burns, maintain fluids (lactated Ringer's solution) to target urine output of 0.5 mL/kg per hour if the patient has clear urine and is at low risk for rhabdomyolysis. If the patient has dark urine and is at risk for rhabdomyolysis, aim for a higher urine output of greater than 1.0 mL/kg per hour. Note that the fluid resuscitation amounts indicated in standard burn resuscitation formulas do not account for deeper tissue injuries that can occur in electrical injuries. Resuscitation should proceed as it would for any other trauma or injury, with the goal being to reestablish appropriate cellular perfusion and restore the oxygen deficit. Most commonly, this should be performed with the least amount of fluid required and global/regional parameters of perfusion are serially analyzed to evaluate effectiveness of resuscitation.

Although compartment syndrome from flame burns is associated with constriction of the tissue associated with burn eschar, the constricting tissue in electrical injury patients is the fascia due to deep tissue and muscle swelling resulting from heat energy caused by the current running through bone. Signs of compartment syndrome are not different from other causes of compartment syndrome; however, pain on passive extension and pain out of proportion to physical

TABLE 1 List of Potential Systems Involved in Electrical Injuries

Systems	Potential Injuries
Cardiovascular	Arrhythmias, including asystole, ventricular fibrillation, bradycardia, and electromechanical dissociation Heart muscle injury Thrombophlebitis
Respiratory	Respiratory arrest Paralysis of diaphragm Inhibition of brain control of respiration
Skin	Burns Infection Dehydration
Neurologic	Loss of consciousness Impaired recall Cognitive deficits Paralysis Spinal cord injury Sensory losses Weakness Chronic pain syndromes
Musculoskeletal	Fractures and dislocations Compartment syndrome Tetany Muscle necrosis Rhabdomyolysis Contractures
Renal	Myoglobin tubular necrosis Renal failure
Other	Cataracts Tympanic membrane injury Visceral injuries including perforations Cholelithiasis and cholecystitis Pancreatitis Posttraumatic stress disorder and other psychiatric disabilities

examination are early signs. Paresthesias and pulselessness are late signs indicating an advanced problem. In extreme cases, the patient might present with flexion contractures and mummification of the extremity, which will usually result in the need for amputation. Any absolute pressure greater than 30 or diastolic pressure–compartment pressure less than 30 indicates compartment syndrome. Fasciotomies should be performed in the presence of compartment syndrome, making sure to decompress all compartments affected. Debridement and ultimately surgical decompression of the hand and upper extremity should only be performed by those surgeons comfortable and familiar with this anatomy. This may include general, burn, plastic, or trauma surgeons.

When taking the patient to the operating room for debridement and grafting of electrical injuries, the surgeon should perform serial debridements and allow the tissue to completely declare itself. These injuries will often evolve with progressive muscle necrosis over time, thus early grafting (within the first week) is commonly unsuccessful. Experienced clinicians often perform conservative serial debridements with temporary wound vacuum-assisted closure or dressing changes that allow time (sometimes as long as 3 weeks) for the wound to completely declare itself before definitive wound closure. Thoughtful planning for functional amputation lengths and possible future surgical interventions such as flaps or transplants should be considered early in the acute course and appropriate consults undertaken. However, because many of these patients will have a significant necrotic tissue burden, limb preservation should not take precedence of preservation of life.

Long-term follow-up involves coordinated multidisciplinary care for these patients from onset of injury through injury recovery and rehabilitation. Complications such as chronic pain interfering with work, issues with amputations, contractures, and neurologic issues, ranging from paralysis to Guillain-Barré type syndromes, paresis, and transverse myelitis have been reported. Central manifestations including cognitive, emotional, and psychiatric changes can be seen. In patients with extensive burns including deep burns to the upper extremity and head and neck areas, lymphedema ambulation is a risk. Cataract formation is the most frequent ocular complication after electrical injury, occurring in 5% to 30% of electrically injured patients. Baseline and follow-up eye examinations are indicated because these cataracts can arise in a delayed fashion, several years after the injury. Auditory examinations are helpful, particularly in the case of an arc blast. Both cholecystitis and cholelithiasis are reported to be associated with electrical injury long term. Ideally, these patients should be followed in an outpatient burn center with capabilities for surgical reconstruction, access to psychiatric and psychological support services, as well as physical, occupational, vocational, and social therapists. Peer support and online resources are also useful.

SPECIFIC CLINICAL SITUATIONS

Lightning Injury

Lightning is one of the most dramatic examples of high-voltage direct electrical injury. Its injuries account for a small subset of electrical injuries, but lightning is responsible for an average of 409 injuries and approximately 90 deaths per year in the United States. The odds of being struck by lightning in a lifetime (estimated 80 years) are 1 in 3000. Estimated fatality from lightning is 30%, and 70% to 80% of survivors may have permanent disabilities.

In addition to tissue injury related to direct contact with an electricity source, injuries noted from the various lightning strike patterns include thermal burns through clothing or other heated material, ruptured tympanic membranes caused by shock wave from a thermoacoustic phenomenon (i.e., thunder), concussive or blast-type injuries secondary to the rapidly expanding air near a lightning strike, and injury caused by a subsequent fall.

Lightning injury can be minor, moderate, or severe.

1. Minor: often awake and alert, may have confusion or amnesia, dysesthesia, hearing or vision changes. Physical findings may be temporary, and complete recovery can occur.
2. Moderate: disorientation, confusion, unconsciousness, paralysis, skin swelling, hypotension, respiratory failure, secondary cardiac arrest. Physical symptoms may resolve over time. Long-term sequelae such as cognitive and sleep disorders, weakness, dysesthesia, and peripheral neuropathy can develop.
3. Severe / serious injury or death in 30% of victims. Blunt trauma, contusion from shock wave, cardiac dysrhythmias, cardiac arrest (primary or secondary), CNS dysfunction. Asystole may be transient, and spontaneous rhythm may recover because of cardiac automaticity. Hypoxia related to central apnea may lead to secondary cardiac arrest. Long-term sequelae such as cognitive and sleep disorders, weakness, dysesthesia, and peripheral neuropathy can develop without direct evidence of initial direct anatomic brain injury.

Keraunoparalysis is transient paralysis that can occur after a lightning strike and is characterized by signs and symptoms of motor and sensory loss (affecting lower limbs more than upper limbs), pulselessness, and pallor associated with vasospasm. Keraunoparalysis typically resolves within several hours after the injury

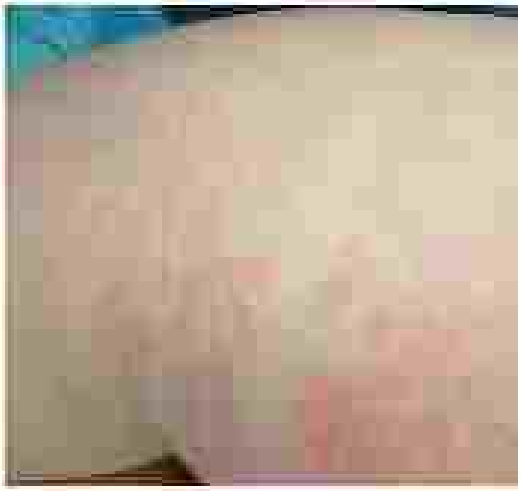

FIG. 2 Lichtenberg figure. (Courtesy Andrew R. Dalton, MD.) (A.S.)

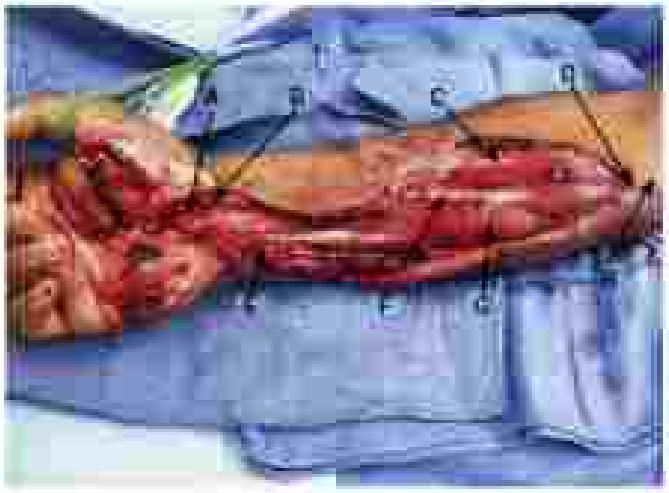

FIG. 3 Fasciotomy of right forearm and hand after electrical injury. (A) Median nerve. (B) Flexor retinaculum. (C) Flexor pollicis longus. (D) Proximal incision. (E) Ulnar nerve and artery. (F) Palmaris longus. (G) Flexor digitorum profundus. (H) Medial epicondyle.

but can mimic spinal cord injury and temporarily mask underlying musculoskeletal injury.

Unlike high-voltage electrical injuries, in which massive internal tissue damage may occur, lightning seldom causes substantial burns. Historically, most burns related to lightning are caused by other objects (moisture, metal on a belt, jewelry or coins in a pocket) being heated and causing a contact burn rather than by the lightning itself. The transformation of the electrical energy to heat can generate temperatures as high as 50,000°F. However, the duration of this transmission is only 1 to 2 milliseconds, as a result, the insulating properties of the skin do not have time to break down.

The two most common causes of death related to lightning injury are (1) cardiopulmonary arrest caused by an interruption of the cardiac cycle by the direct current, resulting in asystole; and (2) apnea from the direct current's interference with the brain's respiratory center, which if left untreated will result in hypoxia, arrhythmia, and secondary cardiac arrest. There is an estimated morbidity 5 to 10 times higher than for non-lightning related electrical injury. A pathognomonic fern-like pattern called keraunographic markings or Lichtenberg figure (Fig. 2) may appear on the skin of lightning strike victims. This is not a burn and often disappears within 24 hours.

Upper and Lower Extremity Compartment Syndrome

Most high voltage injuries are associated with deep tissue injury that is often more extensive than initially appreciated. Management of acute compartment syndrome involves immediate surgical decompression, primarily via fasciotomies of the involved compartment(s). Unlike external burn injuries, which result in a constrictive eschar as the cause of the compartment syndrome and therefore can often be decompressed with escharotomies, electrical injuries typically require fasciotomies because compartment edema from injury and fluid resuscitation is often the cause of the compartment syndrome.

Indications for surgical decompression for any extremity include progressive neurologic dysfunction, vascular compromise, increased compartment pressure, and systemic clinical deterioration from suspected ongoing myonecrosis. Delayed exploration and decompression in the compromised extremity can result in increased amputation rates as well as increased organ failure and mortality.

Fasciotomy of the Upper Extremity

Decompression of the upper extremity includes forearm fasciotomy and assessment of muscle compartment integrity. The decision to include carpal tunnel release should be made on a case by case basis. Initial fasciotomy should be performed in the areas of contact and conduction; for instance, carpal tunnel release should be considered if the injury occurs in the wrist.

There are four compartments in the forearm (superficial volar, deep volar, dorsal, mobile wad), and each should be released with a forearm fasciotomy. One classic technique for the forearm fasciotomy uses a lazy S incision (Fig. 3). The incision begins 1 cm proximal and 2 cm lateral to the medial epicondyle and is continued obliquely across the antecubital fossa toward the mobile wad. It then curves distally and ulnarly reaching the midline at the forearm at the junction of the mid and distal one-third of the forearm and then continuing distally just ulnar to the palmaris tendon and then distally incorporating Guyon canal and the carpal tunnel. The reason for curving the distal fasciotomy incision ulnarly is because the median nerve can give off a separate proximal branch in the thenar area, so by staying ulnarly it reduces the risk of injury. Volar release must include the pronator quadratus and deep flexor compartments as well.

In the hand, all 10 compartments (8 dorsal interossei, 3 palmar interossei, hypothenar, thenar, and adductor pollicis) can be accessed through 4 separate incisions: 2 incisions along the second and fourth dorsal meta-carpal, and 1 each on junction of the glabrous-nonglabrous skin of the thenar and hypothenar eminence (Fig. 3). Additionally, carpal tunnel release is often performed at the same time using a standard carpal tunnel incision. The landmark for the distal portion of the carpal tunnel is the intersection of a line between the ulnar border of the fourth fully abducted (Kaplan cardinal line) and the ulnar border of the middle finger. This can be done as a separate incision 2 to 3 cm in length or continued to join the forearm fasciotomy incision of the forearm.

The fingers have no true fascial compartment, and thus a fasciotomy is not indicated. In the rare instance an escharotomy is needed for the fingers, it can be performed between the extensor tendon and neurovascular bundles. Sometimes one release is sufficient, but on other instances releases are needed dorsal to both neurovascular bundles.

Fasciotomy of the Lower Extremity

Diagnosis of compartment syndrome in the lower extremity is similar to diagnosis in the upper extremity. There are four compartments in the lower extremity: superficial posterior, deep posterior, lateral, and anterior. These compartments can be released through a double-incision fasciotomy with one incision centered between the fibular

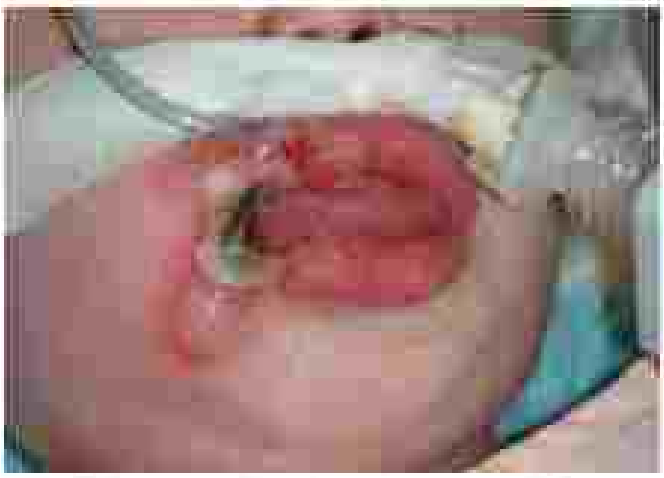

FIG. 4 Oral commissure burn resulting from contact with a household electrical wire. Associated complication: labial artery rupture may occur 7 days after burn.

shaft and the crest of the tibia overlying the intramuscular septum between the anterior and lateral compartments. After the skin is incised, subcutaneous flaps are developed medially and laterally to expose the fascia of the intramuscular septum and fascia of the anterior and lateral compartments. Care must be taken to avoid injury to the peroneal nerves. The medial incision is placed 2 cm medial to the tibia between the anterior intramuscular septum and tibial crest, taking care to avoid the saphenous vein and nerve. The superficial posterior compartment is decompressed by incising the gastrocnemius fascia, and the deep posterior compartment is decompressed by dividing the attachments of the soleus to the tibia, providing access to the posterior tibialis muscle.

Pediatric Commissure Burns

Commissure burns typically occur in the young patient and commonly result from biting or kissing on a household appliance cord. Although considered a relatively low voltage (120–240 V) injury, this soft tissue injury can be devastating and lead to significant tissue loss (Fig. 4). The burn is a result of the saliva permitting the local conduction and arcing of electricity. The electrical energy is primarily concentrated to the oral commissure and the anterior tongue. As with any trauma, the initial management follows Advanced Trauma Life Support guidelines, but these are usually isolated injuries that rarely require intubation.

The contact burn wound, often a grayish white eschar, should be cleansed gently and dressed with an ointment of choice. On examination of the vestibule of the mouth, digital palpation may reveal a "woody," indurated buccal mucosa as far posterior as the maxillary pillars. Early surgical intervention can lead to loss of potentially salvageable tissue that may be necessary for the reconstructive surgery and thus should be avoided. The goal of early treatment is to maintain a clean, moist environment that allows tissue to heal, while ensuring that the airway is not compromised. The child should be encouraged to eat and drink. Involvement of a speech pathologist can be of significant help from the onset. The use of custom-made splints can help reduce contracture and should be initiated early after injury (within 2 weeks if possible). The eschar will demarcate and slough within 7 to 21 days. Based on the proximity of the labial artery to the oral commissure, vessel rupture can be expected to occur in about 10% patients. Parents and caregivers should be educated that should labial artery rupture bleeding occur, compression of the site between the index and thumb should be performed to minimize the hemorrhage, and they should immediately return to the hospital. Seldom do these need surgical intervention for ligation.

The continued healing from the burn can result in tissue scarring and contracture. Contracture can interfere with normal vocalization, facial expression, eating, and oral hygiene (including dental care), not to mention the psychologic sequelae of the trauma. Long-term burn injuries to the mouth can result in microstomia. Contracture of the angle of the mouth is generally treated approximately 1 year after the burn injury has occurred because it takes at least 1 year for the burn to become stable because of the spherocytal action of the orbicularis oris muscle. Subsequent reconstruction of the oral commissure is best addressed with Z-plasty, V-Y flaps, trapezoid flaps, or cervical tongue flaps.

Large Cranial Defects

Deep, large electrical burns to the scalp are often some of the most challenging reconstructive cases in surgery. Necrotomy, decompression, aggressive debridement, and attempts at skin grafting are often insufficient to adequately close the wounds. Often, areas of unstable bone and other significant challenges complicate these wounds. Early involvement of plastic reconstruction services for consideration of major rotation flap and free flap planning is warranted.

Suggested Readings

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Preoperative and Postoperative Care

Fluid and Electrolyte Therapy

Alessandro Fichera, MD, FACS, FASCRS, and Theodoros J. Pu [illegible] MD

F[illegible]ow and the [illegible] of its movement [illegible] a critical c[illegible]p must be tak[illegible] care of [illegible]th a medical and surgical pati[illegible]. The clinical [illegible]pe[illegible]ment that [illegible]ows [illegible]ssessment and understanding of fl[illegible]uid and el[illegible]ctr[illegible]ytes [illegible]ehavior in cellular and s[illegible]ystemic level. [illegible]nderstanding the clinical implications of [illegible]mechanisms and [illegible]ssessment [illegible]apy in the [illegible]urgical patient. This [illegible]apter discusses fluid and electrolyte distribution in the [illegible]body, normal [illegible]ns and [illegible]s as well as [illegible]ssessment and [illegible]ppropriate therapy of fluid and electrolyte disorders.

Fluid [illegible]ompartments and Electrolytes

[illegible]ater [illegible]ounts for [illegible]pproximately [illegible]% of an adult human's total body [illegible]ght and is referred to as total body water (TBW). Adipose tissue [illegible]ater content [illegible]muscle. Therefore, individuals have a lower TBW as a percentage of body [illegible]ght. In addition, [illegible]s tend to have a greater lean muscle [illegible]ass as a percentage of total body weight, resulting in TBW accounting for approximately [illegible]% of total body weight in [illegible]ale patients and [illegible]% in females.

TBW is distributed throughout multiple body [illegible]partments, with the [illegible]ajority residing within the cellular [illegible]partment, as shown in Fig. 1. These percentages [illegible]ange depending on the status of illness and inflammation, but a healthy adult can approximately [illegible]ook at fluid resides in the intracellular space and [illegible]/3 resides in the extracellular space. The extracellular compartment is subdivided into [illegible]nterstitial and intravascular or plasma compartments. The latter is [illegible]/4 of fluid within the extracellular compartment, [illegible]or a healthy 70-kg male patient this would amount to 3 L (one-fourth of 12 L). The interstitial volume is 8 L (two-thirds of 12 L) and the intracellular volume [illegible]s the third TBW.

The balance of TBW is dictated by a complex interplay between membranes and solutes. Membranes separating intracellular and extracellular compartments are freely permeable to water such that the osmolality of the intracellular, interstitial and intravascular compartments remains equal. This is the guiding principal that dictates TBW balance. However, [illegible]ifferential permeability to different solutes [illegible]ists, resulting in a non-[illegible]qual distribution of solutes. These impermeable solutes are known as effective osmoles. They have the ability to create osmotic forces that direct the movement of water across membranes. Water moves across membranes via intracellular junctions or transcellular pores. Lipid rich cell membranes result in the diffusion of water, whereas [illegible]ransmembrane water channels known as aquaporins are [illegible]ndicated in cell membranes. [illegible]ese channels [illegible]ovement

[illegible]apillary membranes are freely permeable to [illegible]ost small solutes (less than 30 kDa) including sodium, potassium, glucose, and low molecular weight proteins. As a result these small solutes have [illegible]ittle to no effective osmolarity in the setting of capillary fluid movement. Movement of water across capillary membranes is dictated by competing forces as described by Starling's law. Transcapillary water movement is the result of the balance between osmotic pressure (an effective osmole) and hydrostatic pressure from blood flow. Osmotic pressure is exerted by plasma proteins [illegible]arge to cross the capillary wall. Starling's law states that net filtration is the difference between the hydrostatic and osmotic pressures of both the interstitial and the capillary fluids. Plasma proteins provide osmotic pressure that tends to draw fluid into the intravascular space, whereas the hydrostatic pressure is thought to push fluid out of the interstitial space. On the arteriolar end of a capillary bed, intravascular hydrostatic pressure exceeds osmotic pressure, resulting in net outward fluid movement. The opposite occurs at hydrostatic pressure decreases along the length of the capillary bed, resulting in net fluid influx into the intravascular compartment near the venous side.

Although most solutes do not contribute to water movement across capillary membranes, they do function as osmotic agents that direct water movement between the intracellular and extracellular spaces across cell membranes. Sodium (Na^+) and potassium (K^+) are the principal determinants of extracellular tonicity and intracellular osmolality, respectively. Na^+ and K^+ are unable to pass freely across the lipid membrane, [illegible]ntrations maintained and maintained by the Na^+–K^+ adenosine triphosphatase (ATPase) pump mechanism. This [illegible]ransmembrane transport exchanges three Na^+ molecules for [illegible]ecules, generating a net negative charge potential. Manipulation of either of these ions results in water movement [illegible]ross [illegible]ts [illegible]ctive osmolality compartment in order to reestablish equilibrium. For example, administration of hypertonic

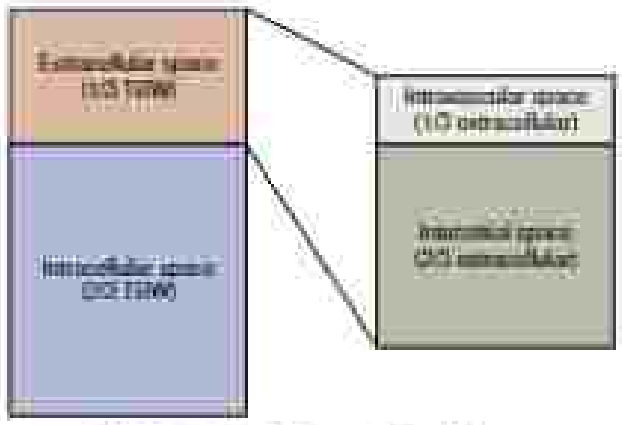

FIG. 1 Body fluid [illegible]ns [illegible]ns [illegible]ns and [illegible]ir [illegible]ns

solution (e.g., 0.25% NaCl solution) results in decreased extracellular osmolality as water moves from the extracellular space to the intracellular space, resulting in cellular swelling. In contrast, administration of a hypertonic solution (e.g., 3% NaCl solution) results in increased extracellular osmolality, as water moves from the intracellular space to the extracellular space, resulting in cellular dehydration.

Serum osmolality is maintained within a narrow range through osmoregulation and is calculated using the following formula:

$$\text{Serum osmolality} = 2 \times (\text{Na} + \text{K}) + \frac{\text{BUN}}{2.8} + \frac{\text{glucose}}{18}$$

where BUN is blood urea nitrogen and mOsm/kg is serum osmolality. Normal serum osmolality ranges from 275 to 290 mOsm/kg, with a threshold of 1% to 2% variation before activation of mechanisms to restore normal levels. Variations in serum osmolality are detected by osmoreceptors within the hypothalamus. Increases in plasma osmolality result in stimulation of thirst along with antidiuretic hormone (ADH) secretion from the posterior pituitary gland. ADH release results in upregulation of aquaporin channels in the luminal membrane of distal collecting tubules in the kidney, promoting free water reabsorption down its established gradient. As a result of increased aquaporin insertion, urine osmolality increases, with variations from 100 to 1,400 mOsm/kg depending on the serum osmolality. ADH secretion is also triggered by central baroreceptors that detect decreased plasma volume. The result of ADH secretion is free water reabsorption in the body's attempt to restore normal osmolality and maintain homeostasis.

Osmoregulation can be viewed as a separate but related process from volume regulation. Changes in osmoregulation result in sodium shifts. Hormones that influence total body sodium content are the principal mediators of volume regulation. The renin-angiotensin-aldosterone (RAA) axis promotes volume expansion. Renin is secreted by the juxtaglomerular cells in response to renal hypoperfusion or low sodium concentration in the macula densa region of the distal tubule. Renin secretion promotes formation of angiotensin from angiotensinogen and the eventual production of aldosterone, which promotes sodium reabsorption. Contrary to the RAA axis, atrial natriuretic peptide (ANP) results in net diuresis. ANP is a hormone released in response to cardiac atrial stretch and results in increased renal blood flow through dilation of the afferent glomerular arteriole and inhibition of sodium reabsorption in the kidney.

Fluid Status and the Management of Volume: The Data

Assessment of Fluid Status

In the immediate postoperative period, patients may have fluid deficits resulting from preoperative or intraoperative fluid losses. Continued fluid losses in the extended postoperative period from urine, skin, and the gastrointestinal (GI) tract are common. Fluid management requires close assessment of fluid status and selection of an appropriate type and rate of fluid replacement. It should be recognized that intravenous (IV) fluids are a therapy capable of providing benefit when utilized appropriately but also able to cause harm when used inappropriately.

Commonly seen in the postoperative period, inflammatory states result in a low effective intravascular volume despite an overall positive fluid balance due to cytokine-induced permeability, which increases extracellular volume. Common signs and symptoms of low effective circulatory volume include abnormal mentation, excessive thirst, dry mucous membranes, poor skin turgor, tachycardia, hypotension, orthostatic changes in vital signs, and oliguria. Daily weights, serum and urine electrolyte levels, acid-base balance, and invasive monitoring can be used to assess a patient's volume status and the adequacy of resuscitation. Urine output is an excellent measure of volume status; adults should produce at least 0.5 mL/kg/hr, whereas children should produce nearly 1 to 2 mL/kg/hr. However, in the setting of renal insufficiency, those receiving diuretics, or those in hyperglycemic states, urine output may be an inaccurate measure of volume status and resuscitation.

Additional indicators of intravascular depletion include an elevated hematocrit, low serum bicarbonate level with a base deficit, blood urea nitrogen/creatinine ratio greater than 20:1 (prerenal azotemia), and a fractional excretion of sodium (FE_{Na}) of less than 1%. Elevated urine osmolality may suggest intravascular hypovolemia, but in the setting of renal insufficiency or use of diuretics it is not an accurate measure. The equation for fractional excretion of sodium is as follows:

$$FE_{Na} = \frac{(\text{Urine Na} \times \text{Plasma Cr})}{(\text{Plasma Na} \times \text{Urine Cr})} \times 100$$

...milar to urine output and urine osmolality assessments, in the setting of renal dysfunction or use of diuretics FE_{Na} is not a useful indicator of volume status. Instead, fractional excretion of urea (FE_{Urea}) provides a useful tool. FE_{Urea} is calculated in the same fashion as FE_{Na}:

$$FE_{Urea} = \frac{(\text{Urine urea} \times \text{Plasma Cr})}{(\text{Plasma urea} \times \text{Urine Cr})} \times 100$$

FE_{Urea} less than 35% is suggestive of a prerenal condition.

Forms of IV Fluid Therapy

IV fluid therapy in the broadest sense is divided into two categories based on its composition and overall goal. Maintenance fluids are used to replace normal and insensible losses. They typically contain dextrose to maintain plasma osmolality and prevent glucagon depletion. Resuscitative, or replacement fluids, replace abnormal or excessive losses and correct for any water or electrolyte deficits. These are utilized in the immediate postoperative period, dehydration, sepsis, and other situations with large fluid deficits.

Maintenance Fluids and Daily Electrolyte Requirements

Sensible losses can be quantified and occur primarily in urine (~800 to 1500 mL daily) and stool (~250 mL daily). Insensible losses are unable to be quantified and include cutaneous losses from the skin (75%) and upper respiratory tract (25%). Insensible losses alone are quantified roughly at 8 to 12 mL/kg per day. Sensible and insensible losses vary greatly in different physiologic states and pathologic conditions, including fever, hyperventilation, burns, tachycardia, and other hypermetabolic states. Cutaneous insensible losses increase by 10% per day for each 1°C increase in body temperature above 37.1°C. Laparotomy and thoracotomy increase insensible losses from the operative site at rates that approach nearly 1 L/hr.

Daily maintenance fluid administration in both pediatric and adult populations can be calculated for a 24-hour period utilizing the 100-50-20 rule or hourly utilizing the 4-2-1 rule (Table 1-3). By definition, maintenance fluids contain dextrose. Their electrolyte composition is variable and allows for replacement of these lost from insensible and sensible losses but these levels should be closely monitored in perioperative patients. In general, the most common postoperative maintenance fluid for adults consists of 5% dextrose in one-half normal saline (D5 ½NS) with 20 mEq/L KCl. In children the standard maintenance fluid is D5 ¼NS or D5 lactated Ringer's solution (LR). This is to avoid hyponatremia, which has been shown to be of critical significance in the pediatric population. Children younger than 2 years usually receive D5 ¼NS, with 20 mEq/L. The reason for this is that until age 2 years, the kidney has a glomerular filtration rate (GFR) that is one-quarter the adult level, and the distal nephrons are unable to effectively concentrate the urine, leading to a difficulty in excreting high sodium loads.

TABLE 1 Electrolyte Composition (mEq) of Parenteral Fluids

Fluid	Na^+	K^+	Cl^-	Ca^{2+}	HCO_3^-	Lactate	pH	Osmolality
Extracellular fluid	142	4	103	5	27	0	7.4	280
Lactated Ringer's solution	130	4	109	2.7	28	0	6.5	275
Normal saline (0.9% NaCl)	154	0	154	0	0	0	4.5	308
One half normal saline (0.45% NaCl)	77	0	77	0	0	0	4.5	154
One quarter normal saline (0.22% NaCl)	34	0	34	0	0	0	4.5	77
3% Saline	513	0	513	0	0	0	4.5	1026
5% Dextrose in water	0	0	0	0	0	50g	5.0	278
5% Albumin	145	0	0	0	0	0	7.4	290
Normosol	140	5	98	0	0	0	6.6	294
Plasma-Lyte	140	5	98	0	0	0	7.4	294

Ca^{2+}, Calcium; Cl^-, chloride; HCO_3^-, bicarbonate; K^+, potassium; Na^+, sodium.

TABLE 2 Electrolyte Composition (mEq) of Gastrointestinal Fluids

Source	Daily Production (mL)	Na^+	K^+	Cl^-	HCO_3^-
Saliva	1000	30–80	20	20	30
Gastric	1000–2000	60–80	15	100	0
Pancreas	1000	140	5–10	60–90	80–100
Bile	1000	140	5–10	100	80
Small bowel	2000–3000	140	20	100	25–60
Large bowel	200–1500	75	30	30	0

Cl^-, Chloride; HCO_3^-, bicarbonate; K^+, potassium; Na^+, sodium.

When administering maintenance fluids, utilizing a 4-2-1 dosing regimen in a 70 kg male (110 mL/hr) results in a total sodium load of 203 mEq in a 24-hour period, which is greater than the required 1 to 2 mEq/kg/day. Although patients with normal kidney function are able to excrete the excess sodium load, caution should be utilized in patients with underlying renal dysfunction, cardiac failure, or other serious comorbidities to not cause iatrogenic hypervolemia. In general, maintenance fluids should be reassessed at least daily to ensure that correct electrolyte and fluid volume needs are met but not exceeded.

Resuscitative Fluids

Resuscitative fluids are most commonly used the immediate postoperative period, after injury, and in the setting of hypotension. The rate of fluid administration is determined by the severity of the existing deficit, presence of ongoing losses, and the patient's comorbidities. NS and LR closely approximate the composition of extracellular fluid and therefore are the most commonly used resuscitative fluids. The composition of various resuscitative fluids is shown in Table 1. LR has a pH of 6.5 and provides 28 mEq of bicarbonate (HCO_3^-) per liter, making it preferential in the setting of acidosis. NS, at a pH of 4.5, does not contain HCO_3^- but has a greater concentration of Na^+ and Cl^- (154 mEq/L making it preferential in patients with a metabolic alkalosis. However, it can create hyperchloremic metabolic acidosis in the setting of high volume resuscitation. Severe fluid losses resulting in hemodynamic instability should be replaced with isotonic resuscitative fluid boluses of 0.9% sodium chloride (NS solution) or LR solution at volumes of 10 to 20 mL/kg, with boluses repeated until adequate resuscitation is reached. Colloid solutions, such as 5% albumin, theoretically provide an advantage when restoring intravascular volume because of the oncotic pressure afforded by the protein content. However, clinical use of colloid solutions is less cost effective and has not demonstrated improved patient outcomes in randomized studies.

ENHANCED RECOVERY AFTER SURGERY (ERAS) PROTOCOLS AND FLUID MANAGEMENT

Enhanced recovery after surgery (ERAS) programs are evidence-based multidisciplinary pathways designed to accelerate postoperative recovery and shorten time to discharge from the hospital without compromising patient safety. The basic hallmarks of ERAS programs are evidence-based, standardized, preoperative assessment and teaching, as well as intraoperative and postoperative management. One of the basic tenants of colorectal ERAS programs focuses on minimizing both intraoperative and postoperative IV fluids. Balanced fluid administration to provide intraoperatively through goal directed therapy that utilizes vasopressors in addition to fluids and closely monitors hemodynamic parameters. Excessive IV fluid in the perioperative period has been linked to delayed return of bowel function and increased postoperative complications. In addition to fluid restriction, data supports restricting sodium intake in attempt to avoid hyperchloremia, which has been associated with renal dysfunction. The data on this field is likely to grow as the number of ERAS programs expand and the literature accumulates.

DIAGNOSIS AND TREATMENT OF ELECTROLYTE DISORDERS

Sodium

Hemostasis and Cl- and Na+ Balance

Sodium is the principal determinant of serum osmolality and free water balance. Sodium is predominately located in the extracellular space and its normal physiologic range is 135 to 145 mEq/L. It functions as an effective osmole, stimulating free water movement across cellular membranes secondary to cell wall impermeability to sodium. Recognizing volume status and osmolarity is vital in the safe and effective treatment of sodium abnormalities.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration greater than 145 mEq/L. It can be subdivided further into mild, moderate, or severe (> 160 mEq/L). Symptoms of severe hypernatremia are related primarily to central nervous system depression as a result of cellular dehydration and include muscle weakness, restlessness, insomnia, lethargy, and coma. Unlike hypovolemia, in which mild to moderate similar states can exist, hypernatremia is always associated with a hypertonic state but can be seen in hypervolemic, euvolemic, and hypovolemic states. Assessment of volume status is the key to successfully understanding the etiology and proper management of hypernatremia.

The most common cause of hypervolemic hypernatremia is seen in patients in dehydrated states and with uncontrolled fluid losses. Older patients, infants, and patients with end stage liver disease are particularly vulnerable. Patients with diarrhea from nasogastric suction, vomiting, diuretics, or lactulose administration are particularly at risk and can become dehydrated quickly. Iatrogenic hypernatremia must often occurs due to inappropriate urinary loss of free water (inappropriate low urine osmolality) seen with neurogenic or nephrogenic diabetes insipidus (DI). In the setting of head injury, pituitary surgery, or cerebral hemorrhage, iatrogenic DI should be suspected for patients who exhibit persistent hypernatremia. A significant response (50% increase in urine osmolality) after administration of desmopressin (DDAVP) in the setting of DI suggests a neurogenic origin. Treatment of nephrogenic DI is more difficult as the kidney responds inappropriately to DDAVP. Finally, hypervolemic hypernatremia is usually iatrogenic in nature, resulting from fluid resuscitation with hypertonic solutions. Other medical causes include mineralocorticoid excess, such as with Conn's or Cushing's syndrome.

Treatment of hypernatremia begins with calculation of the free water deficit:

$$\text{Free water deficit: (L)} = 0.6 \times \text{weight (kg)} \times \left[\frac{\text{Serum Na}}{140} - 1\right]$$

Patients with severe hypernatremia (>160 mEq/L) or symptomatic hypernatremia should undergo treatment with IV water replacements. Those with mild or moderate hypernatremia can be corrected utilizing isotonic NS. *Rate of correction* is critically important and is influenced by the rate in which hypernatremia developed. Those with acute development (<24 hours) should be replaced more rapidly, whereas those with chronic hypernatremia (48 hours) should be approached cautiously. Acute hypernatremia should be corrected at an initial rate of 2 to 3 mEq/L per hour but should not exceed a maximum correction of 12 mEq/L per day. Chronic hypernatremia should be corrected at a rate not to exceed 0.5 mEq/L per hour, with a total change of 8 to 10 mEq/L per day. Serum sodium measurements should be obtained every 2 hours until the patient is neurologically stable.

Hyponatremia

A commonly accepted definition of hyponatremia is a serum sodium concentration lower than 135 mEq/L. Hyponatremia can be subdivided further into mild (130–135 mEq/L), moderate (120–130 mEq/L), or severe (<120 mEq/L). It is estimated that approximately 1% of postoperative patients develop moderate to severe hyponatremia, with upward of 20% of these cases deemed clinically significant. Severe hyponatremia or acute changes in serum sodium concentrations can result in cellular edema and cerebral swelling, leading to clinical manifestations of headaches, lethargy, seizures, and coma. Clinical manifestations of hyponatremia are related to the rate in which the derangement develops. Significant hyponatremia can remain asymptomatic if chronic, as in the case of cirrhosis or heart failure, as the nervous system can adapt. Conversely, patients with acute mild hyponatremia may manifest with symptoms. Additionally, previous work has demonstrated the roles of gender (females worse than males), age (young worse than old), and the presence of hypoxia (worse with hypoxia) as factors that influence the severity of hyponatremia symptoms.

To guide corrective therapy, calculation of the sodium deficit is required utilizing the patient's TBW estimate:

$$\text{Na deficit} = [140 - \text{Serum Na}] \times \text{TBW}$$

TBW is estimated utilizing 0.6 times total body weight for males and 0.5 times total body weight for females. When correcting hyponatremia, the rate of correction is important, as rapid corrections can lead to central pontine myelinolysis (CPM) with potential for permanent spastic quadriparesis and pseudobulbar palsy. Patients with liver disease are particularly susceptible to demyelination. In patients with severe liver disease, the upper limit for a safe rate of correction is unknown. In the majority of patients, serum sodium correction should not exceed 0.25 mEq/L per hour or 9 mEq/L per day. Severe manifestations of hyponatremia (active seizures, respiratory failure, etc.) require immediate treatment with the goal of raising the serum sodium by 2 to 4 mEq/L through a 100 mL bolus of 3% saline over a 10 minute period. If the clinical manifestations do not improve, repeat bolus is indicated. For those patients with less severe manifestations of hyponatremia but who demonstrate hyponatremic encephalopathy (recent seizure, altered mental status, headache, nausea, emesis, etc.), infusion of 3% saline given at a rate of 1 mL/kg per hour is recommended. As a general rule, infusion of 3% saline at a dose of 1 mL/kg provides a serum sodium increase of 1 mEq/L.

In the setting of asymptomatic hyponatremia or as an adjunct to hypertonic saline, furosemide reduced diuresis can aid in a more gradual correction of serum sodium. Treatment of asymptomatic hyponatremia requires assessment of serum osmolality, as it can occur in high, normal, or low serum osmolality states. Aside from osmotic variations, hyponatremia can be present in hypovolemic, euvolemic, or hypervolemic states. Assessment of serum osmolality and volume status is extremely important when determining the appropriate corrective therapy. In the postoperative period, abnormalities in volume status are most common.

Hypovolemic hyponatremia: hyponatremia is the most common form of hyponatremia in the perioperative setting. When hypovolemia is suspected, urine sodium levels less than 20 mmol/L suggest hyponatremia secondary to sequestration of isotonic fluids in the extracellular space or loss from the GI tract or skin. Contrary to treatment of hypervolemic or euvolemic hyponatremia, fluid restriction in the setting of hypovolemia will worsen the clinical picture. Thus, mild to moderate cases are treated utilizing isotonic saline solution.

Hypervolemic hyponatremia is the least common type in the postoperative period, as it is most commonly the iatrogenic result of excessive hypotonic fluid administration. To avoid hypervolemic hyponatremia, hypotonic fluid administration should be reserved primarily for correction of free water deficits in the setting of hypernatremia. Treatment for hypervolemic hyponatremia can be accomplished easily with a combination of water restriction and gentle diuresis. Euvolemic hyponatremia is uncommon in the perioperative period, as it is often the result of syndrome of inappropriate ADH secretion (SIADH), hypothyroidism, or excessive water intake (psychogenic polydipsia). In the postoperative period, transient increases in ADH as the result of pain, stress, narcotic medications, and volume depletion promote free water reabsorption, but not typically at a level sufficient to create a hyponatremic state. SIADH occurs in the setting of traumatic brain injury, pulmonary malignancies (carcinoma and small cell), and lung infections. Diagnosis of SIADH usually is made on findings of high urine osmolality (>150 mmol/kg) and high urine sodium (>25 mmol/L). The absence of hypokalemia helps to differentiate SIADH from adrenal insufficiency. In the setting of SIADH, administration of isotonic saline often worsens hyponatremia, as the sodium is diluted out with reabsorption of free water. Treatment for

euvolemic hyponatremia consists of fluid restriction (<1 L/day) for gradual correction of serum sodium levels.

Assessment of osmolality in addition to volume status is important. Hyperosmolar states can occur in the setting of hyponatremia; however, in the setting of hypertonic hyponatremia it is important to evaluate serum BUN and glucose levels. Elevations in BUN or glucose create increased extracellular osmotic pressure, resulting in an influx of water into the extracellular space, resulting in a relative hypervolemic state. The first step in assessment of hypertonic hyponatremia is to determine the true serum sodium level. In the setting of hyperglycemia, for every 100 mg/dL increase in glucose over 100 mg/dL, 2 mEq/L should be added to the reported sodium.

$$\text{Corrected Na} = \text{Na (mg/dL)} + \left[\frac{\text{glucose}\left(\frac{\text{mg}}{\text{dL}}\right) - 100}{100}\right]$$

Factitious hyponatremia, also known as pseudohyponatremia is rarely seen anymore, as it is now often corrected for by most laboratories. It is caused by elevated chemicals such as proteins and triglycerides, resulting in a false lowering of the serum sodium measurement. Finally, hypotonic hyponatremia occurs most commonly in the setting of a hypervolemic state resulting from expanded extracellular and interstitial volumes with relative intravascular depletion resulting in ADH release. This is seen most commonly in the settings of congestive heart failure, chronic renal insufficiency, nephrotic syndrome, cirrhosis (often in the setting of hepatorenal syndrome), and hypoalbuminemia. Treatment of hypotonic hyponatremia most commonly includes sodium (1500–2000 mg/day) and fluid (<1 L/day) restriction.

Potassium

Homeostasis and Clinical Significance

Serum potassium levels are maintained in a narrow range (3.5–5 mmol/L) via tight regulation at the level of the kidney. The renin-angiotensin-aldosterone system is the body's major feedback system for maintaining potassium homeostasis. Aldosterone acts on the distal renal tubule to cause secretion of potassium. Approximately 98% of the body's potassium is sequestered within the intracellular compartment. Given the relative lack of potassium in the extracellular space, transcellular shifts in potassium are the primary culprit for the development of potassium abnormalities.

Metabolic acidosis, and less commonly lactic acidosis, results in influx of potassium into the extracellular space in exchange for intracellular movement of hydrogen (H^+) ions in an attempt to buffer serum pH. On the contrary, insulin and β-receptor stimulation result in an influx of potassium intracellular.

Hyperkalemia

Hyperkalemia is defined as K^+ above 5.5 mEq/L. Hyperkalemia is cardiotoxic and can lead to ventricular arrhythmias and death. Electrocardiographic (EKG) findings include, in order of progression, peaked T waves, QRS widening, shortened QT intervals, and ventricular ectopy. Hyperkalemia develops through two distinct mechanisms; total body excess or translocation of extracellular potassium into the extracellular space. Acute rises in potassium are not well tolerated, but chronic elevations as seen in chronic renal failure are fairly well tolerated. Notable causes of acute hyperkalemia include acidosis, rhabdomyolysis, cell lysis, and insulin deficiency. A unique surgical cause includes ischemia reperfusion injuries, where revascularization after 4 to 6 hours of ischemia, severe systemic hyperkalemia may occur. Many surgeons utilize prophylactic bicarbonate administration before reperfusion. Additional patients in whom the risk of hyperkalemia is increased include those with profound atrophy (often secondary to prolonged bed rest), neuralgia, denervation syndromes, severe burns, or muscular trauma. Additionally, some medications such as spironolactone and succinylcholine can cause iatrogenic hyperkalemia.

Treatment of hyperkalemia is multifaceted and the degree to which it is treated depends on the presence or lack of symptoms. Treatment consists of promoting either intracellular shift of potassium or overall excretion of potassium from the body. For patients in whom cardiac instability is detected on EKG, the FIRST step in treatment is administration of intravenous calcium gluconate 1 to 2 g over 2 to 3 minutes with continuous cardiac monitoring. This step stabilizes cardiac membranes to prevent arrhythmias but has no effect on serum potassium levels. If EKG changes remain, calcium bolus may be repeated. To quickly affect serum potassium concentration, intracellular shift of potassium can be achieved by administering 10 units of regular insulin IV plus 1 ampule of 50% dextrose (D50) to prevent hypoglycemia and/or administering an ampule of sodium bicarbonate ($NaHCO_3$) and/or administering a β_2 agonist (albuterol). Intracellular shifts temporizes the situation, but ultimately excretion of excess potassium from the body is accomplished with administration of loop diuretics or cation exchange resins (hypernatremia). Exchange resins can be given orally or as a retention enema (contraindicated with immunosuppression) with sorbitol but have an associated risk of colonic ischemia. In critically ill patients, hemodialysis can be utilized to reduce serum potassium.

Hypokalemia

Hypokalemia is defined as serum K^+ below 3.5 mEq/L and is commonly encountered in the perioperative period. It is often the result of renal and GI losses and can be see with loop diuretics, vomiting, diarrhea, and nasogastric suctioning. Signs and symptoms of hypokalemia include generalized fatigue, weakness, atrial arrhythmias, and ileus. EKG findings include flattening of T waves or the formation of prominent U waves. As stated previously, 98% of total body potassium is stored within the intracellular compartment; thus, small changes in serum K^+ reflect large changes in total body stores. Low potassium frequently is associated with hypomagnesemia and acidosis. Magnesium first must be replenished before K^+ is corrected to achieve adequate serum K^+ levels. In patients who are both hypokalemic and acidemic, potassium administration should precede correction of acidemia with bicarbonate because increasing pH will cause an intracellular shift of potassium and overall decrease in serum potassium. Potassium can be replenished via oral or IV routes. Treatment of mild hypokalemia should be accomplished via oral replacement, however, oral therapy often is poorly tolerated. Given the high oral bioavailability of KCl, IV administration should be reserved for patients who do not tolerate the oral form or for those who have severe hypokalemia. Severe hypokalemia should be treated utilizing IV KCl at a rate of 10 to 20 mEq/hr with simultaneous replacement of any magnesium deficits. Given the large total body deficit reflected by serum abnormalities, serial replacements often will be necessary.

Calcium

Homeostasis and Clinical Significance

Calcium is the most abundant electrolyte in the body, with the vast majority found in bone stores. The normal range of serum calcium is 8.5 to 10.5 mg/dL. Serum concentrations are tightly maintained by processes that increase serum calcium via bone demineralization and intestinal absorption and decrease serum calcium via urinary excretion and bone formation. This homeostasis is regulated through complex hormonal regulation, with the majority via parathyroid hormone and calcitriol. Nearly 50% of calcium exists in a biologically active ionized state; the other 50% exists in a minimized inactive state bound to albumin. With such a large portion of circulating calcium bound to albumin, serum calcium measurements must be adjusted for serum albumin levels by the following equation:

$$\text{Corrected calcium} = (0.8 \times (\text{Normal albumin} - \text{Patient's albumin})) + \text{measured calcium}$$

Although this correction generally is utilized, true measurement of ionized calcium in critically ill patients is necessary for patient care and is readily available in all laboratories.

Hypercalcemia

Hypercalcemia is defined by total calcium level greater than 10.4 mg/dL or ionized concentration greater than 5.6 mg/dL. It most commonly is seen with malignancy (breast cancer most common) or in hyperparathyroidism. Other causes include thiazide diuretics, lithium, familial hypocalciuric hypercalcemia, excess intake, vitamin A and D overdose, and immobilization. Symptoms of hypercalcemia include headache, nausea, emesis, altered mental status, lethargy, myalgias, arthralgias, polyuria, and abdominal flank pain secondary to renal stones.

Treatment should be sought for all individuals with total serum concentration greater than 14 mg/dL or those with symptoms. The initial step in treatment includes volume expansion with normal saline (rate of 200 to 300 mL/hr) to dilute circulating calcium and increase renal excretion of calcium. Noninvasive diuretics such as furosemide given IV is used to increase renal excretion of calcium and assist with excess fluid removal to prevent volume overload. An additional treatment for severe or symptomatic hypercalcemia includes calcitonin (4 IU/kg), which will acutely inhibit bone resorption and inhibit renal resorption of calcium. Bisphosphonates, such as zoledronic acid (4 mg IV over 15 minutes) and pamidronate (60 to 90 mg IV over 4 hours) are the best choice for long-term calcium control and for hypercalcemia from enhanced bone resorption. They inhibit osteoclast-induced bone resorption, providing prolonged control with onset of action between 24 and 48 hours.

Hypocalcemia

Hypocalcemia is defined as total serum concentration below 8.4 mg/dL or ionized calcium concentration below 4.5 mg/dL. Causes of hypocalcemia are broken into two broad categories: increased efflux from the extracellular space or decreased influx into the extracellular space. Common causes include hypoparathyroidism and vitamin D deficiency. Additionally, alkalosis increases albumin affinity for calcium and severe pancreatitis results in saponification of calcium intracellular, both resulting in a hypocalcemic state. Hyperphosphatemia and hypomagnesemia also alter calcium homeostasis. In the postoperative period, large volume resuscitation or rapid transfusion of blood products before removal of citrate from blood can result in hypocalcemia.

Symptoms of hypocalcemia include perioral numbness and tingling, hyperreflexia when mechanically stimulating the facial nerve (Chvostek's sign), muscle spasm of the hand and forearm with inflation of a blood pressure cuff proximally (Trousseau's sign), and prolonged QT and arrhythmias on ECG. Treatment should be pursued in the setting of symptoms, (corrected) total serum calcium below 7.0 mg/dL, or ionized calcium below 3.0 mg/dL. Treatment with IV calcium gluconate or calcium chloride should be reserved for cases of severe hypocalcemia or cases with serious symptoms, including overt tetany, laryngospasm, and seizures. Treatment with 10% calcium chloride provides three times as much elemental calcium as 10% calcium gluconate but this requires central venous access. Additionally, administration of calcium chloride requires a monitored setting to avoid associated bradycardia or hypotension. Oral replacement for chronic hypocalcemia in adults can be done through either calcium carbonate or calcium gluconate (1 to 2 g Ca/day). Resistant or severe hypocalcemia may require concurrent vitamin D_3 supplementation. As with hypokalemia, replacement of magnesium concurrently is critical when replacing calcium.

Magnesium

Homeostasis and Clinical Significance

Magnesium is essential for energy metabolism, protein synthesis, calcium homeostasis, and potassium homeostasis. Magnesium primarily is stored intracellular, with less than 1% contained in the extracellular compartment. Normal serum magnesium level is 1.8 to 2.0 mEq/L.

Hypermagnesemia

Hypermagnesemia is a rare event usually seen with burns, trauma, or long-term hemodialysis. Symptoms are uncommon unless serum magnesium levels reach 4.0 mg/dL or greater, with the most common symptom being lethargy. Treatment usually consists of normal saline to expand plasma volume and decrease serum concentration with loop diuretics to reduce renal excretion. Severe hypermagnesemia is treated with IV 10% calcium gluconate (10–20 mL given over 10 minutes).

Hypomagnesemia

Hypomagnesemia often is seen in the postoperative period secondary to dilution. Patients at high risk for hypomagnesemia include alcoholics and critically ill patients. Alternatively, hypomagnesemia may occur as a result of poor intake or GI losses, including diarrhea and biliary and enteric fistulae. Signs and symptoms rarely occur unless serum levels are below 1.0 mEq/dL. Postoperative monitoring is necessary, as severe hypomagnesemia may cause ventricular arrhythmias such as torsades de pointes. Magnesium can be replaced with IV therapy in the form of magnesium sulfate ($MgSO_4$) and is well tolerated. Oral magnesium oxide is an alternative replacement option but it can cause diarrhea, which should be taken into consideration in the postoperative patient.

Phosphorus

Homeostasis and Clinical Significance

Normal serum phosphate ranges from 2.2 to 4.7 mg/dL and it is important in many of the basic cellular processes within the body. Given phosphate's role in cellular metabolism, levels often are altered in critically ill individuals and in the postoperative setting. Individuals who have a poor nutritional status, including critically ill individuals, may experience deficient phosphate levels. Approximately 80% of body stores for phosphate reside within bone, with less than 1% within the intravascular compartment. The renal system is crucial to homeostasis, as thyroid hormone and insulin favor reabsorption of phosphate, whereas parathyroid hormone plays a role in the excretion of excess phosphate. Reabsorption is principally at the proximal tubule through NPT2 sodium/phosphate transporters.

Hyperphosphatemia

Hyperphosphatemia is defined as serum phosphorus levels above 5.0 mg/dL but rarely occurs in the postoperative period. Typically, hyperphosphatemia is seen in patients with renal insufficiency and is the result of a deficiency in 1,25-dihydroxyvitamin D production. Typically, these patients also experience hypocalcemia from increased precipitation resulting from the elevated phosphate levels. The predominant symptoms associated with hyperphosphatemia are mostly those associated with the hypocalcemic state. Treatment of hyperphosphatemia includes plasma volume expansion with normal saline followed by renal stimulation with acetazolamide. In patients with extremely poor renal function or in severe cases, hemodialysis provides corrective therapy. For those with chronic renal failure with chronic hyperphosphatemia, treatment with phosphate binders such as aluminum hydroxide is standard.

Hypophosphatemia

Hypophosphatemia is defined as the serum phosphate level below 2.5 mg/dL and symptoms include arrhythmias, platelet dysfunction, abnormal glucose metabolism, and cardiopulmonary arrest. Hypophosphatemia is much more common in the postoperative period and among individuals in the intensive care unit. Causes of hypophosphatemia include internal redistribution, deficient intake, or excessive loss. Internal redistribution is the result of increased insulin secretion, epinephrine, acute respiratory alkalosis, or bone hunger

TABLE 3 Signs, Symptoms, and Treatment of Electrolyte Disorders

Disorder	Neurologic	Cardiovascular	Gastrointestinal	Renal	Therapy
Hypovolemia	Confusion, seizures, coma	Hypotension, hypertension	Salivation	Oliguria	Fluid resuscitation 0.9% NaCl Hypertonic saline + diuretic
Hypernatremia	Confusion, seizures, coma	Fluid overload	Thirst		Free water 0.45% NaCl
Hypokalemia	Fatigue, weakness	Atrial arrhythmias, flat T waves or U waves	Ileus	Nephrotoxicity	Oral/IV potassium Magnesium replacement
Hyperkalemia	Confusion, paralysis, arrhythmia	Ventricular arrhythmias, peaked T waves, prolonged PR, wide QRS	Nausea, vomiting, abdominal pain		Insulin + 50% dextrose 10% Calcium gluconate
Hypocalcemia	Paresthesia, perioral tingling, carpopedal spasms, Chvostek's sign	Ventricular arrhythmias, prolonged QT interval			IV calcium gluconate 1,25-Dihydroxyvitamin D
Hypercalcemia	Confusion, fatigue, coma	Shortened QT	Abdominal pain	Renal stones, nephrogenic DI (long term)	0.9% NaCl Furosemide
Hypomagnesemia	Weakness, cramping, hyperreflexia	Atrial ventricular arrhythmias (torsades de pointes)	Dysphagia		IV magnesium Magnesium sulfate
Hypermagnesemia	Sedation, paralysis, areflexia	Atrial, ventricular arrhythmias	Diarrhea		0.9% NaCl Furosemide
Hypophosphatemia	Confusion, seizures, weakness	Heart failure, respiratory failure			Sodium or potassium phosphate
Hyperphosphatemia	Symptoms of hypocalcemia				0.9% NaCl Diuretics *Acetazolamide*

DI, Diabetes insipidus; *IV*, intravenous; *NaCl*, sodium chloride.

Dietetic intake can result from intestinal malabsorption (phosphate-binding medications, GI tract surgery), vitamin D deficiency, or starvation and chronic diarrhea. Increased excretion can result from diuretic therapy (acetazolamide), hyperparathyroidism, and acute hepatic reaction.

Refeeding syndrome is a potentially life-threatening condition that occurs when chronically nutritionally depleted individuals receive nutrition. Carbohydrate administration triggers an insulin surge that causes redistribution of phosphate intracellular, further lowering serum phosphate levels. This leads to depletion of adenosine triphosphate and can cause respiratory failure and death. Phosphate levels need to be closely monitored when chronically malnourished individuals are given nutrition.

Hypophosphatemia can also be seen postoperatively after large hepatic resections. Emerging evidence suggests that hypophosphatemia in the setting of liver resection is not the result of increased use by the regenerating liver, but rather a transient hyperphosphaturia secondary to deranged hepatorenal signaling. These patients should have close monitoring and replacement of phosphate postoperatively.

Appropriate treatment of hypophosphatemia should include assessment of the etiology for hypophosphatemia and the cause is often clinically apparent. For cases of symptomatic or severe hypophosphatemia (<1.0 mg/dL), treatment with IV phosphate should be utilized until serum levels exceed 1.5 mg/dL, followed by oral therapy. One millimole (mmol) of phosphate equals 31 mg of phosphorus. IV dosing varies, but for most cases 0.25 to 0.50 mmol/kg given over 8 to 12 hours with a maximum dose of 80 mmol is recommended. Oral therapy, administered as a sodium or potassium salt, usually is dosed at 1 mmol/kg of elemental phosphorus (maximum dose of 80 mmol) divided into 3 doses over 24 hours. In cases where serum phosphate levels are between 1.0 and 1.9 mg/dL, treatment with oral therapy alone is sufficient. Given that only 1% of total body phosphate resides in the intravascular compartment, continuous therapy with phosphate for 5 to 7 days is often indicated. Replacement in patients with renal failure should be done judiciously given the significant risk for development of hyperphosphatemia.

SUMMARY

Fluid status and electrolyte disorders (Table 3) are complex clinical problems that require frequent assessment and correction in critically ill patients. It should be recognized that both IV fluids and electrolytes are therapies capable of providing benefit when utilized appropriately, but also able to cause harm when used inappropriately.

Suggested Readings

Gums M., Rathmann M., Wright C.S. An integrated view of ... examination ... Am J Med ... 2013;...

Jacob ..., Chaput D., Rehm M. ... fiscal update: pelvic, rectal and meningeal ... Cancer. 2013;...

Myburgh J.A., Mythen M.G. ... Anesthesiology. 2013;...

... integration of acid-base and electrolyte disorders. N Engl J Med. 2013;...

Sterns R.... Treatment of plasma sodium ... causes, consequences, and correction. Am J Med. 2015;...

Optimizing Perioperative Care of the Older Adult

Thomas N. ... MD, MS, FACC ... and ... A. ... MD, FACS, ... Michael A. ... MD, FACS

The demographic inevitability of the aging population requires surgeons to acquire basic understanding of geriatric specialty care issues related to the perioperative needs of older adults. Currently, nearly 40% of all inpatient operations in the United States are performed on individuals aged 65 years and older. Older adults are physiologically unique from younger adults.

Surgical quality programs rely on implementation of hospital-wide processes to improve perioperative care. To date, surgical quality programs have focused on certain surgical specialties (e.g., bariatrics, trauma) or individual complications (e.g., infections, readmissions). There are currently no surgical quality programs directly targeting the frail elderly—the population that most commonly undergoes operations and is the most vulnerable to adverse outcomes.

The purpose of this chapter is to provide an overview of the hospital-wide processes required to provide high quality surgical care across the entire perioperative period to frail older adults. The framework of the described care plan for the oldest old is based on the current National Surgical Quality Improvement Program (NSQIP) Coalition for Quality in Geriatric Surgery initiative. Four major clinical domains describe the areas of concentration for optimal perioperative care of the oldest old: function, cognition, goals of care, and nutrition/hydration. Fig. 1 provides an overview of geriatric specialty across the surgical phases of care.

PREOPERATIVE CARE OF THE OLDER ADULT

Risk Screening and Modification

Surgical risk for older adults requires geriatric specialty assessment. For nongeriatric adults, uncomplicated single organ disease (e.g., coronary artery disease) and multimorbidity are used to define risk. Older adults may have a unique surgical risk termed frailty. By definition, a frail older adult is disproportionately at higher risk for adverse healthcare outcomes including disability, major morbidity, and death. Characteristics necessary to quantify the frail vulnerable older adult include cognition, function, mobility, nutrition, and social vulnerability (Fig. 2). Identification of positive characteristics of the frail older adult should trigger geriatric specialty assessment and risk modification prior to the operation. The following characteristics of the frail older adult should be screened for and addressed if present.

Cognition

Cognition describes a patient's thinking, or mental function. Dementia is a chronic decline in mental function (particularly memory) that can lead to inability to live independently. Because older adults have reduced brain function, their brain is more vulnerable to acute brain dysfunction, or delirium, which is the most common postoperative complication in older adults. Delirium is associated with adverse surgical outcomes of death, major morbidity, prolonged hospitalization and institutionalization. Cognition screening tools include the Mini-Cog Test (combination of a three-item recall and clock draw) and the Montreal Cognitive Assessment (MoCA) tool. Positive screens should trigger postoperative delirium prevention bundle ordering (see section on inpatient delirium and Table 1) and counseling on the increased risk of poor postoperative outcomes.

Function

Function describes an older adult's ability to live independently and is typically measured by the ability to perform six activities of daily living (ADLs): bathing, grooming, dressing, feeding, toileting, and transferring. Major operations and hospital stays promote functional disability, an adverse outcome, which studies have shown, that older adults specifically want to avoid. Screening for functional impairment include assessing ADLs and instrumental activities of daily living (IADLs). Older adults screened negative are independent in all activities. Older adults who screen positive are classified as partially dependent or fully dependent. Adults who screen positive should be considered for preoperative exercise therapy, need postoperative physical therapy consultation and require counseling of increased risk of adverse events (notably risk for institutionalization) following an operation.

Mobility

Mobility describes an individual's ability to ambulate. Impaired mobility is reflected by an older adult's need to use walking aids or a slowed walking speed. Major operations result in impaired postoperative mobility. Screening tools to detect impaired mobility include the timed up-and-go (a timed test of rising from a chair, walking 10 feet, turning around and returning to a seated position in the chair), gait speed test (measuring time to walk a ¼ in distance), or use of a mobility aid. Older adults screening positive should be considered for preoperative physical therapy for mobility training and should be counseled of their increased risk of adverse postoperative outcomes, including worsening mobility and increased fall risk.

Malnutrition

Physiologic anorexia occurs in frail older adults resulting in weight loss, decreased lean muscle mass, and poor nutrition. The frailty literature terms this phenomenon as "shrinking." The Mini Nutritional Assessment tool screens for malnutrition. Older adults who screen positive for malnutrition should be considered for preoperative nutritional supplementation, require postoperative nutrition support and should be counseled of the increased risk of poor postoperative outcomes.

Polypharmacy

Taking multiple medications simultaneously makes older adults at high risk because polypharmacy is a surrogate for multimorbidity, increases risk of drug-drug interactions and is associated with adverse drug events. There is not universally agreed upon number of medications that defines polypharmacy. Older adults taking 10 or more medications should undergo medication review prior to their

Suggested Readings

Gums M, Rabinowitz L, Wright CC. An integrated view of potassium homeostasis. *N Engl J Med*. 2015;373:60–72.

Jacob M, Chappell D, Rehm M. Clinical update: perioperative fluid management. *Lancet*. 2007;369:1984–1986.

Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243–1251.

Seifter JL. Integration of acid-base and electrolyte disorders. *N Engl J Med*. 2014;371:1821–1831.

Sterns RH. Disorders of plasma sodium—causes, consequences, and correction. *N Engl J Med*. 2015;372:55–65.

Optimizing Perioperative Care of the Older Adult

Thomas N. Robinson, MD, MS, FACS, Ronnie A. Rosenthal, MD, FACS, and Michael A. Zenilman, MD, FACS

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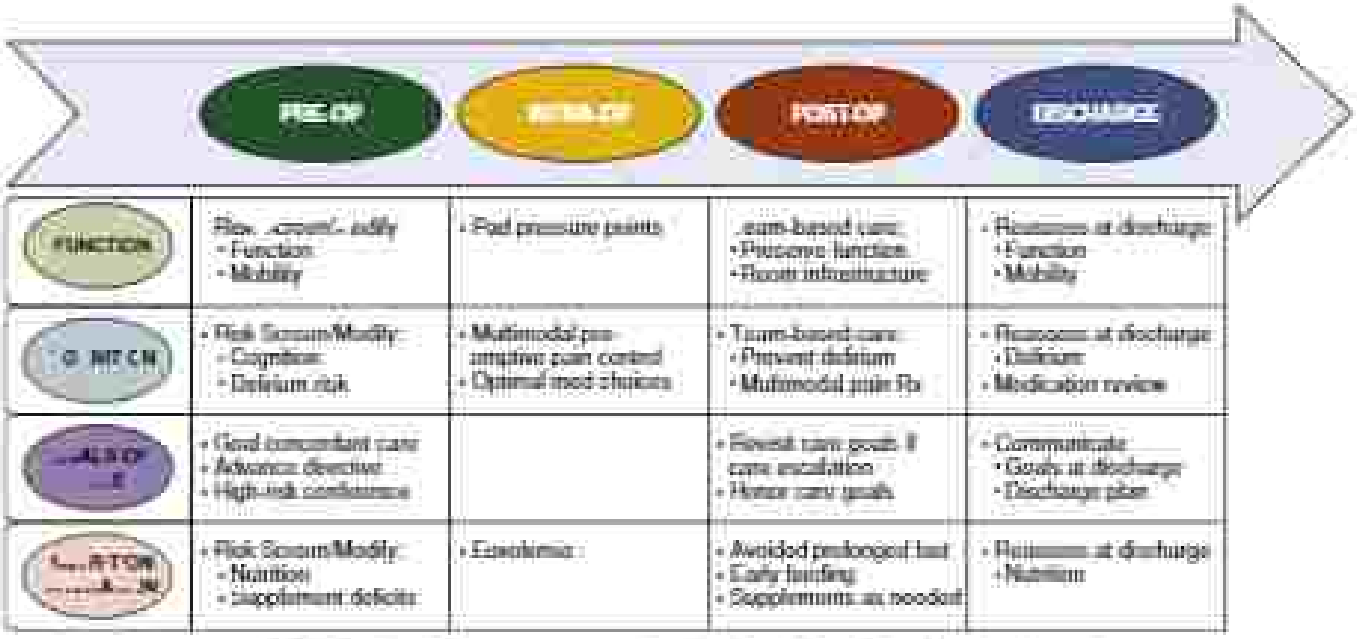

FIG. 1 Overview of the process necessary for optimal surgical care of the vulnerable older adult.

FIG. 2 Clinical characteristics used to identify the frail older adult.

operation. Unnecessary drugs may should be eliminated prior to the operation, including over the counter products.

Goal Concordant Surgical Decision Making

An older adult's values and preferences should guide surgical decision making with the goal of aligning the patient's surgical plan with the anticipated outcomes most valued by the patient. Historically, quantity of life has dictated surgical care plans. This strategy needs to be reconsidered in older adults with limited lifespan who often value quality of life over quantity of life for their remaining lifespan. Surgical decision making should incorporate both forecasted health span (the period of life during which one is healthy and active) and lifespan (life expectancy or chronologic survival) (see Fig. 1). Surgical decision making needs to allow the older adult to discuss overall health goals (ones relating to issues beyond the current condition related to the proposed operation), treatment goals related to the current condition, and the impact of both surgical and nonsurgical treatments on anticipated long-term outcomes. The four outcomes that need to be addressed in addition to those specific to the disease related to the proposed operation include long-term symptoms, function, living location, and survival. The surgeon is responsible for aligning the treatment plan with the patient's overall healthcare goals. Because of the complexity of the information provided to the elderly patient and the substantial potential impact on his or her life, the decision to undergo a major surgical intervention should be revisited sometime between the preoperative consultation and the operation to ensure that the surgical plan is aligned with the patient's goals.

Multidisciplinary High-Risk Conference for Older Adults

A multidisciplinary conference designed to review surgical decision making in at-risk older adults provides valuable insight from a variety of specialists into surgical decisions. Analogous to a tumor board conference, which provides a multidisciplinary approach to cancer management, a high-risk older adult conference provides a multidisciplinary approach to decisions and management of surgical care for vulnerable older adults. Regular attendees at this meeting include geriatrics, surgical leadership, primary surgical team, palliative care, geriatrics, anesthesia, hospital medicine, critical care, and social work. Geriatric high risk committee membership may vary at individual institutions. The overarching goal of this conference is to move the surgical decision making in the most vulnerable older adult from a single provider's recommendation to a more systematic, multidisciplinary approach. As a minimum, the geriatric surgery high risk conference should review all patients 75 years and older undergoing inpatient operations. Older adults who have high mortality risk (e.g., >5% 30-day mortality) based on surgical risk calculator results (https://riskcalculator.facs.org/RiskCalculator/) also have particularly high benefit from being presented at this multidisciplinary conference.

Advance Care Planning

Preoperative planning for adverse perioperative events is essential. The elderly patient's treatment goals should be elicited and an approach to life-threatening problems should be outlined that are consistent with the patient's values and preferences. At a minimum, an older adult's healthcare representative, surrogate, or proxy must be clearly identified with both the name and contact information documented in the medical record prior to all elective operations. If advance directives exist, the existing advance directives must be revisited preoperatively in the context of the proposed operation. For an older adult with planned postoperative admission to the intensive care unit, the extent of the

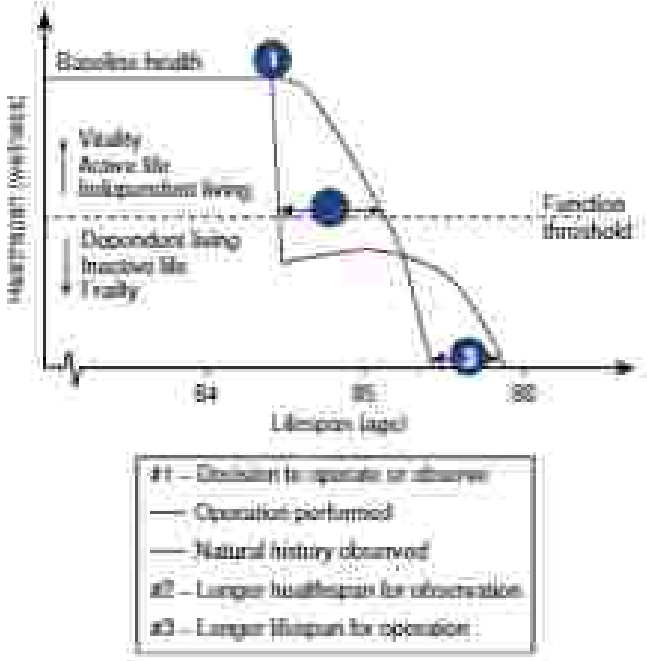

FIG. 3 Conceptualizing health gain versus lifespan in the context of [illegible]

advance directive discussions needs to expand to specifically delineate the patient's preferences for life-sustaining measures including cardiopulmonary resuscitation, mechanical ventilation, feeding tubes, renal replacement therapy, and blood transfusion. It is not mandated that the patient sign and his or her do not resuscitate (DNR) order prior to the operating room or for the intraoperative phase of care. However, the proposition of an elective operation should trigger reconsideration of an existing DNR order.

The advance directive orders established prior to the operation need to be communicated and followed in the postoperative setting. Processes to ensure advance directives are followed postoperatively (e.g., unique wrist bands, prominent documentation in the electronic medical record) should be implemented. Postoperatively, established goals of care must be revisited upon events leading to an escalation of care and for unintended intensive care unit stays of longer than 3 days.

INTRAOPERATIVE CARE OF THE OLDER ADULT

The recommended intraoperative care of the older adult does not significantly differ from the care of other adults. Specific management strategies important for older adults include:

1. To take extra care in padding during patient positioning to prevent skin breakdown, which older adults are particularly susceptible.
2. To use preemptive nonopioid multimodal preventive pain management strategies (e.g., regional blocks, acetaminophen 1000 mg, gabapentin 300 mg) prior to the incision to decrease anesthesia medications during the operation and postoperative pain.
3. To avoid prescribing high-risk medications in the immediate pre- and intraoperative phases of care (e.g., routine use of high-risk antiemetic medications). For a list of commonly prescribed high-risk medications in the perioperative setting see Table 1.

TABLE 1 Common Perioperative Medications With High Risk of Adverse Events in Older Adults

Medications	Comments
PAIN MEDICATIONS	
Meperidine (Demerol)	Related to postoperative delirium
Indomethacin (Indocin)	NSAID with most CNS side effects
Pentazocine (Talwin)	Associated with hallucinations and confusion
Ketorolac (Toradol)	Increased risk of GI bleeding and peptic ulcer disease
GI STRESS ULCER PROPHYLAXIS	
Cimetidine (Tagamet)	Anticholinergic properties predispose delirium
Famotidine (Pepcid)	Anticholinergic properties predispose delirium
Ranitidine (Zantac)	Anticholinergic properties predispose delirium
NAUSEA MEDICATIONS	
Scopolamine	Anticholinergic properties predispose delirium
Promethazine (Phenergan)	Anticholinergic properties predispose delirium
INSOMNIA MEDICATIONS	
Benzodiazepines	CNS toxicity, increase fall risk and fracture
Zolpidem (Ambien)	Increase risk of delirium and falls
OTHER MEDICATIONS	
Diphenhydramine (Benadryl)	Anticholinergic properties predispose delirium
Cyclobenzaprine (Flexeril)	Drowsiness, confusion
Metoclopramide (Reglan)	Extrapyramidal effects

CNS, Central nervous system; NSAIDs, nonsteroidal antiinflammatory drugs; GI, gastrointestinal.

POSTOPERATIVE INPATIENT CARE OF THE OLDER ADULT

Multidisciplinary Inpatient Care Team

The foundation of high-quality postoperative inpatient care of older adults depends on daily rounding of a multidisciplinary team that focuses on geriatric specialty care issues. The surgical and medical teams charged with the hospitalized care of elderly patients disproportionately focus their efforts on the primary disease process leading to the current hospitalization. In contrast, the multidisciplinary geriatric team will focus their efforts on issues central to optimal recovery of the older adult—functional preservation, delirium prevention,

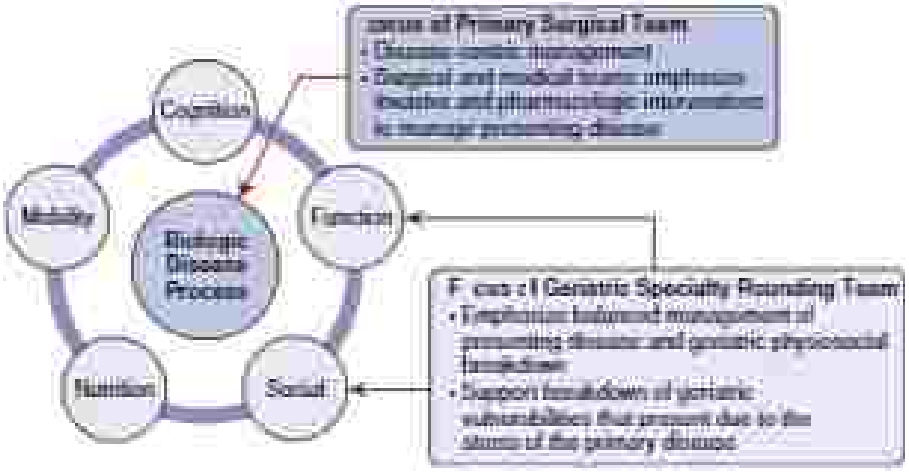

FIG. 4 Uniting the paradigm of hospitalized surgical care of the older adult. The unique vulnerability of the older old requires a paradigm shift in hospitalized care. Traditionally surgical teams focused on the primary disease process alone and disproportionately relied on medical and pharmacologic interventions to manage the presenting disease. In contrast, the frail older adult requires a balanced approach between treating the primary disease and proactively addressing the vulnerability unique to the older adult that lead to postoperative functional, mental and social decline.

nutritional support and discharge transition planning (See Fig. 4). Emphasis on both primary disease management and support of geriatric specialty issues is necessary for optimizing recovery. The composition of the multidisciplinary team may include surgery, geriatrics, hospital medicine, social work, physical therapy, occupational therapy, nutrition, pharmacy, and discharge planner/utilization management.

While rounding may be simultaneous or separate, the care provided by the multidisciplinary team requires direction and coordination. The leadership responsibility of coordinating the care of all these teams will typically be held by a nurse or advance care provider (e.g., physician assistant or nurse practitioner), but could also be managed by a physician team member (e.g., surgeon, hospitalist, geriatrician) depending on the institution. Daily rounds by the team focused on the geriatric vulnerabilities unique to the elderly compliment the primary surgical team, which focuses on surgery specific recovery pathways and avoidance of major morbidity. Existing hospital care models that exemplify this geriatric centric care model include the Hospital Elder Life Program (HELP) and the Acute Care Elderly (ACE) program.

Delirium Prevention

Delirium represents acute brain dysfunction and is the most common postoperative complication in hospitalized older adults. Delirium is closely associated with the adverse outcomes of serious morbidity, prolonged length of stay, need for institutionalization, death, and increased healthcare costs (Box 1). Delirium is an ideal candidate for quality improvement programs because delirium is common and deleterious. One-third of cases of delirium are preventable by simple supportive protocols.

Interventions to prevent delirium include bedside supportive protocols including re-orientation, mobilization, sleep hygiene, and sensory deficit support (Table 2). Delirium prevention "bundles" are constructed in the electronic medical record and should be ordered on all high-risk patients. A common threshold to order the delirium prevention order set bundle is on all patients 75 years and older undergoing an inpatient operation. Targeting this population versus a larger group to start the delirium prevention quality program allows the nursing staff to focus their efforts on a limited, truly high-risk population of inpatients. Prior to launching the delirium prevention order sets, nursing education programs aimed to teach the bedside interventions included in the bundled delirium prevention order set must occur.

In addition to bedside supportive measures to prevent delirium, there are iatrogenic promoters of hospitalized delirium that need to be addressed to allow a more comprehensive delirium prevention program. The clinical team can also target uncontrolled pain, postoperative infections, and use of deliriogenic medications (see next section and Table 1 for high-risk medications) as strategies to reduce delirium rates.

BOX 1 Important But Less Common Drivers of Delirium

Hypotension
Acute blood loss anemia
Myocardial infarction
Pyrexia
Abnormal sodium
Hypoxia
Hypercarbia
Pulmonary embolus
Dehydration
Metabolic acidosis
Urinary retention
Constipation
Stroke
Malnutrition

Postoperative pain control should include multimodal opioid-sparing pain regimens. These pain regimens should include ice packs, massage, standing acetaminophen (1000 mg tid), liberal use of regional blocks and finally opioids. This strategy utilizing opioids as the last line therapy is different from traditional postoperative pain management in which opioids are first line therapy. An important concept is that the delirium risk of uncontrolled pain is far greater than the delirium risk of opioids. Therefore, opioid use is superior than leaving an older adult with uncontrolled pain.

Function Preservation

Functional decline from baseline to discharge occurs in 40% of adults 65 years and older undergoing inpatient operations and in nearly two-thirds of hospitalized 90 year olds. To avoid functional decline, proactive processes to avoid deconditioning must be employed. Avoiding deconditioning requires more than simply mobilizing the patient from the bed to a chair or performing passive range of motion therapy. Early in-hospital physical rehabilitation interventions typically focus on strength, mobility, and balance training. The intensity and duration of physical rehabilitation should increase with ongoing therapy. For example, strength exercises progress in terms of numbers of repetitions and sets, and walking (mobility) exercises can increase in both distance and time. These interventions have been shown to improve physical function

TABLE 2 Modifiable Causes of Postoperative Delirium

Delirium Promoter	Management Strategy
Disorientation	Orient to person, place, time three times daily minimum* Encourage family presence at bedside*
Disrupted sleep	Sleep hygiene: awake during daytime, uninterrupted sleep overnight* Windows allowing natural light in room*
Immobility	Early ambulation: walk in hallway minimum three times daily* Avoid tethers, minimize catheters, tubes, lines that discourage walking*
Sensory deficits	Vision: wear glasses* Hearing: hearing aids/pocket talker*
Uncontrolled pain	Nonpharmacologic pain adjuncts (e.g., ice, massage)† Opioid sparing multimodal pharmacologic pain management†
Medications	Avoid anticholinergic medications and Beers list medications Avoid starting multiple new medications simultaneously
Infection	Avoid iatrogenic infections Diagnose source and actively treat infections

*Commonly used in bedside delirium prevention bundle order sets.

at discharge, decrease need for nursing home disposition, and reduce length of stay.

Appropriate Medication Usage

Medications are a major source of adverse events in hospitalized older adults. Potentially inappropriate medications for older adults should not be used as first line pharmacologic treatment. Vulnerable older adults are more sensitive to medication side effects, have less robust metabolism, and have altered pharmacokinetics. Multiple medications, a phenomenon termed polypharmacy, is both common and deleterious due to drug–drug interactions. For example, starting five new medications puts an older adult at a threefold delirium risk. The Beers list is a medication list considered the gold standard reference for pointing out which medications to avoid in older adults. Table 3 reviews a subset of medications from the Beers List that are relevant to the perioperative setting.

Nutrition and Hydration

Close attention to the nutritional status of vulnerable older adults is important to optimize surgical outcomes. In the postoperative setting, an initial bedside screening for swallowing dysfunction is important to prevent aspiration. Resumption of oral diet should occur as soon as clinically indicated. Inclusion of a nutritional supplementation beverage with meals is a common strategy to increase postoperative caloric intake. Common reasons that limit an older adult's ability to consume food include missing teeth, lost dentures, and lack of appetite due to the normal physiologic anorexia of aging. Ongoing evaluation of adequate food intake should occur throughout the hospital stay.

POSTDISCHARGE CARE OF THE OLDER ADULT

Older adults' physiosocial vulnerability makes them especially vulnerable to hospital readmission and other adverse postdischarge outcomes. Core issues include a poor understanding of what actually happened during the hospital stay, noncompliance with the recommended discharge medical regimen, and a lack of communication with outpatient primary care providers.

Optimizing safe discharge practices requires:

- Clear discharge instructions: Clear review of discharge medical instructions with particular attention paid to newly prescribed medications.
- Written instructions: Written documents reviewing hospital course and potential post discharge adverse events including the occurrence of potential geriatric syndromes including delirium and falls.
- Communication: Written communication sent to the older adult's outpatient primary care provider(s) including operation performed and postoperative course, as well as laboratory and diagnostic test results.
- Follow up: Prearranged follow up with both surgical team, primary care provider, and any new consultants relevant to inpatient stay.

PROGRAM MANAGEMENT TO OPTIMIZE GERIATRIC SURGICAL CARE PROCESSES

Infrastructure to support the optimal surgical care of the older adult is necessary to optimize a continuous quality improvement program aimed to improve the care of vulnerable older adults. The program support necessary is similar to that of trauma or cancer programs.

Personnel

Personnel include a geriatric surgery director (a practicing surgeon with additional expertise in geriatric care) and geriatric surgery manager (a registered nurse with managerial experience and with additional geriatric training).

Clinical Data Collection

Measurement of geriatric specialty care variables (e.g., delirium, function) in addition to traditional 30 day mortality and morbidity variables is necessary to allow assessment and subsequent improvement of outcomes important to older adults perioperatively.

Committee Oversight

A Geriatric Surgery Quality Committee must oversee system wide processes, implement care plans, and actively work to improve surgical quality as dictated by outcomes measurements.

education

All healthcare professionals involved in perioperative care need basic education on the aspect of aligning healthcare goals, cognitive prevention, functional mobility, and nutrition/hydration relevant to older adults.

SUMMARY

Surgical care of older adults requires system wide processes to support the physiosocial vulnerabilities unique to the older adult. This chapter has outlined care plans in all phases of surgical care required to optimize the surgical care of the high risk, frail, older old patient. Knowledge of specialty care topics relevant to geriatric patients is the responsibility of all surgeons.

Suggested Readings

American College of Surgeons National Surgical Quality Improvement and American Geriatrics Society Optimal preoperative assessment of the older surgical patient: a best practice guideline. Soc. . W . . ll. R. Rosenthal, R. . Mirlow . . V. Ko, N. E. ' mands. *J A . C. Surg* 2012 215(4): 453–66.

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Perioperative Optimization

John R. Montgomery, MD, and Mich . el J. Englesbe, M.D

The perioperative period from initial office visit to after surgical recovery represents a significant period in a patient's life. Patients are uniquely engaged in their health and attentive to improving their wellbeing. Perioperative optimization can not only improve surgical outcomes and decrease costs but also improve health outcomes long after the operative procedure. This chapter focuses on eight high-yield domains of perioperative care and provides evidence-based recommendations for optimization.

PERIOPERATIVE CARE MANAGEMENT DOMAINS

Smoking Cessation

According the Centers for Disease Control and Prevention, smoking is the leading cause of preventable death in the United States, with over 480,000 deaths annually. On average, smokers die 10 years earlier than nonsmokers. In the perioperative period, smoking is linked to poor wound healing, surgical site infections, increased inflammatory response, pneumonia, respiratory failure, cardiovascular events, and mortality. In the long term, it increases the risk of stroke, myocardial infarction, emphysema, stomach ulcers, periodontal disease, blindness, infertility/impotence, multiple cancers, and death. The scheduling of elective operations presents an optimal time for smoking cessation counseling and intervention.

Potential barriers to cessation include patient belief that quitting is not important, lack of confidence that attempted smoking cessation will be successful, high perceived cost of intervention methods, lack of social support, and lack of engagement or urging by the surgical team. Evidence-based measures to increase chance of smoking cessation include direct physician advice, prescription of approved medication(s), structured counseling sessions, and plans for follow-up. Approved medications include varenicline, bupropion, and nicotine replacement therapy. There is no evidence for superiority of any of these medications over the others in the perioperative period. Contrary to previous belief, inclusion of nicotine replacement therapy in perioperative care is not linked to inferior surgical outcomes. Compliance with smoking cessation can be assessed with measurement of urine cotinine levels, which are not influenced by nicotine replacement therapy.

Of note, smokers have a better chance of successful smoking cessation in the perioperative period than at other time points. Furthermore, longer periods of nonsmoking preoperatively are associated with increased chances of remaining nonsmoking postoperatively. Therefore, early and direct patient counseling with inclusion of approved medication(s) is crucial to the perioperative and long-term health of the surgical patient.

Recommendations

- Surgeon should urge all patients to quit smoking prior to surgery
- Smoking cessation intervention for all smokers, ideally 2–6 weeks before surgery
- Urine cotinine testing if clinically indicated
- Further postoperative follow-up with primary care provider to decrease chance of recidivism

Frailty

Frailty is an emerging concept used to describe generalized poor functional status and reduced physiologic reserve that results in increased vulnerability to adverse outcomes. Although more prominent in elderly populations, it can also be found in younger patients who suffer from chronic illness, persistent inflammatory states, poor nutrition, or sedentary lifestyle. In the general population, it is independently associated with accelerated progressive functional decline, loss of independence, need for hospitalization, and all-cause mortality. These risks are compounded in the perioperative period due to the stresses of surgery, akin to a debilitated person attempting to run a marathon with no previous physical training. Frail patients are particularly prone to in-hospital mortality, 1-year mortality, pneumonia, infection/sepsis, longer hospital length of stay, higher costs of care, hospital readmission, and need for discharge to rehabilitation center.

Frailty should be evaluated before considering major elective surgery. Common clinical assessments include questionnaires such as the Modified Frailty Index (MFI) and Clinical Frailty Scale (CFS), although numerous additional indices exist. Often, these questionnaires are augmented with objective data such as 6-minute walking distance (6MWD) or hand-grip strength test. Improvement in these objective measurements over time has been shown to improve outcomes.

If a patient screens positive for frailty, enrollment in a "prehabilitation" program to improve functional status and endurance is recommended. These programs take many forms but often include elements of aerobic/anaerobic exercise and nutritional optimization. Prehabilitation has been shown to reduce postoperative complications, decrease hospital length of stay, lower healthcare costs, and increase health-associated quality of life. Even if patients screen negative for frailty, it is still important to encourage preoperative physical activity, as this has been associated with improved postoperative outcomes and patient empowerment. After surgery, these activities should be continued and be incorporated into the lifestyle changes in partnership with the primary provider.

Recommendations

- Every patient should train for surgery by intentionally increasing his or her activity levels.

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Recommendations

- Every patient should train for surgery by intentionally increasing his or her activity levels

- Clinical assessment of poor physical activity levels and frailty for all major elective surgery patients
- Formal prehabilitation programs should be used for patients who screen positive for frailty

Nutritional Status

Optimization of nutritional status is an integral component of perioperative care. Malnutrition is a significant predictor of adverse postoperative outcomes including infection, renal/cardiac complications, gastrointestinal fistula formation, poor wound healing, increased hospital length of stay, higher healthcare costs, and death. Interestingly, obesity is not protective from malnutrition, and it is possible for overweight patients to have micro- and macronutrient deficiencies. Therefore, it is important for all patients to be screened for malnutrition before inpatient and some outpatient elective operations.

Multiple validated risk questionnaires exist for malnutrition screening, including the Nutritional Risk Score 2002 and Malnutrition Screening Tool. Historically, certain laboratory values have been used to support a diagnosis of malnutrition (i.e., albumin, prealbumin, or transferrin); however, reliance on these values in isolation is inadequate and can be misleading. While screening for malnutrition, the surgeon must consider the overall clinical presentation with recent weight changes and healing progress. Presence of chronic inflammatory conditions such as diabetes mellitus, rheumatoid arthritis, and Crohn's disease should heighten concern for malnutrition.

Positive screening necessitates a full nutritional assessment, usually via referral to a registered dietitian. A dietitian can also assist with individualized supplementation of micronutrients and/or macronutrients (e.g., selenium, glutamine) that have been shown to decrease postoperative infectious complications. The surgeon must be aware of the differences between a dietitian and nutritionist in the community setting. A dietitian is legally considered an expert in nutrition after having received a bachelor's degree or higher, completed an internship, passed standardized examinations, and maintained ongoing credentials in the field. A nutritionist is not required to have any formal education or licensing. Once diagnosed, malnutrition should be aggressively managed with early intervention and frequent monitoring to minimize risks of postoperative complications.

Recommendations

- Balanced diet for all surgical patients
- Preoperative screening for malnutrition to allow for referral to dietitian and immediate intervention if screening positive

Cardiac Disease

Heart disease is the leading cause of death for both men and women in the United States and is a significant risk factor for morbidity and mortality in the perioperative setting. In particular, postoperative myocardial infarction is one of the most common causes of increased mortality. Risk assessment requires interrogation of patient-specific risk factors, surgery-specific risk factors, and exercise tolerance. The Revised Cardiac Risk Index is the most commonly used and broadly validated tool for predicting major cardiac complications; a score of 3 or greater confers an 11% chance of major postoperative cardiac event. The American College of Cardiology and the American Heart Association (ACC/AHA) have published extensive clinical practice guidelines regarding the perioperative work-up and management of cardiac disease. The complete guidelines can be found in published documents from the ACC/AHA (http://my.americanheart.org/professional/StatementsGuidelines/_y.xpx).

Recommendations

- Preoperative screening and management of cardiac disease as per the most recent ACC/AHA guidelines

Alcohol Use

According to the 2015 National Survey on Drug Use and Health, 6.2% of adults ages 18 and older have alcohol use disorder and 26.9% of adults engaged in binge drinking within the last month. Furthermore, an estimated 88,000 people die from alcohol-related deaths annually, making alcohol the third leading preventable cause of death in the United States. For the surgical patient, chronic alcohol use poses significant risks in the postoperative period including withdrawal, delirium tremens, pneumonia, and increased wound infection rates. Symptoms of withdrawal can range from mild tremors, confusion, and fever to severe electrolyte abnormalities (hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia), hemodynamic instability, seizures, and death.

Screening tools for alcohol use disorder include the CAGE questionnaire and Alcohol Use Disorders Identification Test (AUDIT-C). If positive, the patient should undergo assessment and treatment by their primary care provider before elective surgical intervention. Laboratory monitoring for chronic heavy alcohol use is available and includes the serum carbohydrate-deficient transferrin and ethyl glucuronide levels. Abstinence for 8 weeks prior to surgery has been shown to decrease postoperative complications from 74% to 31%.

If surgery is needed in an urgent fashion, patients with known alcohol use disorder should be systematically monitored for evidence of withdrawal. Utilization of an institutional protocol for withdrawal monitoring and treatment should be implemented. At our institution, the Michigan Alcohol Withdrawal Severity (MAWS) Assessment Scale is both a scoring and a treatment protocol that utilizes frequent patient assessment for signs and symptoms of withdrawal, including central nervous system excitation, adrenergic hyperactivity, and delirium. Nearly all prescribed patients are initiated on thiamine and folate supplementation with the addition of benzodiazepines or haloperidol based on MAWS and clinical assessment. It is strongly encouraged to quickly transfer patients to higher level care centers if symptoms of withdrawal worsen.

Recommendations

- Preoperative screening for alcohol use disorders via questionnaires such as CAGE and AUDIT-C
- Multimodal abstinence in partnership with addiction professionals is recommended prior to elective surgery
- Monitoring and prompt treatment for withdrawal in perioperative period

Chronic Narcotic Use

Preoperative narcotic use and addiction are increasingly common phenomena in the setting of a nationwide opioid epidemic. In 2015, an estimated 2 million Americans had an opioid use disorder involving prescription pain medications and 591,000 had a substance use disorder involving heroin. The next year, narcotics killed more than 42,000 Americans, with 80% of those deaths coming from prescription narcotics. Preoperative narcotic use is linked to increased hospital length of stay, postoperative ileus, and increased readmission rates. Poor postoperative pain control is also common given the frequent association of chronic narcotic use with hyperalgesia. There is growing evidence for opioid-induced immunosuppression and increased infectious complications, especially in cancer and total joint arthroplasty patients.

In the preoperative period, a multidisciplinary approach should be pursued to minimize narcotic use. This process should include the patient's primary care provider and possible referrals to an anesthesia pain clinic, physical therapist, and mental health professional. Inclusion of nonnarcotic pain medications such as acetaminophen, nonsteroidal antiinflammatory drugs, gabapentinoids, selective serotonin reuptake inhibitors, tricyclic antidepressants, and steroid injections should be considered based on the etiology of the pain and the patient's particular comorbidities. In Michigan, the Overdose Risk

Score is commonly used to estimate the risk of unintentional opioid death. Developed from a large case series of over 5000 unintentional overdose deaths, this score incorporates 12 variables, including number of pharmacies visited per unit time, maximum morphine milligram equivalence prescription in the last year, number of opioid prescriptions in the last 2 years, and various signs of opioid and sedative use to compute a score from 000 to 999. Using 000 to 199 as a reference point, every 100 point increase is associated with an approximate double in risk of unintentional opioid death (Table 1). This score can then be used to provide recommendations on patient counseling and interventions (Table 2).

The physician who principally cares for the patient's pain must be involved in the perioperative care. Narcotic weaning is possible before planned surgical intervention, but total narcotic abstinence can be difficult to achieve. Although narcotic cessation may be beneficial, there is a paucity of evidence to show that total abstinence results in improved outcomes. Patients should not be precluded from surgery if total abstinence is not obtained. In the early perioperative period, a multidisciplinary approach with inclusion of nonnarcotic medications should be utilized to return patients to preoperative narcotic use or lower as quickly as possible. Discharge prescriptions should not exceed a 1-week supply for most operative procedures, and providers should consider addition of an opioid antagonist prescription (e.g., naloxone) and teaching for patients at increased risk of overdose.

Recommendations:

- Pain planning and involvement of pain specialists prior to surgery
- Utilize multidisciplinary approach for preoperative narcotic weaning with inclusion of nonnarcotic medications
- Incorporation of risk calculators to identify patients at risk of unintentional overdose and guide interventions appropriately

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is now recognized to affect between 25% and 30% of Americans, with up to 90% of those being undiagnosed. Mild symptoms include excessive daytime sleepiness, impaired work performance, and decreased health-related quality of life. More serious associations include systemic hypertension, pulmonary hypertension, cardiac arrhythmias, myocardial injury, stroke, depression, metabolic syndrome, and sudden death. In the perioperative period, OSA is also associated with increased incidence of cardiac arrest, cardiac shock, respiratory failure, need for reintubation, and longer hospital length of stay.

Clinical screening tools for OSA include the Berlin questionnaire, American Society of Anesthesiologists checklist, STOP-Bang questionnaire, and Sleep Apnea Clinical Score. Any patient who screens positive for OSA should have an informed discussion with the surgeon about the perioperative risks of OSA and options for preoperative referral to a sleep specialist. Previous studies have shown that preoperative initiation of continuous positive airway pressure (CPAP) therapy for severe OSA patients decreases the risk of perioperative cardiovascular complications by >50%. However, there is insufficient evidence to support postponing an operation for patients with untreated OSA or CPAP noncompliance so long as other major comorbidities and problems with ventilation or gas exchange are optimized (i.e., hypoventilation syndrome, severe pulmonary hypertension, and resting hypoxemia).

In the perioperative period, anesthesiology should be notified of the patient's OSA status so that the anesthetic plan can be optimized.

TABLE 1 Opioid Risk Score and Odds Ratio of Unintentional Death

Risk Score	Odds Ratio
000–199	1
200–299	10
300–399	32
400–499	75
500–599	44
600–699	86
700–799	141
800–899	194
900–999	329

From www.cms.hhs.gov/Medicare/Fraud-and-Abuse/Physician-Self-Referral/Publications-and-Guidance-Advisory-Opinions.html. [accessed 5/6/23].

*Opioid Risk Score from 0–0 to 999 is used as reference point.

TABLE 2 Overdose Risk Score Clinical Guidance*

Overdose Risk Score	Approximate CDC MED Equivalent	Recommended Clinical Guidance
<400	<50 MED	Consider other sources of overdose risk outside of ORS data.
400–599	50–89 MED	Consider naloxone prescription.
≥600	≥90 MED	Consider naloxone prescription. Review use patterns for unsafe conditions. If multiple providers involved in unsafe prescribing, discuss concern with patient and consider contacting other providers directly. If multiple pharmacies involved in unsafe prescribing, discuss concern with patient and consider pharmacy lock-in program. If overlapping medications of same or different type, discuss concern with patient and consider taper to lower dose and/or discontinuation of potentiating medications. If patient has evidence of a substance use disorder, consider inpatient admission or referral for outpatient evaluation and treatment.

From www.cms.hhs.gov/Medicare/Fraud-and-Abuse/Physician-Self-Referral/Publications-and-Guidance-Advisory-Opinions.html. [accessed 5/6/23]. Opioid Risk Score.

*The recommended clinical guidance points have not been independently validated and should not supplant individualized clinical decision making.

CDC, Centers for Disease Control and Prevention; MED, morphine equivalent dose; ORS, overdose risk score.

Occasionally, choice of local block or spinal anesthesia can be selected if safe and feasible. Patients who use CPAP should also be encouraged to bring their own machine into the hospital for use. Finally, choice of multimodal and narcotic minimizing analgesia to mitigate risks of opioid-induced respiratory depression should be considered.

Recommendations

- Clinical screening for OSA in all patients, as majority of cases are undiagnosed.
- If screening positive, informed discussion of risks and benefits of proceeding with surgery versus sleep specialist referral.
- Inform anesthesia colleagues of OSA status before operation so anesthetic plan can be optimized.

Diabetes Mellitus

Type 2 diabetes mellitus is an increasingly common condition affecting 30.3 million or 9.4% of the US population according to the American Diabetes Association. Of these, 7.2 million are undiagnosed. For surgical patients, hemoglobin A_{1c} (HbA_{1c}) greater than 8% is associated with postoperative infectious complications such as pneumonia, surgical site/wound infection, and sepsis. Additionally, diabetics usually have longer hospital lengths of hospital stay. Diabetics are also more likely to have other comorbidities such as cardiovascular disease, obesity, and renal disease.

For patients with known diabetes, HbA_{1c} should be drawn within 3 months of the planned operation. If this value is greater than 8%, the patient should be referred back to their managing clinician for medication optimization. If hyperglycemia is discovered on routine preoperative labs, showing a HbA_{1c} and referred to primary care physician or endocrinologist for management is warranted. There is no evidence for routine blood glucose level screening independent of the procedure specific preoperative labs for average risk patients.

In the immediate postoperative period, glucose levels should be closely monitored for diabetic patients. Goal blood glucose levels are less than 140 mg/dL for stable patients and less than 180 mg/dL for critically ill patients. Given the stresses of surgery and periods of fasting, blood glucose levels can vary widely. Therefore, most clinicians will convert oral medications to a sliding scale insulin for inpatient and reduce long acting insulin doses. The exact changes are dependent on the anticipated postoperative course and patient-specific factors. Before discharge, patients should be converted back to their baseline diabetic medications unless otherwise contraindicated. Management of patients with type 1 diabetes is beyond the scope of this chapter. Expert consultation is recommended if the surgical team is not familiar with management of this condition.

Recommendations

- Referral of surgical patient to primary care physician or endocrinologist for glycemic optimization if preoperative HbA_{1c} greater than 8%.
- Perioperative goal blood glucose level less than 180 mg/dL in stable patients and less than 180 mg/dL in critically ill patients.

CONCLUSION

The perioperative period provides an unparalleled opportunity to impact the overall health of the surgical patient. Interventions at this time should be geared to not only optimize the chance of short term operative success but also facilitate durable changes to the patient's life. Surgeons must recognize their pivotal role in this process and reach out to other providers for multidisciplinary action on comorbid conditions. The aforementioned domains of care provide eight high-yield areas for perioperative optimization; however, this list is not all inclusive and care must be personalized to each individual patient. Unfortunately, most care pathways and policies do not support perioperative medicine as a key component of durable population health interventions. Comprehensive efforts to optimize patients should be supported by providers, policymakers, and payers.

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Chung F, Memtsoudis SG, Ramachandran SK, et al. Society of Anesthesia and Sleep Medicine guidelines on preoperative screening and assessment of adult patients with obstructive sleep apnea. Anesth Analg 2016;123(3):452–473.

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IS NASOGASTRIC TUBE NECESSARY AFTER ALIMENTARY TRACT SURGERY

Travis J. Webb, MD, MHPE

The nasogastric tube (NGT) historically has been used in the postoperative period for patients undergoing surgery on the alimentary tract. The long standing belief held by many surgeons has been that nasogastric decompression allows the bowel to rest, prevents air and fluid accumulation, decreases postoperative nausea and vomiting, prevents abdominal distention, and protects the patient from aspiration, pneumonia, anastomotic leak, and fascial dehiscence. Pervasive use of NGTs coincided with significant advances in the administration of anesthesia, the development of germ theory and aseptic technique, and improvements in hemostasis that revolutionized surgery at the turn of the twentieth century and allowed surgeons to successfully operate in the abdomen. However, evidence has accumulated over the past 40 years repeatedly demonstrating that prophylactic NGT use after alimentary tract surgery is not necessary and may contribute to increased morbidity and hospital length of stay (LOS).

HISTORICAL PERSPECTIVE

Originally described by John Hunter in the eighteenth century as oil skin wrapped around whalebone, the NGT initially was used to feed liquid nutrients to the sick. The first description of a flexible

Occasionally, choice of local block or spinal anesthesia can be selected if safe and feasible. Patients who use CPAP should also be encouraged to bring their own machine into the hospital for use. Finally, choice of multimodal and narcotic minimizing analgesia to mitigate risks of opioid-induced respiratory depression should be considered.

Recommendations

- Clinical screening for OSA in all patients, as majority of cases are undiagnosed
- If screening positive, informed discussion of risks and benefits of proceeding with surgery versus sleep specialist referral
- Inform anesthesia colleagues of OSA status before operation so anesthetic plan can be optimized

Diabetes Mellitus

Type 2 diabetes mellitus is an increasingly common condition affecting 30.3 million or 9.4% of the US population according to the American Diabetes Association. Of these, 7.2 million are undiagnosed. For surgical patients, hemoglobin A_{1C} (HbA_{1C}) greater than 8% is associated with postoperative infectious complications such as pneumonia, surgical site/wound infection, and sepsis. Additionally, diabetics usually have longer hospital lengths of hospital stay. Diabetics are also more likely to have other comorbidities such as cardiovascular disease, obesity, and renal disease.

For patients with known diabetes, HbA_{1C} should be drawn within 3 months of the planned operation. If this value is greater than 8%, the patient should be referred back to their managing clinician for medication optimization. If hyperglycemia is discovered on routine preoperative labs, drawing a HbA_{1C} and referral to primary care physician or endocrinologist for management is warranted. There is no evidence for routine blood glucose level screening independent of the procedure-specific preoperative labs for average-risk patients.

In the immediate postoperative period, glucose levels should be closely monitored for diabetic patients. Goal blood glucose levels are less than 140 mg/dL for stable patients and less than 180 mg/dL for critically ill patients. Given the stresses of surgery and periods of fasting, blood glucose levels can vary widely. Therefore, most clinicians will convert oral medications to a sliding scale insulin formulation and reduce long-acting insulin doses. The exact changes are dependent on the anticipated postoperative course and patient-specific factors. Before discharge, patients should be converted back to their baseline diabetic medications unless otherwise contraindicated. Management of patients with type 1 diabetes is beyond the scope of this chapter. Expert consultation is recommended if the surgical team is not familiar with management of this condition.

Recommendations

- Referral of surgical patient to primary care physician or endocrinologist for glycemic optimization if preoperative HbA_{1C} greater than 8%
- Perioperative goal blood glucose level less than 140 mg/dL in stable patients and less than 180 mg/dL in critically ill patients

CONCLUSION

The perioperative period provides an unparalleled opportunity to impact the overall health of the surgical patient. Interventions at this time should be geared to not only optimize the chance of short-term operative success but also facilitate durable changes in the patient's life. Surgeons must recognize their pivotal role in this process and reach out to other providers for multidisciplinary action on comorbid conditions. The aforementioned domains of care provide eight high-yield areas for perioperative optimization; however, this list is not all-inclusive and care must be personalized to each individual patient. Unfortunately, most care pathways and policies do not support perioperative medicine as a key component of durable population health interventions. Comprehensive efforts to optimize patients should be supported by providers, policymakers, and payers.

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HISTORICAL PERSPECTIVE

Originally described by John Hunter in the eighteenth century as eel skin wrapped around whalebone, the NGT initially was used to feed liquid nutrients to the sick. The first description of a flexible

tube (Levin tube) used to decompress the gastrointestinal (GI) tract after surgery was in 1921 by American gastroenterologist Dr. Abraham Louis Levin. In 1926 Meltzer hypothesized that postoperative abdominal distension resulted from swallowed air, which could be prevented by an indwelling NGT. Despite the lack of scientific evidence to support the benefit of routine prophylactic NGT use after GI tract and abdominal surgery, it remained common practice into the twenty first century. Cuthbert and colleagues were the first to challenge prophylactic NGT use in 1958 when they published results showing that in their cohort of 600 patients with postoperative ileus, the half managed without an NGT had lower morbidity and mortality as well as fewer respiratory tract complications. Their data were nonrandomized but started the conversation that perhaps NGTs were not mandatory postoperatively. The first prospective randomized trial comparing patients with ulcers, anastomoses was published in 1084, and although it showed no difference in complication rates between patients with and without NGTs, it was limited by small sample size and too much heterogeneity.

Cheatham and colleagues published the first meta analysis on the topic in 1995. Their study included 26 clinical trials (3968 patients) that compared the use of selective versus routine NGT decompression after elective laparotomy. Routine use was defined as an NGT placed preoperatively or intraoperatively that remained in place until an unspecified point in the patient's postoperative course (usually return of bowel function, flatus, or decreased output). Selective use was defined as either no NGT used or an NGT placed intraoperatively but removed in the operating room or in the recovery room and replaced only if the patient developed the need for decompression clinically in the postoperative course. The authors demonstrated a significantly lower rate of overall complications as well as a decreased incidence of postoperative pneumonia, aspiration, and fever. There was no significant difference between groups in the incidence of anastomotic leak, wound infection, wound dehiscence, or LOS. The authors reported that 30.5 patients could be spared nasogastric decompression for every 1 patient who required NGT reinsertion postoperatively. The main limitation of their meta analysis was that it included a large number of nonrandomized studies.

In the 20 years since that first meta analysis, numerous randomized controlled trials and subsequent meta analyses have repeatedly shown that prophylactic NGT decompression after surgery on the abdomen does not afford the benefits ascribed to it by surgical dogma. In fact, the majority of studies indicate that the liberal use of an NGT prolongs hospital postoperative LOS and actually increases the risk of certain complications, especially respiratory complications. A 2010 Cochrane review excluding laparoscopic abdominal surgery identified 27 studies (3211 patients) and showed that prophylactic NGT decompression is ineffective at (1) hastening return of bowel function, (2) decreasing risk of aspiration and subsequent pulmonary complications, (3) improving patient comfort by lessening abdominal distension, (4) protecting intestinal anastomoses from leakage, and (5) shortening hospital LOS. The use of NGTs also is associated with significant morbidity related to both placement and prolonged use, as well as significant patient discomfort.

Evidence based medicine has transformed all aspects of patient care, including surgical decision making, which traditionally was highly subjective, individualized, and primarily emulated the practice of prior master surgeons. The historical practice of prolonged bed rest, NGT decompression, and delay of oral intake to allow the alimentary tract time to heal and recover has been refuted repeatedly in the scientific literature. The 1980s and 1990s saw significant advances in perioperative pain control and minimally invasive surgical techniques that aimed at other outpatient or reduced LOS surgery. The Danish surgeon Henrik Kehlet pioneered the idea of fast track surgery in the 1990s, with the intent of developing a multidisciplinary approach to reduce surgical stress and achieve a smoother and faster recovery. This move toward streamlining care has proven successful and beneficial to patients, providers, and society. One of the cornerstones of surgical care to be eliminated by fast track pathways is the prophylactic use of NGTs.

COLORECTAL SURGERY AND ENHANCED RECOVERY AFTER SURGERY

Fast track surgery, as described by Kehlet, perhaps has been most successfully translated into colorectal surgery, specifically elective surgery for colorectal cancer (CRC). Enhanced recovery after surgery (ERAS) pathways significantly reduce postoperative morbidity and decrease LOS and healthcare expenditures. Consensus ERAS Society guidelines developed in 2005 and updated most recently in 2017 have become the standard of care for colorectal surgery. The current guidelines include 24 recommendations for preoperative, perioperative, and postoperative care. The elements included in ERAS for colorectal surgery focus on ensuring appropriate preadmission counseling, utilizing prehabilitation, avoiding prolonged fasting, providing carbohydrate loading, using appropriate antibiotic and thromboembolic prophylaxis, using short acting anesthetic agents and optimal analgesia, maintaining euvolemia with balanced resuscitation, preventing nausea and vomiting, and using postoperative early mobilization and nonopioid analgesia. In addition, the use of laparoscopic or laparoscopic assisted technique should be the first choice when appropriate.

Another critical component of ERAS is early resumption of oral nutrition by offering patients a regular diet immediately after surgery. A 2010 publication titled "The Evidence Against Prophylactic Nasogastric Intubation and Oral Restriction" reviews the current literature surrounding prophylactic NGT decompression in colorectal surgery. The study provides evidence that prophylactic NGT decompression (1) does not improve time to return of bowel function or LOS (in some studies it prolongs time to flatus and LOS); (2) does not reduce the incidence of anastomotic leak, wound infection, dehiscence, or incisional hernia; (3) does not prevent pulmonary complications of fever, atelectasis, or aspiration pneumonia and likely promotes pulmonary complications; and (4) does not prevent abdominal discomfort as measured by nausea, vomiting, or distension (and NGT reinsertion rates are low). The study also argues that early feeding, which is tolerated by 80% to 90% of patients within 24 hours after colorectal surgery, (1) enhances recovery time and decreases LOS; (2) reduces the risk for any type of postoperative infection; (3) decreases the risk for hyperglycemia; and (4) results in no difference in duration of ileus, although it does increase risk for vomiting.

For ERAS pathways to realize the expected benefits on patient outcomes there must be significant collaboration, buy in, and communication between all members of the healthcare team—surgeon, anesthesiologist, patient, nurses, and others. Compliance with the steps of the pathway cannot be assumed, and studies have found that adherence rates drop over time without repetitive education of staff. A web based survey of colorectal and general surgeons found that only about 30% were actively following a perioperative protocol for elective bowel resections. With regard to NGT removal, 61% reported avoidance of NGT completely and 15% reported removal of NGT on postoperative day zero. Another study found that despite the development of a multidisciplinary fast track protocol and training sessions for all staff, only 3 of the 7 key elements of the pathway met 80% compliance after implementation. The authors hypothesized that more time is needed to overcome the deep seated beliefs taught by tradition. This study and others highlight the need for continued monitoring of compliance with ERAS pathways and evidence based medicine.

FOREGUT AND PANCREATIC SURGERY

Whereas ERAS pathways after colorectal surgery have become widely utilized, the introduction of fast track protocols for upper GI

tract and pancreatic surgery has only gained traction over the past few years. As expected, there is often hesitation by surgeons regarding early removal of NGTs and earlier oral feeding after an esophagectomy, gastrectomy, or pancreaticoduodenectomy (Whipple's procedure). This is because of concern over the integrity of the anastomosis as well as the duodenal stump and, especially in the case of pancreaticoduodenectomy, the fact that multiple enteric anastomoses are involved. Traditional surgical training has taught that an NGT is necessary after an esophagectomy to prevent overdistention of the gastric conduit, protect the esophagogastric anastomosis from dehiscence, and prevent vomiting and aspiration. Surgeons also harbor concern that feeding too early after a pancreaticoduodenectomy will increase the risk of pancreatic leak and fistula formation.

Recently, a number of studies examining ERAS programs after elective esophagectomy have been published. In most of these studies the NGT is removed on postoperative day 2, and some studies forego NGTs altogether. A 2017 review of the literature and meta-analysis including 7 studies and 688 patients found no significant difference in rates of anastomotic leak, pulmonary complications, or mortality. Included in this meta-analysis was one study that found no difference in complication rate or in admission rate when comparing an ERAS study group of 103 patients, in which the NGT was removed on postoperative day 2, with a historical control group of 78 patients. Furthermore, another study that compared early removal (postoperative day 2) with delayed removal (postoperative days 6 to 10) found no difference in pulmonary complications, anastomotic leak rates, need for reintubation, mortality, or LOS between groups. The authors did note that patient discomfort scores were higher in the delayed removal group and that only about 10% of patients required NGT reinsertion for postoperative ileus, with no complications from reinsertion despite the fresh anastomosis. They concluded that early removal is safe and affords two-thirds of patients relief of NGT discomfort early in the postoperative course.

The ERAS Society has published official consensus guidelines for fast track care after gastrectomy for gastric cancer (2016) and after pancreaticoduodenectomy (2013). The guidelines after gastrectomy are based on nine randomized controlled trials and two meta-analyses and present strong evidence against the routine use of NGTs. The cited studies repeatedly have shown no difference in time to flatus, anastomotic leaks, pulmonary complications, morbidity, or mortality, and many demonstrated a longer LOS in patients with routine NGT decompression compared with those without an NGT postoperatively. The guidelines after pancreaticoduodenectomy also recommend against routine NGT decompression. The most common complication after a pancreaticoduodenectomy is delayed gastric emptying (DGE), which occurs in up to 30% of patients. Multiple studies comparing a fast track program with historical controls actually have demonstrated that DGE rates are higher when routine NGT decompression is used.

EMERGENCY SURGERY AND NASOGASTRIC TUBES

The data for fast track protocols and use of NGT in emergency abdominal surgery are sparse, however, in the absence of bowel obstruction or the need for NGT for gastrointestinal access there is no evidence to support routine use of NGT. One single institution study of emergency abdominal surgery randomized 367 patients to early oral feeding (soft diet given within 24 hours) and left to a traditional care pathway. The traditional care group of patients was further stratified as high risk (evidence of peritonitis, GI tract obstruction or perforation, or an anastomosis) and placed on nothing by mouth status for 3 days postoperatively or as low risk (none of the high risk criteria) and given liquids and then a soft diet once they passed either flatus or stool. The authors found no difference between the early and traditional groups in complication rate, LOS, or need for reoperation. The early feeding group did experience a significant increase in postprandial vomiting; however, there was no difference in the need for NGT reinsertion between any of the groups.

Another institution performed a prospective randomized trial to evaluate the safety and efficacy of ERAS pathways after emergency laparoscopic surgery for perforated peptic ulcer disease (excluded if ulcer >10 mm). The 21 patients assigned to the ERAS group had their NGT removed in the operating room and were given liquids on postoperative day 1. The control group had their NGT removed only after the output was less than 300 mL a day. The study demonstrated no difference in morbidity or mortality and a significantly shorter LOS for the ERAS group (5.8 vs 8.9 days). However, the exclusion criteria were numerous—American Society of Anesthesiologists class 3 or 4, evidence of septic shock, conversion to an open procedure, and others—which limits the generalizability of the results. Finally, a study in Nepal randomized 115 patients after emergency laparotomy for perforation with peritonitis, intestinal obstruction, or abdominal trauma to two groups with or without an NGT postoperatively. The authors found no difference in the rate of wound complications, gastric ileus, respiratory complications, anastomotic leaks, or NGT reinsertions. Similarly, they demonstrated a shorter LOS in the group managed without an NGT.

COMPLICATIONS OF NASOGASTRIC TUBES

Avoiding unnecessary morbidity from NGT complications is another matter to urge routine NGT decompression. Complications can occur during the placement of an NGT or as a result of prolonged NGT use. Some adverse effects, such as patient pain and discomfort, sinusitis, epistaxis, and pharyngeal pain, are likely under-recognized and under-reported. Despite the seemingly simple technique for insertion, serious complications can arise from misplaced NGTs. Pneumothorax, even a tension pneumothorax, can occur from inadvertent tracheobronchial intubation. Pharyngeal, esophageal, duodenal, and other GI tract perforations have been reported. Intracranial placement of NGTs also has been observed; thus, care must be taken when inserting an NGT in a patient with basilar skull fractures or significant maxillofacial trauma.

Prolonged use can lead to esophageal strictures, nasal ulcerations, and NGT syndrome—ulceration and infection in the posterior cricoid region that causes vocal cord dysfunction and may seriously compromise a patient's airway. Other described complications include middle ear effusions, phlebitis, hypesthesia, aspiration, bleeding, esophageal obstruction from a tangled NGT, incarceration of an NGT into a GI tract anastomosis, reflux, tracheal rupture, arteroesophageal fistula, tracheoesophageal fistula, intramural esophageal dissection, cleft nose deformity, and retropharyngeal infected hematoma.

WHY ARE SURGEONS STILL ROUTINELY USING NASOGASTRIC TUBES?

Despite the preponderance and strength of the scientific evidence against routine NGT decompression after alimentary tract surgery, it is still relatively common for surgeons to leave NGTs in place after a variety of abdominal surgeries. Why is this the case? The answer is likely multifactorial. Perhaps there is a lack of awareness of the current evidence among practicing surgeons. Possibly surgeons are aware of the evidence but do not believe that the results are generalizable to their patient population. It is also likely that many surgeons, even today, tend to base their clinical practice and decision making on the anecdotal experience of their senior teachers or partners rather than on scientific evidence. However, in the absence of bowel obstruction, ileus, or the need for enteral feeding access, the use of NGTs is unnecessary and likely detrimental to optimal outcomes.

CONCLUSION

Routine prophylactic NGT decompression of the GI tract after surgery is not supported by data and is not recommended. Many studies have now demonstrated the safety and efficacy NGT removal immediately post-operatively and initiation of early feeding. The NGT remains an important tool in the surgeon's armamentarium as therapy in the setting of a bowel obstruction or postoperative ileus with vomiting and as a conduit to provide medications and enteral nutrition. Although much progress has been made in the past several years, further work is needed to decrease the utilization of routine NGT use.

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Alkan RHM, ter Horst M, Kruisbrink WA, et al. Initial experiences of an enhanced recovery protocol in esophageal surgery. World J Surg 2013;37:2572–2579.

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SURGICAL SITE INFECTIONS

Jaime A. Espinosa, MD, and Robert Sawyer, MD, FACS, FIDSA, FCCM

Surgical site infections (SSIs) are common postoperative complications, with an annual incidence of approximately 300,000 to 750,000 in the United States alone. They are an expensive burden on the world's economy. It is estimated that in the United States approximately $10,000 to $25,000 dollars are spent per SSI, leading to over $7 billion per year being spent on their management. Thus, within the past few years the Centers for Disease Control and Prevention (CDC), the American College of Surgeons (in conjunction with the Surgical Infection Society), and the World Health Organization (WHO) have published guidelines/recommendations on preventative strategies against surgical site infections based on evidence-based medicine. These are an update from previous recommendations, which were mostly based on expert opinion.

EPIDEMIOLOGY

SSIs occur in approximately 1% to 5% of patients worldwide. However, the incidence is likely underestimated as a large number of SSIs are diagnosed in the outpatient setting. The bacterial pathogens causing SSIs are closely monitored by the CDC via the National Healthcare Safety Network (NHSN). The NHSN is a surveillance system that was created in 2005 to closely track healthcare-associated infections, including antibiotic susceptibility. Interestingly, for SSIs, the percentage of Staphylococcus aureus that was oxacillin, methicillin, and/or cefoxitin resistant (i.e., methicillin-resistant Staphylococcus aureus) was relatively unchanged from 2011 to 2014 (~ 42.7% resistance in 2011 and 43.6% in 2014), while the percent of vancomycin resistant Enterococcus species went down from 68% to 58.4%. The most common bacteria isolated from SSIs from 1990 to 2014 are given in Table 1.

DEFINITION

SSIs are most commonly defined based on CDC definitions, which divide cases into superficial incisional, deep incisional, and organ space infections (Fig. 1 and Table 2).

RISK FACTORS

Risk factors for SSIs have been extensively studied and identified. They include both patient related factors and non-patient related factors as seen in Table 3.

CLASSIFICATION

Surgical wounds are assessed based on the classification system listed below, which was created by the CDC in 1999 (Table 4). Previous data suggested a much higher risk of surgical site infection with surgical wounds, with class IV (dirty) wounds having greater than 27% risk of becoming infected. However, more recent data have displayed a much lower risk, with class IV (dirty) wounds having a 5.1% to 8.5% risk of SSI.

PREVENTION

The increasing number of surgical procedures and the fact that perhaps 60% of SSIs are avoidable has increased the focus on SSI prevention. Thus, the CDC, the WHO, and the American College of Surgeons (in conjunction with the Surgical Infection Society) have recently published guidelines on preoperative, intraoperative, and postoperative recommendations for SSI prevention. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to evaluate the validity and strength of the CDC and WHO published guidelines (Tables 5 and 6).

TREATMENT

All surgical wounds with clinical evidence of infection (calor [heat], dolor [pain], rubor [redness], and/or tumor [swelling]), as first described by the Roman encyclopedist Aulus Cornelius Celsus, should be opened, debrided, cultured, and packed with a wet to dry or vacuum-based dressing. The wound should be fully explored for underlying abscesses, fluid collections, necrotizing infection, debris, and enteric contents. In addition, all necrotic and infected tissue should be meticulously debrided down to healthy bleeding tissue, and the wound should be thoroughly irrigated with normal saline.

The use of oral and intravenous antibiotics is recommended based on the United Kingdom's National Institute for Health and Care Excellence (NICE) surgical site infection guidelines. These antibiotics should be tailored based on wound cultures and local/regional

CONCLUSION

Routine prophylactic NGT decompression of the GI tract after surgery is not supported by data and is not recommended. Many studies have now demonstrated the safety and efficacy NGT removal immediately post-operatively and initiation of early feeding. The NGT remains an important tool in the surgeon's armamentarium as therapy in the setting of a bowel obstruction or postoperative ileus with vomiting and as a conduit to provide medications and enteral nutrition. Although much progress has been made in the past several years, further work is needed to decrease the utilization of routine NGT use.

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The increasing number of surgical procedures and the fact that perhaps 60% of SSIs are avoidable has increased the focus on SSI prevention. Thus, the CDC, the WHO, and the American College of Surgeons (in conjunction with the Surgical Infection Society) have recently published guidelines on preoperative, intraoperative, and postoperative recommendations for SSI prevention. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to evaluate the validity and strength of the CDC and WHO published guidelines (Tables 5 and 6).

TREATMENT

All surgical wounds with clinic evidence of infection (calor [heat], dolor [pain], rubor [redness], and/or tumor [swelling]), as first described by the Roman encyclopedist Aulus Cornelius Celsus, should be opened, debrided, cultured, and packed with a wet to dry or vacuum based dressing. The wound should be fully explored for underlying abscesses, fluid collections, necrotizing infection, debris, and enteric contents. In addition, all necrotic and infected tissue should be meticulously debrided down to healthy bleeding tissue, and the wound should be thoroughly irrigated with normal saline.

The use of oral and intravenous antibiotics is recommended based on the United Kingdom's National Institute for Health and Care Excellence (NICE) surgical site infection guidelines. These antibiotics should be tailored based on wound cultures and local/regional

TABLE 1 Percentage Distribution of Most Common Bacteria to Cause Surgical Site Infections Based on National Healthcare Safety Network Data

	2006–2008	2009–2010	2011–2014
Staphylococcus aureus	30%	30.4%	20.7%
Escherichia coli	9.6%	9.8%	13.2%
Coagulase-negative staphylococci	13.7%	13.2%	7.9%
Enterococcus faecalis	11.2%	11.6%	7.5%
Pseudomonas aeruginosa	5.6%	5.5%	5.3%
Klebsiella (previously Enterobacter) species	3%	4%	4.7%
Enterococcus species	4.2%	5%	4.4%

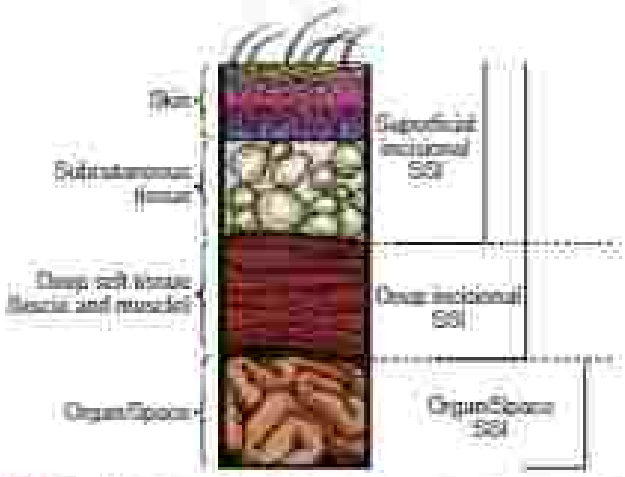

FIG. 1 Pictorial depiction of surgical site infections [illegible]

TABLE 2 Surgical Site Infection (SSI) Definitions

	Definition
Superficial incisional SSI	Infection that occurs within 30 days of surgery and includes only the skin and subcutaneous tissue of the incision. Plus at least ONE of the following: • Purulent drainage, with or without laboratory confirmation, from the superficial incision • Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision • At least one of the following signs/symptoms of infection and superficial incision is deliberately opened by the surgeon (unless incision is culture negative or not cultured) • Pain, tenderness, localized swelling, redness, or heat • Diagnosis made by surgeon or attending physician The following are not considered superficial incisional SSIs: • Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration) • Infection of an episiotomy or newborn circumcision site • Infected burn
Deep incisional SSI	Infection that occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is left in place and the infection appears to be related to the operative procedure and infection involves deep soft tissues (i.e., fascial and muscle layers) of the incision, and at least one of the following is present: • Purulent drainage from the deep incision, but not from the organ/space component of the surgical site • A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: • Fever (>38°C), localized pain or tenderness, unless culture of the incision is negative • An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination • Diagnosis made by surgeon or attending physician
Organ space SSI	Infection that occurs within 30 days after the operative procedure if no implant is left in place or within 1 year of implant is left in place and the infection appears to be related to the operative procedure and infection involves any part of the anatomy (i.e., organs or spaces) other than the incision, which was opened or manipulated during the operation and at least one of the following is present: • Purulent drainage from a drain that is placed through a stab wound into the organ space • If the area around a stab wound becomes infected, it is NOT a SSI. It is considered a skin or soft tissue infection, depending on its depth. • Organisms isolated from an aseptically obtained culture of fluid or tissue from the organ space • An abscess or other evidence of infection involving the organ space on direct examination, during reoperation, or by histopathologic or radiologic examination • Diagnosis made by surgeon or attending physician

*Implant, nonhuman-derived implantable foreign body (i.e., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.

From Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992;13(10):606–608.

TABLE 3 Surgical Site Risk Factors

	Risk Factors
Patient related • Nonmodifiable • Modifiable	Older age, recent radiotherapy, history of skin or soft tissue infection Diabetes, obesity, alcoholism, current smoker, immunosuppression, total bilirubin >1.0 mg/dL, preoperative albumin <3.5 mg/dL
Non patient related • Preoperative • Facility related • Procedure related	Inadequate antibiotic choice, timing, or dosing, inadequate skin preparation, glycemic control, surgical scrub, or hair removal method Inadequate ventilation, increased operating room traffic, nonsterile equipment Emergent procedure, complex procedure, high wound classification, long procedure, blood transfusion, breach in asepsis, poor glycemic control

Modified from Sun RA, Ishani IP, Carango G, et al. American College of Surgeons and Surgical Infection Society surgical site infection guidelines, 2016 update. J Am Coll Surg. 2017;224:59-74.

TABLE 4 Surgical Wound Classification

	Definition	Examples	Risk of Infection (1991)	Risk of Infection (2014)
Class I: clean	Surgical wound in which there is no breach of the respiratory, GI, GU, or genital tracts, and no inflammation is encountered.	Hernia repair (inguinal, femoral, ventral, incisional) Thyroidectomy CABG Mastectomy Laminectomy Total knee replacement Total hip replacement Port placement Axillary lymph node dissection	1%–5%	1.8%–2.4%
Class II: clean contaminated	Surgical wound in which there is a controlled entrance of the respiratory, GI, GU, or genital tracts without a major break in sterile technique.	Small bowel resection Lobectomy (lung) Hysterectomy Colectomy Colostomy reversal Roux en Y gastric bypass Whipple procedure Laryngectomy TURP	3%–11%	4.8%–6.7%
Class III: contaminated	Surgical wound that is open, fresh (less than 4 hours old), and/or accidental with a major break in sterile technique and/or uncontrolled gross spillage from the GI tract. Surgical wound in which acute, nonpurulent inflammation is met.	Cholecystectomy for acute cholecystitis Appendectomy for nonperforated appendicitis Nonsterile equipment or debris found on operative field Small bowel resection for infarcted or necrotic bowel	10%–17%	5.6%–8.6%
Class IV: dirty/infected	Surgical wound that is old (>4 hours old), and/or accidental/traumatic with a major break in sterile technique and/or uncontrolled gross spillage from the GI tract.	Peritonitis Appendectomy for perforated appendicitis Repair of perforated gastric ulcer Repair of perforated small bowel Open fracture repair	>27%	8.5%–13.8%

GI, Gastrointestinal; GU, genitourinary; TURP, transurethral resection of the prostate.

TABLE 5 ACS/SIS, CDC, and WHO Guidelines for Surgical Site Infection Prevention

Recommendation	Agency	GRADE
Administer preoperative antibiotics only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration is established in the serum and tissues when the incision is made. Refer to guidelines in Table 4.	ACS, CDC, WHO	Strong recommendation Low-quality evidence Accepted practice
Administer prophylactic IV antibiotics within 120 minutes before the incision while considering the half-life of the antibiotics. Antibiotics with a shorter half-life such as penicillin and cefazolin should be administered closer to incision time (within 60 minutes).	ACS, WHO	Strong recommendation Moderate-quality evidence
Administer prophylactic IV antibiotics prior to skin incision in all cesarean sections.	CDC	Strong recommendation High-quality evidence
Do not administer additional prophylactic IV antibiotics in clean and clean-contaminated cases after the incision has been closed, even in the presence of a drain. Also applies to prosthetic joint arthroplasty.	ACS, CDC, WHO	Strong recommendation High-quality evidence
Do not administer additional prophylactic IV antibiotics because of the presence of a wound drain. No evidence was found regarding optimal timing for drain removal.	WHO	Conditional recommendation Low-quality evidence
Do not apply antimicrobial agents to the surgical incision for SSI prevention (i.e., ointments, solutions, or powders). In addition, do not irrigate surgical wounds intraoperatively with antibiotic solutions (can lead to antibiotic resistance, WHO).	ACS, CDC, WHO	Strong recommendation Low-quality evidence
Administration of autologous platelet-rich plasma is not necessary for SSI prevention.	CDC	Weak recommendation Moderate-quality evidence
Consider the use of triclosan-coated sutures for SSI prevention.	ACS, CDC, WHO	Weak recommendation Moderate-quality evidence
Glycemic control: Implement perioperative glycemic control protocols in both diabetic and nondiabetic patients. CDC recommends blood glucose levels <200 mg/dL. ACS recommends blood glucose levels between 110 and 150 mg/dL. Except in cardiac surgery (goal <180 mg/dL). The WHO does not have an optimal target concentration, instead they recommend intensive protocols to prevent hyperglycemia (which has been shown to also increase morbidity and mortality).	ACS, CDC, WHO	Strong recommendation High- to moderate-quality evidence
Normothermia: the use of warming devices to maintain perioperative normal body temperature is recommended for SSI prevention.	ACS, CDC, WHO	Strong recommendation High- to moderate-quality evidence
Patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation for surgical procedures should receive 80% FiO_2 (hyperoxia) intraoperatively and in the immediate postoperative period.	ACS, CDC, WHO	Strong recommendation Moderate-quality evidence
Full-body shower or bath with soap (antimicrobial or nonantimicrobial) is advised on at least the morning before the operative day.	CDC, WHO	Strong recommendation Moderate-quality evidence Accepted practice
Perform intraoperative skin preparation with an alcohol-based antiseptic solution (based on chlorhexidine gluconate is recommended by the WHO), unless contraindicated.	ACS, CDC, WHO	Strong recommendation High- to moderate-quality evidence
Application of a microbial sealant immediately after intraoperative skin preparation is NOT necessary for SSI prevention.	CDC, WHO	Weak recommendation Low-quality evidence
Plastic adhesive drapes with or without antimicrobial properties should not be used for SSI prevention.	CDC, WHO	Weak recommendation High- to moderate-quality evidence

TABLE 5 ACS/SIS, CDC, and WHO Guidelines for Surgical Site Infection Prevention—cont'd

Recommendation	Agency	GRADE
Consider intraoperative surgical wound irrigation with an aqueous iodophor povidone-iodine solution. Intraperitoneal lavage with aqueous iodophor solution is not recommended (CDC).	CDC, WHO	Weak recommendation Moderate quality evidence
It is not recommended to withhold transfusion of necessary blood products in an attempt to prevent SSI.	CDC	Strong recommendation Accepted practice
Normovolemic maintenance of adequate circulating blood volume via goal-directed fluid therapy is recommended.	WHO	Conditional recommendation Low quality evidence
Either sterile disposable nonwoven or sterile reusable woven drapes and surgical gowns may be used in surgery to prevent SSI.	WHO	Conditional recommendation Moderate- to low-quality evidence
Consider the use of wound protector devices (wound edge protectors) intraoperatively in clean contaminated, contaminated, and dirty abdominal surgeries to prevent SSI.	ACS, WHO	Conditional recommendation Very low-quality evidence
Consider the use of ciNPWT on primarily closed surgical incisions in high-risk wounds (bleeding, hematoma, intraoperative contamination, dead space, decreased blood flow, or skin or soft tissue damage) in order to prevent SSI.	WHO	Conditional recommendation Low-quality evidence
Laminar airflow systems should not be used to reduce SSI for patients undergoing total arthroplasty surgery.	WHO	Conditional recommendation Low- to very low-quality evidence
Advanced dressings, such as hydrocolloid, hydrogels, vapor-permeable films, etc., are NOT recommended over standard dressings on primarily closed surgical wounds.	WHO	Conditional recommendation Low-quality evidence
Do not discontinue immunosuppressive agents prior to surgery.	WHO	Conditional recommendation Low-quality evidence
Consider the use of oral or enteral multiple nutrient-enhanced formulas (arginine, glutamine, omega-3 fatty acids, and nucleotides) to underweight patients undergoing major surgeries for SSI prevention.	WHO	Conditional recommendation Very low-quality evidence
For orthopedic and cardiothoracic surgery patients, it is recommended that all patients who are known carriers of *Staphylococcus aureus* should receive perioperative intranasal applications of mupirocin 2% ointment with or without chlorhexidine gluconate body wash. Consider same treatment to patients who are known carriers and are undergoing other types of surgery. Conditional recommendation on moderate evidence (WHO).	ACS, WHO	Strong recommendation Moderate quality evidence
Preoperative oral antibiotics should be given with a MBP to adult patients undergoing elective colorectal surgery. MBP should NOT be used alone (without oral antibiotics) in these patients.	ACS, WHO	Strong recommendation Moderate quality evidence
Patients undergoing any surgical procedure should either not have their hair removed OR if absolutely necessary the hair should be removed using a clipper. Shaving is STRONGLY discouraged at all times, whether preoperatively or in the operating room.	ACS, WHO	Strong recommendation Moderate quality evidence
Surgical hand preparation should be done by either scrubbing the hands with antimicrobial soap and water or an alcohol-based hand rub solution prior to donning sterile gloves. Neither is superior to the other (ACS).	ACS, WHO	Strong recommendation Moderate quality evidence

ACS, American College of Surgeons; CDC, Centers for Disease Control and Prevention; FiO_2, fraction of inspired oxygen; N_2, nitrogen; MBP, mechanical bowel preparation; ciNPWT, prophylactic negative-pressure wound therapy; SSI, surgical infection society; WHO, World Health Organization.

TABLE 6 Recommendations for Antibiotic Prophylaxis Based on Surgical Procedure

Surgical Procedure	Recommended Antibiotic	Alternative for Patients With β-Lactam Allergy
Cardiac • Coronary artery bypass • Cardiac device insertion procedures (i.e., pacemaker) • Ventricular assist devices	Cefazolin or cefuroxime	Clindamycin or vancomycin
Thoracic • Lobectomy, pneumonectomy, thoracotomy, etc. • VATS	Cefazolin or cefuroxime	Clindamycin or vancomycin
Vascular	Cefazolin	Clindamycin or vancomycin
Gastroduodenal • Procedures involving entry into the GI tract (e.g., bariatric, Whipple procedure) • Procedures not involving entry into the GI tract (e.g., Nissen, vagotomy) for high-risk patients	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract:		
Open surgery	Cefazolin or cefotetan or cefotetan or cefuroxime or ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Laparoscopic, elective	None	None
Laparoscopic, elective, high risk	Cefazolin or cefotetan or cefotetan or cefuroxime or ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Small bowel:		
Nonobstructed	Cefazolin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
Obstructed	Cefazolin + metronidazole or cefotetan or cefoxitin	Metronidazole + aminoglycoside or fluoroquinolone
Colorectal	Cefazolin + metronidazole or cefotetan or cefotetan or ampicillin-sulbactam Or cefotetan + metronidazole or erythromycin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone Or metronidazole + aminoglycoside or fluoroquinolone
Appendectomy for uncomplicated appendicitis	Cefotetan or cefoxitin or cefazolin + metronidazole	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone Or metronidazole + aminoglycoside or fluoroquinolone
Hernia repair	Cefazolin	Clindamycin or vancomycin
Head and neck:		
Clean	None	None
Clean with placement of prosthetic (excludes tympanostomy tubes)	Cefazolin or cefuroxime	Clindamycin
Clean-contaminated with exception of tonsillectomy and functional endoscopic sinus procedures	Cefazolin + metronidazole Or cefuroxime + metronidazole or ampicillin-sulbactam	Clindamycin
Neurosurgery		
Elective craniotomy and CSF shunting procedures	Cefazolin	Clindamycin or vancomycin
Intraocular prosthesis implantation	Cefazolin	Clindamycin or vancomycin
Cesarean section	Cefazolin	Clindamycin + aminoglycoside

TABLE 6 Recommendations for Antibiotic Prophylaxis Based on Surgical Procedure—cont'd

Surgical Procedure	Recommended Antibiotic	Alternative for Patients With β-Lactam Allergy
Hysterectomy (vaginal or abdominal)	Cefazolin or cefoxitin or cefotetan or ampicillin sulbactam	Clindamycin Or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Or metronidazole + aminoglycoside or fluoroquinolone
Ophthalmic	Topical neomycin polymyxin B gramicidin or fourth-generation topical fluoroquinolone	None
Orthopedic:		
Clean cases of hand, knee, or foot without implantation of foreign materials	None	None
Spinal procedures with or without instrumentation	Cefazolin	Clindamycin or vancomycin
Hip fracture repair	Cefazolin	Clindamycin or vancomycin
Implantation of internal fixation devices (i.e., nails, plates, screws)	Cefazolin	Clindamycin or vancomycin
Total joint replacement	Cefazolin	Clindamycin or vancomycin
Urologic:		
Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)	Cefazolin or fluoroquinolone or TMP/SMX	Aminoglycoside + clindamycin
Clean with entry into urinary tract	Cefazolin	Fluoroquinolone or aminoglycoside + clindamycin
Clean without entry into tract	Cefazolin	Clindamycin or vancomycin
Involving implanted prosthesis	Cefazolin + aminoglycoside Or cefazolin + aztreonam or ampicillin sulbactam	Clindamycin + aminoglycoside Or aztreonam Or vancomycin + aminoglycoside
Clean-contaminated	Cefazolin + metronidazole or cefoxitin	Fluoroquinolone Or aminoglycoside + metronidazole or clindamycin
Heart transplantation	Cefazolin	Clindamycin or vancomycin
Lung transplantation	Cefazolin	Clindamycin or vancomycin
Liver transplantation	Piperacillin tazobactam or Cefotaxime + ampicillin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Pancreas transplantation and pancreas kidney transplantation	Cefazolin + fluconazole (for patients at high risk of fungal infection)	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Plastic surgery, clean with risk factors or clean-contaminated	Cefazolin or ampicillin sulbactam	Clindamycin or vancomycin

CSF, Cerebrospinal fluid; GI, gastrointestinal; "MRSA", methicillin-resistant Staphylococcus aureus; VATS, video-assisted thoracic surgery.
Based on guidelines developed by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA).

antifungal agents. Of note, the NICE recommends against the use of topical antibiotics for prevention and treatment of surgical site infections. The most appropriate duration of antimicrobial use is unclear and is frequently based on the severity of local and systemic inflammation.

The use of negative pressure wound therapy (NPWT), also known as a wound vacuum, is now considered an effective treatment to promote healing in open wounds. NPWT decreases local edema by extracting fluid out of the wound and promotes angiogenesis by promoting blood flow to the region. Within the last 20 years, NPWT has become a popular commodity for the treatment of infected wounds. Previously, NPWT was used mostly after the wound was clean and sutured; nowadays, however, the use of NPWT with instillation (NPWT-i) of normal saline, sodium hypochlorite, or 0.5% polyhexanide plus 0.1% betaine is commonly used for the acute treatment

of open abdominal SSIs. NPWT-i works by instilling one of these solutions into the wound, allowing the solution to dwell in the wound for a certain amount of time (called the dwell time), and finally removing the fluid with negative pressure. Much of the published literature on NPWT-i recommends the use of 0.1% polyhexanide plus 0.1% betaine based on its broad spectrum antibiotic activity. However, Kim et al. recently showed in a prospective, randomized effectiveness study that normal saline can work just as effectively, with a shorter time to a final surgical procedure.

SUMMARY

Surgical site infections are the commonest postoperative complication and the most expensive healthcare associated condition in the United States today. Diagnosis is frequently made on clinical grounds, and treatment should be prompt. Due to the importance of SSI, several evidence based prevention guidelines have recently been published. Future progress in the prevention and management of this condition will depend on optimizing the host immune response and understanding and controlling the bacterial pathogens that are frequently involved.

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Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27(2):97–132.

National Institute for Health and Care Excellence. Surgical site infections: Prevention and treatment; 2008. https://www.nice.org.uk/guidance/cg74/chapter/1-Guidance.

MANAGEMENT OF INTRA-ABDOMINAL INFECTIONS

Mahreen T. Khan, MD, MS, and Adil H. Haider, MD, MPH, FACS

CLASSIFICATION

Intraabdominal infections (IAIs) result from contamination and invasion of microorganisms into the sterile abdominal cavity. IAIs were traditionally categorized as primary, secondary, and tertiary infections. Primary IAIs occur due to invasion of the peritoneal cavity from a distant source or direct bacterial inoculation. This is commonly seen in patients with cirrhosis and ascites or immunocompromised hosts. Most of these infections are monomicrobial and do not require surgery. Secondary IAIs are seen in patients with perforation or severe inflammation of an intraabdominal organ such as appendicitis or diverticulitis. These can also occur due to contamination caused by perforation of hollow viscus or anastomotic leak. Most of these infections are polymicrobial and generally need to go to the operating room. Thus, secondary IAIs require prompt attention of a surgeon. Tertiary IAIs are due to persistent or recurrent infections and are usually seen in immunocompromised patients. These are most commonly sequelae of previous operative attempts to treat secondary IAIs. Tertiary IAIs are less well understood, are polymicrobial, and usually do not require surgery.

The new recommendations by the Surgical Infection Society (SIS) task force encourage differentiating patients with community-acquired intraabdominal infections (CA-IAI) from those with healthcare/hospital acquired intraabdominal infections (HA-IAI), to select appropriate treatment strategies. Within the CA-IAI group, patients should be divided into low risk and high risk categories. Identifying patients at high risk takes into account patient age, comorbid conditions, and physiologic derangements. There are scoring systems to differentiate between low risk and high risk patients. However, for individual patients, clinical judgment is equivalent to a scoring system. An example of a low risk patient is a 20 year old man with no comorbid conditions with perforated appendicitis. A high risk patient is defined as a patient who is at risk of treatment failure. Older age, comorbidities, immunosuppression, and presence of malignancy make a patient high risk (Fig. 1). Patients with HA-IAI are at an increased risk for infection with resistant or opportunistic organisms. The SIS has also developed criteria for identifying patients with healthcare- or hospital-acquired intraabdominal infection (see Fig. 1).

Classifying patients into one of these groups (low risk CA-IAI, high risk CA-IAI, or HA-IAI) helps optimize selection of antimicrobial therapy.

DIAGNOSIS

Presentation

Diagnosis of IAI should be suspected in any patient presenting with sepsis and gastrointestinal and/or genitourinary dysfunction. Obtaining a detailed history and physical examination are key. Patients can present with variable symptoms, most commonly with abdominal pain and fever. Other symptoms include nausea, abdominal distention, obstipation, and diarrhea. Past surgical history, especially recent interventions such as bowel resection and anastomoses are important to elucidate from the patient.

Physical examination can be challenging, as it is often nonspecific. Particular findings on examination may give clues for the underlying pathology. Pain out of proportion with physical exam is suspicious for ischemic bowel. Pain can be localized to a particular quadrant, such as the left lower quadrant, in uncomplicated diverticulitis of the sigmoid colon, or generalized when the infection has progressed, such as an anastomotic leak. Patients may also present with an unreliable physical examination, such as those with an altered mental status or an immunosuppression. In these patients, one should consider IAI if the patient presents with evidence of infection from an unknown source.

Vital signs may be within normal limits in a patient with localized infection. However, when the host's ability to contain the infection is overcome and the infection continues to progress, the patient may quickly progress to sepsis or septic shock.

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Physical examination can be challenging, as it is often nonspecific. Particular findings on examination may give clues for the underlying pathology. Pain out of proportion with physical exam is suspicious for ischemic bowel. Pain can be localized to a particular quadrant, such as the left lower quadrant, in uncomplicated diverticulitis of the sigmoid colon, or generalized when the infection has progressed, such as an anastomotic leak. Patients may also present with an unreliable physical examination, such as those with an altered mental status or an immunosuppression. In these patients, one should consider IAI if the patient presents with evidence of infection from an unknown source.

Vital signs may be within normal limits in a patient with localized infection. However, when the host's ability to contain the infection is overcome and the infection continues to progress, the patient may quickly progress to sepsis or septic shock.

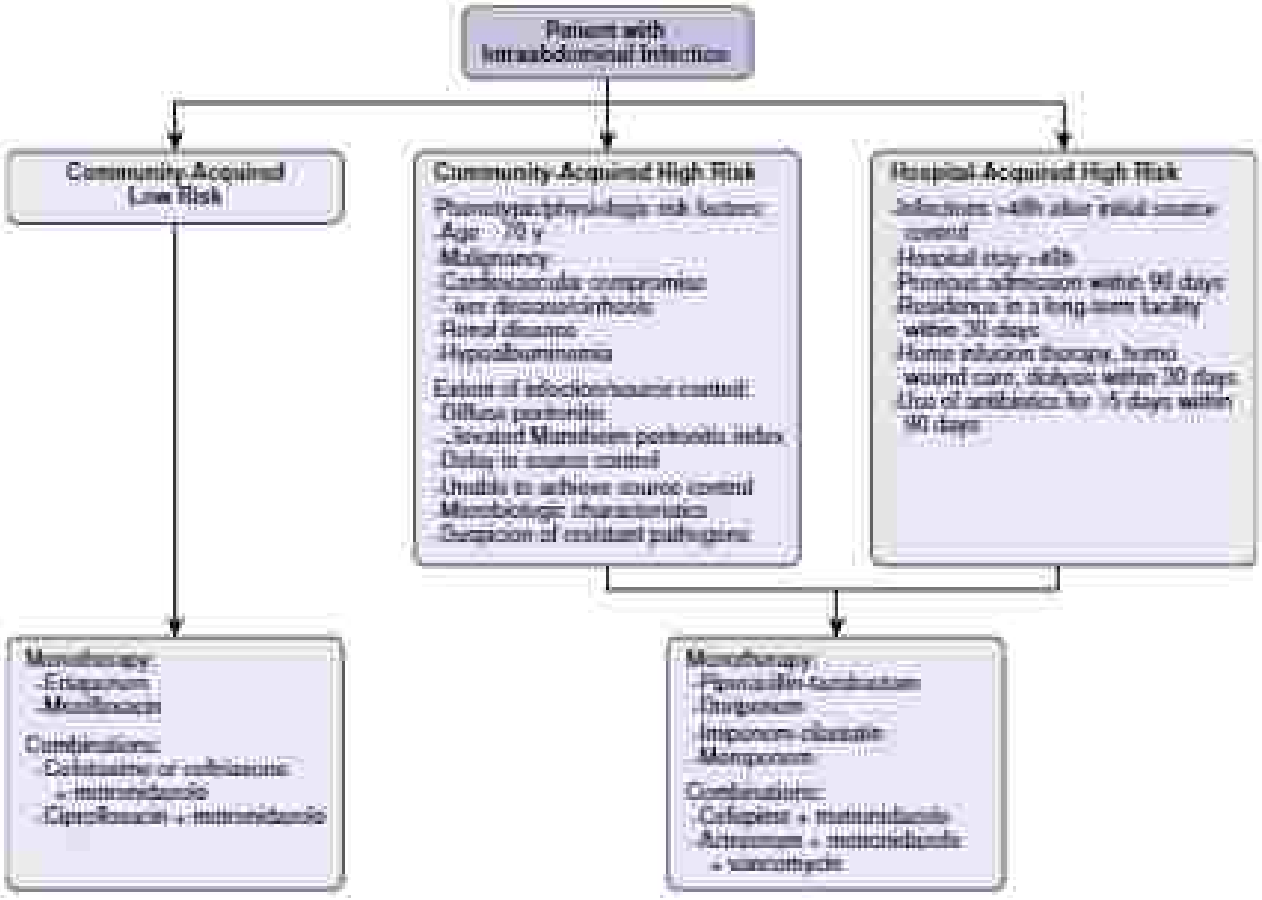

FIG. 1 Classification of intraabdominal infections and empirical antimicrobial regimens for community-acquired (low risk and high risk) and hospital-acquired IAIs. (Modified from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010;11(1):79–109.)

Diagnostic Workup

Laboratory tests such as complete blood count (CBC) and serum electrolyte levels are beneficial to determine potential bleeding and metabolic derangement. Liver function tests, amylase and lipase may be added if there is clinical suspicion of hepatobiliary or pancreatic pathology. In patients with sepsis, serum lactate levels need to be assessed. Blood, urine, and any catheter cultures should be obtained, but pending culture results should not delay therapy or treatment.

In a patient presenting with peritonitis, chest and abdominal radiographs may be the only tests needed before proceeding to the operating room for exploration. For example, in a patient with hollow viscus perforation, upright films are useful for identifying free air under the diaphragm.

Computed tomographic (CT) scan of the abdomen and pelvis with contrast is helpful in identifying the potential source of infection as well as in planning a potential surgical or radiologic intervention. Oral contrast helps to differentiate between bowel loops and intra-abdominal fluid collection. For example, in patients with perforated diverticulitis with an abscess, it can help delineate the abscess and guide subsequent drainage procedures. Intravenous (IV) contrast helps characterize inflammation, necrosis (such as liver or pancreas), and abscess wall. CT is also helpful in identifying small areas of pneumoperitoneum due to hollow viscus perforation, which may not be seen on plain films.

It is not necessary to perform a CT scan on every patient with IAI and different imaging modalities may be more beneficial in certain instances, such as acute biliary disease. In patients presenting with right upper quadrant (RUQ) pain, workup should include a RUQ ultrasound scan to evaluate the gallbladder. Biliary disease may require further imaging modalities such as magnetic resonance imaging. For female patients with right lower quadrant pain, a pregnancy test should be added to the diagnostic tests.

MANAGEMENT

The principles of treatment of IAIs are resuscitation, antimicrobial treatment, and source control. It is very important to recognize and manage IAIs aggressively, as delays in treatment can cause IAIs to progress to sepsis, shock and death. A thorough workup for identification of potential source and antimicrobial treatment should be pursued simultaneously. It is important not to withhold antimicrobial treatment while waiting for diagnostics such as microbial cultures as this may result in worse outcomes for the patient.

Resuscitation

This is a critical step in the management of IAI. Patients with IAI are susceptible to intravascular volume depletion. This can be assessed based on history and physical examination. For example, patients with appendicitis may present with nausea and vomiting causing metabolic alkalosis. Patients presenting with fever or increased respiratory rate have increased insensible fluid losses. In addition, patients with peritonitis have local and systemic fluid sequestration, which further contributes to intravascular volume depletion. High risk patients or those patients who appear to be decompensating should be managed in the intensive care unit. IV lines should be established. A Foley catheter should be placed to monitor and ensure adequate perfusion. If necessary, central venous access should be established to ensure appropriate resuscitation.

Nasogastric tubes should be considered in patients who are at risk of aspiration or have small bowel obstruction. If there is strong suspicion of a perforated gastric or duodenal ulcer, care should be taken when placing the tube. Placement of arterial lines may be beneficial in patients who require active titration of vasoactive substances or those in need of serial laboratory tests.

The 2016 Surviving Sepsis Campaign (SSC) Guidelines recommend the following goals for the first 3 hours after presentation: (1) measuring serum lactate levels, (2) obtaining blood culture, and (3) resuscitating with 30 mL/kg crystalloid for patients with hypotension or serum lactate levels 4 mmol/L or higher. The new sepsis guidelines also emphasize the following strategies for the first 6 hours after presentation: (1) frequently reassessing volume status and tissue perfusion in patients with persistent hypotension and/or initial lactate of 4 mmol/L or higher, (2) adding vasopressors for patients with persistent hypotension (mean arterial pressure <65 mm Hg), and (3) remeasuring lactate.

Antimicrobial Therapy

Antimicrobials should ideally be initiated within 1 hour of diagnosis of sepsis, according to the SSC Guidelines. Empirical broad-spectrum antimicrobials should be administered. The SIS and the Infectious Disease Society of America published recommendations on antibiotic choice for management of IAI in 2010. Since then, new challenges have arisen in the management of patients with IAIs, such as an aging population, sicker patients, increase in resistant bacteria and fungi, and the SIS revised their guidelines in 2017 to meet these needs. Categorizing patients with IAIs into low risk community acquired, high risk community acquired, or healthcare/hospital acquired groups can guide choice of antibiotics.

Within patients with CA IAI, low risk patients can be empirically treated with a single antimicrobial agent or combination therapy. Appropriate single agents are ertapenem and moxifloxacin. Options for combination therapy for low risk patients are metronidazole with cefazolin, cefuroxime, or ciprofloxacin. These antimicrobial agents have activity against microorganisms usually associated with these infections, including gram-negative Enterobacteriaceae, aerobic streptococci, and obligate anaerobes. The routine use of additional agents to provide antipseudomonal, antienterococcal or antifungal coverage is not recommended.

High risk CA IAI can also be empirically treated with single agent or combination therapy. Appropriate single agents are piperacillin-tazobactam, doripenem, meropenem, ceftazidime, moxifloxacin. Options for combination therapy for high risk patients are cefepime or combination with metronidazole or aztreonam in combination with metronidazole and vancomycin (in patients with a severe reaction to β-lactam agents). The flora of high risk patients with CA IAI is similar to those of lower risk patients. However, some high risk patients are infected with *Enterobacter* spp., *Pseudomonas aeruginosa*, and *Bacteroides* spp. These organisms are resistant to narrower-spectrum antimicrobials used in low risk patients. Thus, it is recommended to use broader spectrum empirical antimicrobial agents (see Fig. 1). The use of ampicillin or vancomycin for empirical antimicrobial treatment should be considered in high risk patients not being treated with piperacillin-tazobactam or meropenem-vaborbactam. The use of antifungal agents for empirical treatment is not recommended. It should be considered for critically ill patients with an upper gastrointestinal source.

Patients with HA IAI are at risk for infection from resistant or opportunistic organisms. At minimum, patients with HA IAI should be empirically treated with broader spectrum therapy recommended for CA IAI high risk patients. Each patient should also be assessed for their risk of infection with *Enterococcus* spp., methicillin-resistant *Staphylococcus aureus*, resistant gram-negative bacilli, and *Candida* spp., and empirical treatment provided accordingly. It is also important to know the local trends of antimicrobial susceptibility to help guide treatment of HA IAIs. Appropriate single agents are piperacillin-tazobactam or a broad-spectrum carbapenem. Options for combination therapy are cefepime plus metronidazole, ceftolozane plus metronidazole, or aztreonam plus metronidazole plus vancomycin. Other agents should be added to this basic regimen based on individual patient's assessment for resistant gram-positive, resistant gram-negative, or fungal pathogens.

The duration of antibiotics is debatable. New data support limiting antimicrobial treatment to 4 days in patients who have had adequate source control. In patients who have not had definitive source control, antimicrobial treatment can be continued for 5 to 7 days. Antimicrobial therapy should be changed based on culture results in selected patients. For low risk CA IAIs, antimicrobial therapy does not need to be changed in patients who have had a good clinical response to source control and empirical treatment. For high risk CA IAIs, antimicrobial therapy should be deescalated once culture results are available.

Source Control

The basic principles of source control are to eliminate infectious foci, control ongoing peritoneal contamination and restore anatomic and physiologic function. Majority of IAIs require an intervention in addition to antimicrobial treatment. The exception is patients with clinical problems for which there is evidence that nonintervational approach is associated with better outcomes. Source control should be achieved by the least invasive approach in a patient with IAI.

The use of percutaneous drainage to achieve source control results in significantly less physiologic alterations for the patient and can possibly eliminate or reduce the need for a surgical intervention. CT guided percutaneous drainage is useful in perforated appendicitis with an abscess or complicated diverticulitis. It is important for the surgeon to be involved in the care of the patients with IAI, even when patients are treated with percutaneous drainage initially, as additional therapy may be needed if repeat imaging shows worsening collections or the patient decompensates. In such patients, laparotomy may still be necessary for source control.

Surgical intervention should ensure complete removal of affected tissue. Any infected fluid collection or abscess should be completely evaluated. Necrotic tissue should be debrided until viable tissue is seen. If there is an anastomotic leak, a diversion should be considered. An abbreviated laparotomy and temporary abdominal closure should be done in critically ill patients if closing the abdomen results in significant intraabdominal hypertension, if the patient is hemodynamically unstable, if source control cannot be achieved in the index operation, or if a second look laparotomy is planned in patients with mesenteric ischemia. Routine planned reoperations should be avoided if source control is adequate. Thus, patients should be treated with on-demand instead of scheduled reoperations.

CONCLUSION

IAIs occur due to contamination and invasion of microorganisms into the sterile abdominal cavity. IAIs should be evaluated for risk of adverse outcomes to guide resuscitation, selection of antimicrobial therapy, and source control. Early intervention improves outcomes.

Suggested Readings

Mazuski JE, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect. 2017;18(1):1–76.

Singer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–810.

Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996–2005.

Solomkin JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect. 2010;11(1):79–109.

Epidemiology, Prevention, and Management of Occupational Exposure To Bloodborne Infections

Ethel D. Weld, MD; and Samuel Shoham, MD

Each year, there are 600,000 to 800,000 reported cases of occupationally related percutaneous injuries among US healthcare workers. Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are by far the most important bloodborne pathogens to which healthcare workers (HCWs) might be exposed. At one academic medical center, on the general surgery service, 20% to 30% of operative cases were found to involve patients infected with HBV, HBV, or HCV. This chapter will focus on these three viruses. With careful attention to the epidemiologic risks at hand, knowledge of current guidelines, and timely evaluation by clinicians with expertise on the topic, the harm from such exposure can be minimized or averted entirely. Major gains have been made over the past several decades in prevention of occupational bloodborne infection transmission. Safer medical equipment has reduced sharps injuries, robust universal HBV vaccination programs have reduced the number of occupationally acquired cases of HBV from 17,000 annually in 1983 to 263 cases in 2010, and occupationally transmitted HIV has been all but eliminated. Nonetheless, occupational exposures remain a common problem, and it is estimated that each year over 300,000 HCWs sustain a percutaneous sharps injury. Moreover, complacency on the part of HCWs and facilities must be avoided to avoid preventable harm to HCWs.

While exposure can happen in virtually any site where health care is delivered, there are certain scenarios where risk is particularly high. Sharps injuries are twice as common at teaching hospitals compared with nonteaching facilities; the operating room and postanesthesia units are the highest risk settings. Nurses are at highest risk, accounting for nearly half of cases, followed by residents, fellows, and attending surgeons. Junior clinicians with less experience and/or who are fatigued are more likely to be exposed. The annual rate of percutaneous exposure for trainees is ~20% and nearly all (99%) surgical residents sustain at least one needlestick injury by the end of their training, with the mean of 7.7 total injuries sustained by the fifth postgraduate year.

Victims of such exposure frequently feel a range of emotions including anxiety, posttraumatic stress disorder, fear, embarrassment, anger, and even a sense of betrayal by the profession to which they have devoted themselves. This is further compounded by rates of reporting of such exposures of approximately 50%. Fear of being reprimanded, concerns regarding confidentiality of the process, and time constraints have been identified as possible reasons for this. Out of concern for both employee health and patient safety, institutions must ensure that their staff and trainees are knowledgeable about what to do in case an exposure has happened and that there are practical mechanisms in place to help them access postexposure care in a timely and efficient fashion. In addition, occupational health practices that interface with surgeons directly in or immediately outside of operating rooms are a practical stepping measure while working to change a surgical culture that strongly discourages scrubbing out of cases at the time of needlestick. The champions for improving the safety of surgical trainees can and should include attending surgeons at the highest levels, particularly those present in the operating room at the time of a needlestick injury.

Complacency about risks of bloodborne disease after percutaneous or mucocutaneous exposure must be vigilantly guarded against, both from an employee safety and patient safety perspective. It is true that the rate of perioperative transmission of HBV and HCV is low across populations of HCWs, but this is only true because of decades of concerted effort and policy to safeguard the occupationally exposed. Furthermore, a HCW facing an accidental needlestick or other percutaneous injury should rightly be far less concerned with population health statistics than with the individual particulars (ie, of the exact source patient and viruses) involved, some of which can escalate that HCW's risk dramatically over that estimated in epidemiologic trends. It is also true that HBV cannot be transmitted to HBV immune individuals, which is reassuring in the era of universal HBV vaccination for HCWs. However, 10% to 20% of vaccinated individuals are immune nonresponders (by some estimates, even higher), often without being aware of this, and these individuals are at risk of occupational transmission of HBV—also a chronic, incurable, and deadly disease. Of paramount importance is that the decision about reporting and managing exposures should be taken out of the hands of the exposed individual, who is likely to be in the throes of numerous external stressors.

EPIDEMIOLOGY

Assessment of an occupational exposure to bloodborne infection should start with an assessment of the level of risk of the individual exposure. Knowledge of the relative risk of infectious transmission after an exposure can often be reassuring to the exposed individual (Figures 1 and 2).

The following factors are critical determinants of whether transmission will occur after exposure to a bloodborne pathogen (see also Box 2):

- The pathogen: HBV is by far the most transmissible bloodborne pathogen, with rates of developing clinical hepatitis in unvaccinated individual being as high as 30% and serologic evidence of HBV infection that are twice those (Fig. 1). This far exceeds those of HCV and HIV, which are as low as 0.2% and 0.3%, respectively, for percutaneous exposures.
- The inoculum (determined by the following factors):
  - Amount of circulating virus in the source patient's body
    - Among individuals who have detectable HBV e antigen in serum (a sign of significant viral replication) the percutaneous risk of transmission is 22% to 31%, and risk for developing serologic evidence of HBV infection is 37% to 62%.

BOX 1 Factors That Increase the Risk of Transmission of all Infectious Bloodborne Pathogens

- *High-risk exposure:* percutaneous, mucous membranes exposed, nonintact skin exposed, bites with blood exposure, visible blood on device, deep injury, large volume, hollow needles, blood from vessel
- *High-risk body substance:* Blood, bloody fluid, potentially infectious tissue
- *High-risk source patient:* hepatitis B virus surface antigen (HBsAg)+, HBeAg+, HCV Ab+ with HCV RNA PCR at high levels, HIV Ab+, HIV RNA PCR at high levels, noncompliant drug user, clinical or epidemiologic risks, advanced disease (likely a proxy for high viral load in HIV)

On the other hand, if exposure is to blood from HBeAg-negative source, the risks of developing clinical hepatitis is 1% to 6%, and the risk for developing serologic evidence of HBV infection is 23% to 37%.

BOX 2 Relative Average Risk of Infection Transmission After a Percutaneous Exposure to Blood (Based on Aggregate Data)

By source patient correlates

HBV (HBsAg+): risk varies according to e antigen positivity (chronic infectiousness)
- HBeAg+: 37%–62% transmission risk per exposure
- HBeAg−: 23%–37% transmission risk per exposure

HCV: Historically risk of transmission after percutaneous exposure has been reported as 1.8%, newer data suggests risk is much lower (0.2%)
- HIV coinfection in source patient may increase risk of HCV transmission
- One study *only* found transmission (1.2%) with hollow bore needles

HIV: 0.33% transmission risk for a percutaneous exposure (1 in 300)
- 0 cases reported after intact skin exposure
- 0.23%–0.3% transmission risk from needlestick injury
- 0.09%–0.09% transmission risk for a mucocutaneous exposure (~ 1 in 1000)

- Patients with advanced HIV infection and high viral loads are more likely to transmit virus than are those whose viral loads are undetectable. However, transmission is still possible even when source patient is on antiretroviral drugs.
- Amount and identity of the source fluid.
  - Blood has the highest concentrations of transmissible bloodborne viruses and is by far the most important fluid for transmission of bloodborne pathogens.
  - Semen, vaginal fluid, cerebrospinal fluid, breast milk, pericardial fluid, synovial fluid, and pleural fluid can also transmit HIV, but these are far less common in the healthcare setting.
  - Unless visibly bloody, other body fluids (e.g., saliva, urine, vomitus, feces, nasal or respiratory secretions, sweat, and tears) will not transmit HIV and rarely transmit HBV or HCV. For the special scenario of Ebola, which is also considered a bloodborne infection, it is worth noting that the disease can be transmitted through exposure to feces and vomitus as well as blood, and while live virus has been isolated from saliva and tears as well, though studies of transmissibility via these latter two routes are limited by their small size.
- Mechanism of injury/exposure. Needlestick injuries with hollow bore needles that had been placed within the vein or artery of a source patient carry the highest risk for transmission.
- Site of exposure.
  - The most important site is percutaneous, particularly with deep tissue injury. However, bloodborne infections can also be transmitted following exposure to mucous membrane and across nonintact skin barriers.

Healthcare personnel status	Postexposure testing		Postexposure prophylaxis		Postvaccination serologic testing[†]
	Source patient (HBsAg)	HCP testing (anti-HBs)	HBIG[*]	Vaccination	
Documented responder[§] after complete series (≥ 3 doses)	No action needed				
Documented nonresponder[¶] after 6 doses	Positive/unknown	—[**]	HBIG ×2 separated by 1 month	—	No
	Negative	No action needed			
Response unknown after 3 doses	Positive/unknown	<10 mIU/mL[††]	HBIG ×1	Initiate revaccination	Yes
	Negative	<10 mIU/mL	None		
	Any result	≥10 mIU/mL	No action needed		
Inactivated/incompletely vaccinated or vaccine refusers	Positive/unknown	—[**]	HBIG ×1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

FIG. 1 Postexposure management of healthcare personnel after occupational percutaneous and mucosal exposure to blood and body fluids by healthcare personnel hepatitis B vaccination and response status and, as appropriate to hepatitis B surface antigen (HBsAg) status of source patient. *HBIG*, hepatitis B immune globulin; *HBsAg*, hepatitis B surface antigen; *HCP*, healthcare personnel. [*]HBIG should be administered intramuscularly as soon as possible after exposure when indicated. The dose of HBIG is 0.06 mL/kg. [†]Should be performed 1 to 2 months after the last dose of the HepB vaccine series (and 4–6 months after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL). [§]A responder is defined as a person with anti-HBs ≥10 mIU/mL after ≥3 doses of HepB vaccine. [¶]A nonresponder is defined as a person with anti-HBs <10 mIU/mL after ≥6 doses of HepB vaccine. [**]If HCP titer was anti-HBs <10 mIU/mL or who are unvaccinated or incompletely vaccinated and sustain an exposure to a source patient who is HBsAg positive or has unknown HBsAg status, should undergo baseline testing for hepatitis B virus infection as soon as possible after exposure, and follow-up testing again 6 months later. Ideally 6 months after initial baseline tests consist of total anti-HBc testing in approximately a 6 months duration of HBsAg and total anti-HBc. (From Jatla N, Gilbert C, Spiegel ... *et al*. Recommendations for Prevention of Hepatitis ... after Exposure to the Clinical Guidelines Recommendations of the Advisory Committee on Immunization Practices, MMWR 1991 ... Recommendations Rep. 2001;50(RR-11):1–42.)

- In the scenario of a human bite, it is imperative to consider that both the biter and the victim may have been exposed to bloodborne pathogens.
- The HCW's level of protective immunity
  - Immunocompromised HCWs are at higher risk for acquisition of bloodborne pathogens.
  - Immunocompetent HCWs who have received three or more doses of the HBV vaccine series and have achieved anti-HBs levels of ≥10 mIU/mL (vaccine responders) are protected against infection.
    - This vaccine is mandatory for all HCWs, and approximately 90% of HCWs attain seroprotective levels with vaccination. However, there do wane over time.

At the time of exposure, it is not always known whether the source patient is infected with HBV, HIV, or HCV. Exposure to blood or infectious fluids of a patient with known HIV or hepatitis is one situation, the management of which is discussed later in the chapter. Exposure to blood or infectious fluids of a patient whose infectious status is unknown is a separate scenario in which the risk of transmission of infectious illness reflects the risk of undiagnosed infection in the general population, and the particular population that a given hospital or healthcare setting serves.
The following statistics are relevant in that regard:

- In the general US population, an estimated 1.1 million people are living with HIV, of whom 15% are unaware that they have HIV. In the youth population, among 13- to 24-year-olds, 54% of those with HIV are unaware that they have HIV.
- Transmission of HIV to occupationally exposed individuals is increased when the virus is detectable in the source patient's blood; therefore, it is highly relevant that only 49% of the US population living with HIV have achieved and sustained viral suppression.
- In the United States, 862,000 people are chronically infected with HBV. It is estimated that about one fifth of those infected with HBV in the United States are unaware of it. HCV infects 3.5 million persons in the United States, of whom approximately 50% are unaware of their infection.

Efforts to increase diagnosis of all these infections in the general population are underway. Routine screening of all individuals between 13 and 65 for HBV and all individuals born between 1945 and 1965 (or in other age groups but with HCV risk factors) for HCV is now recommended by the Centers for Disease Control and Prevention and the US Preventive Services Task Force.

PREVENTION

In general, robust efforts at prevention of occupational exposures to bloodborne infections should include universal HBV vaccination for all HCWs, personnel education and protection with universal precautions including the use of eye shields and gloves (and double gloves when necessary), rigorous procedure training, eliminating needle recapping, and minimizing exposure to sharps. Interventions that enable this include vigilant use and regular emptying of sharps containers, and engineering fixes such as needleless devices, automatic retracting needles, and safety knives, among others.

MANAGEMENT OF ANY EXPOSURE TO BLOODBORNE INFECTION

Postexposure Immediate Care

Cleansing Affected Area

Once an occupational exposure has occurred, facilitate local wound care should be performed as follows:

- Clean wounds (scrub, with soap and water, in a prolonged, thorough fashion).
- Use alcohol-based agents on exposed area.
- Flush any exposed mucous membranes with water.
- Flush eyes with water if exposed.
- Avoid use of bleach or caustic products, which can further irritate and abrade skin.
- No evidence that squeezing or milking the site helps.
- As mentioned, after a percutaneous injury that occurs through a surgical glove, surgeons should duplicate and replace, and follow standard protocols for when sterility is breached.

Management of a Human Immunodeficiency Virus Exposure:

Testing the Source Patient

- Rapid HIV-1 and -2 testing should be performed on the source patient's serum (rapid tests on oral secretions or blood are often available that have a less than 20-minute turnaround time).
- Window period of detection of HIV is 2 weeks after acute infection (fourth-generation HIV Ag/Ab testing may be followed with HIV RNA polymerase chain reaction [PCR] if source patient is high risk or had a recent high-risk exposure).
- The recent history and clinical picture of the source patient should be investigated, with particular attention to whether there is any recent syndrome that could be consistent with acute HIV (such as fever, sore throat, rash, headache, fatigue, enlarged cervical lymph nodes, etc.) If yes, *HIV RNA PCR should be ordered.*
- Negative predictive value >99% for negative rapid HIV test.
- In cases where there is incomplete or missing data on the source patient, the exposed person should be actively involved in the decision-making process. Sometimes postexposure prophylaxis (PEP) is withheld in situations of epidemiologic low risk. However, often in these scenarios of incomplete information, the exposed person chooses to proceed with taking PEP, as the potential benefits likely outweigh the risk, even in situations of low risk.

Postexposure Prophylaxis

The evidence for the efficacy of PEP of HIV rests on animal transmission models, retrospective observational human data, and the analogies with the efficacy of prevention of maternal to child transmission and perinatal prophylaxis. Retrospective case control studies in exposed individuals given zidovudine (azidothymidine [AZT]) PEP demonstrate an 81% reduction in transmission; the regimens of today are far better tolerated and far more potent, and if taken properly should reduce the risk of transmission to virtually zero (Table 1).

For effective prevention of transmission, both the timing of initiation and the duration of therapy matter (Fig. 2). The initiation of PEP should take place within 1 to 2 hours of exposure; efficacy drops off after 24 hours and is negligible after 72 hours, so initiation of PEP is not recommended if 72 hours have elapsed (see Tables 1 and 2). The exposed HCW should be counseled to abstain from or practice safe sex until the source patient's HIV serology returns negative. The CDC-recommended acceptable regimens for PEP are displayed in tabular form in Box 3. The guidelines no longer recommend an assessment of risk of HIV transmission to determine whether to initiate a two drug or three drug regimen, and instead recommend a three drug antiretroviral therapy regimen in all cases where PEP is initiated. This is largely because the available three drug regimens in the current era are exceedingly well tolerated. If the source patient is HIV positive with a virus that is known to be resistant to certain antiretrovirals, it is advisable to choose PEP regimens that are active against the source patient's virus. For guidance with the time sensitive initiation of PEP, the PEP line is a telephone hotline that can be a valuable resource: 888-448-4911 or http://www.nccc.ucsf.edu/.

Failures of Multidrug Postexposure Prophylaxis Reported to Centers for Disease Control and Prevention Through 2005

All were older regimens such as PEP and all were with follow-lists results.

Exposed source patient

- Pregnancy does not alter the calculus for PEP (high risk of transmission to fetus during acute infection, so the benefits outweigh the risk)
- Medications used in PEP are safe in pregnancy (AZT/3TC + lopinavir has most safety data in pregnancy)
- Discontinue breastfeeding during acute (postpartum)
- Consult with experts in obstetric infection

TABLE 1 Effect of Zidovudine (Azidothymidine [AZT]) on Prevention of Occupationally Acquired HIV in Humans

Human Study*	Cases (n = 33)	Controls (n = 479)
No AZT	24 (73%)	455 (95%)
AZT	9 (27%)	244 (36%)

*Adjusted odds ratio for acquisition of HIV after AZT postexposure prophylaxis: 0.2 (0.1–0.3).

From Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med.* 1997;337(21):1485–1490.

Monitoring

Follow-up testing for HIV is recommended at 6 weeks, 12 weeks, and 6 months postexposure.

Management of Hepatitis B Virus Exposure

There is a 90% protective response to the three-vaccine series for HBV immunization, and those who have had natural infection with HBV in the past should also be considered immune to reinfection. HCWs at risk of HBV acquisition after an exposure are those who have not been vaccinated or who have had inadequate response to vaccine. The highest concentration of HBsAg is found in blood. HBsAg is also found in CSF, saliva, semen, and breast milk, but most other body fluids do not contain infectious levels of HBsAg. Therefore, exposures to blood are highest risk for HBV transmission.

***Prevention: Hepatitis B Virus Vaccination** (See Figs. 1 and 2 for "Vaccination Algorithms")*

- Now two-dose HEPLISAV-B(Hyun Vac) HBV vaccine granted Food and Drug Administration approval in 2017 is more effective (95%) than older vaccines, increases completion rate as it is only 2 doses separated by 1 month, and should be considered for unvaccinated or nonresponder HCWs exposed to a patient with HBV.
- Older HBV vaccines (Recombivax HB, Engerix-B, Heplisav-B, Twinrix-B, etc.) are administered in a three-dose series at 0, 1, and 6 months.
- Anti-HBs titers decline to less than 10 mIU/mL in 30% to 50% of adults 8 to 10 years after immunization.
- Despite this, immune memory to nonresponders remains intact for at least 20 years after immunization.
- Very rare for prior responders (+ anti-HBsAb after vaccination) to acquire chronic HBV infection.

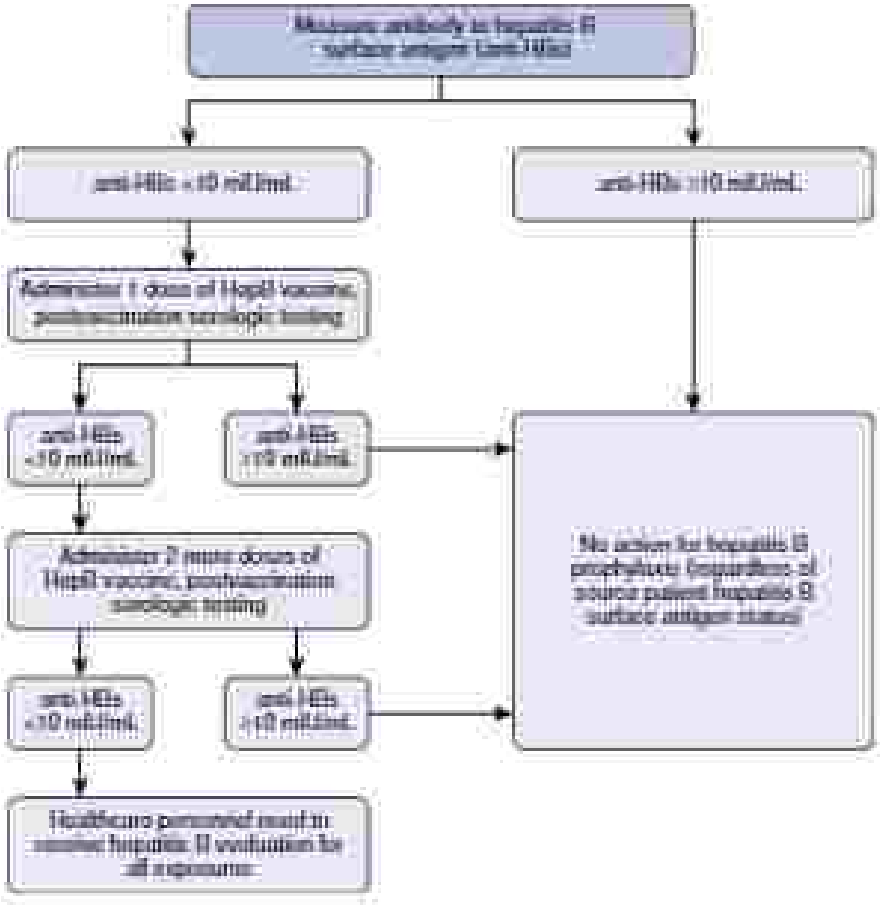

FIG. 1 Postexposure evaluation for healthcare personnel previously vaccinated with complete, 3-dose HepB vaccine series who have not had postvaccination serologic testing. Testing should be performed 1 to 2 months after last vaccine dose using quantitative method (e.g., enzyme-linked immunosorbent assay) to detect protective concentrations of anti-HBs (also known as anti-HBsAb). (Modified from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2018;67(RR-1):1–31.)

TABLE 2 Timing to Tenofovir (PMPA) Postexposure Prophylaxis Initiation and Duration of Treatment Both Affect Efficacy of Prevention of HIV Transmission of SIV in Macaques

TDF Treatment		
Initiation Delay (Hours)	Treatment Duration (Days)	No. HIV Infected
–	–	10/10
48	28	8/10
8	28	6/8
24	28	6/9
48	28	2/4
72	28	2/4
24	10	5/9
24	5	3/4

HIV, human immunodeficiency virus; TDF, tenofovir disoproxil fumarate.
Data from Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. *Science*. 1995;270(5239):1197–1199.
Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus type 1 infection depends critically on timing of initiation and duration of treatment. *J Virol*. 1998;72(5):4265–4273.

- Important to check anti-HBs response after completing 3-vaccine series (5%–10% do not seroconvert after).
- Booster doses of HBV vaccine are recommended for seroresponders who do not become HBsAb positive.
- Booster doses of HBV vaccine among known prior responders are not recommended.

Immediate Management of Occupational Exposure to Hepatitis B Virus

1. Verify HBsAb status of exposed HCW
   - Ask HCW if he or she has been vaccinated against HBV
   - If HCW gives permission, look up anti-HBsAb status in medical record
   - If HCW is positive for HBsAb (i.e., has antibody titers anti-HBs ≥10 mIU/mL), then STOP. No need for further intervention regardless of HBsAg status of source patient.
2. If HCW is unvaccinated, ascertain HBV serologic status of source patient.
   - Ascertain previous HBsAg and anti-HBcAb for source patient and proceed as follows:
     - HBsAg unknown: send HBsAg from source patient
     - HBsAg positive
       - Immediately administer both HBIG 0.06 mL/kg IM × 1 and HBV vaccine to HCW
       - Optional: draw HBsAg from source patient to get a sense of the magnitude of transmission risk
     - HBsAg negative
       - Optional: initiate HBV vaccination series in source patient.
3. If HCW vaccinated, but seroresponse is unknown (i.e., no anti-HBs available)
   - Test HCW for anti-HBsAb
   - Determine HBsAg status of source patient
     - HBsAg positive: administer HBIG × 1 plus vaccine booster to HCW
     - HBsAg unknown: test source patient for anti-HBs
       - If source patient anti-HBs positive, no treatment needed
       - If source patient anti-HBs negative: administer vaccine booster to HCW and check titer in 1 to 2 months
     - HBsAg negative: no treatment necessary
4. If HCW vaccinated against HBV but is a known nonresponder after vaccination (HBsAb-negative, anti-HBs <10 mIU/mL)
   - Determine HBsAg status of source patient
     - HBsAg positive: administer HBIG × 2 (separated by 1 month) and HBV vaccine
     - HBsAg unknown
       - Test source patient for anti-HBsAb
       - If source patient anti-HBsAb positive, no treatment needed
       - If high risk, treat as though HBsAg positive
     - HBsAg negative: No treatment needed

BOX 3 Centers for Disease Control and Prevention Recommended Regimens for Postexposure Prophylaxis (PEP) of Human Immunodeficiency Virus*

Preferred

Tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC)* 300 mg/200 mg daily + dolutegravir (DTG) 50 mg PO daily

or

Tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC)* 300 mg/200 mg daily + raltegravir (RAL) 400 mg PO BID

Alternatives

Elvitegravir (EVG)-cobicistat-TDF-FTC* 150 mg/150 mg/300 mg/200 mg daily

or

TDF-FTC 300 mg/200 mg* + pharmacologically boosted† protease inhibitor (darunavir [DRV] or atazanavir [ATV]) daily*

or

Rilpivirine (RPV)-TDF-FTC* 25 mg/300 mg/200 mg daily with food

PEP should be started within 1 to 2 hours from the exposure, and transmission blocking efficacy drops off significantly after 24 hours. PEP should be administered for a total duration of 28 days. In the United States, the PEP Hotline is a useful resource when making decisions surrounding PEP: telephone 888-448-4911.

*For patients with glomerular filtration rate (GFR) ≥30 mL/min, dose adjustment of TDF and FTC will be necessary and single-tablet coformulations cannot be used.
†Available as single-tablet coformulations.
‡EVG should not be prescribed to women of childbearing potential who are sexually active and not using a >99% effective method of contraception, nor should it be prescribed to individuals in the early first trimester of pregnancy (within 8 weeks since last menses), pending further data.
§With cobicistat 150 mg or ritonavir 100 mg, to increase levels of protease inhibitor. DRV dose 800 mg daily. ATV dose 300 mg daily. DRV should not be prescribed to individuals with sulfa allergy but ATV may be.
¶Regimens containing both cobicistat and TDF should not be prescribed to anyone with CrCl <70 mL/min.

Management of Hepatitis C Virus Exposure

Because 20% to 30% of cases of acute HCV spontaneously clear, it is important that HCV Ab positivity be followed by HCV RNA PCR to confirm that the source patient indeed has chronic HCV rather than spontaneously cleared HCV with residual antibody positivity.

Appropriate management of HCV exposure depends on the status of the source patient, as follows.

If HCV Ab positive

- Check to see if HCV RNA has previously been ordered, to determine chronicity.
- If no HCV RNA available, order HCV RNA PCR.

If HCV RNA is undetectable

- Source patient previously treated and cleared infection, attaining sustained virologic response,
  or
- Source patient independently spontaneously cleared HCV
- HCW not at risk for acquiring HCV

If HCV RNA detectable

- Source patient is at risk for transmitting HCV to HCW.

If source patient is of unknown HCV status

- Draw HCV Ab.
- HCV Ab should be followed by HCV RNA PCR if positive.
- If high risk patient, can draw HCV RNA PCR with initial draw.

If source patient has chronic HCV (HCV Ab and HCV RNA positive), exposed HCW should have:

- HCV Ab test and LFT at baseline (time of exposure) and at 6 months post exposure.
- HCV RNA at 4 to 6 weeks postexposure.

Because of the high rates of spontaneous clearance of acute HCV by 6 months, there is some variance in recommendations on timing of treatment. The American Association for the Study of Liver Diseases and Infectious Disease Society of America joint guidelines on acute HCV recommend that the patient and their clinician jointly decide whether a delay in treatment initiation while monitoring for spontaneous clearance is favored, and even if the decision is instead to initiate treatment during acute infection, monitoring HCV RNA first for a minimum of 12 to 16 weeks before starting treatment is recommended. In such cases, the same HCV regimens used for chronic HCV are used for acute HCV, are safe and well tolerated, and are >90% likely to result in cure. However, we advocate immediate treatment of acute HCV for HCWs who are found to have HCV RNA positive at 4 weeks postexposure. Risk benefit ratio favors this, especially with regard to the availability of safe, well tolerated, and highly effective treatment regimens with acceptable cost, which minimize the impact on the HCW, their potentially exposed family, and their patients over the period of high HCV viral load.

No preexposure or postexposure prophylaxis for HCV is currently recommended.

1. Immune globulin not recommended by CDC
   - Little evidence that humoral response critical in clearance
   - No efficacy in chimpanzees to prevent infection
2. Interferon (IFN) ± ribavirin not recommended
   - Trials:
   - IFN may only be effective to established infection
   - No effect in (underpowered) Japanese study
   - Early identification and treatment of infection offers best course of action currently for occupationally acquired HCV.

Suggested Readings

AASLD & IDSA joint guidelines on Management of Acute Hepatitis C Infection. http://www.hcvguidelines.org/sites/default/files/full_guidance_pdf_0.pdf.

CDC. Diagnoses of HIV infection in the United States and dependent areas, 2010. HIV Surveillance Supplemental Report. 2012;17(3).

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Spradling PR, Rupp LB, Moorman AC, Lu M, Tedder RS, Gordon SC, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. Clin Infect Dis. 2012;55(8):1047–1055.

Updated US Public health service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR. 2001;50(RR-11):1–42.

Weiss EL, Mahary MA, Wang C, et al. Prevalence of blood-borne pathogens in an urban, university-based general surgical practice. Ann Surg. 2005;241(6):905–908.

Antifungal Therapy in the Surgical Patient

Ashley D. Meagher, MD, MPH, and Heather L. Evans, MD, MS

Nosocomial fungal infections are an increasing problem in hospitalized surgical patients. These infections are frequently seen in critically ill surgical patients, with bloodstream infection the most common etiology. The most commonly seen infections are caused by *Candida* species. Other significant fungal pathogens in surgical patients include *Aspergillus*, *Cryptococcus*, mucormycosis, and emerging pathogens such as *Fusarium*. Superficial fungal infections are rarely dangerous, but invasive fungal infections continue to be associated with serious complications and a high mortality. Surgical patients frequently have many of the risk factors associated with invasive fungal infection, including critical illness, recent abdominal surgery, solid organ transplantation, exposure to broad-spectrum antibiotics, as well as any additional immunocompromised states. Identification and diagnosis of infection can be difficult, which frequently delays initiation of appropriate antifungal therapy. Surgeons may be involved in the care of patients with invasive fungal infections in many settings, from debridement of infected tissue to treatment in a critical care unit. This chapter summarizes fungal infections typically encountered, with special emphasis on the use of antifungal therapy as treatment (Table 1).

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TABLE 1 Patient Types and Treatment Options for Fungal Infections

Infection	Patient Type	Primary and Alternative Treatments	Duration of Therapy	Comments
Candidemia	Critically ill, abdominal surgery, cancer chemotherapy, vascular access, burns, parenteral nutrition	Primary Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg × 1, then 100 mg/day IV Micafungin 100 mg/day IV Fluconazole 800 mg × 1, then 400 mg/day IV or PO Alternative Deoxycholate AmB 0.7–1.0 mg/kg/day IV Lipid AmB 3–5 mg/kg/day IV Voriconazole 6 mg/kg BID × 2 doses, then 4 mg/kg BID	14 days after clearance of blood cultures Longer if ocular involvement. If possible, can switch to oral agent to complete therapy once patient has stabilized.	Remove vascular access devices, if possible. Do not use fluconazole for critically ill patients. Evaluate for ocular involvement with funduscopic examination.
Candiduria/UTI	Urinary catheter, DM, kidney transplant recipients	Primary Fluconazole 200–400 mg/day IV or PO	14 days	Patients with asymptomatic candiduria do not routinely need to be treated. Exceptions are neutropenia or planned instrumentation.
		Alternative Deoxycholate AmB 0.5–0.6 mg/kg/day IV	1–7 days	
		Flucytosine 25 mg/kg QID PO	7–10 days	
Oropharyngeal candidiasis	Immunocompromised, radiotherapy, ill-fitting dentures	Primary Clotrimazole 10 mg 5 times/day PO Nystatin suspension (100,000 U/mL) 4–6 mL QID PO Fluconazole 100–200 mg/day PO Alternative Fluconazole solution 200 mg/day PO Posaconazole 400 mg BID × 2 days, then 400 mg/day DID PO Voriconazole 200 mg BID PO Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg × 1, then 100 mg/day IV Micafungin 100 mg/day IV Deoxycholate AmB oral suspension 100 mg/mL QID PO or 0.3 mg/kg IV daily	7–14 days	Use topical therapy for mild disease; relapses more common with echinocandins.
Esophageal candidiasis	Immunocompromised	Primary Fluconazole 200–400 mg/day PO or 400 mg/day IV Alternative Micafungin 150 mg/day IV Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg/day IV Deoxycholate AmB 0.5–0.7 mg/kg/day IV Posaconazole 200 mg/day PO Voriconazole 200 mg BID IV or PO Posaconazole 400 mg BID PO	14–21 days	Relapses may be more common with echinocandins.

TABLE 1 Patient Types and Treatment Options for Fungal Infections—cont'd

Infection	Patient Type	Primary and Alternative Treatments	Duration of Therapy	Comments
Vulvovaginal candidiasis	Antibacterial therapy, DM	Topical therapy (e.g., clotrimazole, nystatin, miconazole) Fluconazole 150 mg × 1 PO	Schedules vary by agent	Vulvovaginal candidiasis, even if recurrent, usually does not result from an immunocompromised state.
Aspergillosis	Abnormalities of neutrophil number or function, structural lung abnormalities, burns	Primary Voriconazole 6 mg/kg IV/1 × 2, then 4 mg/kg/day × others Caspofungin 70 mg × 1, then 50 mg/day IV Posaconazole 800 mg/day in 2–4 divided doses IV or PO	Length of treatment not clear	Consider monitoring voriconazole and posaconazole levels to help guide therapy.
Mucormycosis	Systemic immunosuppression, burns, trauma, near drowning, neutropenia, DM, deferoxamine use	Primary Lipid AmB 5–7.5 mg/kg/day + posaconazole	Length of treatment not clear	Debridement and excision are often needed. If patient is stable, consider switching to posaconazole after 3 weeks AmB.

AmB, Amphotericin B; BID, twice daily; DM, diabetes mellitus; IV, intravenously; PO, orally; QID, four times daily; UTI, urinary tract infection.

SPECIFIC FUNGI

Candida

Candida species are the most common fungal pathogens in surgical patients, comprising approximately 80% of fungal nosocomial infections. These fungi are commensals of the human gastrointestinal (GI) tract, genital tracts, and skin. Infections are almost always of endogenous origin, particularly when host defenses break down or are breached. Patients with a central venous catheter, prolonged exposure to broad-spectrum antibiotics, or those who have had a recent operation, particularly when there has been GI contamination, are at greater risk for candidiasis. Iatrogenic spread between patients by healthcare workers can affect fungal colonization patterns and subsequent infecting species, as can exposure to antifungal agents.

There are at least 15 species of *Candida* identified; however, more than 90% of invasive infections are caused by *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei*. There are increasing infectious complications with other *Candida* species such as *C. dubliniensis*, *C. lusitaniae*, and *C. auris*. *C. albicans* still comprises approximately one half of infections, and the prevalence of non-*albicans* species vary based on geographic location and special populations. *Candida* is the third most common bloodstream pathogen, and accounts for 9% to 10% of all bloodstream infections in hospitalized patients. Awareness of non-*albicans* species is crucial because they frequently have reduced susceptibilities or intrinsic resistance to common antifungal therapies.

Infection resulting from *Candida* can be broadly divided into mucosal and systemic disease. Mucocutaneous infections are generally benign and limited to local overgrowth. These are mediated by changes in local flora. Oropharyngeal and candidal esophagitis generally occur in immunocompromised patients, including those with human immunodeficiency virus (HIV), those receiving chemotherapy, or being treated with corticosteroids. Cutaneous and vulvovaginal candidiasis are sometimes triggered by antimicrobial use, poor glycemic control, or may be spontaneous.

Surgical patients at elevated risk for invasive candidiasis are frequently critically ill with need for central venous catheter, broad-spectrum antibiotics, hemodialysis, or total parenteral nutrition. In addition, surgical diseases, such as perforation of the gastrointestinal tract, intestinal anastomotic leak, or pancreatitis, increase the risk for invasive candidiasis. Most frequently, invasive infection is in the form of candidemia; however, peritonitis, endocarditis, mediastinitis and meningitis may occur in certain postsurgical patient populations. Approximately 50% of blood cultures fail to demonstrate candidemia, so critically ill patients with the risk factors of upper gastrointestinal perforation, prolonged broad-spectrum antibiotic treatment, or known *Candida* colonization should be empirically treated with antifungal therapy.

Other Fungi

Other invasive fungal infections, once rare, are on the rise, likely secondary to the increasing number of immunocompromised patients. Patients with advanced malignancy, hematologic disease, HIV, as well as organ transplant recipients and those with autoimmune conditions are at increased risk for invasive fungal infection. *Aspergillus* is the most common species encountered. Patients with abnormal lung anatomy or function, such as with cystic fibrosis, chronic lung disease, lung transplantation, or prolonged mechanical ventilation may be chronically colonized with *Aspergillus* or other molds. These may progress to invasive or saprophytic disease. Invasive aspergillosis most commonly manifests as a progressive, cavitary pulmonary infection that can result in hemoptysis. Cavitary lesions usually are seen on chest radiograph or computed tomography of the chest. Cutaneous infection may occur after a break in the skin barrier, either because of burn injury or after an operation in a severely immunocompromised patient. *Mucormycosis*, *Cryptococcus*, and infection with endemic fungi (*Coccidioides*, *Blastomyces*) are rarely seen in primary surgical patients outside of organ transplantation or following burn or traumatic injuries contaminated by soil. These infections may

be reactivated with initiation of immunosuppressive medications or in severe critical illness.

ANTIFUNGAL AGENTS

Azoles

The azoles are a commonly used class of antifungal agents with activity against a broad range of fungi. These drugs inhibit ergosterol biosynthesis, thereby impairing formation of the fungal cell membrane. Azoles are available in oral, intravenous (IV), or topical forms, depending on the specific agent. Azoles have the potential for multiple drug interactions via the cytochrome P450 system, and care must be taken when they are administered at the same time as other drugs metabolized by these mechanisms.

Fluconazole

Fluconazole is the predominant azole used to treat fungal infections in surgical patients. It is effective against most species of *Candida* and is used often as first-line therapy. It is available in oral and IV formulations and is generally well tolerated. Fluconazole has excellent activity against *C. albicans* but has variable activity against *C. glabrata*, which can account for up to 25% of candidal infections. It is inactive against *C. krusei*. Fluconazole is a first-line agent for oropharyngeal and esophageal candidiasis as well as for urinary tract infections resulting from *Candida*. It also has a role in cases of invasive candidiasis in moderately ill, nonneutropenic patients, although dosing needs to be significantly higher (800–900 mg/day). Dose adjustment is required with renal dysfunction. The use of fluconazole has been associated with hepatic toxicity, GI upset, rashes, and drug interactions. Resistance to fluconazole is on the rise, so sensitivity testing should be performed in high-risk patients.

Voriconazole

Voriconazole is effective against most species of *Candida* and *Aspergillus* and multiple other filamentous fungi. It is available in oral and IV formulations. Voriconazole is the first-line treatment for invasive aspergillosis and can be used in cases of invasive candidiasis. It has excellent bioavailability, allowing for oral administration. Steady-state levels are reached more rapidly with IV loading doses of 6 mg/kg every 12 hours for 2 doses, followed by 4 mg/kg IV every 12 hours or 200 mg orally every 12 hours. Patients with renal dysfunction should receive the oral form of voriconazole for maintenance because the cyclodextrin carrier used in the IV formulation can accumulate and may damage the kidneys. Patients with hepatic impairment should receive the standard loading dose, but the maintenance dose should be decreased by 50%. Voriconazole is associated with multiple adverse reactions, most commonly visual changes such as photophobia, reduction in visual acuity, and blurred vision. Routine monitoring of drug levels is not recommended; however, monitoring can be helpful when there are concerns about efficacy or toxicity. Like fluconazole, voriconazole is associated with multiple drug interactions.

Posaconazole

Posaconazole is effective against a broad range of fungi, including most species of *Candida* and *Aspergillus* and many filamentous fungi, including the zygomycetes. It is available in oral suspension, delayed-release tablets, and IV formulations. Oral suspension or delayed-release tablets are indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients at high risk of developing these infections because of being severely immunocompromised (e.g., recipients of hematopoietic stem cell transplant with graft-versus-host disease, those with hematologic malignancies with prolonged neutropenia from chemotherapy). Attainment of steady-state levels can take a week or longer, and for this reason it generally is not recommended as first-line therapy for established infections. The dose for invasive fungal infections varies depending on the formulation used, and it is imperative that this be taken into account. As with voriconazole, IV dosing should be reduced in patients with renal impairment because of toxicity from accumulation of the associated vehicle. Side effects of posaconazole are common and include fever, nausea, diarrhea, headache, hypokalemia, and thrombocytopenia. Long QT syndrome and hepatotoxicity are less common but serious complications. Posaconazole also is associated with multiple drug interactions similar to those with other azoles.

Itraconazole

Itraconazole's spectrum of activity is similar to that of fluconazole. It is active against *Candida* but also against some filamentous and dimorphic fungi, including *Aspergillus*, *Blastomyces*, and *Histoplasma*. It also can be used to treat onychomycosis. In some countries, itraconazole is available for IV therapy. Itraconazole has been of limited use in surgical patients because of the erratic bioavailability of the oral capsule, which has improved with the oral cyclodextrin solution. Additional factors limiting its use include the need for drug-level monitoring, GI upset (particularly with the cyclodextrin solution), hepatic toxicity, and negative inotropic cardiac effects that can cause or worsen congestive heart failure.

ECHINOCANDINS

The echinocandins (caspofungin, micafungin, and anidulafungin) are an important class of antifungal agents, and they have emerged as a preferred treatment class for many fungal infections. They act by inhibiting fungal cell wall formation and have fungicidal activity against almost all *Candida* species. Echinocandins are most widely for the treatment of invasive candidiasis, especially in critically ill and neutropenic patients. They also are used for empiric antifungal therapy in immunocompromised patients with neutropenic fever. Echinocandins are first-line therapy against invasive candidiasis because they are fungicidal against a variety of *Candida* species, including fluconazole-resistant *C. glabrata* and *C. krusei*. Treatment failures have been reported with *C. parapsilosis*, which has some innate resistance to the echinocandins. Under selective pressure, other species of *Candida* may develop resistance. They are not ideal for cases of oropharyngeal and esophageal candidiasis. The echinocandins inhibit growth of *Aspergillus*, but they are not fungicidal against this species. There may be a role for their use as salvage therapy in refractory *Aspergillus* infections, but should be used in combination treatment. Experience suggests that this class is among the safest and best tolerated of the antifungals available. They are available via the IV route only.

Polyenes

Polyene antibiotics are a class of antimicrobial compounds that bind to ergosterol, the main sterol in the fungal cell membrane, and cause depolarization. This increases membrane permeability and leads to leakage of intracellular cations causing cell death. Amphotericin B and nystatin are examples of polyene antimycotics. Amphotericin B deoxycholate, which was the standard drug for the treatment of candidiasis for decades, demonstrates rapidly fungicidal in vitro activity against most species of *Candida* but is associated with significant nephrotoxicity. Because of this adverse effect, it is rarely used. Instead, most physicians use a lipid-based amphotericin B formulation, either liposomal amphotericin B or amphotericin B lipid complex, when selecting a polyene agent. These lipid-based compounds have much less toxicity than amphotericin deoxycholate, but are significantly more expensive. Because of this, amphotericin B is now primarily used in salvage therapy of the most refractory invasive fungal infections. Nystatin is frequently used to treat mucocutaneous candidiasis in a powder, cream, or oral liquid form.

COMMON FUNGAL INFECTIONS

Mucocutaneous Disease

Mucocutaneous fungal infections are very common, and their risk factors, including diabetes mellitus, obesity, treatment with antibiotics or steroids, and inflammatory skin diseases, are found frequently in surgical patients. These infections can cause significant discomfort but are rarely dangerous. Typical sites of infection include the skin, oropharynx (thrush), genitalia, and esophagus. Patients with symptomatic superficial infections should be treated, but because *Candida* species normally exist on the skin and mucosal surfaces as commensals, culturing the organism from a superficial surface in the absence of symptoms is not an indication for treatment.

Cutaneous Candidiasis

Cutaneous candidiasis is almost always caused by *C. albicans* and may occur anywhere on the body but typically involves intertriginous areas (candidal intertrigo). Warm, moist, and macerated skin sites, such as inframammary crease, large abdominal folds, the axillae, or the groin, are common sites of involvement and must be examined and treated. Open incisions, wounds, or decubitus ulcers being treated with moist dressings are also at risk for infection. The affected area may be ruby red and moist. The skin can be eroded with scalloped scaling at the borders. Satellite lesions just beyond the border of the grossly affected area are common.

Diagnosis generally is based on clinical appearance. Superficial candidiasis can be treated with topical therapy. For moist macerated skin, an antifungal powder formulation is preferable because of its drying properties. Nystatin (100,000 units/g) and miconazole (2%) are available as either a powder or a cream. A variety of other antifungal creams are also available, such as ketoconazole (2%) and clotrimazole (1%). More extensive infections may require oral azole drugs in conjunction with topical treatments.

Candidal Vulvovaginitis

Candidal vulvovaginitis is common, and most women will have at least one episode during their lifetime. Most infections are caused by *C. albicans* and represent a patient's own organisms. Risk factors include antibiotics, diabetes mellitus, and pregnancy. Vulvovaginitis may be seen with local irritation, itching, erythema, thick white vaginal discharge, dysuria, and dyspareunia. Patients often make a self-diagnosis of "yeast" vaginitis. This can be confirmed by identifying *Candida* elements (pseudohyphae and blastoconidia) on microscopic evaluation of a 10% potassium hydroxide–treated sample. Fungal cultures are usually neither necessary nor helpful.

There are multiple intravaginal treatment options, including oral nystatin tablets (100,000 units/tablet), various topical azole creams and vaginal suppositories (e.g., miconazole 2%, butoconazole 2%, clotrimazole 1%, terconazole 0.4% and 0.8%, tioconazole 6.5%, miconazole cream 2% and 4% or suppositories at 100 and 200 mg) and oral fluconazole (150 mg as a single dose). The duration of treatment varies with different agents and concentrations. Most infections can be treated with a single dose of oral medication or a 1- to 3-day course of topical therapy. Some patients with recurrent or severe disease require longer treatment with either 7 to 14 days of topical azole or 150 mg of fluconazole in two sequential oral doses (second dose 72 hours after initial dose).

Oropharyngeal Candidiasis

Oropharyngeal candidiasis mainly presents in immunosuppressed patients, particularly after organ transplantation and in those with advanced HIV. Additional risk factors include extremes in age, poorly controlled diabetes mellitus, nutritional deficiencies, inadequately fitting dentures, systemic or inhaled steroids, radiotherapy, and cytotoxic chemotherapy. Presentation of oropharyngeal candidiasis in a patient without risk factors should spark a search for underlying disease. This may be the first manifestation of advanced HIV. Clinical manifestations include thrush, which is characterized by curd-like, white patches on multiple surfaces of the oral mucosa, and erythematous candidiasis (acute atrophic candidiasis), which occurs by itself or in association with the white patches. Symptoms include local pain, burning, and changes in taste perception. Microscopic examination of scrapings of the involved area may help with the diagnosis if it is doubtful.

Oropharyngeal candidiasis is almost always caused by *C. albicans* and usually responds to topical treatments such as clotrimazole troches, 10 mg 5 times daily, or nystatin suspension (nystatin "swish and swallow"). Systemic antifungal medication such as fluconazole 100 to 200 mg daily, or itraconazole 200 mg daily, may be necessary for oropharyngeal infections that do not respond to topical therapy. Treatment is typically for 7 to 14 days but may need to be extended, depending on response to therapy.

Esophageal Candidiasis

Esophageal candidiasis usually occurs in patients with a highly compromised immune system. Additional risk factors include advanced liver disease and inhaled steroids. Usual symptoms include odynophagia, dysphagia, and retrosternal pain. Concurrent oropharyngeal candidiasis is common but not always present. Infection is generally limited to the mucosa. Complications include dehydration and malnutrition resulting from poor oral intake, esophageal strictures, and even esophageal perforation.

Treatment is with oral fluconazole 200 to 400 mg daily. If the patient is unable to tolerate oral therapy, fluconazole 400 mg daily should be delivered intravenously. Therapy is typically for 14 to 21 days, depending on patient response. Oropharyngeal and esophageal candidiasis refractory to fluconazole occasionally may develop in patients who are highly immunosuppressed or those previously treated with an azole and have developed resistance. Alternative oral options include voriconazole solution 200 mg/day, posaconazole 200 mg twice daily, and posaconazole 400 mg twice daily. These regimens are more and are potentially more toxic than fluconazole. Treatment may be ineffective if resistance has developed to the entire azole class. IV antifungal therapy with echinocandins (micafungin 150 mg daily, caspofungin 70 mg loading dose, then 50 mg daily, and anidulafungin 200 mg daily) can be effective, but use is associated with higher relapse; therefore, recommended dosages are higher. Systemic amphotericin B deoxycholate or lipid formulations are another option, but can be associated with substantial toxicity. Patients at significant risk for oropharyngeal and esophageal candidiasis, such as those receiving cytotoxic chemotherapy or high-intensity immunosuppression or those who have advanced HIV, should be treated with prophylaxis. Topical agents such as nystatin or clotrimazole are generally effective. Systemic fluconazole 400 mg by mouth or IV daily also may be effective as suppressive therapy in cases of recurrent infection.

Candiduria

Candiduria is a common finding in hospitalized surgical patients, or those with long-term indwelling urinary catheters. This may represent a spectrum of clinical scenarios, from colonization and cystitis to more serious conditions such as upper urinary tract infection or disseminated disease. It is often difficult to distinguish true urinary infection from mere colonization, particularly in patients with indwelling urinary catheters. The decision to treat should be based on the clinical scenario and not solely on the presence of yeast in urine cultures.

Treatment is indicated in patients who are symptomatic, neutropenic, have renal allograft, or those with urologic manipulation. Removal or exchange of urinary catheters may be helpful in clearing candiduria. Oral fluconazole (200 mg or 3 mg/kg daily) for 7 to 14 days is recommended for the treatment of cystitis resulting from *Candida*. Alternatives include systemic amphotericin B deoxycholate or oral flucytosine, although the latter frequently results in the rapid development of resistance. Bladder irrigation with amphotericin B

deoxycholate may be useful in cases of refractory cystitis from azole-resistant strains. Lipid formulations of amphotericin B should be avoided because they do not achieve adequate concentrations in the urinary system. Patients with persistent candiduria and additional risk factors should be evaluated for presence of a fungus ball or renal parenchymal disease.

FUNGAL BLOODSTREAM INFECTIONS

Fungi are the fourth most common pathogen isolated in bloodstream infections overall and the third most common pathogen in intensive care units in the United States. The majority of cases are attributed to *Candida* species, in particular *C. albicans*. Candidemia occurs more commonly at the two extremes of age. Despite advances in pharmacologic agents, fungal bloodstream infections continue to carry an associated mortality rate of between 40% and 60%.

As with other candidal infections, risk factors include prolonged antibiotics treatment, total parenteral nutrition, neutropenia, immunosuppression, hemodialysis, previous fungal colonization, presence of an intravascular catheter, major surgery, and burns. Prolonged critical illness increases the risk of colonization with *Candida*, which then increases the risk of bloodstream infection. It is believed that once colonization occurs, *Candida* obtains access to the bloodstream via translocation across the mucosal barrier in the GI tract, IV catheter, or from an invasive localized infection. Blood cultures remain the gold standard for diagnosis; however, sensitivity of blood cultures is less than 50%. Newer diagnostic assays, including polymerase chain reaction, beta-D-glucan, and T2Candida, are still undergoing investigation and are not widely used. *C. glabrata* has been increasing and now comprises about one fourth of bloodstream isolates. This organism has an increased likelihood of resistance to azoles and potential for multidrug resistance. Sensitivity testing should be performed on all candidal bloodstream isolates.

Treatment recommendations vary for specific patient populations, taking into consideration recent drug exposure and risk factors for infection due to resistant strains. Fluconazole remains a reasonable option for noncritically ill patients who have no previous exposure to azoles and lack additional risk factors for *C. glabrata* (e.g., advanced age, malignancy, diabetes mellitus). Fluconazole should be given with an initial loading dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) daily. Echinocandins are preferred for treatment of patients with greater risk factors, including neutropenic patients, and those at risk for infection with *C. glabrata* or *C. krusei* isolates. Echinocandin dosing recommendations include caspofungin at a loading dose of 70 mg, then 50 mg daily; micafungin 100 mg daily; or anidulafungin at a loading dose of 200 mg, then 100 mg daily. First-line therapy in neutropenic patients remains echinocandins; however liposomal amphotericin B formulations (3–5 mg/kg daily) also may be used. Patients should have blood cultures drawn every 1 to 2 days to monitor for clearance. Treatment should continue for 2 weeks after the first documented negative blood culture.

Central venous catheters should be removed as early as possible in patients with candidemia because it may be primary source of infection or become infected secondarily. Retention of the catheter may be considered in patients with implanted access devices and candidemia in the setting of cytotoxic chemotherapy and neutropenia. All patients with candidemia should have a dilated funduscopic examination by an ophthalmologist within the first week after diagnosis to evaluate for chorioretinitis or endophthalmitis.

Intraabdominal Fungal Infections

Intraabdominal fungal infections occur as a result perforation of the upper gastrointestinal tract, as a complication of an intraabdominal operation or, less commonly, from disseminated disease. *Candida* is the most commonly isolated species, and mortality rates range from 20% to 40%. Risk factors for *Candida* intraabdominal infections include pancreatic necrosis, recurrent abdominal operation, upper gastrointestinal tract perforation, anastomotic breakdown, and multifocal colonization. Patients should be classified as low or high risk, based on the presence of these risk factors.

Diagnosis of an intraabdominal fungal infection should be based on culture results from intraoperative samples or by percutaneous aspiration. Intraoperative fungal cultures or percutaneous aspiration should be obtained for patients at high risk of intraabdominal fungal infection to identify the presence of resistant organisms and to guide antimicrobial therapy. The presence of yeast in samples obtained from an existing surgical drain may simply represent colonization and not necessarily an intraabdominal infection. The Surgical Infection Society recommends against empiric antifungal treatment in low-risk patients, as well as most high-risk patients. However, patients with upper gastrointestinal perforation who are critically ill seem to be at even higher risk; so empiric antifungal therapy should be considered in this specific population.

Early source control is essential in managing these infections. Antifungal treatment with fluconazole is appropriate for most patients with infection due to *C. albicans*. An echinocandin should be used for critically ill patients and those with isolates likely to be resistant to the azoles. The optimal duration of treatment is unclear. A recent multinational expert panel recommended treatment for 10 to 14 days for intraabdominal *Candida* infections. However, the Surgical Infection Society's Study to Optimize Peritoneal Infection Therapy evaluated the duration of treatment for patients with complicated intraabdominal infections and demonstrated that 4 days of treatment following adequate source control resulted in similar outcomes compared with patients who received a longer course of therapy. Although patients with fungal infections were included in that study, it is unclear whether these recommendations apply to this group. The current Infectious Diseases Society of America guideline for management of candidiasis recommends that duration of treatment be determined by the adequacy of source control and clinical response.

FUNGAL SURGICAL SITE INFECTIONS

Approximately 3% of surgical site infections (SSIs) are fungal, with *C. albicans* being the most common fungal pathogen. Although infrequent, these infections are important to recognize because there have been case reports of *C. albicans* causing necrotizing infections at a surgical or central line site. Certain patient populations, such as those suffering from traumatic injuries, burns, or secondary or tertiary peritonitis are at higher risk of developing fungal SSIs.

Burn patients are at particularly high risk, with fungus responsible for approximately 20% to 25% of burn wound infections, often as one isolate of a polymicrobial infection. Fungal wound infections in this population typically occur approximately 2 weeks after burn injury and have been associated with a greater mortality. It is unclear if fungal SSIs are the direct cause of death or simply represent a more severe disease state in these patients. Diagnosis of a fungal wound infection in burn wounds requires histopathologic evidence of fungal invasion into viable tissue. The presence of fungi in necrotic tissue is considered to represent colonization. These patients require both surgical debridement as well as systemic antifungal therapy.

Both *Candida* and *Aspergillus* have infrequently been implicated in posttransplantation wound infections, including osteomyelitis and mediastinitis. The mainstay of treatment is surgical debridement and several months of antifungal therapy.

FUNGAL PULMONARY INFECTIONS

Fungi represent only a small fraction of pathogens responsible for pulmonary infections, but they are important to recognize in light of the growing population of immunosuppressed patients. Opportunistic organisms most commonly cause fungal pneumonias, whereas pulmonary infections due to endemic fungi are rare in surgical patients.

Candida

Candidal pneumonia is very rare, despite *Candida* being a common organism found in respiratory secretions. Most cases are related to disseminated *Candida* infection arising from distant sites and usually occur among patients with additional risk factors. As with most *Candida* infections, prolonged antibiotic use, hematologic malignancies, and other immunocompromised states are the primary risk factors. Definitive diagnosis of *Candida* pneumonia is based on isolating the organism from lung tissue samples because growth of *Candida* from respiratory secretions generally indicates asymptomatic colonization and should not be treated. There are no clear guidelines for treatment of primary *Candida* pneumonia. Most cases have been treated with amphotericin B deoxycholate or lipid formulations, although milder cases have been treated successfully with fluconazole. Disseminated disease should be treated similarly to candidemia.

Aspergillus

Invasive aspergillosis is an increasingly important problem in surgical patients, particularly the immunocompromised patient. It remains an uncommon disease but carries significant mortality. Early epidemiologic studies in the United States have estimated its incidence to be 12 cases per 1 million people per year.

Invasive aspergillosis is most commonly seen as a progressive, cavitary pulmonary infection that can result in hemoptysis. Common symptoms include fever, dyspnea, cough, and pleuritic chest pain. However, one third of patients are asymptomatic initially. Cavitary lesions are usually identified on plain radiographs or computed tomography of the chest. Other radiologic findings such as the "halo" sign and "air crescent" sign are highly suggestive of *Aspergillus* pneumonia but nonspecific. Diagnosis can be difficult because of the relative insensitivity of microscopy and culture to detect *Aspergillus*. A definitive diagnosis requires both histopathologic evidence of infection and culture of the organism from a sterile site. Galactomannan antigen detection, beta-D glucan detection, and polymerase chain reaction are additional laboratory studies that may improve detection in certain high-risk populations. Voriconazole remains the treatment of choice; amphotericin B is second line if voriconazole is not available. Echinocandins (alone or in combination) should be reserved as salvage therapy. Surgical resection of a pulmonary lesion may be indicated in patients with hemoptysis, bacterial superinfection, or as salvage in refractory infection; however, many patients with this level of disease are too ill to safely undergo surgery.

Mucormycosis

Mucormycosis, also referred to as zygomycosis, is another very rare infection caused by one of the organisms belonging to the order Mucorales, most commonly *Rhizopus* spp. or *Mucor* spp. It has an incidence of less than 2 per 1 million people per year.

Although this infection typically affects immunocompromised patients, it may also be seen after traumatic injuries, near drownings, or burns. Additional risk factors include poorly controlled diabetes mellitus, malignancy, and treatment with the iron chelator deferoxamine. Because of its invasive nature, this infection carries significant morbidity, with mortality rates greater than 50%. The most common sites of mucormycosis include the sinuses, respiratory tract, and skin. Less commonly, the GI tract may be involved. Infection is commonly locally invasive to adjacent structures such as the orbits, brain, and blood vessels, leading to extensive tissue destruction. Vascular invasion may result in serious complications such as massive hemorrhage. Pulmonary mucormycosis is characterized by angioinvasion and a high degree of tissue necrosis leading to rapidly progressive pneumonia, development of cavitations, and hemoptysis. Reversed "halo" signs may be an early radiographic finding but is nonspecific and also may be seen in aspergillosis. Symptoms of pulmonary infection are nonspecific, with patients typically having fever and hemoptysis.

Definitive diagnosis of mucormycosis requires histologic evidence of tissue invasion, but bronchoalveolar lavage is helpful in making a diagnosis. Management of this disease requires a multidisciplinary approach. This includes correction of metabolic abnormalities, reduction of immunosuppression medications, and excision or debridement of infected tissues. Aggressive surgical debridement is key to preventing further invasion. This is particularly important if there is angioinvasion or necrosis. Liposomal amphotericin B at doses of at least 5 mg/kg per day is recommended. Posaconazole may be used in combination with liposomal amphotericin B in refractory cases or for chemoprophylaxis and suppression. Echinocandins have not been shown to have in vitro activity against this species and are therefore not recommended.

Suggested Readings

Kanj SS, Kanafani ZA, Chakrabarti A, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med. 2013;39:2002–2010.

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Use of Opioids in the Postoperative Period

Richard J. Barth Jr, MD

CURRENT OPIOID EPIDEMIC

Opioid overdose is now the leading cause of injury-related death in the United States. There were 42,600 deaths from opioid overdose in 2016 compared to 37,000 deaths from motor vehicle crashes. Unfortunately, young people are most afflicted by this problem—20% of all deaths in persons between the ages of 24 and 35 were due to opioids. The death rate from prescription opioid overdose has quadrupled between 2000 and 2016. In addition, deaths from heroin and fentanyl are skyrocketing; the vast majority of people who use these drugs start with prescription opioids.

The rise in opioid overdose deaths has been temporally linked to rising rates of opioid prescriptions, which have similarly quadrupled between 2000 and 2015. In 2012 in the United States, 82 opioid prescriptions were written per 100 persons. Over 5 million Americans report current opioid abuse (within 30 days), and 18 million report abuse during their lifetime.

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The rise in opioid overdose deaths has been temporally linked to rising rates of opioid prescriptions, which have similarly quadrupled between 2000 and 2015. In 2012 in the United States, 82 opioid prescriptions were written per 100 persons. Over 5 million Americans report current opioid abuse (within 30 days), and 18 million report abuse during their lifetime.

Surgeons play an important role in this epidemic. Surgeons are responsible for a significant number of opioid prescriptions, and a substantial number of overdose deaths can be linked to opioid prescriptions written by surgeons. Although it was previously taught that prescribing opioids to patients for acute pain rarely resulted in long-term opioid use, recent studies have shown that 5% to 10% of opioid-naïve patients prescribed an opioid after surgery become long-term users. Furthermore, the size of the prescription matters. In one study, patients given a 1-day prescription had a 6% chance of being on opioids at 1 year after surgery, compared to a 13% chance if given an 8-day prescription. Thus, surgeons expose their patients to the risk of becoming long-term opioid users when they prescribe opioids for postoperative pain. Another problem arises when opioids are over-prescribed, excess pills can be diverted to others who were not the recipients of the original prescription. It is estimated that over 70% of chronic opioid users receive their medications through methods of diversion.

IN-HOSPITAL OPIOID-RELATED ADVERSE EVENTS

In addition to the risk of death from outpatient opioid overdose, the use of opioids in the inpatient setting is also associated with significant morbidity. Although opioids are effective analgesics, opioid-related adverse drug events occur in 5% to 10% of surgical patients. These adverse events include respiratory depression, ileus, nausea and vomiting, confusion, delirium, and dependence. Patients experiencing adverse opioid effects have a higher rate of inpatient mortality, length of stay, and cost of hospitalization.

NONOPIOID PAIN MANAGEMENT PLANS

Several alternatives to opioids are available for use in comprehensive pain management strategies and are implemented in enhanced recovery protocols. Pain from many operations can be decreased through the use of regional blocks. Regional blocks are highly effective in relieving pain and in decreasing opioid requirements, and have little morbidity. Regional blocks are well described for many operations, from mastectomies to hernia repairs to hemicolectomies. The use of epidural anesthetics to provide analgesia in the postoperative period for major abdominal surgery has also been shown to have several advantages, including decreased need for opioids. Infusion of local anesthetic into the wound prior to incision and the use of transdermal lidocaine patches should also be considered as part of the perioperative pain management plan.

Studies of patients with acute pain from surgery have indicated that ibuprofen and acetaminophen are more effective pain relievers than opioids. Meta-analyses by the Cochrane Database of Systematic Reviews have evaluated the effectiveness of various analgesics to determine the proportion of patients who achieved at least a 50% reduction of acute pain for 4 hours. They found that the combination of ibuprofen 400 mg and acetaminophen 1000 mg relieved pain in 79% of patients. Ibuprofen 400 mg alone relieved pain in 52% of patients. In contrast, oxycodone 5 mg alone relieved pain in only 23% of patients, similar to the 17% of patients whose pain was relieved by placebo. Randomized trials of emergency room patients with acute pain from extremity injuries have also shown that combinations of acetaminophen and ibuprofen are as effective as acetaminophen plus opioids. Most patients undergoing elective surgery have no contraindications to the use of acetaminophen and ibuprofen. Liver toxicity is very rare if acetaminophen is dosed correctly. Ibuprofen needs to be carefully used in patients with renal dysfunction. A meta-analysis has shown that the intraoperative use of ketorolac does not result in increased bleeding rates. The use of these medications can enable many patients to use less opioids and especially in the outpatient setting can enable some to avoid opioid use completely.

A wealth of studies have also demonstrated that the preoperative use of gabapentin can also decrease pain and decrease postoperative opioid use.

Studies in cognitive psychology have shown that establishing the expectation with patients that their pain is going to be relieved by the proper and acetaminophen is likely to contribute to the success of this approach. Indeed, discussing with patients prior to surgery what level of pain is expected, and what the pain management strategy is going to be, lets them know that their surgeon cares about their discomfort and has a thoughtful plan about how to both manage their pain and minimize complications from excessive opioid use.

APPROPRIATE OPIOID PRESCRIBING

The problem for surgeons is that they must balance their desire to adequately relieve their patients' postoperative pain with a responsibility for their patients' long-term wellbeing and for overall population health. The goal of appropriate opioid prescribing is to prescribe the optimal number of opioid pills so that patients' pain is adequately relieved and leftover pills are minimized.

Several recent studies that have queried patients about how many opioids they actually used have documented that opioids are being overprescribed for most operations. These studies have shown that only 25% to 40% of opioids that are prescribed are actually consumed by patients. Over three-quarters of patients have unused opioids left over after surgery. Why are surgeons overprescribing? Several factors probably come into play. Primarily, it is likely due to a lack of knowledge regarding how many opioids were required for adequate pain control; until recently data on postoperative opioid use was lacking. Indeed, most studies on overprescribing also report wide variations in the number of opioids prescribed by different providers, reflecting a lack of evidence-based data to guide decisions. Lacking knowledge, surgeons might just choose the default number of pills that appears on an electronic medical record prescription, which in some cases is quite high. Until recently, opioids could not be electronically prescribed, so surgeons prescribed an excess to prevent patients from having to return to the clinic to obtain opioid refills. Surgeons may be concerned that if they do not adequately treat patients' pain they themselves will be negatively impacted by poor provider satisfaction scores on patient surveys of postoperative patients. All of these factors are being addressed by recent initiatives.

Emerging data on actual opioid use has enabled clinicians to form guidelines for appropriate opioid prescribing. Once the median and range of opioid use is known, guidelines can be developed that satisfy a certain proportion of patients' needs. For example, after establishing opioid usage for several outpatient general surgery operations, we set a guideline to fulfill the opioid usage of 80% of our patients. As shown in Fig. 1, we initially observed that a median of 30 5-mg oxycodone pills were being prescribed to laparoscopic cholecystectomy patients, with a range of 0 to 100 pills. We established a guideline recommendation of 15 pills, as this would satisfy the opioid usage of over 80% of our patients. When this guideline (which called for 50% reductions in the number of opioids we had previously been prescribing) was implemented, we were concerned that we would be undertreating 20% of our patients. We observed, however, that this was not a problem: fewer than 1% of patients required a refill prescription. Why were we able to satisfy almost all patients' opioid needs despite targeting only 80%? We queried the outlier patients who took more than our guidelines recommended, and found that over half of their opioid usage was for reasons other than surgical pain. We also found that some patients took more than the guideline number because they were initially prescribed more than the guideline and patients dutifully thought they were supposed to take all that they were prescribed. In fact, once we routinely set patient expectations, maximized use of local anesthetics and pre- and postoperative nonopioid analgesics, we have found that patients are using far less than our initial guidelines called for. Although we recommended 30 5-mg opioid pills after

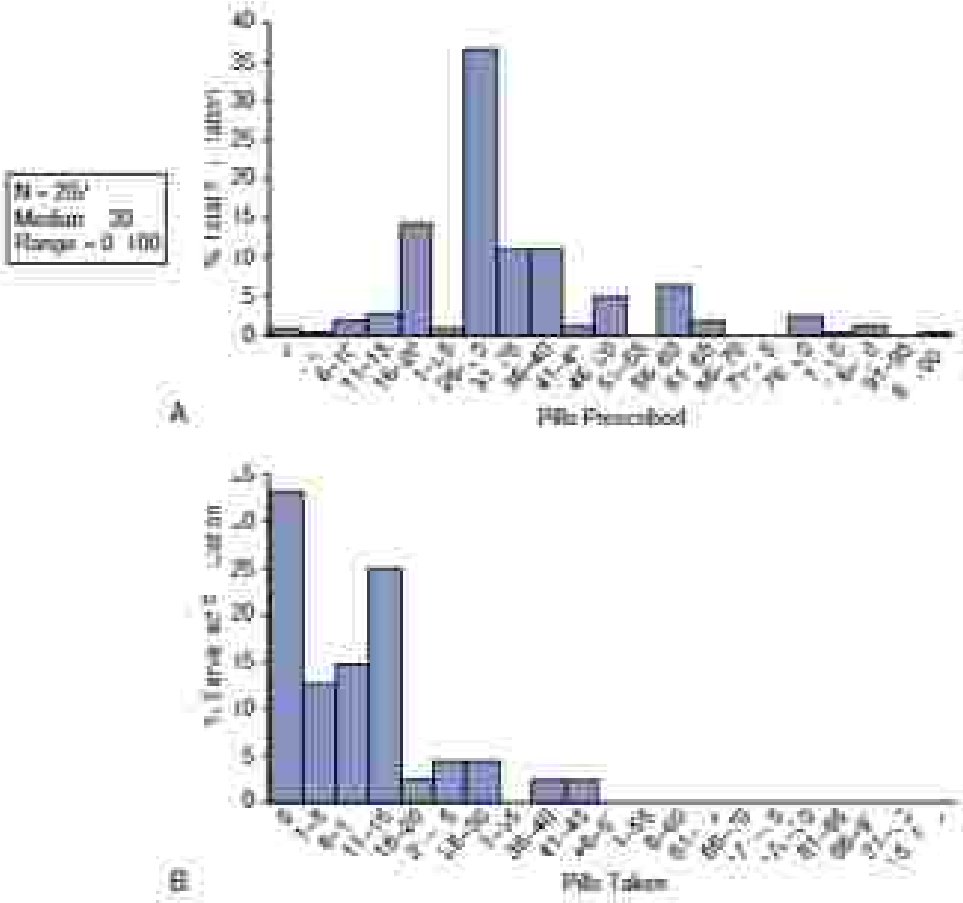

FIG. 1 Frequency of opioid pills prescribed and taken after laparoscopic cholecystectomy.

partial mastectomy and sentinel node excision in our initial guideline formulation, with the use of preoperative acetaminophen and gabapentin, intraoperative local anesthetic and ketorolac, and postoperative acetaminophen and ibuprofen, it is rare now for any of our partial mastectomy sentinel node patients to require an opioid.

The Mayo Clinic guidelines (http://links.lww.com/SLA/B67) are based on their observations of opioid use for several operations and were designed to supply enough pain medications for 80% of the middle two quartiles of patients (Tables 1 and 2). Procedure specific guidelines, based on evidence from usage studies, have also been made available by the University of Michigan (https://michigan.qures.org/prescribing-recommendations/). Opioid potency is expressed in oral morphine milligram equivalents (MME). For ease of conversion, a 5 mg tablet of oxycodone is 7.5 MME; 2 mg hydromorphone is 8 MME; 5 mg Vicodin is 5 MME; 30 mg codeine is 4.5 MME, and 50 mg tramadol is 5 MME.

Some guidelines, like the Mayo and Michigan guidelines, are procedure specific. This is particularly appropriate for outpatient procedures, some are just more painful than others and may require more opioids. These guidelines also give procedure specific recommendations for how many opioids to prescribe when patients undergoing a particular procedure are discharged after an inpatient stay. We have found, in multivariate analysis, that the best predictor of opioid use after a procedure that required an inpatient stay was the number of opioid pills taken the day prior to discharge. In our study of surgical inpatients, the particular operative procedure did not predict opioid usage post discharge. This allowed us to formulate an easy to remember guideline for discharge opioid prescriptions (Table 3). For patients discharged on postoperative day 2 or later, the discharge prescription is based on the number of pills taken the day prior to discharge: zero pills the day prior to discharge are prescribed none, 1 to 3 pills the day prior to discharge are prescribed 15, and 4 or more pills the day prior to discharge are prescribed 30. (1 pill = 5 mg oxycodone = 7.5 MME). In addition to its simplicity, another advantage of this guideline is that it takes individual variability in response to pain into account.

Several factors influence opioid usage after discharge. Patients who are opioid naive, older, have lower pain scores and who take few opioids while admitted are much less likely to require postoperative opioids than patients who are chronic opioid users, younger, have higher pain scores and who take more opioids in the hospital. Recognition of these factors is built into the Mayo Clinic guideline, which delineates low and high dose recommendations in addition to the standard, procedure specific dose (see Table 1).

PATIENT EDUCATION

Now that we have data on postoperative opioid use we can have a data driven discussion with patients preoperatively regarding the level of pain that they should expect after surgery and the methods (opioid and nonopioid) that we plan to use to minimize their pain. Those who are prescribed opioids should be clearly instructed on the risks of use, including both short term adverse events and the risks of becoming a long-term user. Clear instructions should be given to all about Food and Drug Administration (FDA) compliant forms of opioid disposal.

ASSESSMENT OF RISK OF OPIOID ABUSE

It is particularly important to prescribe the appropriate number of opioids to patients who have a high risk of becoming long term opioid users/abusers. At this point, we do not have molecular markers that will predict which patients, when prescribed opioids for surgery, are at risk of becoming long term opioid users. Certain patient characteristics, however, can be used to predict risk. The Webster Opioid Risk Calculator, for example (Table 4), takes into account family and personal history of abusing alcohol, illegal or prescription drugs, age,

and psychologic disorders like bipolar disease, depression, schizophrenia, and attention deficit disorder obsessive compulsive disorder to determine risk levels for long term opioid use. At some hospitals, risk calculators have become required elements for opioid prescribing through the electronic medical record. Several states have made it mandatory for surgeons to do a Physician Drug Monitoring Program (PDMP) search prior to prescribing opioids. The concept is that patients who have "doctor shopped" for opioids can be identified prior to surgery. However, even when one identifies a patient as high risk due to a high opioid risk calculator score or a suspicious PDMP record, these patients are still going to have pain from their surgery and are likely to require at least as many opioids as patients who are at low risk or have clear PDMP records. For surgeons it is likely that the most efficient use of our time would be to use the PDMP selectively for patients requesting refills after their initial prescription.

POSTOPERATIVE OPIOID PRESCRIBING FOR CHRONIC OPIOID USERS

Patients who are chronic opioid users are tolerant of opioids and therefore pose a particular challenge for perioperative pain management. With over 5 million such patients in the United States, it is not uncommon to have to manage their perioperative pain. Optimal management of chronic opioid users is not well defined. For patients requiring elective operations, innovative perioperative programs that utilize the expertise of both pain medicine physicians and psychiatrists may be beneficial. Some patients may be able to have depression or anxiety medications optimized, allowing them to be weaned off high dose opioids prior to surgery. Close collaboration between pain physicians and surgeons in the perioperative period is likely to lead to optimal results.

TABLE 1 Mayo Clinic Surgical Outcomes Program Recommendations for Adult Discharge Opioid Prescriptions (Number of Tabs of 5 mg Oxycodone or 50 mg Tramadol)

	Low Dose[a]	Standard Dose[a]	High Dose
GENERAL SURGERY			
Endoscopy (± PEG)	NSAID/acetaminophen only	NSAID/acetaminophen only	NSAID/acetaminophen only
Muscle biopsy or excisional biopsy			5 tabs oxycodone or 6 tabs tramadol
MIS cholecystectomy or appendectomy MIS inguinal hernia repair (TAPP or TEPP) Open inguinal hernia repair MIS bariatric, hernia repair, or adrenal surgery		8 tabs oxycodone or 12 tabs tramadol	20 tabs oxycodone or 30 tabs tramadol
SURGICAL ONCOLOGY			
Wide local excision or lumpectomy ± SLN	NSAID/acetaminophen only	5 tabs oxycodone or 10 tabs tramadol	10 tabs oxycodone or 15 tabs tramadol
Simple mastectomy only ± SLN		10 tabs oxycodone or 15 tabs tramadol	15 tabs oxycodone or 25 tabs tramadol
Mastectomy with tuboabdominal reconstruction ± SLN/ALND		20 tabs oxycodone and 40 tabs tramadol	40 tabs oxycodone and all tabs tramadol
Mastectomy with submuscular reconstruction ± SLN/ALND (recommend diazepam 2mg tabs every 6 hours, dispense #40)		30 tabs oxycodone and 80 tabs tramadol	60 tabs oxycodone and 60 tabs tramadol
MIS abdominal solid organ resection (e.g., kidney, spleen, or liver wedge)		15 tabs oxycodone or 25 tabs tramadol	25 tabs oxycodone or 40 tabs tramadol
Open major abdominal resection (e.g., Whipple, esophagectomy, or liver resection)		30 tabs oxycodone or 60 tabs tramadol	50 tabs oxycodone or 80 tabs tramadol
CRS			
MIS or open bowel resection (colon or small bowel) (rectal surgery, resection w/ ostomy, larger incisions, concurrent surgery, and major MIS cases may require higher dose)	NSAID/acetaminophen only	15 tabs oxycodone or 25 tabs tramadol	30 tabs oxycodone or 45 tabs tramadol

TABLE 1 Mayo Clinic Surgical Outcomes Program Recommendations for Adult Discharge Opioid Prescriptions (Number of Tabs of 5 mg Oxycodone or 50 mg Tramadol)—cont'd

	Low Dose*	Standard Dose†	High Dose‡
VASCULAR, THORACIC, AND ENDOCRINE			
Bronchoscopy or upper endoscopy (+ ablation)	NSAID/acetaminophen only	NSAID/acetaminophen only	NSAID/acetaminophen only
Percutaneous endovascular or vascular access procedures (cut-downs, complex endovascular, and AV superficialization may require additional opioids)			5 tabs oxycodone or 10 tabs tramadol
Carotid endarterectomy			8 tabs oxycodone or 12 tabs tramadol
Thyroid/parathyroid surgery, mediastinoscopy, or POEM		5 tabs oxycodone or 10 tabs tramadol	10 tabs oxycodone or 15 tabs tramadol
VATS procedure (pulmonary or mediastinal)		20 tabs oxycodone or 30 tabs tramadol	40 tabs oxycodone or 60 tabs tramadol
Thoracotomy (pulmonary, pleural, or chest wall)	5 tabs oxycodone or 8 tabs tramadol	30 tabs oxycodone or 90 tabs tramadol	60 tabs oxycodone or 100 tabs tramadol

*Prescribing a combination of tramadol and oxycodone is accepted as described, but the total number of pills should be reduced. For example, if 20 tabs oxycodone or 30 tabs tramadol is recommended from prescribing 10 tabs of oxycodone and 15 tabs of tramadol would be appropriate. However, prescribing a total of 50 tabs would be more than the patient would be expected to need. In addition, patients receiving opioids should still be encouraged to use NSAID/acetaminophen, if not contraindicated, and these should be taken around the clock with opioids being used only as needed for breakthrough pain.

†**Consideration for low-dose opioid dosing.** When collecting patients for low-dose opioid dosing it is important to note that prospective survey data on opioid use at mine suggests that a significant proportion of patients do not need any opioids after discharge. However, consideration should be made for anticipated intensity of pain associated with the patient's condition, patient access to clinical follow-up, and the extent to which nonopioid analgesics may be utilized for adjunct. For pain management (e.g., patients with contraindications to NSAID/acetaminophen) may require a prolonged level of opioids. Also consider using regional analgesia/anesthesia techniques in patients going home without opioids. It is also important to note that while providing refills requires extra care and time to providers, internal data somewhat strongly supports that patients found it easy to get a refill after discharge when needed. Prescribing higher opioids to avoid the inconvenience of a refill should be avoided.

‡**Consideration for standard opioid dosing.** If opioids are deemed appropriate to manage postoperative pain, the prescription should be for the lowest possible strength of a short acting opioid for the shortest duration of time based on anticipated pain, with a goal to taper as healing progresses. The recommended amounts in this group exceed self-reported use of 75% of patients; however, many patients use only 0 to 5 pills. Prescribing less opioids has not been shown to increase refill rates. Recommendations are for patients with no preoperative opioid use.

§**Consideration for high opioid dosing.** Preoperative opioid users should in general be included in these groups. Patients who are taking high doses of opioids, long-acting opioids, or have a pain management contract preoperatively fall outside of these recommendations and a postoperative pain management plan should be developed before surgery in coordination with their primary prescriber. When prescribing high doses of opioids it is important to discuss the risk of opioids, including respiratory depression and addiction, with the patient.

¶**Counseling.** Patients should be instructed before the procedure about their anticipated healing time, and that pain is a normal and expected part of the recovery process. Patients should be instructed on the expected duration of needing opioids, and that most patients should be off opioids 5 to 7 days after discharge. All patients should be instructed on the use of nonopioid pain medications if they are not contraindicated, regardless of dosing group selected. Patients should be instructed on the risk of opioids, including the risk of addiction. Very few patients dispose of unused opioids appropriately. Providers should instruct patients on the safe disposal of opioids.

ALND, Axillary lymph node dissection; BMI, body mass index; CRS, cytoreductive surgery; LOS, length of stay; NSAIDs, nonsteroidal anti-inflammatory drugs; POEM, per oral endoscopic myotomy; SLN, sentinel lymph node; TAPP, transabdominal preperitoneal; VATS, video assisted thoracoscopic surgery.

TABLE 2 Factors Shown to Influence Opioid Usage After Discharge

Less Use	More Use
Opioid naïve	Preoperative opioid users
Older age, lower BMI, longer length of stay	Younger age
Lower pain score at discharge	Higher pain score at discharge
Less in-hospital opioid use	High in-hospital opioid use

TABLE 3 Dartmouth Guideline for Discharge Opioid Prescription After Inpatient Surgical Procedures

Opioid Pills Taken Day Prior to Discharge	Opioid Discharge Prescription Pill Number
0	0
1–3	15
≥4	30

TABLE 4 Webster Opioid Risk Calculator

	Female	Male
FAMILY HISTORY OF SUBSTANCE ABUSE		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
PERSONAL HISTORY OF SUBSTANCE ABUSE		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16 and 45 years	1	1
History of preadolescent sexual abuse	3	0
PSYCHOLOGIC DISEASE		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Total score:		

From Webster LR, Webster R. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. Pain Med 2005;6(6):432.

This tool should be administered to patients upon an initial visit prior to initiating opioid therapy for pain management. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse. ADD, Attention deficit disorder; OCD, obsessive compulsive disorder; Rx, prescription.

DISPOSAL OF EXCESS OPIOID PILLS

Appropriate disposal of excess opioids is a critical issue because when opioids are overprescribed, many patients will have left over pills and excess pills are then available for long-term use by the patient, or for diversion to others. Two methods of opioid disposal are approved by the FDA. One may return excess pills to drop boxes, which are commonly located at police stations and fire departments. Alternatively, one may dissolve pills in water in an unlabeled plastic bag to which dirt or cat litter is added and dispose of the bag in the trash. Several studies have shown that 10% or less of patients dispose of excess opioids in an FDA compliant manner. Even with intensive patient education about the dangers of excess opioids, compliant disposal rates of only 20% were achieved. Potential interventions to improve the proportion of pills disposed in a compliant fashion are under active investigation.

EFFECTIVENESS OF METHODS TO DECREASE OPIOID PRESCRIBING

In recognition of the link between opioid overprescribing and soaring death rates from overdose, many states have instituted legislation limiting the amount of opioid pills that can be given to patients for acute or chronic conditions. In general, these efforts have been based on expert and legislative opinion rather than rigorous evidence. Massachusetts and several other states have recently passed legislation that limits new opioid prescriptions for acute pain to "not more than a 7-day supply." This type of legislation, however, raises questions in its application. Does a 7-day supply mean 84 opioid pills (if 2 pills are taken every 4 hours), or 21 pills (if 1 pill is taken every 8 hours while awake)? Does one assume that the patient will slowly wean off the pills, thereby requiring less over time? Is a 7-day supply the appropriate duration for opioid pain control, or is it 5 days, or 10 days? Guidelines that are based on empirical data on patient opioid consumption, whether it be procedure based, or based on inpatient usage on the day prior to discharge, as described above, bring evidence-based precision to postoperative opioid prescribing decisions. There is some evidence that educational interventions about the dangers of opioid overprescription and providing surgeons with evidence-based prescription guidelines can dramatically change prescribing practices, without state legislative enforcement.

CONCLUSION

The epidemic of opioid overdose deaths and morbidity from adverse events from opioid use demands that surgeons use alternative methods to control postoperative pain and to responsibly prescribe appropriate amounts of opioids to their patients.

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SURGICAL PALLIATIVE CARE

Geoffrey P. Dunn, MD, FACS

S[illegible] the pr[illegible] under [illegible] work for [illegible] [illegible] the [illegible] [illegible] treatment.

[illegible] In 2006, the National Quality Forum published its *National Framework and Preferred Practices for Palliative and Hospice Care* based on consensus guidelines authored by the leading hospice and palliative care organizations. In 2006, the Accreditation Council for Graduate Medical Education recognized hospice and palliative medicine as a subspecialty of 11 parent Boards including the American Board of Surgery.

PRIMARY PALLIATIVE CARE AND REFERRAL TO PALLIATIVE CARE SERVICES

The indication for palliative care in surgical practice is the seriously ill patient's desire for relief of distress in any of its forms as well as promotion of quality and promise of life regardless of diagnosis or prognosis. The choice of therapy is based on the ability of the treatment to meet the agreed upon goals of care, not its impact on the underlying disease process. Even highly invasive surgical treatments can be consistent with the purview of palliative care if shared decision making has adequately determined the relevance of the treatment. To date the majority of situations in surgical care for which palliative care would be appropriate do not trigger the services of palliative care teams or specialists. This has necessitated the concept of *primary palliative care*, the minimum deliverables of palliative support that can be secured by a surgeon and surgical team. These include (1) skilled communication about goals of care, unwelcome news, prognosis, and code status; (2) acute and uncomplicated chronic pain management; (3) management of common nonpain symptoms such as dyspnea, nausea, vomiting, anorexia, delirium, and anxiety; (4) recognition of syndrome of imminent demise; (5) appropriate and timely referral to specialty palliative care and hospice services. Palliative care consultation should be considered for patients with serious illness even when the surgeon has addressed the basic problems germane to palliation.

Shared decision making has become the preferred method for healthcare choices (including palliative care consultation) in situations attended by significant risk and uncertainty. Shared decision making is a collaborative process in which both the patient's preferences based on personal physical, socioeconomic, psychologic, and spiritual needs are aligned with the surgeon's presentation and explanation of available treatment options. It is not to be confused with informed consent, which is primarily an instructive, not a collaborative process. The operational platform for shared decision making is the family conference, which in the intensive care unit setting should occur within the first 5 days of admission, even in the absence of palliative care specialists. The primary nurse for the patient, social worker, and others active in the care of the patient (e.g., chaplain), should be invited to attend. During the meeting patients or their surrogates can identify the personal parameters for medical intervention while the clinician shapes a treatment recommendation, based on the prognosis, values, and priorities of the individual patient. In cases of doubtfully beneficial treatments the time-limited trial of therapy with a follow-up meeting is an invaluable maneuver that offers the chance but fires the warning shot. In the joint assessment of risk and benefit of operative intervention for seriously ill older patients the outcomes to be considered should go beyond the obvious and immediate (prolonged institutional care, burdensome symptoms, life support dependency) and include social and psychologic concerns such as being a burden, prolonged functional dependency, loss of personhood, and death away from home.

Palliative care consultation services, which are increasingly available in hospital and outpatient settings in the United States, have been shown to improve symptom control, enhance patient and family satisfaction, lower costs, and even improve survival. Triggers (see Box 2) for referral to specialty palliative care services have been proposed though may be of limited utility in resource poor settings or when consultation would duplicate primary palliative care.

BOX 1 Statement of Principles of Palliative Care

- Respect the dignity and autonomy of patients, patients' surrogates, and caregivers.
- Honor the right of the competent patient or surrogate to choose among treatments, including those that may or may not prolong life.
- Communicate effectively and empathically with patients, their families, and caregivers.
- Identify the primary goals of care from the patient's perspective, and address how the surgeon's care can achieve the patient's objectives.
- Strive to alleviate pain and other burdensome physical and nonphysical symptoms.
- Recognize, assess, discuss, and offer access to services for psychologic, social, and spiritual issues.
- Provide access to therapeutic support, encompassing the spectrum from life-prolonging treatments through hospice care, when they can realistically be expected to improve the quality of life as perceived by the patient.
- Recognize the physician's responsibility to discourage treatments that are unlikely to achieve the patient's goals, and encourage patients and families to consider hospice care when the prognosis for survival is likely to be less than 6 months.
- Arrange for continuity of care by the patient's primary and/or specialist physician, alleviating the sense of abandonment patients may feel when "curative" therapies are no longer useful.
- Maintain a collegial and supportive attitude toward others entrusted with care of the patient.

[illegible] Principles of Palliative Care [illegible]. [illegible]. 2004;[illegible]:[illegible]. Adapted with permission from [illegible] et al. [illegible] Surg. 2000;[illegible]:[illegible].

Assessment and Intervention

A conceptual model for pain and suffering is helpful for framing a workable strategy for palliative intervention. The primary target for palliative intervention is distress, not disease. Useful models of pain and suffering widely recognized in clinical palliative care are Cicely Saunders's model of "total pain" and Eric Cassell's concept of suffering. Saunders's model outlines four cardinal dimensions of pain (physical, socioeconomic, psychologic, and spiritual) that in aggregate are referred to as "total pain" and contribute to suffering. Cassell described suffering as the feeling that arises from a threat to integrity (wholeness) of the person. The elements of personhood include the individual's past, present, and future; his or her social role, private life, and a transcendent dimension. Suffering is not relieved until the threat to personhood has passed or is diminished.

Skillful and empathic communication is the core intervention of palliative care. It is analogous to the proper conduct of an operation—it requires creation of the right physical and social context, assessment of the individual's preparedness, permission to proceed, definitive action with economy of delivery, acknowledgment of the impact of the action upon the recipient, closure, and follow-up.

Palliative care assessment includes identification of decision-making capacity, previous illness and treatments, sources of pain in all its dimensions, sources of personal strength, vulnerabilities, and individual values and wishes. Surrogacy and advance medical directives may be addressed at this time. Relief of pressing symptoms should be done prior to or concurrently with assessment. Patient's goals of care that emerge from this discussion set the parameters for the surgeon's involvement. In cases where operative intervention is anticipated, preoperative anesthesiology consultation is helpful in planning intraoperative and perioperative analgesia (especially if use of regional anesthesia is anticipated), reviewing patient's goals of care in light of what anesthesia expertise can offer, and reconsideration of existing do not resuscitate (DNR) orders.

BOX 2 Center to Advance Palliative Care General Referral Criteria: Triggers for Specialist Palliative Care Referral

- Presence of a serious illness and one or more of the following:
  - New diagnosis of life-limiting illness for symptom control, patient/family support
  - Declining ability to complete activities of daily living
  - Weight loss
  - Progressive metastatic cancer
  - Admission from/to long-term care facility
  - Two or more hospitalizations for the same illness within 3 months
  - Difficult to control physical or emotional symptoms
  - Patient, family, or physician uncertainty regarding prognosis
  - Patient, family, or physician uncertainty regarding appropriateness of treatment options
  - Patient or family requests for futile care
  - DNR order uncertainty or conflicts
  - Uncertainty or conflicts regarding the use of artificial feeding/hydration in cognitively impaired, seriously ill or dying patients
  - Limited social support in setting of serious illness (e.g., no family support system, lives alone, homeless, chronic mental illness)
  - Patient, family or physician request for information regarding hospice appropriateness
  - Patient or family psychologic or spiritual distress

DNR, Do not resuscitate.

Physical symptom relief takes immediate priority of action over intervention for nonphysical distress, even if nonphysical issues are ultimately more important to the patient. Symptom management is the primary work of palliative care and requires an interdisciplinary approach. A strong liaison with clinical pharmacists is particularly helpful because of the effectiveness of pharmacotherapy for most symptoms and the frequency of adverse drug reactions, including costs, that add to total symptom burden. Because the elderly represent a substantial portion of patients receiving palliative care it is helpful to be mindful of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, also known as the Beers List, which are guidelines for improving safety in prescribing medications for the elderly.

Tables 1 through 3 show medications and their conversions commonly used for control of major symptoms encountered during palliative care in the hospital setting. For nonphysical symptoms, the surgeon's role is to identify, triage, and refer appropriately and promptly. The importance of colleagueship with individuals entrusted with spiritual care of the individual cannot be overemphasized, particularly if spiritual anguish is the predominating form of the patient's distress. For specific ethical concerns frequently encountered in surgical palliative care, see Table 4.

The armamentarium of surgical palliative care includes palliative surgery, which is no longer defined as noncurative surgery but, instead, the more affirmative concept of deliberate symptom control and restoration of quality of life. This transition has been guided by increased emphasis on determining personal relevance for symptom relief, minimizing morbidity, improvement in nonphysical domains, and durability of symptom relief.

Considerations for palliative surgery include the expected course of the disease, the psychology of the patient, the effectiveness of the given operation, and the capacities of the surgeon/surgical team. Therapeutic benefit from palliative surgery must achieve symptom control, durability of symptom control, and symptom control with minimal morbidity (including social morbidity of hospitalization of an individual during the last weeks of life). After operative

TABLE 1 Overview of Pain Symptoms, Assessment, and Management

Symptom	Assessment	Treatment
Somatic pain	• Easily localized; includes acute postsurgical pain • Prescribe standing regimen with immediate release rescue doses available for breakthrough or uncontrolled pain • Unless contraindicated, a bowel regimen should be administered with opioids for prophylaxis against constipation • Symptomatic control should be assessed frequently to guide evaluation and refinement of the treatment regimen	• Mild pain: acetaminophen or NSAIDs • Moderate pain: titrate short acting opioids • Severe pain: titrate short acting opioids until adequately controlled, then transition to long acting opioids of equivalent potency and rescue doses
Bone pain	• Type of somatic pain from highly sensitive nociceptors of periosteum • Can be caused by fractures or irritation from underlying metastases found on radiographs and isotope bone scans • Bone metastases in the spine may lead to spinal cord compression and neurologic deficits • To decrease risk of NSAID induced gastropathy with chronic NSAID use, selective COX-2 inhibitors and coadministration with a gastroprotective agent (i.e., proton pump inhibitors) is advisable	A regimen combining NSAID s and opioids may alleviate generalized bone pain • Radiotherapy is effective for isolated metastases • Orthopedic interventions can be considered to stabilize pathologic fractures
Muscle spasm	• Prolonged, forceful, or sustained involuntary muscle contraction • Can be iatrogenic from medication side effects or because of electrolyte imbalances or dehydration	Pharmacologic therapeutics to include anticonvulsants (e.g., diazepam) and muscle relaxants (e.g., baclofen) • Manipulations to relax the muscle include stretching and massage • Physiotherapy treatments include electrical stimulation of the nerves or ultrasound thermotherapy
Neuropathic pain	• Common examples include post thoracotomy pain, phantom limb pain after amputation, ischemic limb pain, and pain from tumor invasion of nerves (i.e., pancreatic cancer pain) • May be accompanied by altered sensation	• Tricyclic antidepressants (e.g., amitriptyline) and anticonvulsant medications (e.g., gabapentin) may be helpful in combination with opioids • Pancreatic cancer pain may be alleviated temporarily by local neurodestructive (celiac axis blockade) or permanently by celiac axis neurolysis procedures • Anti-inflammatory properties of corticosteroids may reduce peritumoral edema
Visceral pain	• Often diffuse and poorly localized • Can be caused by distension, ischemia, and inflammation of the thoracic, pelvic, or abdominal organs • Solid organ tumor burden may cause stretch or irritation of peritoneal surfaces	• Treatment options are tailored to the site and etiology, and may include anti-inflammatory medications, corticosteroids, and opioids
Intestinal colic	Distension of the small intestine and colon cause visceral pain • Common examples include paralytic ileus, malignant obstruction, and intestinal pseudo-obstruction	• Treatment begins with addressing any reversible causes of distension • Nondestructive distension pain can be treated with antispasmodic agents (e.g., hyoscine butylbromide) and opioids

NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 2 Approximate Opioid Equivalences for Management of Moderate to Severe Pain

Analgesic	IM, SC, IV Route (mg)	Oral Route (mg)
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	NA	20
Hydrocodone	NA	30

...ose is a rough recommendation for opioid... patients. The ratios are... titration, and variability in opioid response between individuals among... Consult an expert before switching... IM, intramuscular; IV, intravenous; NA, not available; SC, subcutaneous.

TABLE 3 Overview of Nonpain Symptoms, Assessment, and Management

Symptom	Assessment	Treatment
Nausea/vomiting	• Rule out reversible causes such as hypercalcemia and infection. Treat underlying cause if nausea and vomiting results from intestinal obstruction or intracranial processes (i.e., increased intracranial pressure from space-occupying lesion or hemorrhage) • Toxins and medications can act centrally to stimulate the CTZ of the brain, inducing nausea and vomiting • Upper gut dysmotility from ineffective and delayed gastric emptying results in gastric distention, nausea, and vomiting	• Antiemetics target different receptors and may be combined • Dopamine antagonists (e.g., prochlorperazine, haloperidol) are effective for vomiting related to the CTZ • Antihistamines (e.g., meclizine) and anticholinergics (e.g., scopolamine) act centrally on receptors in the vomiting center of the vestibular system. They can be combined with dopamine antagonists • Serotonin antagonists (ondansetron) have diffuse inhibitory effects on serotonin receptors of the small bowel, vagus nerve, and chemoreceptor trigger zone. They are indicated for chemotherapy-induced nausea and vomiting • Nausea from dysmotility can be treated with prokinetics (e.g., metoclopramide)
Delirium/agitation	• May be caused by electrolyte imbalances and accumulation of toxic metabolites • Can be produced or worsened by certain medications (e.g., opioids, benzodiazepines)	• Identify underlying causes • Frequent reorientation • Antipsychotics are first-line pharmacotherapy (e.g., haloperidol, chlorpromazine) for moderate symptoms • For severe symptoms, benzodiazepines (e.g., lorazepam, midazolam) can be combined with antipsychotics to achieve sedation
Diarrhea	• First consider infection (e.g., *Clostridium difficile*) and iatrogenic (e.g., laxatives, medication side effect) causes • Diarrhea may be caused by chemotherapy or radiation enteritis • Patients may have altered anatomy (e.g., colectomy, bowel resection, high-output fistula, enteric intruder)	• Dietary modification, electrolyte repletion and adequate hydration • If infectious and reversible causes are ruled out, antidiarrheals can be used (e.g., loperamide, kaolin and pectin) • Patients with steatorrhea from pancreatic insufficiency should receive pancrelipase • Octreotide can be given to patients with secretory diarrhea, high-output stoma, or gastrointestinal fistula • Aspirin or NSAIDs, cholestyramine, and psyllium may be helpful for patients with radiation enteritis
Constipation	• Commonly associated with poor fluid intake, weak or debilitated patients, and those on opioid analgesics • Fecal impaction can cause partial or complete obstruction	• Stimulant laxatives (e.g., senna, bisacodyl) are indicated for patients without complete obstruction and should be given in combination with stool softeners (e.g., docusate sodium, polyethylene glycol, lactulose)
Dyspnea	• Several acute processes may cause dyspnea in surgical patients, including pneumothorax, atelectasis, and uncontrolled pain • The physiologic stressors of surgical treatment may exacerbate chronic conditions, including congestive heart failure and chronic obstructive pulmonary disease • When physical causes of dyspnea have been ruled out, emotional or situational challenges should be considered (i.e., anxiety)	• Reversible causes of dyspnea should be assessed quickly and treated appropriately, i.e., management of fluid overload for congestive heart failure and administration of bronchodilators or steroids for obstructive airway disease • Administration of supplemental oxygen using face masks should be avoided in the terminal setting • "Air hunger" is palliated with opioids and anxiolytics • Particularly when responding respiratory failure is a concern, an immediate conversation about preferences for invasive and noninvasive ventilation should occur with the patient or surrogate, with appropriate documentation in the medical record
Anorexia	Assess for reversible causes such as constipation, untreated pain, and endobronchial wounds	Megestrol acetate, steroids, nutraceutical

CTZ, Chemoreceptor trigger zone; NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 4 Common Ethical Issues in Surgical Palliative Care

Issue	Commentary
Disclosure of bad news	Broad legal and ethical consensus supporting disclosure of bad news when permitted by patient or surrogate. No evidence that disclosure of bad news "takes away hope" if conveyed gently and in the spirit of non-abandonment. Empathic truth telling fosters trust that is the basis of hope
Perioperative DNR orders	The American College of Surgeons, the Association of Operating Room Nurses, and the American Society of Anesthesiologists position papers condemn policies requiring automatic cancellation of existing DNR orders for patient undergoing anesthesia based on the principle of patient autonomy. All recommend preoperative discussion ("required reconsideration") during which patient or surrogate confirms patient's treatment goals and limits of care including revision or implementation of a DNR order, risks of patient's care plan; and recommendations by anesthesiologist and surgeon. During this discussion the anesthesiologist and patient can set the parameters for resuscitation for the procedure itself and in the recovery room
Withhold/withdraw of life support	The withholding and withdrawal of medical treatments are considered legally and ethically equivalent and are based on the right to bodily integrity. It is generally more difficult to withdraw a life supporting treatment once it has been started than to not initiate it at all. A surrogate's persistent reluctance to consider termination of life support is usually related to their fear that they will be "killing the patient" or their fear that withdrawing life support will cause suffering. Legally and ethically, termination of an unwanted medical treatment of the properly informed and uncoerced patient/surrogate is not considered homicide or suicide.
Aggressive symptom management	• Aggressive symptom management of unbearable symptoms is a moral imperative if effective treatment is available, even at the risk of hastening or causing death, as long as causing death is not the intention of treatment. The risk of hastening death is present with any surgical treatment for serious illness, including attempts to cure. • In situations where rapid escalation of dosing is necessary to relieve intractable severe symptoms (pain, dyspnea, agitated delirium) in the imminently dying patient, the DDE, broadly accepted by ethicists, is invoked. DDE is comprised of these elements: • The act must be good or morally neutral • Bad effects are foreseen but not intended • A good end cannot justify a bad means • The risk/benefit ratio must be reasonable
Terminal sedation	Rarely indicated in palliative care. Reserved for severe, intractable symptoms (pain, overwhelming existential distress) where death is imminent. The goal of palliative sedation is to use the minimum amount of sedation necessary to relieve severe physical symptoms to the point of unconsciousness, if necessary, and deliberate induction of coma or hastening of death. Consultation with ethics committee, neuropsychiatric consultant for determine competency), and palliative care specialist are recommended.

DNR, Do not resuscitate; DDE, rule of double effect.

complications dramatically worsen the prospects of achieving durable symptom relief up to the time of death.

Although life expectancy of less than 2 months has been suggested as a contraindication for palliative surgery, prognostication by physicians is notoriously inaccurate, especially if a symptom (e.g., pain) is the reason for loss of function rather than progression of disease. For many palliative intraabdominal procedures, such as malignant bowel obstruction, generally agreed upon relative contraindications include cachexia or hypoalbuminemia, poor performance status, significant comorbidities, diffuse intraperitoneal carcinomatosis, advanced disease refractory to chemotherapy, palpable multiple intraabdominal masses, multiple liver metastases, extraabdominal metastases, pleural effusions, multiple sites of partial obstruction or prolonged transit time of contrast on intestinal radiographic series, advanced age, recurrence following recent laparotomy for malignant obstruction, and previous abdominal radiation therapy.

The availability of stenting, minimally invasive procedures, laparoscopic approaches, and improved adjuvant chemo and radiation therapies have increased flexibility in relieving symptoms related to obstruction, pain, bleeding, fistula, and contaminated wounds. Many of the principles and interventions useful for the palliation of malignant disease can be applied to nonneoplastic disorders encountered in surgical practice such as chronic pancreatitis, congestive heart failure, and chronic liver failure.

Patient self report is the gold standard for outcomes measurement following palliative treatment. Numerous validated measuring instruments exist, some of which offer multiple languages and disease specific modules with ongoing updates. Some of the more commonly used questionnaires include the Functional Assessment of Cancer Control Version (FACT-G), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30), and the McGill Quality of Life Questionnaire (MQOL).

Surgeons should consider the option of hospice referral for patients with an estimated survival of 6 months or less if the illness pursues the expected course without further attempts to reverse it. The hospice option, which includes the patient's understanding of its prognostic criteria for enrollment, should be included for discussion during the informed consent process for palliative and nonpalliative surgery. See Boxes 2 and 4 for screening prognosis and referral criteria for hospice services.

BOX 3 Prognostic Indicators for Palliative Care Patients

General Indicators of Poor Prognosis

- Functional ability, single most important predictive factor
- Median survival of 3 months or less if ECOG ≥ 3 or KPS ≤ 50
- Additional evidence: unintentional progressive weight loss >10% over prior 6 months
- Serum albumin <2.5 g/dL (not to be used in isolation from other factors)

Cancer-Related Indicators of Poor Prognosis

- Patients with solid tumors typically lose 30% of functional skill in the last 3 months of life
- If >50% of time is spent sleeping or lying down and is increasing, median survival is 3 months, less with increasing symptoms, especially dyspnea
- Most solid tumors that progress through 2 rounds of chemotherapy: <6 months
- Hypercalcemia: 8 weeks (except newly diagnosed myeloma or breast cancer)
- Pericardial effusion: 8 weeks
- Carcinomatous meningitis: 8–12 weeks
- Multiple brain metastases: 1–2 months without radiation, 3–6 months with radiation
- Malignant ascites or pleural effusion: <6 months

Most metastatic solid cancers, acute leukemias, high-grade lymphomas not on chemotherapy: <6 mos

ECOG, Eastern Cooperative Oncology Group.

SYNDROME OF IMMINENT DEMISE AND COMFORT MEASURES ONLY

The syndrome of imminent demise or active dying can be easily overlooked in the differential diagnosis of clinical decline attributed to reversible causes such as drug-induced delirium or organ failure. The stages of syndrome of imminent demise can span from less than 24 hours to 2 weeks. The syndrome commences with a (usually) bed-bound patient with diminished oral intake and increased sleep and confusion. This progresses to further cognitive decline and increased somnolence punctuated with periods of lucidity. In the final stage coma, "death rattle" extremity mottling, and variable respiratory patterns including apneas are present. Progression tends to be more rapid for patients who are malnourished and/or infected. Its recognition is crucial because of the implications for its management. To meet the family's desire for privacy and avoidance of suffering of the patient, interventions and paraphernalia not relevant to comfort should be quietly discontinued. When a patient has an automated implantable cardioverter defibrillator, this should be addressed with the patient and/or family to provide the opportunity to program off the defibrillator portion of the device. There is no palliative indication for programming of pacer function.

Family members should be reassured of minimal discomfort of the patient by the medical team, especially because family may fear they have abandoned the patient themselves by discontinuing life-sustaining treatments. As death approaches, dyspnea (air hunger), upper airway secretions (death rattle), altered sensorium (delirium, loss of consciousness, agitation), incontinence, and pain are the likely symptoms that will require proactive management. An important part of preparing the family for what death will look like includes explaining the mechanisms of the death rattle before it occurs. This can be much to reassure family if it does because its occurrence is due to a small amount of pooled secretions around the vocal cords, not "drowning." In addition to preemptive medication with antisecretory drugs, positioning patients on their side or elevating the head of the bed may reduce noisy respirations.

In cases when ventilator withdrawal is necessary to initiate comfort care, paralytics should be discontinued, allowing time for neuromuscular function to return. The patient should be premedicated adequately for sedation with opioids and benzodiazepines to prevent dyspnea and anxiety. Additional medications should be available at bedside for immediate titration. FiO_2 is then lowered to room air and positive end expiratory pressure is discontinued. Further titration with opioids and anxiolytics is based on apparent respiratory distress, not oxygen saturation. If there is no apparent distress after tapering down to an inspiratory rate of 4/minute, extubation can be done with or without family presence. A substantial majority of patients will expire within an hour and most of the remainder within 24 hours. If the patient remains stable for several hours, transfer to a suitable nonmonitored bed can proceed as long as the family is notified before transfer. The possibility of unexpected prolonged survival and its implications for transfer should be addressed before initiation of comfort measures only. After death occurs, the family should be given adequate time and privacy to say goodbye and private at the bedside. Confidential and bereavement support should be offered at this time.

BOX 4 Medicare Hospice Benefit

Eligibility

- Enrolled in Medicare Part A
- Two physicians certify terminally ill status with life expectancy of less than 6 months if illness pursues its natural course
- Patient opts for symptom management care only and forgoes life-prolonging treatments for terminal illness of record and other comorbidities.

From Medicare Benefit Policy Manual, Chapter 9, Coverage of Hospice Services Under Hospital Insurance. www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c09.pdf

BEREAVEMENT

Access to bereavement services is a critical component of surgical palliative care, not only for patients and families but also to hospital caregivers. Hospital-based bereavement services including pastoral care departments and family support services have been shown to affect long-term psychosocial functioning of surviving family members and decisions about organ donation. Surgeons may also benefit from these services as they seek the balance between detachment and overwhelming emotions in response to serial losses. Writing a condolence letter to the deceased patient's family is a simple but significant gesture that supports the family and the surgeon's bereavement.

In summary, the surgical community has too many seriously ill people in its care and has too much unique experience to refer them to not assume an active role as a provider of palliative care to its patients and families regardless of prognosis.

SUGGESTED READINGS

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CARDIOVASCULAR PHARMACOLOGY

Jay G. Shake, MD, MS, and J. Michael Brewer, DO, FS

The need to pharmacologically manipulate the cardiovascular system is relatively common for practicing surgeons and those caring for patients in the perioperative period. Most surgical residents often state to their trainers that we surgeons should strive to be the best doctors in the hospital. And, to be able to operate. This statement probably applies itself well in the familiarity and comfort we should have regarding the use of common cardiovascular medications because this occurs so frequently in our patient population. The most encountered scenarios often involve managing a patient with severe hypotension or shock, heart failure, hypertension, and an assortment of common cardiac arrhythmias. This chapter aims to give the reader an overview of these common conditions and how they can be managed with a few cardiovascular medications.

MANAGEMENT OF SHOCK/ HYPOTENSION

Assessment of Shock

Shock is a disturbance of the adequate forward flow of blood that is essential for the delivery of oxygen and nutrients and removal of carbon dioxide and waste from cells and tissues. Multiple factors contribute to normal blood flow, including heart rate (HR), myocardial contractility, preload, and systemic vascular resistance (SVR)/afterload; and, when perturbed, may result in inadequate blood flow and shock. The surgeon must quickly and accurately assess a patient to determine the etiology of shock (i.e., inadequate preload, cardiac failure, or low SVR [afterload]) to correctly manage the condition, including the correct choice of inotrope or reassessment of preload. Shock is not simply a state when the mean arterial pressure (MAP) is less than 65 mm Hg or the patient requires medications to maintain this parameter, though these factors may be markers of shock. Blood pressure is not a measure of the forward flow of blood in the cardiovascular system. Rather, it is simply a pressure measurement; therefore, we make every attempt to not interchange low blood pressure (or hypotension) and shock if possible. A patient can have a normal or elevated blood pressure and be in cardiogenic shock with a cardiac output (CO) that is not compatible with life. This can be understood by review of a simple physiology equation:

$$CO = HR \times (MAP - CVP)/SVR$$

in which CVP is central venous pressure.

Another simple equation that the reader needs to remember is as follows:

$$CO = HR \times SV$$

in which SV is stroke volume.

The human body can quickly and easily adjust its CO to meet bodily needs by increasing the HR. Similarly, cardiac surgeons often place temporary pacing leads on the surface of the heart to artificially increase the CO in patients with low flow states. Usually 80 to 90 beats/min has been the preferred HR range in these cases or even higher in orthotopic heart transplant patients. SV is particularly influenced by preload, contractility, and SVR (afterload). Although, just to be thorough, a number of other things can directly or indirectly affect SV, including heart rhythm, atrioventricular synchrony, and pulmonary vascular resistance.

To describe what we call the forward flow of blood in the cardiovascular system, some clinicians use CO, but certainly in the cardiovascular intensive care unit, we have become more comfortable using cardiac index (CI) because it adjusts for the size of the patient, more specifically body surface area (BSA). A single value can be the target of any size individual from the young thin teen or emaciated elderly individual to the massive obese adult males that we more commonly care for today.

$$CI = CO/BSA$$

A landmark paper in congenital cardiac surgery simply and eloquently demonstrated that an "inflection point" occurs at about a CI of 2 L/min per m² (Fig. 1). Values consistently below this value were directly proportional to the increased probability of acute cardiac death. It is not surprising that most cardiac centers have developed a practice of treating cardiac medications to target MAPs greater than 65 mm Hg and cardiac indexes greater than 2.0–2.2 L/min per m². In our experience, values below this routinely result in parameters of inadequate perfusion including metabolic acidosis and elevation in lactate levels. Again, remember that a low CI can coexist with a normal or even elevated blood pressure.

Shock patients can be placed in three categories:

1. *Hypovolemic shock.* This form of shock is related to low filling pressures or preload seen by the heart and cardiovascular system. Certainly, hemorrhagic shock is in this category. Resuscitation with crystalloid, colloid, or blood products would be the correct management depending on the etiology of volume loss. Resuscitation of the proper amount of fluid is also important (see the Perioperative Optimization section for more details.) It is important to remember that up to 40% of all causes of hypotension in the intensive care unit can at least initially respond to fluid resuscitation alone. Start with this approach while you are gathering more information to treat a patient in one of the other categories. Other diagnoses that need to be remembered, and clinically behave like hypovolemic shock because they are impeding the appropriate filling of the heart, are cardiac tamponade and pulmonary embolism. Each of these diagnoses has a unique decision tree with appropriate management.
2. *Cardiogenic shock.* This form of shock is related to inadequate CO (or CI), which is directly related to dysfunction of the heart and often some contribution of the systemic vascular system. This can be related to a problem directly related to myocardial contractility such as either acute left heart failure, acute right heart failure, or both. A simple example to demonstrate this would be following an acute myocardial infarction in the perioperative period. More commonly, this can be seen with an acute on chronic process such as chronic systolic heart failure or chronic diastolic heart failure. Unfortunately, the compensatory mechanism to elevate the blood pressure to an acceptable level in this type of patient is elevation of the SVR. This in turn makes the failing heart need to work even harder to eject the blood against the increased resistance. Sometimes these very sick hearts need inotropic supportive medications and also afterload reduction to adequately increase the cardiac indices to a level compatible with life. Our analogy to trainees is that you need to "step on the gas" and also "let off the brake" to a failing car engine. It is thus not surprising that home inotropic therapy in the heart failure patient population has traditionally been with milrinone and dobutamine, both inotropic agents with vasodilatory properties.
3. *Distributive shock.* This form of hypotension is related to vasoplegia or relative loss of arterial vascular tone. Often these patients have a high CO and yet remain hypotensive because of low SVR. Anaphylactic shock and spinal shock would both fall into this category. Septic shock would initially fall in this category too, but in advanced cases, there is also the component of septic cardiomyopathy. The use of vasoconstrictor medications is often necessary to support these patients.

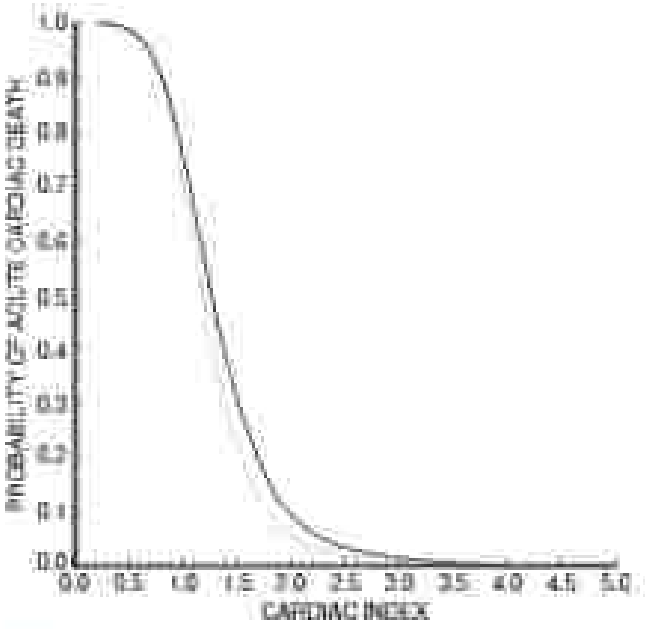

FIG. 1 Mortality and cardiac indexes. [illegible]

Preload Optimization

Although aggressive intravenous fluid resuscitation is often undertaken as an initial measure for a patient in shock, it cannot be stressed enough that there is mounting evidence that too much fluid is also harmful to our patients. Excessive intravenous fluid resuscitation can lead to severe hypoxia (pulmonary edema) or arrhythmias (atrial or ventricular overload) and may increase mortality in critically ill patients. The goal is therefore optimization of the preload, ideally without leaving the patient's intravascular space either underfilled or overfilled. Modern fluid management incorporates the use of dynamic tests to induce brief changes in cardiac preload while assessing for increase in SV and CO.

Historically, physicians have used static parameters such as CVP and pulmonary capillary wedge pressure as predictors of intravascular volume status or a response to fluid bolus challenges to their assessment of an appropriate preload; however, these have repeatedly been shown to be inaccurate and therefore can misguide management. Our line of reasoning is that the CVP is not a gas gauge in which a single predetermined number predicts the correct filling pressure for all patients. As a result of these collective findings, the use of Swan-Ganz catheters has dramatically declined. The use of dynamic parameters such as pulse pressure or SV variation, respiratory variation of the inferior vena cava, mini fluid challenge, and expiratory occlusion test (in mechanically ventilated patients), and passive leg raising test are likely better predictors of which patients will have an increase in SV following administration of intravenous fluids, which is the ultimate goal of fluid resuscitation in patients with shock. These tests can be performed easily at the bedside, though some require a method of measuring changes in SV or CO or special monitors. Surgeons caring for critically ill patients should be familiar with the limitations of any dynamic parameters they wish to incorporate into care of patients.

Left Heart Failure

Perhaps the most ill and difficult to manage patients in the intensive care unit (ICU) is the subset of patients who have left heart failure. This is particularly true when they have additional confounding problems such as sepsis or pulmonary hypertension. The vasoplegia and need for added CO to maintain adequate blood pressures and metabolic needs can amount to the need for a concoction of numerous cardiovascular medications to achieve our desired parameters at doses that are sure to result in end organ injury and likely death. Vasoactive agents (inotropes targeted at increasing the blood pressure often make matters worse by increasing the pulmonary hypertension with their α-adrenergic stimulation.

Also commonly seen in the ICU are patients with hypotension/shock from worsening of preoperative chronic systolic heart failure or new acute myocardial infarction. This is referred to as an acute on chronic disorder. The management is the same except the magnitude of support is often increased a logarithm, or more, and of course the outcomes can be extremely poor.

Although there is no proven outcome benefit for invasive hemodynamic monitoring in these patients, the authors routinely use these invasive devices to achieve reasonable hemodynamic goals, usually MAPs $\geq$ mm Hg or greater and cardiac indexes of 2.2 L/min per m^2 or greater when there is any indication that there is more than one etiology contributing to the hypotension. An example would be a patient with septic shock and significant left ventricular dysfunction. Fortunately, there have been an increasing number of new monitoring devices, some mentioned previously, offering less invasive techniques and with more real-time feedback to adjust management.

If adequate cardiovascular parameters cannot be achieved with multiple high-dosed intravenous medications one could obtain consultation for consideration of an intraaortic balloon pump or even extracorporeal mechanical circulatory support in a select patient population with acute heart failure.

Right Heart Failure

One must attempt to understand the etiology of right heart failure to be able to manage it correctly. Remember, right heart failure is most commonly a result of left heart failure. This needs to be assessed first; however, if elevated pulmonary pressures and right heart failure are found with satisfactory left heart function, then therapy needs to be targeted at decreasing the pulmonary vascular resistance. This would include avoiding α-1 agonists and correcting hypoxemia, hypercarbia, and severe acidosis. Elevated airway pressures from high ventilator settings or positive end-expiratory pressure should also be avoided. Inhaled vasodilator therapy should also be considered.

The guiding principles to improve left heart failure are otherwise nearly identical to right heart failure. An echocardiogram is often indicated to identify if there is a single- or two-ventricle issue and whether there is a cardiac valve problem contributing to the situation. Inotropic therapy would be the mainstay of therapy with the preferred agent to be milrinone or dobutamine due to their increase in inotropy without vasoconstriction.

Single-ventricle mechanical support is now possible with percutaneous right ventricular assist device or venoarterial extracorporeal mechanical circulatory support in extreme cases.

CARDIOVASCULAR MEDICATION CHOICE ALGORITHM

The goal(s) of the cardiovascular medication would be to improve myocardial contractility enough to improve the SV and subsequently the forward flow (CO), without worsening or provoking an acute myocardial infarction. At the same time, the agent might need to increase the afterload to restore the mean arterial blood pressure to an acceptable level. The indications of the commonly used inotropic and vasopressor medications are dependent on the receptors that they activate (Table 1) and the resulting physiologic response. The specific effects of the receptors (Table 2) are important to remember and in combination with the drug's mechanism of action one should be able to more accurately choose an agent to accomplish the desired effect.

A few specific effects of the cardiovascular medications deserve review. β_1 stimulation increases myocardial contractility (inotropy),

an increased HR (chronotropy), and increased conduction of impulses down the heart's conduction system (dromotropy). Additionally, stimulation of α-1 receptors angiotensin II receptors, and vasopressin 1 (V_1) receptors all result in vasoconstriction.

Our medication drip strategies are as follows (assuming preload is optimized):

1. If more forward flow (CO) is needed and the blood pressure is low, use an agent with both β-1 agonist with α-1 activity. We choose epinephrine first for very impaired contractility and norepinephrine first for moderately impaired contractility. Severely impaired hearts often need both. Otherwise, sometimes a second agent is needed such as vasopressin or even angiotensin II for refractory hypotension. Milrinone (phosphodiesterase inhibitor) can be added to the β agents to increase the contractility. Their actions are synergistic because of the separate mechanisms of action.
2. If more forward flow is needed and the blood pressure is elevated or normal use an agent to lower the afterload (vasodilator) and add a β-1 agonist or phosphodiesterase inhibitor if needed to increase the contractility. A single agent that does both, such as dobutamine or milrinone, can be useful.
3. If there is normal or elevated forward flow but hypotension remains, then there is an afterload problem. A vasoconstrictor is needed with α-1 angiotensin II, or vasopressin 1 stimulation with titration targeted to a desired endpoint. If one drug is started and the patient remains refractory, start a second agent that works by a different mechanism. Norepinephrine is currently the drug of choice in sepsis, so this would need to be started first in this patient population. If patients fail to respond adequately to norepinephrine, our practice is to add either vasopressin or epinephrine as a second agent. If further escalation of vasopressor support is needed, intravenous angiotensin II may be considered. Also consider endocrinopathy as a cause for distributive shock. There is some evidence that intravenous hydrocortisone may be helpful in the setting of refractory septic shock. Other medications such as intravenous methylene blue or high dose hydroxocobalamin may be considered for rescue therapy in the most refractory of cases.
4. In a patient with distributive shock and severe pulmonary hypertension, avoid use of any agent with α-1 adrenergic properties. Instead, initiate a trial with vasopressin.

MANAGEMENT OF SYSTEMIC HYPERTENSION

It is relatively common to encounter systemic hypertension in the perioperative period. Often, this is seen with pain as the inciting event, so this should always be addressed first. Then we must ensure that patients are not put at increased risk by the discontinuation of their chronic antihypertensive medication(s). This can be particularly difficult when the gastrointestinal tract is involved during surgery, with accompanying loss of bowel function or ileus. In particular, cessation of β-blockers has been shown to be harmful to patients at risk of ischemic heart disease. Fortunately, there are intravenous medication substitutions that can be ordered as a replacement with similar pharmacologic profile. Other classes of agents, in particular long-acting agents, have no other parental medications and other classes of medications need to be chosen. Sometimes shorter acting agents of the same drug classification can be used. Last, after surgery the need to restart home medications needs to be considered.

Direct vasodilators via the parenteral route are very useful as first line antihypertensive agents in the perioperative period for many patients. Intermittently dosed agents include hydralazine (10–20 mg intravenous [IV] every 2–4 hours as needed) and labetalol (20–80 mg IV every 10 minutes as needed with a maximum dose of 300 mg/d). Usually, the lower range of doses is attempted first and then escalating doses are added as needed. The next step would be a continuous infusion with clevidipine, labetalol, nicardipine, nitroglycerin, or sodium nitroprusside. Clevidipine (1–21 mg/hr IV) is a calcium channel blocker that has a lipid formation so should be discouraged if using other lipid accompanying agents such as propofol as a sedative. Labetalol is also a very effective continuous infusion (0.5–20 mg/min) particularly in β-blocker naïve patients. Nicardipine (1–15 mg/hr IV) is in the same drug class; however, it has a much longer half life (8.6–14.4 hours) so one must anticipate the change in blood pressure and adjust the dosing along with the clinical picture. Nitroglycerin and sodium nitroprusside are both venodilators so should be used to caution in patients with intracranial hypertension. Nitroglycerin (5–200 μg/min IV, start 5 μg/min and increase by 5 μg/min every 3 to 5 minutes until a response is seen) is a rather weak antihypertensive agent and is therefore used more for its antianginal properties in the perioperative period. Sodium nitroprusside (0.4 μg/kg per minute with starting doses 0.3–0.5 μg/kg per minutes IV) is a very effective direct vasodilator with a relatively short circulatory half life (2 minutes); however, cyanide toxicity can be seen with high doses, lengthy duration, or renal impairment due to secondary medicine clearances (thiocyanate half life 3 days). Also, both nitroglycerin and sodium nitroprusside can develop tachyphylaxis with continued use.

Direct vasodilators offered via the oral route include calcium channel blockers and hydralazine (10–50 mg PO four times daily). Several calcium channel blockers are offered as many hospital formularies including amlodipine (2.5–10 mg by mouth [PO] every day), diltiazem (immediate release 30–90 mg PO four times daily), verapamil, and more. Several of these are also offered in a formulation with long acting properties. Usually, we suggest starting the shorter half life agents first to demonstrate stability and then transition to the longer acting medication at a later time.

Parenteral β-blocking agent use has primarily centered on labetalol (mixed α- and β-antagonists), esmolol, and metoprolol. Labetalol, as noted previously, can be a very effective at lowering blood pressure because of its actions on the vascular tone in addition to the β-blocking properties. Intravenous metoprolol tartrate (2.5–10 mg IV every 6 hours) is still a mainstay of therapy to control HR, blood pressure, and even atrial fibrillation prophylaxis in many ICU patients. Esmolol (50–200 μg/kg per minute IV) is a β-blocker worth mention because of its ultra-short half life (9 minutes). Although this implies rapid onset and easy titration, we find a limited subset of patients to which this is really useful, in large part because of the large volume of infusion need to achieve the dosages that are need to get good HR or blood pressure control. Esmolol may be started in the acute setting in an unstable patient, and then we rapidly convert to intravenous infusion of metoprolol with similar effects as able.

There are numerous β-blockers offered in an enteral form; however, again we tend to mostly concentrate on oral labetalol and metoprolol, although other agents could certainly be used. Labetalol (100–800 mg PO bid) is commonly used at many centers for perioperative blood pressure control. We tend to gravitate to metoprolol, and there are two forms that providers must know and be comfortable using. Metoprolol tartrate (Lopressor, 12.5–100 mg PO twice daily) is the most common oral β-blocker formulation that we use in our cardiovascular ICU and has a shorter half life. We start at the lower end of the dosing range and then titrate to effect. Metoprolol succinate (Toprol XL, 25–200 mg/day PO) is a long acting agent that can be used after a period of stability with the shorter acting agent.

Several other antihypertensive classes exist, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers (ARBs), clonidine, diuretics, and some combination medications that contain agents with more than a single drug category. Although angiotensin converting enzyme inhibitors are often held around the time of surgery, sometimes they need to be restarted in a patient that is unable to tolerate oral medications, in this case, enalaprilat is a reasonable choice with a starting dose of 0.625 mg IV every 6 hours and then increased every several doses to maximum of 2.5 mg IV every 6 hours. The most commonly used ARB in our unit

TABLE 1 Commonly Used Intravenous Inotropic and Vasopressor Agents

Medication	Dose range	Mechanism/receptor	Indication
Angiotensin II	1.25–40 ng/kg/min	Angiotensin	Vasoconstrictor
Dobutamine	1–20 μg/kg/min	β 1, β 2	Inotrope, vasodilator
Dopamine	1–20 μg/kg/min	α 1, α 2, β 1, β 2, dopamine	Inotrope, vasoconstrictor
Epinephrine	1–20 μg/min	α 1, α 2, β 1, β 2	Inotrope, vasoconstrictor
Isoproterenol	1–20 μg/min	β 1, β 2	Inotrope, chronotrope
Milrinone	0.125–0.75 μg/kg/min	Phosphodiesterase 3 inhibitor	Inotrope, vasodilator (including pulmonary)
Norepinephrine	1–30 μg/min	α 1, α 2, β 1	Inotrope, vasoconstrictor
Phenylephrine	20–200 μg/min	α 1	Vasoconstrictor
Vasopressin	0.01–0.06 U/min	V1, V2	Vasoconstrictor

TABLE 2 Effects of Adrenergic and Other Receptor Subtypes on the Cardiovascular System

Receptor	Location	Effect
α 1	Systemic arterioles (viscera, coronary, skeletal muscle), veins, pulmonary arterioles	Vasoconstriction
α 2	Presynaptic and postsynaptic sympathetic nerve terminal, central nervous system	Vasodilation
β 1	Heart	Inotropy, chronotropy, dromotropy
β 2	Systemic arterioles (viscera, coronary, skeletal muscle), veins, pulmonary arterioles	Vasodilation
Dopamine	Systemic arterioles (viscera, coronary, skeletal muscle), veins, pulmonary arterioles	Vasodilation
Vasopressin 1	Vascular smooth muscle	Vasoconstriction
Vasopressin 2	Renal distal convoluted tubule and collecting duct	Antidiuresis
Angiotensin II	Systemic arterioles, kidney, adrenal cortex	Vasoconstriction

to losartan (25–100 mg/day PO, divided every day or twice daily). Caution must be taken when using both the angiotensin converting enzyme inhibitors and ARBs in patients with renal artery stenosis, hepatic or renal impairment, and volume depletion. Clonidine (0.1–0.4 mg PO twice daily) can be quite helpful for those patients refractory to a cocktail of several high dose antihypertensives. Several of the combination drugs are helpful but not ideal in the acute settings, but need to be considered later in the hospitalization to simplify the antihypertensive regimen. An example would be isosorbide dinitrate/hydralazine (1 tablet PO three times daily, 20 mg/37.5 mg).

MANAGEMENT OF PULMONARY HYPERTENSION

A common incorrect diagnosis made in the ICU or laboring a patient with pulmonary hypertension just because the pulmonary artery pressures are elevated on the Swan Ganz catheter. If these are seen with concomitant elevated systemic blood pressures, they really mean little. We find the ones that need to be managed are when they approach two thirds of systemic pressures. Moreover, it is helpful to know if this is reversible or not. Attempting inhaled or IV vasodilatory medication is not helpful if there is no response to the medication; therefore, if true pulmonary hypertension is identified, then begin an investigation into the etiology, which might mean consultation with a cardiologist or pulmonologist. Primary pulmonary hypertension can be treated with inhaled medications. To the contrary, elevated pulmonary artery pressures as a result of a left heart valve insufficiency might be worsened by a pulmonary vasodilator and attention would need to be directed to the medical or surgical management of the underlying disease process.

Inhaled nitric oxide (1–80 parts per million) can be used as a potent pulmonary vasodilator through the existing ventilator tubing is helpful, but increasingly expensive. Rarely does one need to go above 20 parts per million. Many centers have moved to inhaled epoprostenol with similar efficacies and at a substantial decrease in cost of the medications. This can often amount to millions of dollars at a large academic facility.

BRADYARRHYTHMIAS

Bradyarrhythmias are probably the least encountered arrhythmia in the ICU setting, at least those requiring medical management. This is because, as a general rule, bradycardia is well tolerated as long as there is an adequate CO; however, bradyarrhythmias can be seen as a result of the administration of nearly any medical blocking agent, particularly when several are used for hypertension refractory to monotherapy or in the case of treatment for tachyarrhythmias (mentioned in subsequent sections). In these cases, removal of the inciting agent(s) is most often the first step, along with correction of any correctable electrolyte abnormality.

In an unstable patient, or one with symptomatic status bradycardia, then management is per advanced cardiac life support (ACLS) protocol. In brief, the first line agent would be atropine at a starting dose of 0.5 mg IV and redosed, as needed, every 3 to 5 minutes to a maximum dose of 3 mg. Additionally, ACLS would recommend the addition of a chronotropic intravenous agent, either epinephrine or dopamine, to achieve an adequate HR. Epinephrine at 2 to 20 μg/min or dopamine 2 to 10 μg/kg per minute IV are the recommended doses. Other less common IV agents to treat bradycardia include glycopyrrolate (0.2–0.6 mg IV) and isoproterenol (2–10 μg/min IV). More commonly, I have seen isoproterenol used on heart transplant

TABLE 3: Common Rate-Control Agents

Medication	Acute Rate Control: Initial Dose	Following Dose(s)	Oral Dosing: Acute or Chronic Rate Control
β-BLOCKERS			
Metoprolol	2.5–5 mg IV over 2 minutes	Repeat every 15–20 minutes up to 3 doses	25–100 mg PO twice daily
Esmolol	0.5 mg/kg IV bolus	0.05–0.25 mg/kg/min	NA
CALCIUM CHANNEL BLOCKER: NONDIHYDROPYRIDINE			
Diltiazem	0.25 mg/kg IV over 10 minutes	Repeat 0.35 mg/kg IV × 1 after 15 minutes, may follow with 5–15 mg/hr IV for <24 hr	30–, 0 mg PO 4 times per day, starting with 30 mg, maximum, 360 mg/d
CARDIAC GLYCOSIDES			
Digoxin	0.25–0.5 mg IV (renal adjust dose)	0.125–0.25 mg IV every 2–6 hr up to 1.5 mg total dose (renal adjust dose)	0.0625–0.25 mg PO every day
OTHER			
Amiodarone	150 mg IV over 10 min	1 mg/min for 6 hours, then 0.5 mg/min for 18 hr 150 mg IV over 10 minutes may be repeated during the infusion	400 mg PO twice daily or 800 mg PO three times daily loading dose, then 200 mg PO every day

IV, Intravenous; NA, not available; PO, by mouth.

response to loss of successful capture of temporary pacemaker leads, although ICE is certainly mentioned in the ACLS pathway.

Temporary pacing can be achieved with several approaches, although transcutaneous with the defibrillation pads is probably the most common in the ICU in emergent situation because it is fast, easy, and nursing staff is well versed in this technique with ACLS training. Of course, this is temporary and usually requires patients to be sedated, often challenging in an unstable patient. With specialized training, an intravenous pacing catheter (several models and types) can be floated to provide pacing, but this is difficult if central venous access is not already achieved. In fact, this is probably limited to a cardiovascular ICU.

TACHYARRHYTHMIAS

Narrow Complex Tachyarrhythmias

Sinus tachycardia is one of the most common perioperative tachyarrhythmias. Assure if the patient has an adequate circulating blood volume and adequate pain control. These should be addressed first and can often correct the abnormality. Once these are ruled out, or corrected, then an agent to control the accelerated rate could be considered if the patient would be thought to have an increased cardiac risk. Rate control for the sake of rate control in each and every patient is unnecessary and could actually confuse this compensatory mechanism from another unrecognized etiology.

There is an array of other narrow complex tachyarrhythmias including accelerated junctional rhythm, paroxysmal supraventricular tachycardia, and certainly the most common arrhythmia in this category and worth mention is atrial fibrillation. In general, atrial fibrillation is very well tolerated in most patients. The loss of atrial contraction and atrial ventricular dyssynchrony only results in hemodynamic instability when there is a setting of decreased ventricle filling capacity. Should the patient become unstable with hemodynamic compromise or develop severe cardiopulmonary symptoms (angina, dyspnea, etc.), then you are hard pressed to take action. Rarely, a patient with paroxysmal atrial fibrillation in the clinical scenario will need light sedation and electrical cardioversion per ACLS protocol. It should be mentioned that attempting cardioversion in a patient with long-standing persistent or permanent atrial fibrillation will be unsuccessful and, in our opinion, a waste of precious time. More commonly, these patients will require the administration of a vasopressor such as phenylephrine or norepinephrine to stabilize the blood pressure and then receive an intravenous agent such as amiodarone (Table 3) for rate control while attempts are made to correct other causes such as electrolyte abnormalities or addressing causes of myocardial ischemia. Amiodarone protocols usually include a 150 mg IV loading bolus over 10 minutes followed by an amiodarone drip at 1 mg/min for 6 hours and then 0.5 mg/min for another 18 hours. Additional amiodarone boluses of 150 mg IV can be given during the infusion period, each over 10 minutes. Digoxin can also be considered in these patients, particularly if the patient has severe pulmonary disease or has already demonstrated a hypersensitivity to amiodarone. We also often use another underappreciated and rather benign antiarrhythmic, intravenous magnesium sulfate (2 × g IV). This can be considered as long as the patient does not have corresponding severe acute or chronic renal dysfunction or elevation of other intracellular cations (potassium). We initially target rate control for less than 100 beats/min. If this is tolerated, we then lower our target to 80 beats/min, which in our experience seems helpful for chemical cardioversion.

Stable patients with new onset atrial fibrillation can often be managed in a stepwise manner. Again, the goal is rate control over rhythm control. The ventricular rate is usually controlled first with a parenteral dose of β blocker (usually metoprolol) or calcium channel blocker (diltiazem). β blockers are especially preferred if the patient has known ischemic heart disease. A single or series of IV doses can also be used to achieve more rapid HR control in acute settings. Once the maximum dose has been given, then a second agent will need to be added to either the diltiazem or metoprolol. If the patient is still hypertensive, then we often add the other agent (add diltiazem if metoprolol given first). Or rather, if the blood pressure is more marginal now, consider adding either digoxin or amiodarone. Either an IV or parental route can be used to load amiodarone. Ten grams is needed if using the oral dosing regimen and 5 g is needed for the IV route. Once the agent is loaded a standard maintenance dose can be given (usually 200 mg PO every day). Digoxin is usually avoided for patients with decreased creatinine clearances because of its renal clearance (or a dose adjustment to avoid digoxin toxicity). Amiodarone is usually avoided in patients with a prior sensitivity or severe lung disease. Last, one must use caution when adding a third high dose nodal blocking agent and using amiodarone in combination with digoxin.

Systemic anticoagulation is usually considered for patients who persist in atrial fibrillation beyond 48 hours. Most commonly, this is with intravenous heparin using a nurse-driven titration protocol. Of course, the benefit of such anticoagulation, to prevent thromboembolism, must be weighed against the individual's risks of bleeding. More long-term oral anticoagulation has been shown to decrease the risk of stroke in persistent atrial fibrillation by more than 60%; however, again, taking risk factors into account, whether or not to anticoagulate a patient long-term most clinicians would calculate a congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke, vascular disease, age 65 to 74 years, and sex score to help steer their management. Specifics of this decision-making regarding continued anticoagulation is not covered in this chapter.

Wide Complex Tachyarrhythmias

Wide complex arrhythmias are much less common in the perioperative surgical patient. Examples include monomorphic ventricular tachycardia, polymorphic ventricular tachycardias such as torsades de pointes, and a wide QRS complex in a patient with a preexisting bundle branch block. An unstable patient should be treated per ACLS protocol, usually with a synchronized cardioversion attempt. Stable patients are usually treated first with a β-blocker or amiodarone. The stable patient with torsades de pointes is managed differently. Precipitating medications that prolong the QTc periods are discontinued first and then parenteral magnesium is given (1–2 g IV over 30–60 seconds and may be repeated in 5–15 minutes) even with normal serum magnesium levels.

Suggested Readings

Cariou A, Combes X, Annane D, et al. Vasopressin for hypotensive shock. Crit Care Clin Spec Rev. 2011;27(1):109–120.

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Glucose Control in the Postoperative Period

Tamara L. Seaver, MD, FACS, MCCM, Benjamin L. Moran, MD, and Ronald Tarpley, MD, FACS

In 2014, the US National Diabetes Statistic Report demonstrated that, in addition to 21 million individuals diagnosed with diabetes, there were approximately 8.1 million with undiagnosed diabetes. These numbers would indicate that roughly 9.3% of the American population may be suffering from diabetes. In addition, approximately 30% of intensive care unit (ICU) patients have preexisting diagnostic criteria for diabetes, and the rate of diabetes was highest among those 65 years of age and older.

Diabetic and nondiabetic surgical patients are at risk for acute hyperglycemia resulting from the body's response to the stress of surgery and acute illness. A causal relationship between hyperglycemia and morbidity and mortality has been demonstrated in the surgical population, and intensive glucose control in postoperative populations has been shown to increase survival and decrease surgical complications. Given the increasing prevalence of diabetes and aging of the population, these findings make postoperative glycemic control an integral part of providing safe quality surgical care. As paradigms in care shift and the surgical acuity and comorbid conditions in patients increase, glycemic control will continue to be of critical importance in the care of the surgical patient. Unfortunately, the appropriate range and variability of blood glucose has more significant debate in the literature and the lack of consensus is further evident by the widespread differences in published blood glucose guidelines. Although some studies have shown a reduction in morbidity and mortality when intensive insulin therapy is used to maintain blood glucose at or below 110 mg/dL in the surgical ICU, other studies have not only failed to reproduce this result, but also have demonstrated increased mortality with intensive insulin therapy. It is clear that a negative impact of hyperglycemia on wound infection and surgical complications exists, but the optimal level of glucose control while avoiding the potential complications of hypoglycemia and glucose variability remains unknown. This chapter will review the pathophysiology of stress-induced hyperglycemia, examine the three tenets of glycemic control (treating hyperglycemia, preventing hypoglycemia, and decreasing glycemic variability), and present targeted glucose guidelines for diabetic and nondiabetic patients in various surgical environments.

INDICATIONS

There is a well-established association between postoperative hyperglycemia and poor outcomes in surgical patients. Elevated postoperative glucose has been strongly associated with respiratory complications, venous thromboembolism, myocardial infarction, cardiac arrest, and need for reoperation. Additionally, hyperglycemia appears to be an independent predictor of surgical site infection, pneumonia, urinary tract infection, and sepsis within 30 days of surgery. Elective surgery patients who develop hyperglycemia have a twofold higher risk of infection, and patients who receive noncardiac general surgery procedures have a 30% increase in postoperative infectious complications for every 40 mg/dL increase in hyperglycemia. The association of hyperglycemia after cardiac surgery, hepatectomy, colectomy, and general and vascular surgeries correlating with worse outcomes in the postoperative period has been repeatedly demonstrated.

Unfortunately, even in the absence of preexisting diabetes, stress-induced hyperglycemia is a common finding in critically ill patients and in patients undergoing major surgical procedures. Stress-induced hyperglycemia in nondiabetic patients has been defined as a blood glucose level greater than 140 mg/dL, and in diabetic patients as a blood glucose greater than 180 to 220 mg/dL.

Hyperglycemia in critically ill patients and those undergoing major surgical procedures occurs as a result of a catecholamine-induced stress response. Catecholamine release is activated by the sympathetic nervous system during acute periods of stress and modulated by the suprarenal glands with additional positive and negative feedback regulated through the pituitary gland (Fig. 1). Glucose production may also be increased because of gluconeogenesis and glycogenolysis. Some degree of hyperglycemia in response to stress is normal and can be initially protective as part of the adaptive response for survival; however, in acute and severe illnesses, the resultant state of hyperglycemia may be too high for the bodies normal mechanisms and require glycemic therapy to manage.

Severe hyperglycemia is a well-documented marker of illness severity. It may be worsened by medical treatments, such as dextrose infusions, parenteral nutrition, and corticosteroids, often are necessary to treat the acutely ill. The patient's hyperglycemic condition

Systemic anticoagulation is usually considered for patients who persist in atrial fibrillation beyond 48 hours. Most commonly, this is with intravenous heparin using a nurse-driven titration protocol. Of course, the benefit of such anticoagulation, to prevent thromboembolism, must be weighed against the individual's risks of bleeding. More long-term oral anticoagulation has been shown to decrease the risk of stroke in persistent atrial fibrillation by more than 60%; however, again, taking risk factors into account, whether or not to anticoagulate a patient long-term most clinicians would calculate a congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke, vascular disease, age 65 to 74 years, and sex score to help steer their management. Specifics of this decision-making regarding continued anticoagulation is not covered in this chapter.

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Suggested Readings

Cuthpert C, Simel C, Arthach J, et al. Vasopressin for hypotensive shock. Cochrane Database Syst Rev. 2010;(2):CD003589.

Richardson L, Hendrich SC, Wood H, et al. Inotropic agents and vasoactive strategies for the treatment of cardiogenic shock or low cardiac output syndrome. Cochrane Database Syst Rev. 2018;1:CD008669.

Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(suppl 2):S444–S464.

Glucose Control in the Postoperative Period

Thomas M. Scalea, MD, FACS, FCCM, Benjamin Moran, MD, and Ronald Tanoriers, MD, FACS

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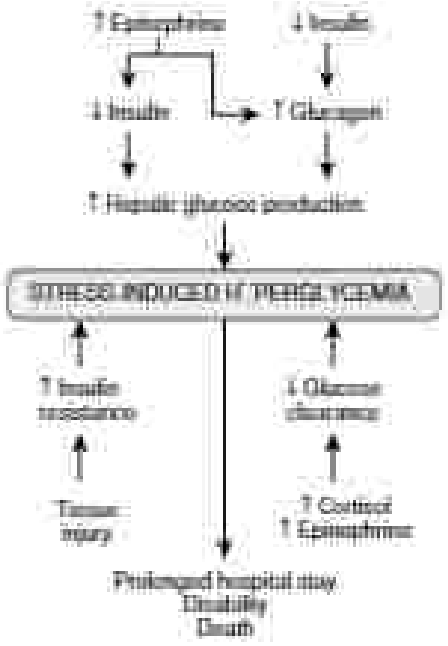

FIG. 1 Hormonal mechanisms of stress-induced hyperglycemia. [illegible]. A. Inzucchi et al., [illegible], *Diabetes Metabolism Research and Reviews* [illegible].

generally subsides after the afflicting illness and periods of stress have resolved. In the acute hyperglycemic patient, the resulting hyperglycemia is a direct correlation to the insufficient insulin secretion needed to overcome the hyperglycemic effects of catecholamines; however, in those with chronic disease, insulin resistance also contributes and patients with significant amounts of tissue injury or surgical stress may require augmented insulin levels.

Hyperglycemia leads to limited vascular reactivity by the angiotensin II and nitric oxide synthase pathways, inhibition of neutrophil chemotaxis and phagocytosis, and increased vascular permeability and leukocyte and platelet activation. Through these mechanisms, hyperglycemia plays a significant role in the development of stroke, myocardial infarction, surgical site infections, and impaired wound healing, increasing morbidity and mortality in surgical patients. In colorectal and nondiabetic patients, one single postoperative elevated glucose value has been associated with infectious and noninfectious complications, with the rates of complications increasing parallel to the degree of hyperglycemia. Given the association of hyperglycemia with increased morbidity and mortality, tight glucose control has become a target to improve outcomes in the postsurgical and critically ill patient.

TECHNIQUES

Management of glycemic control is directed toward treating hyperglycemia, preventing hypoglycemia, and limiting glycemic variability. Derangements in more than one of the domains of glycemic control are associated with a cumulative increase in mortality among patients without diabetes.

Hyperglycemia

The standard management of hyperglycemia was challenged in 2001 when Van den Berghe et al compared strict blood glucose control with the current management of glucose in 263 patients admitted to a surgical ICU. They demonstrated that tight blood glucose of 80 to 110 reduced hospital mortality by 5% to 8% compared with goals less than 180. Tight glucose control was also associated with reductions in bloodstream infections, acute kidney injury, critical illness polyneuropathy, hypercalcitraemia, anemia, and the duration of mechanical ventilation. These results were remarkable; however, they were unable to be reproduced. In 2009, the Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation trial randomized more than 6000 mixed medical and surgical ICU patients to tight glucose control (81–108 mg/dL) vs conventional (<180 mg/dL) but had markedly differing results. They demonstrated a higher 90-day mortality and had a 13-fold increased risk of hypoglycemia with tight glucose control. Other studies have suggested that there should be differences in glycemic targets between diabetics and nondiabetics.

With a rising population of diabetic and prediabetic individuals in the United States, the risk of severe hyperglycemia among critically ill patients is increasing, especially in those with undiagnosed diabetes mellitus. Patients with preexisting diabetes tend to have a persistent state of hyperglycemia resulting from insulin resistance and hyperglucagonemia that are consequences of the disease's natural progression. As a result, these patients are more likely to require control with hypoglycemic medications and strict glucose monitoring. Multiple studies have demonstrated a U-point association between glycemic levels in the ICU and the risk of death, with the lowest risk of death associated with normal glucose levels for age. There are many observations that this U-shaped relationship is flattened in diabetic patients with lower levels of mortality occurring at higher levels of glucose than in nondiabetics; however, Kosiborod and colleagues demonstrated that patients without diabetes had a lower mortality when mean blood glucose was maintained between 80 and 140 mg/dL, whereas a mean blood glucose of 80 to 110 mg/dL was associated with increased risk of mortality compared with ranges of 110 to 140, 140 to 180, and even greater than 180 mg/dL in diabetic patients. These findings suggest that, although nondiabetic patients benefit from glucose levels near normal, the diabetic patient may benefit from higher levels. This may be due to chronic hyperglycemia inducing adaptations, where acutely lowering blood glucose to normoglycemic ranges may activate hypoglycemia like responses. These findings suggest that diabetic ICU patients with chronic poor glycemic control evidenced by elevated hemoglobin A1c (HbA1c) levels may benefit from a more liberal blood glucose range.

Hypoglycemia

Hypoglycemia is a dangerous situation in both diabetic and nondiabetic patients. Hypoglycemia has been associated with increases in cardiovascular mortality thought to be related to QT prolongation and derangements in cardiac cell repolarization. Hypoglycemic episodes have been independently associated with increased risk of mortality among diabetic and nondiabetic patients. Diabetic patients hospitalized with acute myocardial infarction had a 93% increased mortality rate when hypoglycemia was present during their hospitalization. A group of 2601 patients hospitalized in the ICU were evaluated for ICU mortality when moderate or severe hypoglycemia was present and compared with a group with no episodes of hypoglycemia. Patients with severe and moderate hypoglycemia had 34% and 18% increase in 90-day mortality when compared with their normoglycemic counterparts. Patients with multiple hypoglycemic events had a 44% increase in mortality when compared with normoglycemic patients. Optimal therapy expresses need to treat hyperglycemia without inducing episodes of hypoglycemia.

Glycemic Variability

Glycemic variability has been defined as acute glycemic fluctuations. These upward and downward fluctuations are often a direct result of treatment for hyperglycemia. Glycemic variability leads to increased oxidative stress at a cellular level, which causes endothelial dysfunction and vascular damage, and may be associated with worse outcomes than persistent hyperglycemia in critically ill patients. Glycemic variability confers an increased risk of mortality by 25.7% in

critically ill nondiabetic patients. Nondiabetic patients appear to be more affected than diabetic patients; variability of greater than 20% increases the risk of mortality among nondiabetic patients but not in diabetics. There is no current consensus on the range of acceptable glycemic variability. Although a range of 80 mg/dL has been suggested because it corresponds to the normal physiologic variability in nondiabetic patients, this definition has not been validated.

Management of Hyperglycemia

Glycemic control is difficult in the surgical patient because of the multifactorial, complex, and dynamic nature of perioperative hyperglycemia. HbA_{1c} levels indicate average glucose levels over the preceding 4 months, and elevated levels have been associated with worse surgical outcomes. The American Diabetes Association defines prediabetes as HbA_{1c} 5.7 to 6.4%, diabetes as HbA_{1c} greater than 6.4%, and poorly controlled diabetes as HbA_{1c} greater than 7.0%. HbA_{1c} level should be obtained to elective preoperative patients over the age of 45, and in those who are overweight or obese and have an additional risk factor for diabetes. Levels greater than 7.0% have been associated with postsurgical infections, increased morbidity, and prolonged hospital length of stay. Although some have advocated for delays in elective surgery until reduction in levels of HbA_{1c}, whether lowering levels before surgery will lead to improved outcomes remains unknown. Measuring HbA_{1c} in acute hospitalized hyperglycemic patients may allow the differentiation between stress-induced hyperglycemia and undiagnosed diabetes for patients with levels greater or equal to 6.5%.

Intravenous insulin infusion is the most precise way to quickly adjust and control blood glucose levels because of its rapid onset of action, titratability, and potential to avoid glycemic variability. It is particularly useful in critically ill surgical patients whose nutritional intake may be variable and interrupted. There has been demonstrated substantial risk of hypoglycemia in patients who are being managed with tight glycemic control. One developing technology that may ease glycemic management is continuous inline glucose monitoring systems. These systems sample blood from a central venous line every 15 minutes and report glucose levels. Initial studies have shown improved glycemic variability and maintenance of therapeutic glucose ranges compared with 1- and 2-hour intermittent glucose measurements.

The intensive monitoring required for insulin infusion therapy is not possible for most patients outside of an ICU environment; thus, most postsurgical patients will require treatment with subcutaneously dosed insulin. Sliding scale insulin (SSI) regimens, in which patients are administered a set amount of regular insulin in response to degree of hyperglycemia, are increasingly discouraged in favor of basal, bolus, and correctional regimens. SSI regimens treat hyperglycemia after it occurs rather than preventing its development, are associated with increased hyperglycemia, hypoglycemia, and glycemic variability, do not deliver physiologic insulin levels, and may be dangerous in patients with type 1 diabetes. Additionally, they have been associated with adverse outcomes in general surgery patients with type 2 diabetes mellitus. There are several randomized trials in medical and surgical studies that have demonstrated improved glycemic control and decreased complications with basal and bolus insulin regimens compared with SSI. For patients who were managed with an insulin infusion, the 24 hour insulin requirements are calculated and 50% of this is administered as basal long-acting insulin once- or twice-daily divided doses. The other 50% is administered as rapid-acting insulin with meals in divided doses, or as part of a correctional dose based on preprandial glucose. For patients on continuous or parenteral nutrition, basal long-acting insulin plus rapid-acting insulin every 4 hours or short-acting insulin every 6 hours should be used. In noncritically ill patients, initial basal insulin dose range between 0.3 and 0.5 units/kg per day. Dosing should be adjusted daily based on blood glucose response and the amount of insulin administered on the prior day. Pragmatically, a period of correctional dose insulin without basal may be necessary to establish a baseline need in patients whose diabetic status and degree of stress hyperglycemia is unknown.

RESULTS

Although the association with hyperglycemia and postoperative outcomes is clear, the ideal degree of glucose control remains to be determined. Although a tight glucose target range of 80 to 110 mg/dL was found to be associated with a morbidity and mortality benefit by Van den Berghe, subsequent studies have shown worsened mortality with such a tight degree of glucose control due mainly to increased episodes of severe hypoglycemia. At this point, most advocate for a glycemic target slightly above a normal physiologic range to avoid the threat of hypoglycemia. As medicine advances new technology, such as inline glucose monitoring, it may allow for tighter glucose control without the threat of hypoglycemia and be able to produce results similar to those seen in the van den Berghe study.

Multiple medical societies have published recommendations for glycemic control in different patient populations. The Society of Thoracic Surgeons' guideline recommends that patients who have undergone routine cardiac surgery should maintain glycemic levels below 180 mg/dL. For postcardiac surgery patients anticipated to spend greater than 3 days in the ICU, however, and who require mechanical ventilation, myocardial or renal support, or need inotropic or antidysrhythmic medications, a level below 150 mg/dL is recommended. The Society of Critical Care Medicine task force recommends maintaining a blood glucose level below 150 mg/dL (alternately <180 mg/dL) and avoiding levels less than 100 mg/dL to prevent hypoglycemia for critically ill patients. Similar degrees of glycemic control are recommended in neurocritical care patients. Goal ranges of 110 to 140 mg/dL or 140 to 180 mg/dL if hypoglycemia cannot be prevented and an overall emphasis on prevention of hypoglycemia especially in patients with a traumatic brain injury. In patients with neurodistressing sepsis, the Surviving Sepsis Campaign guidelines set a goal blood glucose less than 180 mg/dL. The American Diabetes Association sets its target between 140 and 180 mg/dL in critically ill patients and the Endocrine Society recommends 110 to 140 mg/dL for postcardiac surgery populations. Table 1 summarizes the various societal recommendations for glycemic control.

SUMMARY

Hyperglycemia has been reproducibly associated with worsened outcomes in postsurgical and critically ill patients. Improved glycemic

TABLE 1 Societal Recommendations of Glycemic Control in Critically Ill Patients

Cohort	Glucose Control Goal
Nondiabetic ICU patient	140–180 mg/dL
Diabetic ICU patient	140–180 mg/dL[a]
Cardiac surgery ICU patients	<180 mg/dL (<150 mg/dL if anticipated ICU stay >3 days, ventilator dependent, or requiring renal support, mechanical cardiac support, or inotropic or antidysrhythmic infusions)
Surgical ICU patients	100–150 mg/dL (alternately <180 mg/dL)
Septic ICU patients	<180 mg/dL

[a]Poorly controlled diabetes (HbA_{1c} >7%), may benefit from blood glucose levels <200 mg/dL; however, more data needed.

ICU, intensive care unit.

Modified from Silva Perez LJ, Bonnet-Lopez MA, Varon J, Scnaider S. Management of critically ill patients with diabetes. *Med J Diabetes*. 2017;9(2):80–96.

control improves infectious and noninfectious morbidity as well as mortality in these patient populations; however, the ideal glycemic target remains unclear. Initial enthusiasm for tight glucose control (90–110 mg/dL) has waned in favor of a slightly supranormal glycemic range (100–180 mg/dL) in most patient populations because of worsened outcomes associated with hypoglycemia with lower target ranges. Whether poorly controlled diabetics should have a slightly higher target range, and what the appropriate degree of glycemic variability is, remains unknown. Although insulin infusions are likely the ideal strategy for controlling blood glucose, the need for close monitoring makes them unsuitable for the majority of postsurgical patients outside of the ICU. Most patients will continue to be managed with intermittent dosing of a combination of rapid-, short-, and long-acting subcutaneous insulin analogs ideally using a basal, bolus, and correctional regimen. Noncritically ill patients should have a target premeal blood glucose lower than 140 mg/dL, with random glucose levels lower than 180 mg/dL. Technologic advances in the ICU, such as inline glucose monitoring, allow a lower and tighter glycemic target while avoiding hypoglycemia and may adjust the ideal glycemic range in the future. For now, a target range between 140 and 180 mg/dL in most critically ill patients seems prudent.

Suggested Readings

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Postoperative Respiratory Failure

Rachael A. Callcut, MD, MSPH, FACS

Respiratory dysfunction after operative intervention is the most common postoperative complication seen after both elective and emergency surgery. Postoperative pulmonary complications (PPCs) result in significant increases in morbidity and mortality rates and cost. In fact, it is the leading cause of postoperative death. The most serious of the PPCs is postoperative respiratory failure (PRF). Historically, most definitions of PRF have required the criteria of need for mechanical ventilation exceeding 48 hours after a procedure or need for reintubation in the 30 days after operative intervention. However, this definition excludes the mild forms of PRF, which are exceedingly common, and there has been a growing interest in treating PRF with noninvasive techniques including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and high flow nasal cannula (HFNC). Thus the newest definitions that are most often used to define postoperative respiratory failure include one or more of the following criteria:

- Failure to wean from mechanical ventilation within 48 hours of a procedure
- Need for reintubation in the first 30 days after a procedure
- Partial pressure of oxygen (PaO_2) less than 60 mm Hg
- Partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) less than 40 kPa (PF ratio <300 mm Hg)
- Inability to maintain an oxygen saturation greater than 90% with supplemental oxygen
- New-onset hypoxemia requiring oxygen supplementation for more than 48 to 72 hours

This chapter focuses on the cause and management of PRF, including preoperative identification of high-risk patients, strategies to prevent PRF during and after operation(s), and treatment for the most severe form, acute respiratory distress syndrome (ARDS).

Types of Postoperative Respiratory Failure

PRF includes both hypoxemic and hypercarbic respiratory failure. Hypoxemic respiratory failure (PaO_2 <60 mm Hg on room air), known as type I, is the most common in the postoperative period and is primarily attributed to increased dead space ventilation and shunting. Dead space results from increased ventilation perfusion (V/Q) mismatch. Shunting occurs when the unventilated lung is well perfused. These are both increased in the postoperative period secondary to the effects of decreased functional residual capacity from atelectasis. Atelectasis occurs both related to intraoperative ventilator technique and poor postoperative pain control. Additional causes of postoperative hypoxemia are listed in Box 1.

control improves infectious and noninfectious morbidity as well as mortality in these patient populations; however, the ideal glycemic target remains unclear. Initial enthusiasm for tight glucose control (90–110 mg/dL) has waned in favor of a slightly supranormal glycemic range (100–180 mg/dL) in most patient populations because of worsened outcomes associated with hypoglycemia with lower target ranges. Whether poorly controlled diabetics should have a slightly higher target range, and what the appropriate degree of glycemic variability is, remains unknown. Although insulin infusions are likely the ideal strategy for controlling blood glucose, the need for close monitoring makes them unsuitable for the majority of postsurgical patients outside of the ICU. Most patients will continue to be managed with intermittent dosing of a combination of rapid-, short-, and long-acting subcutaneous insulin analogs ideally using a basal, bolus, and correctional regimen. Noncritically ill patients should have a target premeal blood glucose lower than 140 mg/dL, with random glucose levels lower than 180 mg/dL. Technologic advances in the ICU, such as inline glucose monitoring, allow a lower and tighter glycemic target while avoiding hypoglycemia and may adjust the ideal glycemic range in the future. For now, a target range between 140 and 180 mg/dL is most critically ill patients seems prudent.

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BOX 1 Common Causes of Postoperative Hypoxemia

Atelectasis—most common
Aspiration
Cardiogenic pulmonary edema
Pulmonary embolism
Pneumothorax
Bronchospasm
Mucus plugging
Pulmonary contusion

BOX 2 Common Causes of Postoperative Hypercapnia

Residual inhaled anesthetic
Residual neuromuscular blockade
Opioid use
Sedatives
Neuromuscular disorders
Chronic obstructive pulmonary disease
Sepsis
Obesity

Hypercapnic respiratory failure, known as type II, results from a failure to clear carbon dioxide. This can occur when an increased work of breathing is required to maintain a partial pressure of carbon dioxide ($PaCO_2$) less than 50 mm Hg on room air. This can also result from apnea from failure to clear anesthetics or from the effects of opioids in the perioperative period. Additional causes are listed in Box 2. Those suffering from type II respiratory failure will still require oxygen supplementation.

RISK FACTORS AND PREVENTION STRATEGIES

Numerous authors in recent years have attempted to quantify, using risk prediction scores developed from retrospective cohorts, the modifiable and nonmodifiable risk factors associated with postoperative respiratory complications. Unfortunately, all these risk factor assessments have grouped any type of perioperative pulmonary complication (PPCs i.e., pneumonia, aspiration, pulmonary edema, respiratory failure, pulmonary embolism, bronchospasm, hypoxemia) together, making the scores less useful for determining the specific risk of PRF. At least one PPC occurs in up to 19% of all patients, with PRF occurring in 2% to 3.5%.

Despite the limitations in the studies available, common themes have emerged. The nonmodifiable risk factors most commonly associated include advanced age (>65 years old), functional dependence, emergency surgery, chronic obstructive pulmonary disease (COPD), preoperative low oxygen saturation on room air, major open abdominal or thoracic surgery, neurologic surgery, and vascular surgery (specifically aortic surgery). American Society of Anesthesiologists class greater than 2 is a particularly strong predictor of PPCs. Modifiable risk factors included preoperative rehabilitation, improving nutrition (risk highest with albumin <30 g/dL), smoking cessation, minimizing procedure length (increased risk with procedures >3 hours), intraoperative ventilator strategy, intraoperative volume management, minimization of transfusion, and postoperative multimodality care approaches (adequate pain control, minimization of atelectasis, early mobility).

Intraoperative Strategies

Intraoperative changes occur almost immediately that have deleterious effects on pulmonary function. Volatile anesthetics result in a decrease in mucociliary function, which efficiently creates a more desirable environment for bacteria. Alveolar capillary permeability also increases, as does a decrease in surfactant. This combined impairment has been implicated in the development of postoperative pneumonia, which is a major cause of PRF. There is also a rapid decrease in functional residual capacity that increases V/Q mismatch and leads to significant atelectasis.

Adopting a ventilator strategy that minimizes the effects of general anesthesia has been shown to decrease the risk of PRF. This includes a lung protective ventilation strategy of smaller tidal volumes of 6 to 8 mL/kg. The role of positive end expiratory pressure (PEEP) remains controversial, with some data supporting low PEEP and others higher PEEPs (5–10 cm H_2O). Despite conflicting results, most advocate for an intraoperative PEEP of 5 to 8 cm H_2O. Recruitment maneuvers have been shown to have a limited effect on combating the atelectasis that occurs in nearly 75% of all patients receiving paralytics for induction. Volume controlled ventilation is preferable, especially in thoracic and abdominal surgery where compliance can dramatically change during a procedure. It is particularly important to avoid volutrauma resulting in alveolar overdistention. Often overlooked is the role of hyperoxia (FIO_2 >80%) for prolonged periods intraoperatively. It is important to minimize the time at high FIO_2 concentrations to avoid the development of oxygen associated absorption atelectasis.

In addition to mechanical ventilation strategies, alterative volume management has been shown to be advantageous. Recent studies have also shown that those exposed to colloids (albumin) and greater transfusion exposures are at a higher risk of PRF. However, the key is judicious management of volume needs. It is not advantageous to avoid needed transfusion by increasing exposure to crystalloids. It is well known from the trauma literature that patients exposed to high volumes of crystalloid also have a detrimental effect on posttraumatic pulmonary outcomes. In general, more restrictive fluid resuscitation strategies are preferred over liberal approaches, especially in trauma patients and those undergoing thoracic surgery.

One of the easiest modifiable risk factors for PRF is adequately assessing residual neuromuscular blockade remaining at the end of a procedure. Prolonged neuromuscular blockade or residual effects can result in impaired diaphragmatic strength, poor cough, and a net reduction in the forced vital capacity. These are a setup for developing PRF. Also, extubating a patient who has severe pain that is inadequately controlled can also worsen atelectasis. For abdominal or thoracic procedures, strong consideration to epidural placement should be considered because this has been linked to lower postoperative pulmonary complications.

Postoperative Strategies

In addition to adequate pain control strategies (that achieve optimized comfort while minimizing respiratory depressant medications such as opioids), a multimodality approach to postoperative care has been demonstrated to minimize PRF. This includes nutritional support, selective nasogastric tube decompression after abdominal surgery, careful volume management avoiding fluid overload, and lung expansion maneuvers. Lung expansion maneuvers include incentive spirometry 10 times per hour while awake, deep breathing and coughing every 2 hours, and adjuvant physiotherapy (cough assist, flutter valve, chest physiotherapy, intermittent positive pressure ventilation) for high risk patients. The most important factor for all patients is early mobilization. Early mobilization improves V/Q mismatch. It also passively increases lung volumes because patients are more likely to take a larger breath when in the upright position. It also increases airway clearance and promotes coughing.

There has been growing interest and comfort with using noninvasive ventilation to decrease the need for intubation in patients suffering PRF. Noninvasive ventilation (NIV) includes CPAP (for hypoxemic patients) and BiPAP (for those with concomitant hypoxia and hypercapnia), both of which provide positive pressure

ventilation. It is especially useful in those having preexisting COPD. For these patients, it has been shown to lower mortality rates and decrease intensive care unit length of stay and the need for intubation. It is not useful for patients in whom secretions, aspiration, emesis, or inability to comply with wearing a face mask are issues. NIV can reduce work of breathing associated with pain from upper abdominal or thoracic procedures. It is useful in recruiting atelectatic lung and effectively increases forced vital capacity.

HFNC is a newer strategy to increase positive airway pressure via a noninvasive and well tolerated nasal prongs. Oxygen is delivered at 35 to 60 L/min, which produces 5 to 8 mm Hg of positive pressure. HFNC has been shown to decrease work of breathing and postoperative pulmonary complications. Humidified and heated air can be provided via this mechanism. For specific postoperative respiratory failure, there is no clear evidence that HFNC is superior to other forms of NIV, but a current ongoing clinical trial is investigating this.

Overall, NIV has been shown to be safe in postoperative patients. A recent study recommended 30 minutes of intermittent CPAP over the first 7 postoperative days was advantageous for high risk patients. A total of five CPAP treatments per patient were applied. Although compliance was variable, most patients were able to initiate this therapy within the first postoperative day.

For those unable to be extubated at the end of their procedure, similar approaches to intraoperative ventilator management are keys to avoiding pulmonary complications. This includes lung protective ventilation at 6 mL/kg tidal volume for high risk patients, maximum of 8 mL/kg for low risk patients, a PEEP of at least 5 cm H_2O, and limiting airway plateau pressure to 28 cm H_2O. Intermittent recruitment maneuvers should be used as necessary. Minimizing fraction of inspired oxygen to less than FiO_2 0.6 helps to minimize absorption atelectasis and oxygen radical secondary to lung injury.

Daily sedation interruption (spontaneous awakening) and spontaneous breathing trials (SBTs) are imperative to minimizing the time on the ventilator. A successful SBT includes a patient maintaining adequate work of breathing without tachypnea and oxygenation. SBTs are typically done at a low level of CPAP (5 cm H_2O) for 30 minutes. If the rapid shallow breathing index (breaths per minute divided by tidal volume in liters) remains below 105, there is an 80% chance of a successful extubation. Additional extubation criteria include minimal secretions, ability to protect the airway, minimal airway edema (presence of a cuff leak when tested), adequate pain control, and hemodynamic stability. If patients are not able to be extubated after SBT, they are returned to their prior mechanical ventilator settings.

ARDS

The most severe form of postoperative respiratory failure (PRF) is acute, diffuse, progressive, resulting in acute respiratory distress syndrome. Although ARDS is relatively uncommon after elective operations, it occurs with a higher frequency in those undergoing emergency operations. ARDS can be a lethal condition, with mortality rates exceeding 30% to 50% when it occurs in its most severe form during the postoperative period. Postoperative ARDS tends to occur early as a median of 2 days after surgery. Once a patient develops ARDS, therapeutic interventions are aimed at minimizing further barotrauma or volutrauma while addressing the underlying cause of the ARDS. For those requiring mechanical ventilation, a lung protective ventilation strategy (low tidal volume with 6 mL/kg of predicted body weight) has been shown to be the most effective therapy in the treatment of ARDS for reduction in mortality rates. The vast majority of the remaining treatments, known as rescue therapies, have only short term benefits in improving oxygenation but fail to provide any long term survival benefit. Rescue therapies are particularly important in postoperative ARDS where increased pulmonary shunting from severe atelectasis is one of the major contributing factors to the PRF. These therapies are aimed at reducing the increased pulmonary shunting. Despite having no survival benefit, rescue therapies are vital components in management of severe ARDS.

Definitions

The definition of ARDS has undergone multiple iterations since first described in 1967, and the most current version was adopted in 2011. A consensus panel representing the European Society of Intensive Care Medicine, American Thoracic Society, and the Society of Critical Care Medicine developed the Berlin criteria. The definition requires an interval of onset within 1 week of illness, injury, or surgery. Other criteria include a minimum of 5 cm H_2O for PEEP to required, bilateral opacities involving at least three quadrants by chest radiographs that are not fully explained by effusions, lobar/lung collapse, or nodules, and the degree of hypoxemia must not be fully explained by cardiac failure. The condition is classified as mild (PF 201–300 mm Hg), moderate (PF 101–200 mm Hg), and severe (PF <100 mm Hg).

Therapeutic Targets and Standard Therapies

The treatment of ARDS is largely supportive care focused on minimizing the underlying conditions contributing to the development of ARDS (like pneumonia or sepsis). The mainstay of therapy is to maintain oxygenation while minimizing risk of barotrauma and oxygen toxicity. There are no clear criteria for safe minimum oxygenation criteria; however, most clinicians try to reach an oxygen saturation of 88% or greater, with PaO_2 levels greater than 55 to 60 mm Hg. Oxygen toxicity and further lung injury can result if the PaO_2 is sustained less than 60% to 65% within 48 hours.

Lung protective ventilation has become the standard of care for those patients suffering from ARDS. The ARDS Network of investigation has repeatedly demonstrated a survival benefit when low tidal volume ventilation is used. Tidal volumes at 6 mL/kg or less of ideal body weight are desirable while limiting transpulmonary pressure (plateau pressure <30 mm Hg). This strategy is almost universally applied with high respiratory rates (>30 breaths/min) to maintain adequate minute ventilation and avoid severe acidosis secondary to hypercapnia. The approach of permissive hypercapnia (allowing pCO_2 levels to rise to minimize plateau pressures) is used in most patients. The most commonly recommended mode of ventilation for patients with ARDS is volume control to minimize the risk of ventilatorinduced that can occur with the variable tidal volumes seen in pressure control modes.

Bicarbonate infusions may be necessary if pH levels fall to 7.15 to 7.20 to minimize cardiac dysfunction occurring due to the acidosis from permissive hypercapnia. A conservative fluid volume management approach has also been shown to be advantageous, resulting in fewer ventilator days, lower plateau pressures, lower PEEP, and improved P/F ratio. Steroids remain controversial, with most clinicians recommending that they only be given before 14 days and reserved for patients who are failing to improve. Used in this manner, they have been associated with a favorable improvement in oxygenation and fewer ventilator days without any increase in infectious complications, but they did not result in a long term survival benefit.

Rescue Therapies

Rescue therapies include neuromuscular blockade, recruitment maneuvers, inhaled nitric oxide or inhaled prostacyclins, prone positioning, and extracorporeal membrane oxygenation (ECMO). High frequency ventilation (HFOV) is no longer routinely used for the management of adult ARDS after the findings of the OSCILLATE trial were published in 2013 in the *New England Journal of Medicine*, which showed increased mortality rates for those treated with HFOV compared with conventional ventilation.

Clinically, the question of when and how to use rescue therapies arises frequently when patients are perceived to have refractory hypoxemia. There is no standard definition of refractory hypoxemia. Most would consider it to include the following criteria: PaO_2 less than 60 mm Hg with plateau pressures greater than 30 cm H_2O with an FiO_2 of 0.8 or greater, a P/F ratio less than 100, or a saturation persistently less than 88%. Further complicating treatment is the lack of a clear therapeutic target for a minimum PaO_2 that is safe. Most ARDS protocols target a PaO_2 greater than 55 mm Hg. For those who have

significant neurologic impairment (stroke or traumatic brain injury), a higher PaO_2 goal is desired. Although for brain injured patients guidelines recommend a PaO_2 greater than 100 mm Hg, in those with concomitant ARDS it is usually difficult to achieve this without risk of further lung injury. For these patients, a common practical target is 70 to 80 mm Hg.

Fig. 1 demonstrates a stepwise approach for selecting from the rescue therapies described below. It is important to understand that the goal of rescue therapies is to improve oxygenation while the underlying pathophysiology contributing to ARDS can be addressed. Most rescue therapies provide only short-term benefit for those suffering life-threatening hypoxemia. Only low tidal volume ventilation, higher PEEP, and prone positioning have been shown to improve survival.

Neuromuscular Blockade

Although neuromuscular blockade (neuromuscular blocking agents) is considered standard therapy by some clinicians for those suffering moderate to severe ARDS, it is technically a rescue therapy. It should only be used if prolonged mechanical ventilation is expected and should be used early (<2 days) in the course of ARDS. They are most effective for improving oxygenation in those with significant ventilator asynchrony. There is limited evidence that there may be a small survival benefit at 90 days. Heavy sedation is required if neuromuscular blockade is used.

Recruitment Maneuvers and Higher PEEP

After neuromuscular blockade, recruitment maneuvers and high PEEP are used next to determine whether areas of lung can be "recruited." Significant atelectasis is one of the consequences of lung protective ventilation strategies. Portions of lung may not be well inflated due to the lower pressures and volumes targeted. Hypoxemia results from shunting when there are perfused alveoli that are not aerated.

Recruitment maneuvers are brief sustained inflations of the lungs to higher airway pressures and volumes than ordinarily used in mechanical ventilation. At our institution, we attempt bolusing the inspiratory pressure at 60 mm Hg for 40 seconds. We repeat the maneuver several times over a short 15- to 20-minute interval if the patient tolerates the initial attempt. For patients who are volume deplete, this can result in transient hypotension. Patients also occasionally have worsened hypoxemia initially as the recruited lung is opening up. Alternative strategies include holding the pressure for shorter time intervals (20–30 seconds) and the use of intermittent PEEP. Intermittent PEEP can be used with volume control modes of ventilation typically set for 4 above the baseline PEEP. The ventilator delivers this extra PEEP every few breaths. Additional maneuvers include periodic large tidal volume breaths (or sighs).

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) causes improved ventilation perfusion matching through vasodilation of the pulmonary circulation, occurring preferentially to the alveoli that are well ventilated. One of the major contributors to refractory hypoxia is a consequence of acute pulmonary hypertension secondary to regional hypoxia. iNO has a net effect of reducing the acute pulmonary hypertension. Clinical studies have generally failed to find a universal survival benefit of iNO for all patients with moderate to severe ARDS, but there are minimal improvements in hypoxemia. For those suffering life-threatening hypoxemia, it may provide enough time to allow other therapies to take effect or provide a bridge to more advanced interventions such as prone positioning or ECMO. The typical starting dose is 5 ppm, with titration to 40 ppm. Patients also must be monitored for methemoglobinemia, and improvement in oxygenation is greatest in the first 24 to 48 hours.

Inhaled Prostacyclin

Prostacyclin act as vascular smooth muscle dilators that can target the pulmonary vasculature when given in an inhaled formula. The net result is reduction in afterload for the right heart by reductions in mean pulmonary pressure and pulmonary vascular resistance.

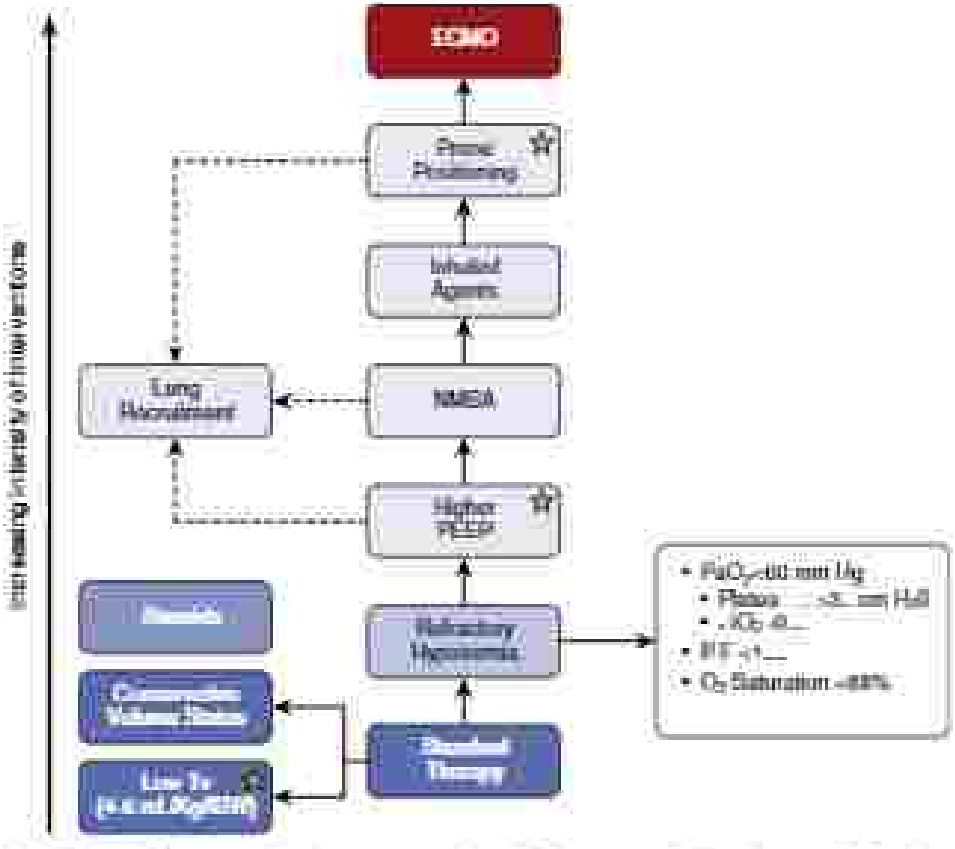

FIG. 1 Rescue therapy algorithm. ECMO, Extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; PEEP, positive end-expiratory pressure.

while attenuating the peripheral effect of hypotension. They may also have a secondary benefit of reducing inflammation in the pulmonary tissue through antiinflammatory properties including inhibiting platelet aggregation and neutrophil adhesion.

The most widely available inhaled prostacyclin is epoprostenol (Flolan). The half-life of epoprostenol is very short, lasting only minutes, and typical dosing ranges from 1 ng/kg per minute to 60 ng/kg per minute. It is given as a continuous nebulized solution hooked in line with the ventilator. Inhaled prostacyclins are typically significantly less expensive than iNO. A recent Cochrane review failed to find any high-quality evidence assessing the survival benefit of inhaled prostacyclins; however, it has been shown to improve short-term oxygenation.

How to Use iNO and Inhaled Prostacyclins

An arterial blood gas (ABG) to assess preexposure PaO_2 should be obtained 5 to 15 minutes before administration of the inhaled agent and again 30 to 60 minutes after exposure. Those with an increase in PaO_2 or oxygen saturation are considered responders. Clinically, occasionally a patient will not respond at 30 to 60 minutes, but a subsequent response will be seen after a longer exposure interval up to 4 hours. If a patient is not a responder, the inhaled agent should be withdrawn. The caveat is that some patients who do not appear to benefit with regard to improved oxygenation will improve when the therapy is coupled with prone ventilation.

Prone Positioning

Prone positioning has been available as a rescue therapy for decades, but until the recently reported PROSEVA study, its survival benefits had been questioned. The results were quite remarkable with a reduction in 28-day mortality from 33% in the supine group to 16% in the prone group. The patients were left in the prone position for at least 16 consecutive hours per day. This study combined with multiple prior works supports that improvements in oxygenation are seen for those placed in the prone position. As with other rescue therapies, the greatest benefit is if it is used early. In the trial, prone positioning was continued until the P/F ratio improved to 150 mm Hg or greater with 10 cm or less of water of PEEP and 60% or less FiO_2 after being in the supine position for 4 consecutive hours.

When prone, the FiO_2 should be weaned to maintain the goal PaO_2 over the 16 hours. Before returning to a supine position the first time, they should be preoxygenated to 100% FiO_2. Once supine, ABGs and oxygen saturation levels should be monitored as FiO_2 is weaned. When weaning PEEP, it should be done slowly with a maximum change of 1 cm of H_2O per 12 hour period. When supine, patients should be returned to the prone position if the PaO_2 falls below the goal or if saturations reach less than 87% to 88%. Typically, the first time the patient is supine, we will limit the patient to 30 to 60 minutes in the supine position. In subsequent intervals of supine positioning, the time supine can be increased stepwise to 4 hours.

ECMO

Venovenous ECMO has been used with success over the last several decades in some centers with specialized expertise (Fig. 2). However, no well-done randomized trials have been completed demonstrating benefit over other rescue therapies. The major drawbacks to ECMO include it being highly invasive compared with other rescue techniques.

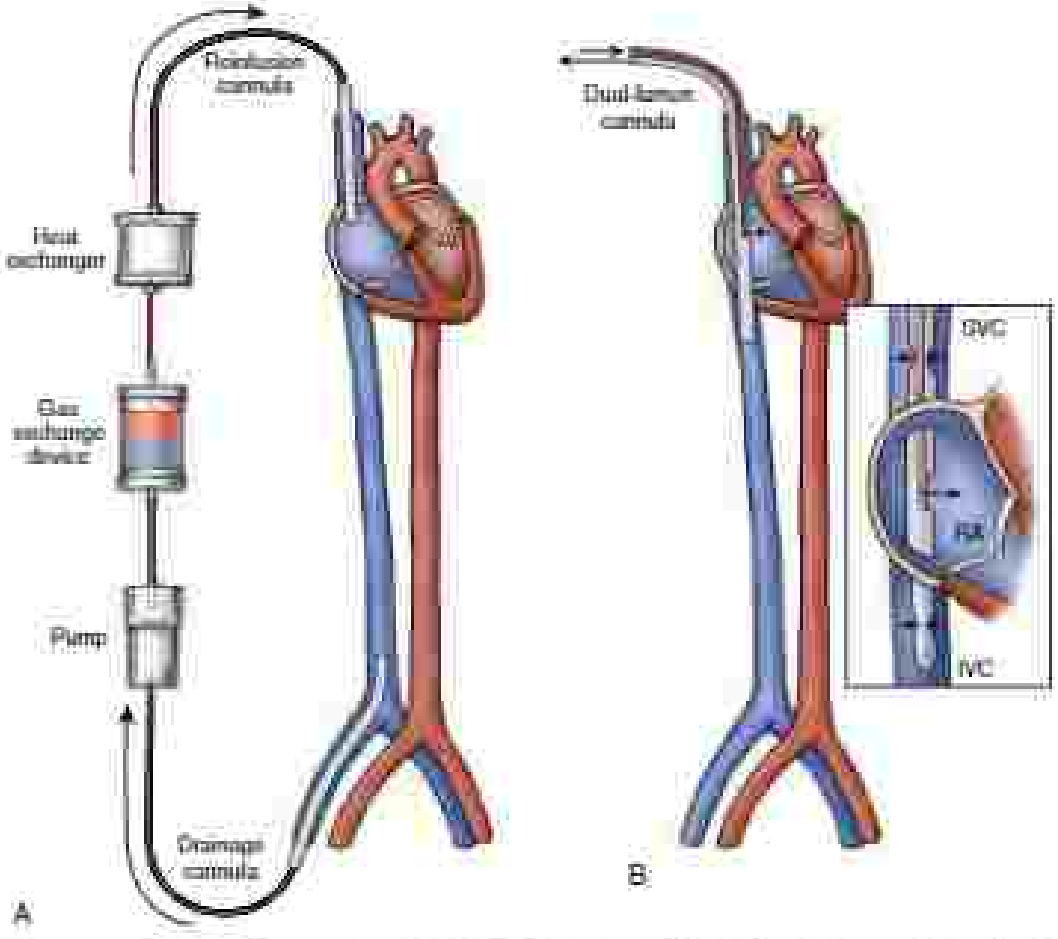

FIG. 2 Venovenous extracorporeal membrane oxygenation. (A) Jugular configuration. Blood is drained from the femoral vein and then passes through a pump, a gas exchange device, and a heat exchanger before returning into the internal jugular vein. (B) Single cannula configuration using a dual-lumen cannula. Blood is drained from the [illegible] and returned to the R[illegible] atrium. IVC, Inferior vena cava; RA, right atrium; SVC, superior vena cava.

expensive, and almost always requiring systemic anticoagulation. These limitations are balanced against the ability of ECMO to allow patients to be ventilated at smaller tidal volumes without the consequences of hypocapnia. This lower ventilation helps to avoid further secondary lung injury that occurs due to volutrauma and barotrauma. This strategy helps to allow the underlying lung to heal. Despite the lack of clinical trials, some centers have had case series with significant benefit, and ECMO is considered as a potentially life saving therapy for patients to consider who do not respond to other rescue therapies.

Suggested Readings

The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–1308.

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Ventilator-Associated Pneumonia

Navpreet K. Dhillon, MD, and Eric J. Lay, MD

Pneumonia remains a continually encountered medical condition that continues to carry significant morbidity and mortality despite advances in medical care. Community acquired pneumonia accounts for 8.4% of primary care physician visits annually with a mortality rate nearing 12% for those who ultimately require hospital admission. Likewise, the associated mortality resulting from hospital-acquired pneumonia is high, with 2016 National Healthcare Safety Network data indicating that 44% of patients die during admission and an additional 23% die within a year of admission, reflecting an overall mortality rate of 67% from the first year from diagnosis. Ventilator-associated pneumonia (VAP) is associated with prolonged mechanical ventilation time, longer hospital stays, and especially high mortality. VAP has classically been defined as pneumonia that developed after at least 48 to 72 hours of endotracheal intubation and leads to the most common intensive care unit (ICU)–acquired infection. Although the high mortality after pneumonia diagnosis is associated with the patient's underlying condition, every measure possible should be considered to reduce pneumonia related mortality.

Respiratory infections constitute one-half of all infections in ICUs. Further, multiple studies have shown that surgical and trauma patients develop VAP at higher rates compared with other patients, highlighting why surgeons should be aware of this condition. Although the incidence of VAP appears to be decreasing, it remains largely an iatrogenic disease. Clinicians continue to encounter several challenges with regards to the prevention, diagnosis, and treatment of VAP.

Risk Factors

Elderly patients, the immunocompromised, and those with lung disease or other comorbidities are at increased risk for VAP. In addition, prolonged supine positioning, use of paralytics, and aspiration are associated with VAP. Several studies have identified risk factors for VAP among trauma patients which include increased injury severity score, emergent intubation, transfusion requirements, spinal cord injury, thoracic injury, and need for operative intervention. Patients presenting with traumatic brain injury are at a particularly high risk and require a high index of suspicion for the diagnosis and treatment of VAP.

Prevention

Many cases of VAP result from iatrogenic causes. Clinicians must understand the methods and strategies that are used to prevent VAP, especially those that minimize or prevent intubation.

Early Extubation

There is a direct correlation between the duration of mechanical ventilation and the risk of VAP occurrence. The surgical intensivist should exhaust all measures to minimize ventilation duration. This includes using daily sedation holidays during which sedation is temporarily held to the point that a patient can follow commands. In addition, a daily spontaneous breathing trial is necessary to allow the patient to demonstrate respiratory ability with the assistance of minimal pressure alone. Daily sedation holidays when paired with spontaneous breathing trials help to facilitate regular assessment of the patient's respiratory status and to determine if the patient is a suitable candidate for extubation. Failure to do so leads to prolonged ventilation and unnecessary ventilator days. The decision to extubate should be made early in the day such that the proper personnel are readily available in case the patient requires reintubation. In addition, awake patients waiting for extubation have a high risk for endotracheal tube dislodgment and the need for urgent reintubation. Anecdotally, our "extubation rounds," in which we briefly walk through the unit before formal rounds to identify potential extubation candidates, leads to early extubations and limits refusal delays. Finally, a surgical ICU team should be available 24 hours a day to evaluate those patients who are young, healthy, and ready to be weaned from the ventilator.

expensive, and almost always requiring systemic anticoagulation. These limitations are balanced against the ability of ECMO to allow patients to be ventilated at smaller tidal volumes without the consequences of hypocapnia. This lower ventilation helps to avoid further secondary lung injury that occurs due to volutrauma and barotrauma. This strategy helps to allow the underlying lung to heal. Despite the lack of clinical trials, some centers have had case series with significant benefit, and ECMO is considered as a potentially life saving therapy for patients to consider who do not respond to other rescue therapies.

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Preventing Reintubation

Another opportunity to reduce the rate of VAP is to reduce reintubation with select noninvasive measures. Noninvasive devices deliver ventilatory support without an endotracheal tube. Noninvasive ventilation (NIV) has been shown to reduce rates of intubation and mortality in select patients admitted with chronic obstructive pulmonary disease exacerbation or acute cardiogenic pulmonary edema. Extubating patients at risk for reintubation to NIV will reduce the rate of reintubation; however, if a patient develops delayed respiratory failure after extubation, there is little role for NIV to prevent reintubation. In fact, a multicenter randomized control trial demonstrated that patients who received traditional NIV therapy after developing respiratory failure within 48 hours from extubation had a higher mortality rate compared with those receiving standard therapy. Attempting to salvage respiratory failure with NIV after a failed extubation is highly dangerous and should be avoided to favor of reintubation.

The use of high flow nasal cannula (HFNC) has emerged recently as an alternative method to standard NIV therapy with potential results in preventing reintubation. HFNC is designed to deliver humidified air and oxygen at a rate that exceeds other traditional oxygen modalities. A large multicenter randomized control trial demonstrated that there was a reduction in mortality and lower intubation rates in patients with acute hypoxemic respiratory failure placed on HFNC. In a single-center retrospective study, HFNC was associated with lower adjusted reintubation rates in critically ill surgical patients specifically. The use of HFNC after extubation is not standard throughout ICUs, but should be considered to select patients who are high risk for reintubation.

Lung Protective Ventilation

Understanding the mechanics of ventilation and how this may facilitate lung injury in critically ill patients is imperative. It is well established that ventilating ventilation with lower tidal volumes carries a lower risk of mortality in patients with acute respiratory distress syndrome (ARDS). Likewise, this strategy during abdominal operations is also associated with lower rates of pneumonia and other complications, presumably resulting from an attenuated inflammatory response from the ventilator itself. In general, lower tidal volumes to reduce barotrauma should be favored to lower the incidence of VAP.

Bundles

VAP bundles have gained popularity over the past decade, and much focus has been given to the development and adherence to these bundles. The original bundle introduced by the Institute for Healthcare Improvement included several interventions with the intention of reducing VAP. Components of the VAP bundle often include head of bed elevation, daily sedation holidays, daily spontaneous breathing trials with routine extubation evaluations, stress gastric prophylaxis, and venous thromboembolism prophylaxis. Variants of the bundle emphasize oral hygiene with chlorhexidine.

Because much of the care required by VAP bundles has become standard, the efficacy of mandatory bundles is uncertain. Some studies suggest that VAP bundles effectively reduce the incidence of VAP and costs, whereas others question their ability to do so. A multiinstitutional study in trauma patients showed that not only was true VAP bundle compliance difficult to attain, VAP rates occurred independent of compliance. Despite questionable benefits, VAP bundles are not detrimental and therefore frequently adopted in ICU settings.

TERMINOLOGY AND DIAGNOSIS

The terminology associated with VAP and the related events can be perplexing, but important for healthcare providers to understand. In fact, a substantial reason why VAP rates have declined significantly nationwide is because of the evolving definition of what constitutes VAP. VAP historically referred to a pneumonia that develops 48 to 72 hours after endotracheal intubation; however, defining a pneumonia can be challenging because the clinical and bacteriologic criteria used are neither sensitive nor specific. The Centers for Disease Control and Prevention's National Healthcare Safety Network introduced new terminology in 2013 (Fig. 1) to better describe the associated conditions.

Ventilator associated events (VAEs) describe several entities including ventilator associated conditions (VACs), infection related VAC (IVAC), and possible VAP (PVAP). VAC occurs after a patient who has been on mechanical ventilation for at least 2 days develops a change in respiratory status manifested by either a need for increased fraction of inspired oxygen or higher positive end expiratory pressure. VAE can derive from both infectious etiologies such as pneumonia, and noninfectious etiologies such as pulmonary edema, atelectasis, ARDS, and pulmonary embolus. A VAE, complicated by either changes in temperature (either <36°C or >38°C) or white blood cell count (either <4000 cells/mm³ or >12,000 cells/mm³), which requires treatment with an antimicrobial agent for at least 4 days is further categorized as an IVAC. IVACs with purulent secretions and/or positive laboratory testing are classified as PVAPs. The specific criteria that results in a positive laboratory test can be found in Fig. 1. Although bronchoalveolar lavage (BAL) in some instances may be superior to endotracheal aspiration for diagnosing VAP, both are effective and diagnosis by either method is associated with similar ventilator days, ICU and hospital length of stay, and mortality.

Despite these definitions, the criteria for VAP remains subjective because there is no universally accepted definition. Some clinicians rely heavily on chest radiographic findings such as the development of consolidations, whereas others may use more objective criteria. Scoring systems, such as the Clinical Pulmonary Infection Score, can be used to determine if a PVAP is VAP (Table 1). Clinical Pulmonary Infection Score accounts for the nature of tracheal secretions, chest radiographic findings, temperature, laboratory values, and ventilator settings. A score of 6 or more correlated with a 100% sensitivity and 93% specificity in one study. Another study, however, revealed a 77% sensitivity and 62% specificity, questioning the utility of the scoring system. Defining VAP will continue to be a challenge as the terminology is expected to evolve with new scoring systems.

TREATMENT

Given the high mortality associated with untreated VAP, clinicians should start broad spectrum empiric antibiotics immediately after the suspicion for VAP arises. In fact, early antibiotic administration is linked with lower mortality rates. Some may be reluctant to start antibiotics without a definitive diagnosis because of concerns for the development of multidrug resistant (MDR) organisms, however, recent evidence suggests that resistance is not as prevalent as previously thought. Ultimately, the liberal or conservative use of antimicrobials is at the discretion of the attending physician. In either case, antibiotics should be deescalated and tailored once culture results and sensitivities become available.

Local antibiograms can guide initial therapy. Antibiograms provide an overview of common pathogen susceptibilities at a certain institution when laboratory results are pending. This report is synthesized by compiling institutional laboratory data periodically. Alternatively, the Infectious Diseases Society of America and the American Thoracic Society developed guidelines in 2016 that can be used when initiating treatment (Fig. 2). Empiric VAP treatment using this algorithm is highly dependent upon the risk for both MDR VAP and the prevalence of resistant gram negative bacilli and methicillin resistant *Staphylococcus aureus* (MRSA) within a given unit. Any patient who either received intravenous antibiotics within the past 90 days, developed septic shock at the time of the presumed VAP incident, had ARDS preceding VAP, was hospitalized for at least 5 days before VAP onset, or required acute renal replacement is deemed high risk and should receive two agents for gram negative and pseudomonal coverage (one β-lactam based and one non β-lactam based antimicrobial) and an additional agent that will specifically cover MRSA. Similarly, individuals who are not considered high risk for MDR VAP

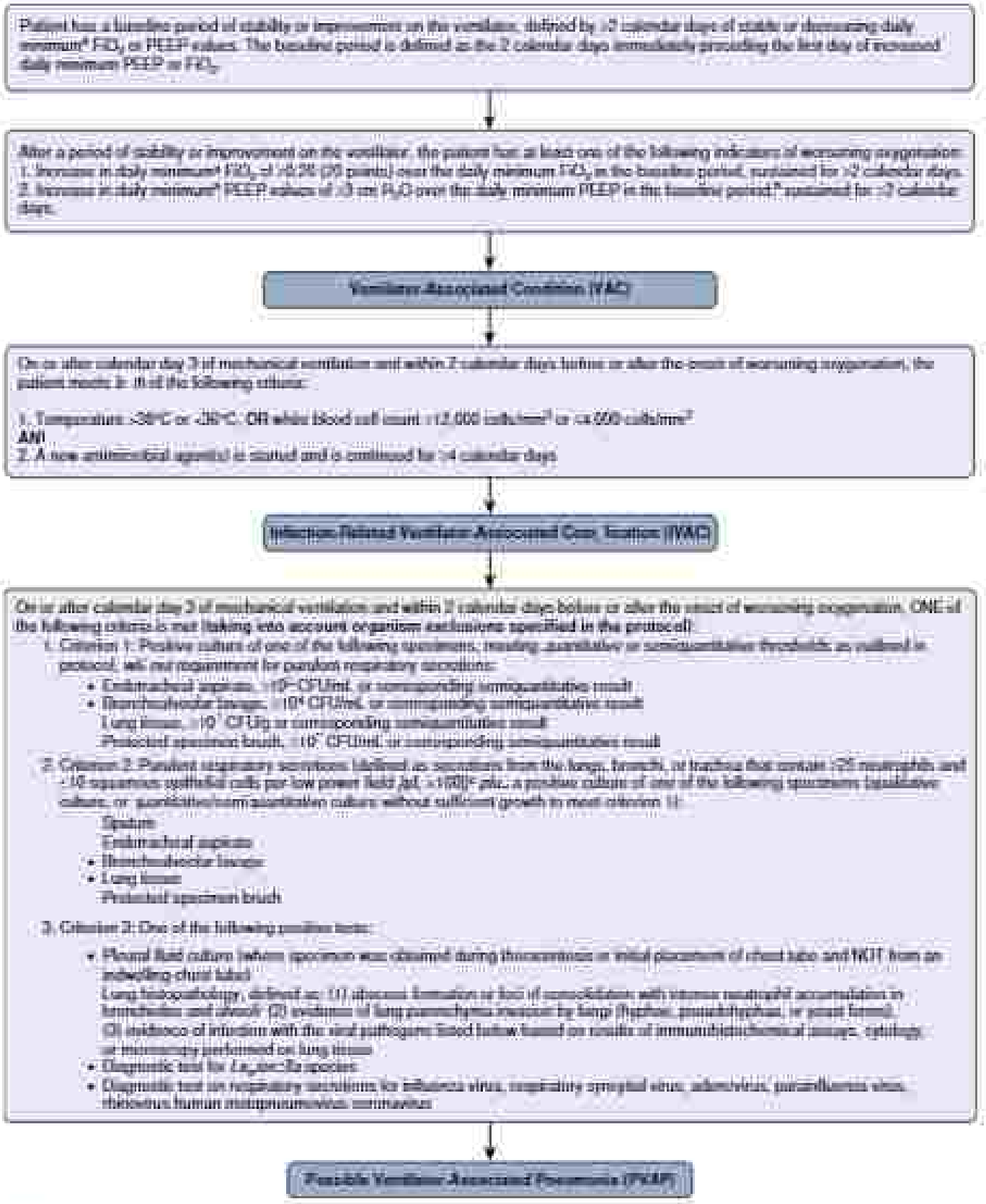

FIG. 1 Ventilator-associated events surveillance algorithm. [a]Lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour. [b]Daily minimum PEEP values of 0 or <5 cm H_2O are considered outliers for the purposes of VAE surveillance. If the laboratory reports some "qualitative" results, those results must convert to the same quantitative thresholds for laboratories for using the purulent respiratory secretions criterion in the IVAC. Abbreviations: FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VAE, ventilator-associated event. [Illegible] Centers for Disease Control and Prevention, National Healthcare Safety Network, Ventilator-associated event [pdf], [illegible] (March 2019). [illegible] Adapted from "[illegible]," by BioRender.com (2020). Retrieved from [illegible].

TABLE 1 Clinical Pulmonary Infection Score

Diagnostic Feature	0	1	2
Tracheal secretions	Rare	Abundant	Abundant and purulent
CXR infiltrate	None	Diffuse	Localized
Temperature (°C)	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39.0 or ≤36.5
White blood cells (× 10⁹/L)	≥4.0 and ≤11.0	<4.0 or >11.0	<4.0 or >11.0 + bands ≥0.5
PaO_2/FiO_2 (mm Hg)	≥240 or ARDS		<240 or no ARDS

ARDS, Adult respiratory distress syndrome; CXR, chest radiograph; PaO_2/FiO_2, partial pressure of oxygen in arterial blood/fractional concentration of oxygen in inspired gas.
From Pugin J. Clinical signs and scores for the diagnosis of ventilator-associated pneumonia. *Minerva Anestesiol.* 2005;71:367–381. Copyright © Edizioni Minerva Medica.

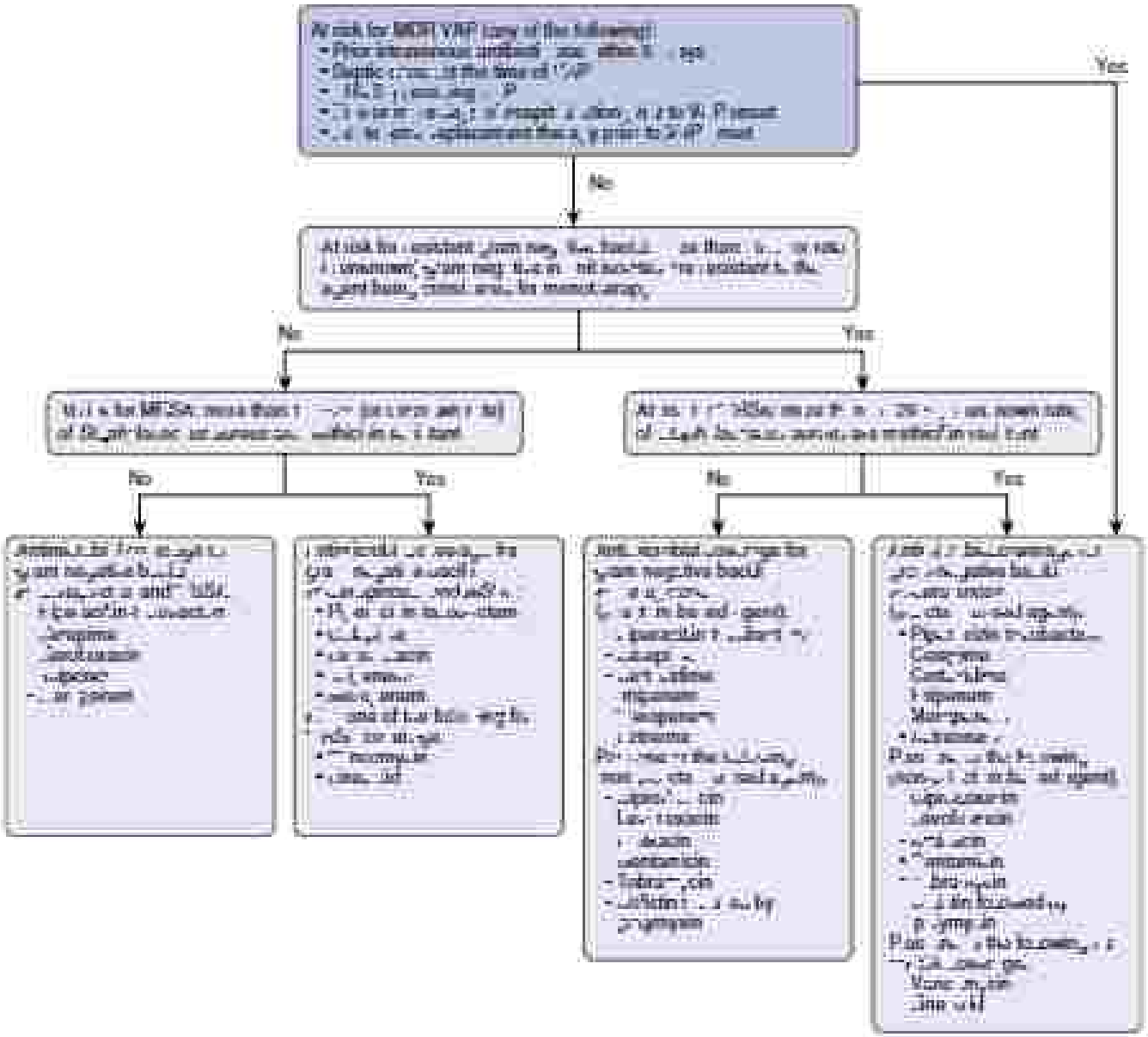

FIG. 2 Proposed algorithm for empiric antibiotic treatment for VAP. ARDS, acute respiratory distress syndrome; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; PSEA, methicillin-sensitive *S. aureus*; VAP, ventilator-associated pneumonia. (Modified from Kalil AC, Metersky ML, Klompas M, et al. Management of adult with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63:e61.)

but are in units where more than 10% (or unknown rate) of the gram-negative bacilli isolates are resistant to monotherapy and more than 10% (or unknown rate) of *S. aureus* isolates are resistant to methicillin should receive the same regimen. MRSA coverage can be removed if there is a low rate of MRSA isolates within the unit. Monotherapy can be used to empirically cover gram-negative bacilli and *Pseudomonas* species if a unit has a low level of gram-negative bacilli resistance. Typical agents used for monotherapy include piperacillin-tazobactam, cefepime, and levofloxacin.

The duration of antimicrobial therapy is another factor that needs to be considered. There is significant variability with how long pathogens remain after the initiation of therapy, with some clearing within 72 hours of treatment and others remaining for nearly a week. At the same time, prolonged treatment may be associated with resistance. Magnotti et al describe a protocol wherein a BAL is obtained on day 4 of treatment; if the BAL demonstrates a growth of less than 10,000 CFU/mL, then antibiotics are continued for a total of 7 days. Antibiotics are otherwise continued for 10 to 14 days if there is more growth. Recent guidelines from the Infectious Disease Society of America and the American Thoracic Society, in contrast, recommend a 7 day course rather than an extended course, irrespective of BAL results. There were no differences in ventilator days, ICU length of stay, or mortality when comparing patients who had shorter antibiotic courses with those with longer courses in a recent meta-analysis. Of note, one third of VAP cases are due to non-glucose fermenting gram-negative bacilli including *Pseudomonas* and *Acinetobacter*, which benefit from prolonged courses to reduce recurrent infection.

CONCLUSIONS

VAP continues to be a condition that occurs in a sizable portion of critically ill surgical patients and carries substantial morbidity and mortality especially when left untreated. Defining VAP can be challenging, but it is important to start therapy with broad-spectrum coverage as soon as the clinical suspicion for VAP arises. Antibiotics should be deescalated and tailored according to study results. Emphasis should also be placed on VAP prevention through early extubation and reducing reintubation.

SUGGESTED READINGS

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EXTRACORPOREAL MEMBRANE OXYGENATION FOR RESPIRATORY FAILURE IN ADULTS

Candice C. Low, MD, Robert J. Morana, MD, and George J. Magovern Jr, MD

Acute respiratory distress syndrome (ARDS), first described nearly 50 years ago, continues to be a major contributor to morbidity and mortality, as well as an important component of resource consumption in the intensive care unit. The syndrome is the most severe manifestation of acute lung injury, which can develop from a wide range of direct pulmonary (aspiration, toxic inhalation, infection, near drowning) or extrapulmonary sources (disseminated sepsis, thoracic trauma, circulatory shock). Ventilator management focuses on minimization of barotrauma and prevention of increasing levels of CO_2 retention. Standard ventilator strategies aimed toward limiting development of pulmonary distention and promoting recruitment of atelectatic alveoli include pressure-controlled ventilation, inverse-ratio ventilation, and low frequency ventilation. Current mortality rates remain high, however, ranging between 39% and 60% in published reports. Ventilator-induced lung injury secondary to barotrauma limits the efficacy of standard therapy, even when used under the direction of respiratory specialists. Theoretically, the technique of extracorporeal membrane oxygenation, or extracorporeal membrane oxygenation (ECMO) is a logical approach to broker the competing problems of lung protection and effective gas exchange in ventilator-dependent patients because it separates these processes and allows control over the degree of native lung function.

ECMO SYSTEM DESCRIPTION

A typical ECMO system is comprised of a membrane oxygenator, heat exchanger, roller or centrifugal pump, circuit tubing, and cannulae appropriate to the mode of access. A parallel circuit containing a second pump and oxygenator may be used to ensure efficient CO_2 removal at low flow rates or to increase oxygenation at higher flow rates. In some systems, a parallel circuit is included to minimize the effects of oxygenator complications and to facilitate oxygenator exchange. Heparin-bonded components are used when possible to decrease anticoagulation requirements. Most systems maintain the circulating blood at normothermic temperatures, but slight hypothermia has been suggested to reduce oxygen consumption requirements when metabolic demand is high.

Indications

Venovenous (VV) ECMO should be considered in any adult patient suffering from acute onset and potentially reversible severe respiratory failure with significant hypoxia or hypercarbia despite maximal ventilator management. Although there are many causes of respiratory failure in adults including pulmonary embolism, acute cardiogenic pulmonary edema, and hypercarbic respiratory failure, the most common etiology is ARDS. The Berlin Definition of ARDS, published in 2012, established the current widely accepted diagnostic criteria based on timing and etiology of respiratory symptoms, radiographic findings, and presence of hypoxemia (Box 1). Several methods for grading the severity of ARDS have been developed, but the most commonly used to predict clinical therapies in ARDS trials has been the Murray Lung Injury Score, which assesses four factors: (1) extent of infiltration on chest film; (2) degree of hypoxemia; (3) level of positive end expiratory pressure (PEEP) required to achieve oxygenation; and (4) respiratory system compliance (Table 1). A Murray score of more than 2.5 is generally accepted as an indication for consideration of VV ECMO in severe ARDS (Box 2).

but are in units where more than 10% (or unknown rate) of the gram-negative bacilli isolates are resistant to monotherapy and more than 10% (or unknown rate) of *S. aureus* isolates are resistant to methicillin should receive the same regimen. MRSA coverage can be removed if there is a low rate of MRSA isolates within the unit. Monotherapy can be used to empirically cover gram-negative bacilli and *Pseudomonas* species if a unit has a low level of gram-negative bacilli resistance. Typical agents used for monotherapy include piperacillin-tazobactam, cefepime, and levofloxacin.

The duration of antimicrobial therapy is another factor that needs to be considered. There is significant variability with how long pathogens remain after the initiation of therapy, with some clearing within 72 hours of treatment and others remaining for nearly a week. At the same time, prolonged treatment may be associated with resistance. Magnotti et al describe a protocol wherein a BAL is obtained on day 4 of treatment; if the BAL demonstrates a growth of less than 10,000 CFU/mL, then antibiotics are continued for a total of 7 days. Antibiotics are otherwise continued for 10 to 14 days if there is more growth. Recent guidelines from the Infectious Disease Society of America and the American Thoracic Society, in contrast, recommend a 7 day course rather than an extended course, irrespective of BAL results. There were no differences in ventilator days, ICU length of stay, or mortality when comparing patients who had shorter antibiotic courses with those with longer courses in a recent meta-analysis. Of note, one-third of VAP cases are due to non-glucose fermenting gram-negative bacilli including *Pseudomonas* and *Acinetobacter*, which benefit from prolonged courses to reduce recurrent infection.

CONCLUSIONS

VAP continues to be a condition that occurs in a sizable portion of critically ill surgical patients and carries substantial morbidity and mortality especially when left untreated. Defining VAP can be challenging, but it is important to start therapy with broad-spectrum coverage as soon as the clinical suspicion for VAP arises. Antibiotics should be deescalated and tailored according to study results. Emphasis should also be placed on VAP prevention through early extubation and reducing reintubation.

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EXTRACORPOREAL MEMBRANE OXYGENATION FOR RESPIRATORY FAILURE IN ADULTS

Candice T. Lee, MD, Robert J. Maraca, MD, and George J. Magovern Jr, MD

Acute respiratory distress syndrome (ARDS), first described nearly 50 years ago, continues to be a major contributor to morbidity and mortality, as well as an important component of resource consumption in the intensive care unit. The syndrome is the most serious manifestation of acute lung injury, which can develop from a wide range of direct pulmonary (aspiration, toxic inhalation, infection, near drowning) or extrapulmonary sources (disseminated sepsis, thoracic trauma, circulatory shock). Ventilator management focuses on minimization of barotrauma and prevention of increasing levels of CO_2 retention. Standard ventilator strategies aimed toward limiting development of pulmonary distention and promoting recruitment of atelectatic alveoli include pressure-controlled ventilation, inverse-ratio ventilation, and low frequency ventilation. Current mortality rates remain high, however, ranging between 39% and 60% in published reports. Ventilator-induced lung injury secondary to barotrauma limits the efficacy of standard therapy, even when used under the direction of respiratory specialists. Theoretically, the technique of extracorporeal membrane oxygenation, or extracorporeal membrane oxygenation (ECMO) is a logical approach to bypass the competing problems of lung protection and effective gas exchange in ventilator-dependent patients because it separates these processes and allows control over the degree of native lung function.

ECMO SYSTEM DESCRIPTION

A typical ECMO system is comprised of a membrane oxygenator, heat exchanger, roller or centrifugal pump, circuit tubing, and cannulae appropriate to the mode of access. A parallel circuit containing a second pump and oxygenator may be used to ensure efficient CO_2 removal at low flow rates or to increase oxygenation at higher flow rates. In some systems, a parallel circuit is included to minimize the effects of oxygenator complications and to facilitate oxygenator exchange. Heparin-bonded components are used when possible to decrease anticoagulation requirements. Most systems maintain the circulating blood at normothermic temperatures, but slight hypothermia has been suggested to reduce oxygen consumption requirements when metabolic demand is high.

Indications

Venovenous (VV) ECMO should be considered in any adult patient suffering from acute onset and potentially reversible severe respiratory failure with significant hypoxia or hypercarbia despite maximal ventilator management. Although there are many causes of respiratory failure in adults including pulmonary embolism, acute cardiogenic pulmonary edema, and hypercarbic respiratory failure, the most common etiology is ARDS. The Berlin Definition of ARDS, published in 2012, established the current widely accepted diagnostic criteria based on timing and etiology of respiratory symptoms, radiographic findings, and presence of hypoxemia (Box 1). Several methods for grading the severity of ARDS have been developed, but the most commonly used to predict clinical therapies in ARDS trials has been the Murray Lung Injury Score, which assesses four factors: (1) extent of infiltration on chest film; (2) degree of hypoxemia; (3) level of positive end-expiratory pressure (PEEP) required to achieve oxygenation; and (4) respiratory system compliance (Table 1). A Murray score of more than 2.5 is generally accepted as an indication for consideration of VV ECMO in severe ARDS (Box 2).

BOX 1 Berlin Definition of ARDS (All Criteria Must be Present)

- *Timing of respiratory symptoms:* onset of symptoms within 1 week of known clinical insult, or new or worsening symptoms arising during the past week
- *Radiographic findings:* bilateral pulmonary infiltrates on chest radiograph or CT scan
- *Rule out other etiologies:* respiratory symptoms that cannot be fully explained by cardiac failure or fluid overload
- *Hypoxemia:* The severity of ARDS is defined by the degree of hypoxemia, as indicated by the ratio of PaO_2/FIO_2
  - *Mild:* PaO_2/FIO_2 >200 mm Hg but <300 mm Hg, on mechanical ventilator settings with PEEP or CPAP ≥5 cm H_2O
  - *Moderate:* PaO_2/FIO_2 >100 mm Hg but <200 mm Hg, on mechanical ventilator settings with PEEP ≥5 cm H_2O
  - *Severe:* PaO_2/FIO_2 ≤100 mm Hg on mechanical ventilator settings with PEEP ≥5 cm H_2O

The Berlin Criteria, established in 2012, replace previously accepted 1994 American-European Consensus definition of ARDS.
ARDS, Acute respiratory distress syndrome; *CPAP,* continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; *PEEP,* positive end-expiratory pressure.

TABLE 1 Murray Lung Injury Score

Category	Score
1. Extent of infiltration on chest radiograph	
No alveolar consolidation	0
Confined to 1 quadrant	1
Confined to 2 quadrants	2
Confined to 3 quadrants	3
Involving all 4 quadrants	4
2. Degree of hypoxemia (partial pressure of oxygen in arterial blood/fraction of inspired oxygen)	
≥300	0
225–299	1
175–224	2
100–174	3
<100	4
3. Level of positive end-expiratory pressure (cm H_2O)	
≤5	0
6–8	1
9–11	2
12–14	3
≥15	4
4. Respiratory system compliance (mL/cm H_2O)	
≥80	0
60–79	1
40–59	2
20–39	3
≤19	4

Final Murray score is calculated by the addition of scores from each component. Score 0 = no lung injury, 1–2.5 = mild-moderate lung injury, >2.5 = severe lung injury.

BOX 2 Indications and Contraindications for VV ECMO

Indications

1. Hypoxic respiratory failure resulting from any cause where there is >80% risk of mortality. Consider VV ECMO when risk of mortality is >50%.
   - PaO_2/FIO_2 <150 on FIO_2 >90%, and a Murray score of 2–3 is associated with a 50% risk of mortality
   - PaO_2/FIO_2 <100 on FIO_2 >90% and a Murray score of 3–4 is associated with an 80% risk of mortality
2. Refractory CO_2 retention despite high pressure mechanical ventilation settings (peak plateau >30 cm H_2O)
3. Intubation in end stage lung disease patient awaiting lung transplant
4. Massive air leak
5. Acute cardiopulmonary collapse secondary to PE, airway obstruction, trauma, etc.

Contraindications

1. Mechanical ventilation with high settings (FIO_2 >90%, peak plateau >30 cm H_2O) for >7 days
2. Recent or expanding CNS hemorrhage
3. Immunosuppressed (ANC <400/mm^3)
4. Non-correctable comorbidity (i.e., terminal malignancy, major CNS damage, end stage lung disease without transplant option)

ANC, Absolute neutrophil count; *CNS,* central nervous system; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; *PE,* pulmonary embolism; *PEEP,* positive end expiratory pressure; *VV, ECMO,* venovenous.

Contraindications

VV ECMO can be a lifesaving tool for severe refractory respiratory failure when appropriate patients are selected. There are no absolute contraindications for VV ECMO; however, factors associated with poor outcomes despite ECMO are considered relative contraindications. These include active intracranial hemorrhage, prolonged high pressure and fraction of inspired oxygen (FIO_2) ventilation beyond 7 days, metastatic malignancy with a short life expectancy, and severe baseline advanced respiratory failure without a treatment option beyond ECMO (e.g., lung transplant, lung volume reduction surgery) (Box 2). Potential conditions in patients considered for VV ECMO are very common; thus, each patient should be evaluated on a case-by-case basis. In particular, patients should be assessed as to their premorbid function, baseline comorbidities, duration of illness, current number of organ system failures, and overall prognosis. Younger patients with few to no medical problems and isolated ARDS will tend to have the best outcomes. Daily multidisciplinary assessment of futility should be evaluated by the progression of illness, subsequent organ failure, and complications.

Technique

Insertion of VV ECMO to establish rapid pulmonary support is of critical importance. There are two well accepted percutaneous configurations.

1. Right femoral vein to the inferior vena cava (IVC) and right internal jugular (IJ) vein to the right atrium, with two separate cannulae (Fig. 1).
2. Right internal jugular vein into right atrium and IVC with a single dual-lumen three-port cannula (Fig. 2).

The goals of both of these approaches are to take deoxygenated blood from the IVC (Fig. 1) or IVC and superior vena cava (SVC; Fig. 2), pass it through an oxygenator, and return oxygenated and decarboxylated blood to the right atrium. Before placing VV ECMO,

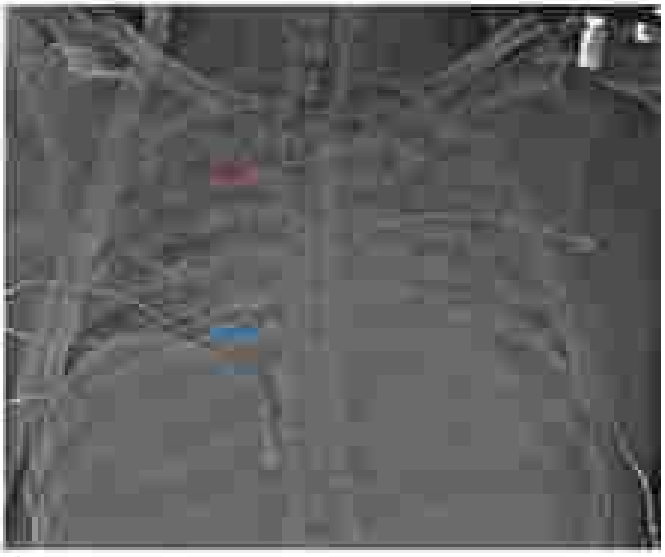


FIG. 1 Standard venovenous extracorporeal membrane oxygenation cannulation. Long venous cannula is inserted with its tip in the inferior vena cava (blue arrow) and inflow cannula in the right internal jugular (red arrow).

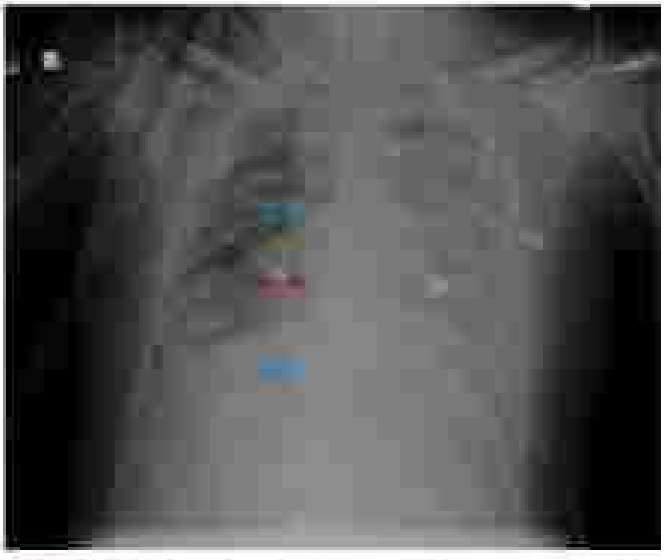


FIG. 2 Single dual-lumen three-port venovenous extracorporeal membrane oxygenation cannulation with two drainage ports (blue arrows) in the superior vena cava and inferior vena cava and one inflow port in the right atrium (red arrow).

patients should have a central line in the left internal jugular or left subclavian vein, as well as an arterial line. In addition, continuous telemetry monitoring during the procedure is crucial because malignant arrhythmias can often occur with wire manipulation within the right atrium of a hypoxic patient. Before insertion, we confirm the planned cannulation sites and supine position with head turned to opposite side of the neck being accessed. The patient is widely prepped with chlorhexidine antiseptic at the neck from the tragus to the sternal notch and bilateral groins to the knees. It is important to use sterile drapes that extend from the patient's head to the feet. It is our preference to access the right femoral vein because the left femoral vein crosses behind the left common iliac artery making the insertion more difficult. Using ultrasound guidance and the Seldinger technique, the right femoral vein and IJV are identified, accessed, and wires are placed. Once both wires have been placed, a bolus of heparin, 100 U/kg intravenous is administered. The IJV vein is serially dilated and an 18Fr cannula is inserted, the wire and dilator are removed, and the cannula is clamped. Either simultaneously or sequentially, the right femoral vein is serially dilated in preparation for cannulation. Before inserting the long 24Fr venous cannula, we estimate the appropriate insertion depth by measuring the distance between the patient's groin to the costal margin. The long venous cannula is inserted and clamped as well. The VV ECMO limbs are then brought onto the field and both cannulas are connected to the circuit. It is critical to ensure that no air bubbles are entrained in the tubing during connection. In addition, communication with the perfusionist should ensure that the inflow outflow from the patient to the pump to the femoral cannula and the outflow into the patient is through the IJV. Cannulas are secured in position with 0 silk sutures at the insertion point and Foley catheter holders along the leg and behind the ear onto the chest. Transient desaturation after the institution of VV ECMO commonly occurs because of the transfer of pump prime into the circulation and should resolve within 1 to 2 minutes.

ECMO flow and oxygenation should provide oxygen delivery and CO_2 removal capable of supporting normal patient metabolism. This usually equates to VV blood flows of about 60 to 80 mL/kg per minute. Typically most patients will flow between 3.5 and 5 L/min with 2000 to 2800 revolutions per minute. If a circuit is planned for CO_2 removal only, flows 50% to 25% of cardiac output should suffice. Maximum inflow suction pressure should not exceed −250 mm Hg and the maximum outflow pressure should not exceed 300 mm Hg. Initial ECMO settings should be set at full support with the oxygenator FiO_2 of 100% and the sweep of 4 to 6 L/min. ECMO settings are then adjusted based on the first arterial blood gas on ECMO. Chest and abdominal radiographs are obtained to confirm cannula position. The long venous cannula should be positioned such that the tip lies just below the right costal margin in the IVC. Systemic heparin infusion is initiated and titrated to maintain an activated partial thromboplastin time (aPTT) of 40 to 50 seconds.

The Avalon cannula (Maquet) is a multiport dual lumen cannula designed to be inserted into the IJV and provide full VV ECMO access. The cannula includes two outflow ports in the IVC and SVC and an additional inflow port in the right atrium (Fig. 2). This configuration affords the advantage of a single cannula and avoidance of groin access with the potential for patient ambulation on VV ECMO. One critical caveat to the Avalon must be inserted under echocardiographic or fluoroscopic guidance to ensure the introducer wire is positioned within the IVC and not in the right ventricle. There have been several case reports of improper wire position and subsequent cannula insertion through the free wall of the right ventricle with frequently fatal consequences.

MANAGEMENT

A critical care nurse and an ECMO specialist (typically a perfusionist, respiratory therapist, or physician) should be assigned to provide 24-hour monitoring and care for the ECMO patient and the patient on support. It is imperative that institutions develop its own protocols based on Extracorporeal Life Support Organization (ELSO) guidelines with the perfusion staff, nursing, critical care, and the surgeons for ECMO-circuit management and issues.

Ventilator Management

The goal of VV ECMO is to minimize both barotrauma from hyperinflation and high airway pressure and to limit pulmonary oxygen toxicity. Following stabilization on VV ECMO, we typically follow ARDSNet ventilator protocols to minimize further barotrauma, including pressure control or assist control mode ventilation, with the goal being low tidal volumes of 4 to 6 mL/kg, maximum peak airway pressures 30 cm H_2O or less, and minimizing FiO_2. From this point, we aggressively wean the ventilator FiO_2 to 40% to maintain a partial pressure of oxygen in arterial blood (PaO_2) greater than all but

and then subsequently wean VV ECMO FIO_2 and sweep. Patients with primary hypercarbic respiratory failure can be maintained on low-flow ECMO (15–30 mL/kg per minute) to effect carbon dioxide removal while providing maximum lung rest.

Baseline lung compliance is calculated and then measured daily to assess improvements in the respiratory system. Static lung compliance is calculated by dividing the tidal volume by the difference in plateau pressure and PEEP and has been shown to correspond with successful weaning from VV ECMO.

$$C_{stat} = \frac{\text{Tidal volume}}{[P_{plateau} - P_{EEP}]}$$

Normal lung compliance is approximately 100 mL/cm H_2O and 70 to 80 mL/cm H_2O for ventilated patients. Patient with acute lung injury and ARDS have decreased lung compliance, ranging from 30 to 50 mL/cm H_2O and less than 30 mL/cm H_2O, respectively. It is our belief that the ventilator should be weaned to compliance of more than 30 mL/cm H_2O and FIO_2 40% before weaning ECMO.

Systemic Anticoagulation

Systemic anticoagulation is maintained with continuous infusion of heparin to maintain an aPTT of 40 to 50. It is not uncommon for platelet counts to drop by more than 50%.

Aggressive correction of coagulopathy and prompt surgical response to bleeding sites can reduce bleeding complications to manageable levels in most patients. To optimize the oxygenation carrying capacity in patients, we maintain a hemoglobin greater than 10 to 12 g/dL. The membrane oxygenator is changed either on a fixed schedule based on experience or when signs of impending membrane failure develop. These signs include decreasing efficiency of gas exchange, fraying, and evidence of deposition on the membrane.

Sedatives and Analgesia

The use of sedation and paralysis is based on patient requirements. In situations where agitation significantly elevates oxygen demand, both may be needed. Airway management is facilitated by sedation, especially before tracheostomy; however, the use of increased levels of sedation hinders neurologic evaluation, which is critical for ongoing survivability assessment. In addition, the prolonged use of sedatives and especially paralytics in the intensive care unit can have deleterious consequences. Recently, studies have demonstrated decreased bioavailability of many sedatives and opioids related to circuit sequestration of these agents. Lipophilic drugs, such as midazolam, diazepam, lorazepam, fentanyl, and propofol, are particularly subjected to this phenomenon, resulting in larger dosages and decreased effectiveness of these drugs while on ECMO. Morphine tends to be less affected by circuit sequestration.

Renal

An attempt should be made to aggressively diurese the patient to dry weight or less to reduce and minimize interstitial pulmonary edema. In situations in which renal function is compromised, early use of continuous VV hemofiltration is used to remove volume. Continuous VV hemofiltration can be integrated into the ECMO circuit, thus eliminating the need for an additional venous catheter.

Infection

Prophylactic antibiotics are given before insertion and discontinued within 24 hours, with further antibiotic or antifungal therapy as directed by the presence of any underlying infectious illness. White blood cell count, C-reactive protein, and systemic vascular resistance are good indicators of ongoing infection. Temperature, on the other hand, may be unreliable while on ECMO because a significant amount of passive cooling occurs and can mask fevers. Therefore, cultures are routinely performed biweekly while on ECMO. Activated protein C has a demonstrated survival benefit in severe sepsis; however, its use with ECMO poses a serious bleeding risk.

TROUBLESHOOTING ECMO

Recirculation

Recirculation is a phenomenon that occurs when the inflow and outflow cannulas are too close together (Table 2). Although not inherently dangerous, it reduces the efficiency of the VV ECMO circuit and may be a cause of persistent hypoxia. This can be assessed by visually examining the cannulas for appropriate color differential (the outflow should be dark and the inflow bright), radiographic location of the cannulas (the tip of the femoral venous cannula should be below the diaphragm, there should be sufficient distance between the inflow and outflow cannulae tips). In addition, the PaO_2 of the outflow cannula should not be higher than the systemic PaO_2 or have a saturation greater than 75%. When this does occur, repositioning the outflow cannula will solve the problem.

SVC Syndrome

SVC syndrome can occur in patients on VV ECMO because of mechanical obstruction of the SVC typically with the ECMO cannula. SVC syndrome is typically seen in smaller patients with a body surface area less than 1.6 m^2 and in patients with significant hardware already lying within the SVC (e.g., pacemaker leads, indwelling dialysis catheters). It may occur rapidly after insertion or insidiously over the first several hours. Manipulation of the patient's position is reverse Trendelenburg is only a temporary measure. Once identified, it is best managed by downsizing and exchanging the SVC cannula. It is important to obtain an echocardiogram to ensure that cardiac misadventures with resulting cardiac tamponade is not the cause.

Persistent Hypoxia

Some patients with severe respiratory failure may require maximal ventilator support in addition to maximal VV ECMO support for several days to weeks before any sign of recovery is seen. If patients are persistently hypoxic, we confirm the oxygenator is functioning. Another cause of persistent hypoxia arises from an increase in deoxygenated blood returning from bronchial arteries. In this instance, conversion to veno-arterial venous (VAV) ECMO cannulation strategy is an option.

Hemolysis

Hemolysis with VV ECMO is a relatively rare event that occurs in 10% of patients, according to ELSO registry data. With the use of heparin bonded circuits and centrifugal pumps, hemolysis is not a common problem. It typically is manifested by refractory anemia and elevated bilirubin and should be considered in instances where there is not an overt source of bleeding. It is confirmed by elevated serum plasma free hemoglobin (>10 mg/dL), elevated lactate dehydrogenase, and decreased haptoglobin. Potential sources of hemolysis include clots in the pump chamber, elevated suction pressures (< −300 mm Hg), high resistance of the outflow cannula, or kinking in the circuit. It is important to identify the source of hemolysis and correct it.

Thrombocytopenia

Thrombocytopenia is a common problem with VV ECMO and is infrequently caused by heparin-induced thrombocytopenia (HIT). A drop in platelet count of greater than 50% from baseline prompts HIT screening with anti-heparin PF4 antibody and serotonin release assay testing. If testing is positive for HIT, we will switch to a direct thrombin inhibitor (e.g., argatroban, bivalirudin). There are many reports of patients being managed safely without systemic heparin; however, this will affect the longevity of the membrane oxygenator. Platelets are transfused as necessary to maintain the platelet count at greater than 25,000.

TABLE 2 Troubleshooting Venovenous ECMO

Problem	Signs	Treatment
Recirculation	Persistent hypoxia Outflow blood saturation >5% or partial pressure of oxygen (outflow) > partial pressure of oxygen (inflow) No color differential between outflow and inflow cannula blood Chest radiograph: cannular tips too close together	Reposition outflow cannula
SVC syndrome	Facial plethora Localized edema of face and upper extremities Rule out cardiac tamponade	Downsize and exchange IJ cannula
Oxygenator thrombosis/failure	Persistent hypoxia Decreased post-oxygenator partial pressure of oxygen in arterial blood Hemolysis Elevated outlet pressure	Exchange oxygenator
Hemolysis	Anemia and hyperbilirubinemia Plasma free hemoglobin >10 mg/dL Elevated lactate dehydrogenase Low haptoglobin	Identify source and treat
Thrombocytopenia	>50% drop in baseline hemoglobin platelet count Onset within 5–10 days of prior heparin exposure New thrombosis or skin necrosis Heparin-induced thrombocytopenia testing: anti-heparin PF4 antibody, serotonin release assay Rule out other causes (e.g., hemolysis, disseminated intravascular coagulation, sepsis, idiopathic thrombocytopenic purpura	Stop heparin Start direct thrombin inhibitor (i.e., argatroban, bivalirudin) Can consider no anticoagulation
Hypovolemia	Elevated inlet suction pressure (< −300 mm Hg) Fluctuating and low flows Hypotension Evaluate for bleeding Confirm correct cannula size, position; look for cannula kinking	Give volume; consider blood transfusion for hemoglobin <10 g/dL
Disseminated intravascular coagulation	Recent trauma, sepsis, malignancy Diffuse bleeding Thrombocytopenia Thrombosis Abnormal coagulation profile: ↑ prothrombin time and activated partial thromboplastin time, ↓ fibrinogen, ↑ D-dimer, ↑ fibrin degradation products	Identify underlying cause and treat Supportive care Transfuse to keep platelet count >50,000 and fibrinogen >100 mg/dL

WEANING AND LUNG RECOVERY

The return of lung function is signaled by improving PaO_2 with ability to wean the ventilator FIO_2, improving lung compliance (>30 mL/cm H_2O) and tidal volumes, and a reduction in the peak airway pressures. The ventilator is set to 7 to 8 mL/kg with peak airway pressure less than 35 mm Hg, and an FIO_2 less than 40%, then VV ECMO FIO_2 is weaned slowly over several days to maintain a systemic PaO_2 greater than 70. Once an ECMO FIO_2 of 21% (room air) is maintained for 24 to 48 hours with PaO_2 greater than 70 on ventilator FIO_2 <40% with a lung compliance of 30 mL/cm H_2O or greater, the heparin infusion is stopped and the ECMO cannulae are clamped and removed at the bedside. Hemostasis is achieved with direct pressure for at least 30 to 45 minutes. In our experience, open surgical repair of the venous access sites is rarely needed. The patient is maintained on the ventilator until a standard ventilator weaning process is instituted.

DISCUSSION

ECMO was first used successfully more than 30 years ago and has become the standard of care for refractory respiratory failure in neonates and older children. Adult ARDS carries a mortality rate that can approach 100% in patients who are failing conventional treatment, and the care of these patients is expensive and resource intensive. Theoretically ECMO support melds well with the needs of the ARDS patient; it provides excellent CO_2 removal while reducing barotrauma and oxygenation demands on the potentially recoverable native lung. ECMO support is associated with significant comorbidity, particularly related to anticoagulation and bleeding, but these complications are usually manageable and occur at a rate that can be reconciled with the high mortality seen in untreated patients.

Strategies for ARDS are quite diverse. ECMO is rarely evaluated in a cohort consistent for diagnosis because these niche populations are usually too small for timely recruitment. Nevertheless, over the past decade, survival to discharge following ECMO appears to be stabilizing at around 50% for patients with respiratory failure without concomitant cardiac failure (Fig. 3). This appears to be related to the development of improved oxygenators and cannulae and use of VV rather than venoarterial cannulation when cardiac support is not necessary. Use of heparin-bonded components in the ECMO circuit have not eliminated serious bleeding events but have reduced the level of heparin infusion required to maintain an acceptable anticoagulation status.

International Summary -January, 2018

ECLS Registry Report

International Summary

January, 2018

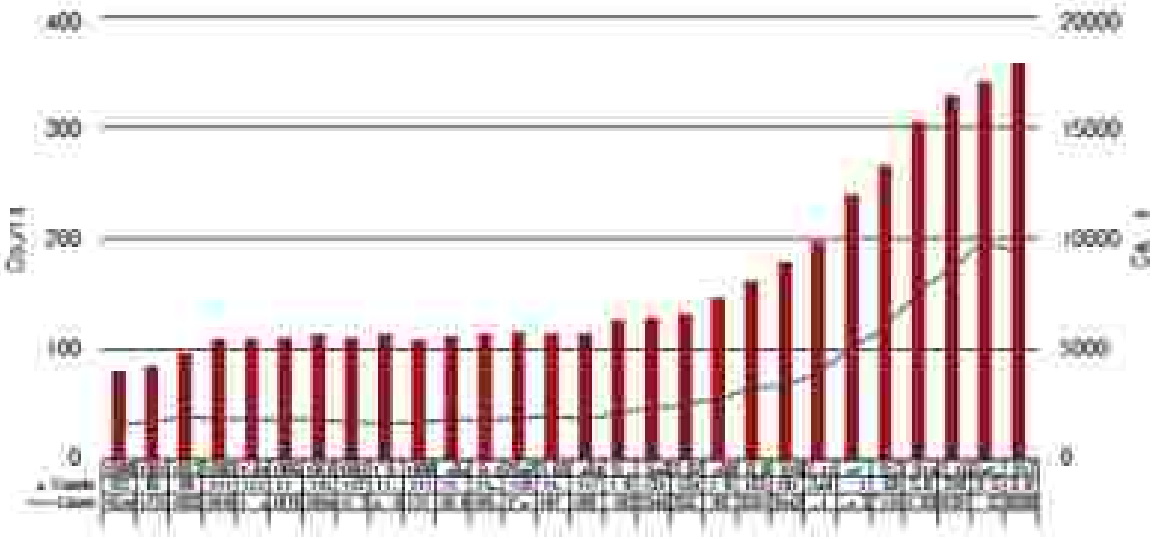
Extracorporeal Life Support Organization
2800 Plymouth Road
Building 300, Room 303
Ann Arbor, MI 48109

Overall Outcomes

	Total Runs	Survived ECLS		Survived to DC or Transfer	
Neonatal					
Pulmonary	38,944	25,922	84%	22,188	73%
Cardiac	7,718	5,011	4%	3,231	41%
ECPR	1,694	1,125	%	654	40%
Pediatric					
Pulmonary	8,726	5,890	7%	5,078	58%
Cardiac	10,232	7,089	8%	5,375	52%
ECPR	3,881	2,220	57%	1,443	40%
Adult					
Pulmonary	15,888	10,463	%	8,7 4	59%
Cardiac	15,201	8,488	55%	6,378	41%
ECPR	4,745	1,830	38%	1,361	29%
Total	98,948	68,041	8%	55, 45	56%

Centers

Centers by year



Wednesday, January 31, 2018 (c) 2018 Extracorporeal Life Support Organization

FIG 3. Extracorporeal life support committee, January 2018. (Courtesy Extracorporeal Life Support Organization.)

Recognition of the role of ventilator-induced barotrauma in limiting the efficacy of mechanical ventilation has led to the development of low-traumatic ventilator management approaches such as pressure-controlled and inverse ratio ventilation. When used as a component of a standardized protocol, these methods can increase the number of patients who recover without transition to ECMO support and may also increase the recovery potential of the native lung in patients who progress to ECMO.

In summary, although the results of a robust randomized clinical trial in a well-defined patient population are awaited, there is evidence that VV ECMO can increase survival in patients with ARDS refractory to conventional therapy. Use of this technique, however, is appropriate only in conjunction with a well-constructed respiratory management protocol that is initiated at the time of ARDS diagnosis.

Suggested Readings

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Tracheostomy

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Tracheostomy is a common procedure performed in intensive care units (ICUs) and the operating room (OR) worldwide. Over 100,000 tracheostomies are performed annually in the United States, a number that appears to have grown steadily up until the 2000s, with a slow rate of decline since. This decline may be explained in part by results from more recent studies on the timing of tracheostomy. Nearly 3% of all hospital admissions in the United States require mechanical ventilation for acute or chronic respiratory failure, the major indications for tracheostomy. Among all patients requiring mechanical ventilation annually, more than 10% undergo tracheostomy as an inpatient, and more than 70% of patients with new tracheostomies are discharged to long-term assisted care facilities. The frequency with which the procedure is performed and its implications for ongoing care in the postacute setting mean that the timing and application of tracheostomy are of major economic importance as well. A recent cost estimate of long-term acute care for chronic critical illness in the United States placed the overall figure at $35 billion annually. Therefore, a general understanding of the indications, risks, benefits, and potential complications of the procedure should be of interest to any medical practitioner or policymaker.

The procedure is typically performed by general, thoracic, or otolaryngology head and neck surgeons, by surgical intensivists, or by medical intensivists with specialized procedural training in the percutaneous dilational technique. A small study found no significant difference in outcomes of percutaneous dilational tracheostomy performed by surgical or interventional pulmonology teams, as long as patients were appropriately selected for the procedure.

Indications and Contraindications

The indications for tracheostomy can be partitioned broadly into three categories, listed in descending order of prevalence: need for prolonged mechanical ventilation, airway protection (i.e., following cerebrovascular accident), and upper airway obstruction (Table 1). Finally, emergency tracheostomy is also a consideration in certain situations in which it is not possible to perform translaryngeal intubation.

The only absolute contraindications to the procedure are soft tissue infection overlying the intended surgical site and operative transport error. Relative contraindications include very high ventilator support settings, uncorrected coagulopathy, and laryngeal cancer prior to definitive treatment given the increased risk of local disease spread.

The contraindications specific to the percutaneous dilational technique are emergency airway, enlarged thyroid, inability to palpate landmarks, unstable cervical spine fracture (or a patient who is otherwise unable to extend their neck), and previous surgery at the site, including prior tracheostomy.

Respiratory Failure with Need for Prolonged Mechanical Support

The most common indication for tracheostomy is the anticipated need for prolonged mechanical ventilation in the context of respiratory failure. Respiratory failure results in over 2 million hospitalizations annually in the United States alone, a number that is steadily growing. Approximately 40% of patients admitted with respiratory failure will require endotracheal intubation with mechanical ventilation, and more than 10% will undergo tracheostomy placement. Two-thirds of all tracheostomy procedures in the United States are performed on mechanically ventilated patients in the ICU, and this is the largest and best-studied population of patients undergoing the procedure. The underlying etiology of respiratory failure is not necessarily an indication or contraindication to tracheostomy, although careful consideration must be given to the expected duration of ventilator support required to avoid unnecessary procedures. Unfortunately, despite considerable study, there is no broad consensus on appropriate timing of tracheostomy after endotracheal intubation.

Common causes of respiratory failure requiring prolonged mechanical ventilator support include sepsis, respiratory failure secondary to other medical problems (i.e., cardiogenic pulmonary edema), and perioperative or traumatic respiratory failure (i.e., after multiple rib fractures). Respiratory failure is often multifactorial and may also result from a combination of conditions; additional risk factors for respiratory failure requiring tracheostomy include increasing age and morbid obesity.

The primary benefit of tracheostomy over translaryngeal tracheal intubation is improved patient comfort and an attendant decrease in sedative and narcotic requirements, which facilitates weaning efforts. This patient-centered outcome has been reiterated in multiple randomized trials and is the only well-established improved outcome over conventional translaryngeal intubation. Tracheostomy also improves ease of pulmonary hygiene and expedites ICU discharge to a ventilator capable step-down unit or post-acute facility with a primary focus on rehabilitation. Most perceived benefits of tracheostomy over translaryngeal intubation have not been consistently demonstrated in prospective studies (ventilator-associated pneumonia, overall mortality).

Recognition of the role of ventilator-induced barotrauma in limiting the efficacy of mechanical ventilation has led to the development of low-traumatic ventilator management approaches such as pressure-controlled and inverse ratio ventilation. When used as a component of a standardized protocol, these methods can increase the number of patients who recover without transition to ECMO support and may also increase the recovery potential of the native lung in patients who progress to ECMO.

In summary, although the results of a robust randomized clinical trial in a well-defined patient population are awaited, there is evidence that VV ECMO can increase survival in patients with ARDS refractory to conventional therapy. Use of this technique, however, is appropriate only in conjunction with a well-constructed respiratory management protocol that is initiated at the time of ARDS diagnosis.

Suggested Readings

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Table: 1 Indications for Tracheostomy

Indication	Condition
Need for prolonged mechanical ventilation	Acute and chronic respiratory failure (i.e., sepsis or degenerative neuromuscular disease)
Airway protection	Neurologic catastrophe Cerebrovascular accidents
Upper airway obstruction	Congenital high airway obstruction Inability to transbronchially intubate trachea Neoplasms of the oropharynx, hypopharynx, or larynx Oral, neck, or maxillofacial trauma or burns Angioedema Laryngeal (i.e., vocal cord paralysis or radiation fibrosis) Infection (i.e., epiglottitis) Obesity hypoventilation syndrome Obstructive sleep apnea Thyroid goiter with compressive signs and symptoms

Importantly, tracheal stenosis and tracheoesophageal fistula, complications most exclusively attributed to prolonged endotracheal intubation, are now also being described following tracheostomy. Additionally, tracheoinominate arterial fistula, once thought to be exclusively a complication of tracheostomy, can also be seen with transtracheal intubation. The complications of tracheal stenosis, tracheoesophageal fistula, and tracheoinominate arterial fistula are more likely related to excessive cuff pressure and pressure necrosis than the means by which ventilation is delivered. Careful consideration of perceived and demonstrated benefits and risks of tracheostomy should be undertaken during discussions with patients or their medical decision makers when pursuing informed consent.

A lack of decisive guidance on timing and a broad range of clinical conditions indicating the procedure underscore the importance of the clinician's role in patient selection and timing of tracheostomy.

Airway Protection

Patients who have had significant head trauma, ischemic stroke, or intracranial hemorrhage may have protracted or permanent dysphagia and are at risk for aspiration. Although lesions affecting the posterior cerebral circulation are classically implicated in post-stroke dysphagia, inability to swallow to present in 30% to 40% of all stroke survivors. In broad terms, neurologic catastrophe resulting in dysphagia with inability to protect the airway is a common indication for tracheostomy. Some patients may respond to nutritional therapy through an enteric tube with oil per os until swallow function and airway protection improve, but many patients with deficits severe enough to require long-term enteral access will ultimately continue to aspirate their own secretions and require tracheostomy.

There have been considerable efforts to predict which patients will require tracheostomy in the neuro-ICU setting. Importantly, many patients in this population also require mechanical ventilation due to central hypoventilation or associated comorbidities. Among patients requiring ventilatory support after intracranial hemorrhage or ischemic stroke, several studies have identified decreased Glasgow Coma Scale scores (typically <8) and severity of radiographic lesions as correlates of need for tracheostomy. However, the heterogeneity of this population and comorbidity between respiratory failure and inability to protect one's airway again ultimately leave the final judgment regarding timing and patient selection to the clinician.

Upper Airway Obstruction

Tracheostomy effectively bypasses functional or mechanical causes of upper respiratory tract obstruction. Congenital causes of upper respiratory tract obstruction include laryngeal atresia (or severe stenosis), a rare condition that may be diagnosed prenatally and important with emergent tracheostomy at the time of birth. The Pierre Robin sequence with severe micrognathia and glossoptosis causing respiratory distress may also be an indication for pediatric tracheostomy.

Obstructing neoplasm affecting the aerodigestive tract is also an indication. Benign and malignant tumors affecting the head and neck can cause respiratory compromise, and tracheostomy may be performed as an adjunct at the time of surgical resection, or as a palliative intervention. Importantly, there is evidence that tracheostomy prior to definitive intervention for laryngeal carcinoma may be associated with increased local disease spread, and the decision to perform tracheostomy and timing relative to definitive treatment should be made with the patient's multidisciplinary oncology team in the context of their treatment plan.

Acquired causes of upper airway obstruction that may be an indication for tracheostomy include stricture from radiation fibrosis or bilateral vocal fold paralysis, for example after iatrogenic recurrent laryngeal nerve injuries or neck malignancy. Any condition causing a difficult or impossible translaryngeal intubation may require tracheostomy. For example, angioedema, burn injury, and trauma to the head and neck in a stable patient with threat to the airway constitute indications for urgent tracheostomy if emergent cricothyrotomy is to be avoided. In the era of vaccination, infectious epiglottitis (i.e., from *Haemophilus influenzae*) is exceedingly rare in the United States but was previously an indication for tracheostomy among children (and less commonly adults). Obesity hypoventilation syndrome and obstructive sleep apnea not responding to conventional management may also require tracheostomy.

Emergency Airway Considerations

In the event that emergent cervical access to the airway is required (i.e., for inability to perform translaryngeal intubation after traumatic injury or cardiopulmonary arrest), cricothyrotomy is the preferred method for expeditiously ventilating unless laryngeal injury is suspected. Surgical or percutaneous (i.e., via needle or hollow catheter) methods may be employed, with the latter preferable among children owing to the relatively small size of affected structures. The speed and reliability of cricothyrotomy makes it the procedure of choice in the majority of urgent surgical airway situations. Conversion of emergency cricothyrotomy to formal tracheostomy should be performed once the patient has stabilized and is able to safely undergo general anesthesia in a controlled environment.

In the event of suspected or confirmed laryngeal injury (i.e., after head and neck trauma), endotracheal intubation and cricothyrotomy should both be avoided. A formal emergent surgical tracheostomy should be performed to decrease risk of extending or otherwise exacerbating the injury. The procedure is performed emergently under local anesthesia when there is concern for impending airway obstruction with suspicion for laryngeal injury based on clinical impression after penetrating or blunt injury. In a stable patient in whom laryngeal injury is suspected without evidence of impending airway compromise, computed tomography and flexible fiberoptic laryngoscopy should be performed prior to any instrumentation of the airway (including endotracheal intubation).

ANATOMY

In the adult, the trachea is a 10 to 13-cm, centrally located, hollow organ with a cervical portion that begins approximately at the sixth cervical vertebral body (Fig. 11.1) traverses the neck and gives way to a thoracic portion that enters the mediastinum and terminates with the carina at the T4–T5 disk level. The hollow and flexible structure of the trachea is supported by the prominent thyroid cartilage, the circumferential

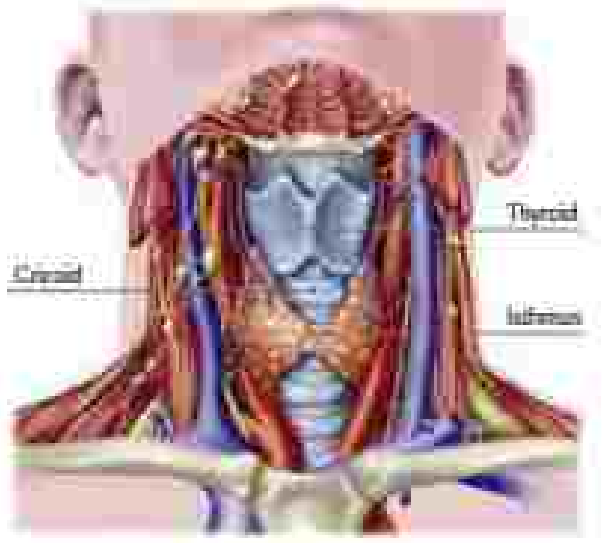


FIG. 1 Safe tracheostomy by any technique requires knowledge of neck anatomy.

cricoid cartilage, and 15 to 20 incomplete cartilaginous rings inferiorly. When viewed in cross section, such as with a bronchoscope, the normal human trachea appears to be nearly cylindrical with posterior flattening. This flattening is evident on histology as the membranous portion of the trachea at the opening of each C-shaped tracheal ring. The posterior wall may also be identified during bronchoscopy by the dense longitudinal folds of the trachealis smooth muscle.

The most superficial and therefore surgically accessible portion of the trachea lies between the thyroid cartilage and the sternal notch. At this point, only the skin, subcutaneous tissue, strap muscles, thyroid isthmus, and pretracheal fascia overlie the organ. The cervical esophagus lies immediately posteriorly, and the lobes of the thyroid and anterior jugular veins border the trachea laterally. The innominate (brachiocephalic) artery crosses over the right anterolateral trachea approximately at the sixth to tenth tracheal rings.

The vascular supply and drainage of the cervical trachea is predominately via the inferior thyroid artery and vein, respectively. Tracheoesophageal branches of the vessels enter the trachea through lateral tissue pedicles, highlighting the importance of midline anterior access during tracheostomy to avoid significant vascular injury. The paired supply and drainage provides some vascular redundancy in the event of significant injury or resection. The supply of the distal trachea may have contributions from subclavian, intercostal, internal thoracic, and bronchial arteries.

The location, length, and anatomic relations of the trachea are less predictable in childhood and normally vary in the adult somewhat with respiration.

OPERATIVE TECHNIQUES

Open Surgical Versus Percutaneous Dilational Tracheostomy

Modern tracheostomy procedures can be described as either open or percutaneous. Conventional "open" or surgical tracheostomy was first described in ancient Egypt over 3600 years ago and remains in use for select patients today. Percutaneous dilational tracheostomy was pioneered using the Seldinger technique to gain access to the trachea in the 1960s by Toye and Wilmoth. However, it was not until Ciaglia described a technique of serial radial dilations in 1985, that percutaneous dilational tracheostomy gained the widespread popularity that is seen today.

Today, percutaneous dilational tracheostomy is recommended over surgical tracheostomy for most adults without contraindications based on evidence for decreased stoma infection, bleeding, and improved scar cosmesis. Although several variations exist, the single-step dilator kits Ciaglia Blue Rhino (Cook Medical) and Portex Ultra-PERC (Smiths Medical) with bronchoscopic guidance are used most commonly. In a 2006 meta-analysis of 17 randomized controlled trials (RCTs) including 1232 patients undergoing tracheostomy, the authors found that percutaneous technique was generally equivalent to surgical tracheostomy with respect to bleeding, major early and long-term complications, and mortality. The only statistically significant benefit of percutaneous technique was a decreased stoma site infection. A more recent 2014 meta-analysis of 973 patients in 14 RCTs agreed with the prior findings of decreased stoma inflammation and infection but cautioned that technical difficulties were more common among percutaneous procedures, perhaps due in part to the increasing prevalence of the procedure and heterogeneity in training among proceduralists.

Preoperative Assessment

Preoperative assessment should include a thorough history and physical examination, and review of laboratory studies and any pertinent imaging or endoscopy. Besides determining if the patient is an appropriate and safe procedural candidate in general, attention should be given to details that may favor surgical (open) tracheostomy over percutaneous dilational tracheostomy.

Relevant historical data include history of malignancy of the head, neck, or upper aerodigestive tract; history of radiotherapy to the head or neck; and any pertinent surgical history. In particular, prior neck surgery (including tracheostomy placement) may lead to scarring that obscures or obliterates anatomic planes and relationships, and therefore increases the complexity of the procedure, and cervical spinal fusion may limit the extension of the neck required for safe percutaneous dilational approach. Although prior neck procedures, including prior tracheostomy, may make the procedure more difficult, they do not necessarily obviate the ability to perform a percutaneous dilational tracheostomy. Fractures of the cervical spine are a relative contraindication to percutaneous tracheostomy, particularly if there is any concern for instability.

For patients in an ICU setting who are intubated and mechanically ventilated, careful attention to hospital course and current and recent ventilator settings is important. The cause of respiratory failure and length of mechanical ventilation, and failed extubation attempts (spontaneous breathing trials or unplanned reintubations) should be considered. Finally, special attention to the fraction of inspired oxygen (FIO_2) and especially the positive end expiratory pressure (PEEP) is critical in planning for a safe tracheostomy. At our institution, patients must generally be able to tolerate FIO_2 less than 0.4 while lying flat at PEEP no greater than 20 mm Hg to be considered for surgical tracheostomy due to the risk and the consequences of potential rapid alveolar de-recruitment during the procedure.

On physical examination, careful attention to the limits of neck extension and palpation of bony and cartilaginous landmarks may ultimately direct the decision to perform surgical tracheostomy. Inability to palpate relevant landmarks or less than 1 cm between the cricoid cartilage and sternal notch are relative contraindications to percutaneous dilational tracheostomy. Generally, an ideal percutaneous dilational tracheostomy candidate will have 2 to 3 tracheal rings palpable below the cricoid cartilage.

It is our practice to check prothrombin time (PT/INR), partial thromboplastin time, and complete blood count within 48 hours of the procedure to ensure that there is no uncorrected severe coagulopathy (PT/INR > 1.5 or platelets < 100,000). The ideal candidate will have normal coagulation parameters. We typically do not interrupt deep venous thrombosis chemoprophylaxis (subcutaneous low molecular weight heparin or unfractionated heparin) or antiplatelet therapies (aspirin, clopidogrel) in preparation for tracheostomy.

For intubated patients, the most recent chest radiograph should be reviewed to ensure that there are no previously unrecognized findings (pneumonia, pneumothorax) preoperatively. If cross-sectional imaging of the neck is available, it should be reviewed to evaluate for aberrant vascular or other anatomy, although there is not a specific indication for preoperative imaging. Similarly, if bronchoscopy or laryngoscopy has been performed, any upper airway pathology should be reviewed prior to performance of the procedure.

Procedural Technique: Surgical Tracheostomy

Although typically performed in the OR with general anesthesia and neuromuscular blockade, surgical tracheostomy may also be performed in the ICU setting. Informed consent from the patient's medical decision maker is garnered preoperatively and a discussion of potential risks should address the most common complications of the procedure including bleeding, infection at the stoma site, accidental decannulation, and pneumothorax. The patient is placed in the supine position with the neck extended using a shoulder roll to improve anterior tracheal exposure if possible. Subtle reverse Trendelenburg position decompresses the veins of the neck, and facial hair is removed using mechanical clippers to the mandible. The patient's skin is prepped from the upper lip to mandible and draped with typical sterile technique. The patient is preoxygenated with 100% FiO$_2$ and ventilator settings that minimize acidosis. Finally, sedation, analgesia, and paralysis are administered by anesthesia staff to improve the safety and efficiency of the procedure.

After a time out for safety that includes discussion of airway and risk mitigation, the relevant landmarks are palpated in preparation for incision (Fig. 2). The preferred 3-cm skin incision may need to be longer for patients with difficult anatomy or obese habitus and is made over the second tracheal ring, or approximately 1 cm below the cricoid cartilage. Although a transverse skin incision (with careful attention to avoid anterior jugular venous injury) is preferred for cosmetic reasons, a vertical incision may be used. The subcutaneous tissues and platysma are divided using a combination of electrocautery and blunt dissection (Fig. 3). Strap muscles (sternohyoid and sternothyroid) are retracted laterally to expose the thyroid isthmus (Figs. 4 and 5). It is our practice to divide the isthmus using electrocautery, although it may be retracted superiorly or inferiorly if it is sufficiently mobile to allow exposure to the trachea. The pretracheal fascia can be divided and dissected bluntly laterally, exposing the trachea (Fig. 6). A cricoid hook is then used to elevate the trachea, which is sharply incised using a scalpel below the first or second tracheal rings. Alternatively, two tracheal "stay" sutures may be placed to facilitate elevation of the trachea; these sutures also may facilitate tracheostomy tube replacement by a trained provider in the event of early inadvertent decannulation (Fig. 7). There are several variations on the tracheal incision itself; some surgeons advocate for a longitudinal "fenestrated H" incision spanning the first through third rings, whereas an alternative approach involves three careful incisions to raise a flap. We make a longitudinal incision involving the second and third tracheal rings approximately 1 cm long, or just sufficient to admit the tracheostomy tube (Fig. 8). The transoral endotracheal tube may need to be retracted slightly to allow placement of a new tracheostomy tube, which is inserted into the new tracheal defect using sterile technique (Fig. 9). The inner cannula is placed, the

FIG. 2 Palpation of surface landmarks facilitates the procedure. The thyroid and cricoid cartilages are outlined with ease and the sternal notch is marked with a cheerful lobotomy. The planned 3-cm cricothyroid incision is marked approximately over the second or third tracheal rings.

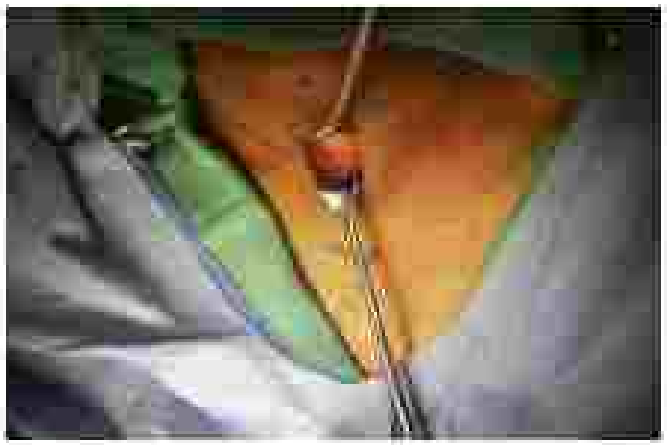


FIG. 3 After skin incision, electrocautery and blunt dissection reveals the platysma.

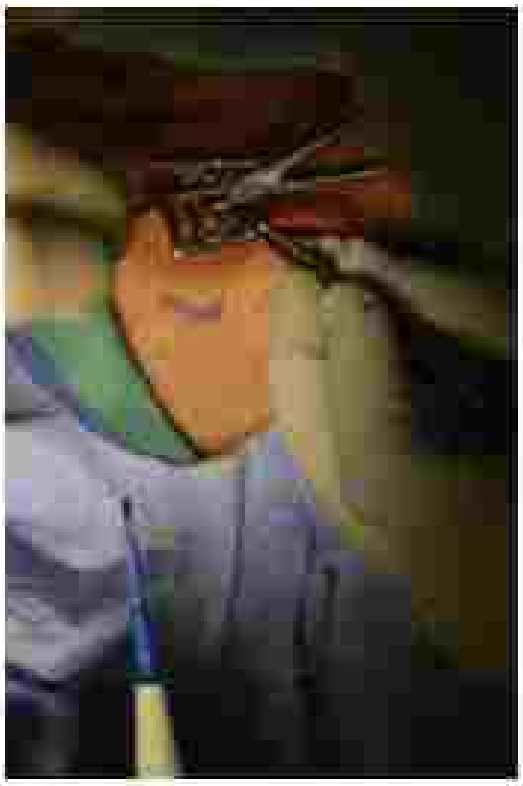
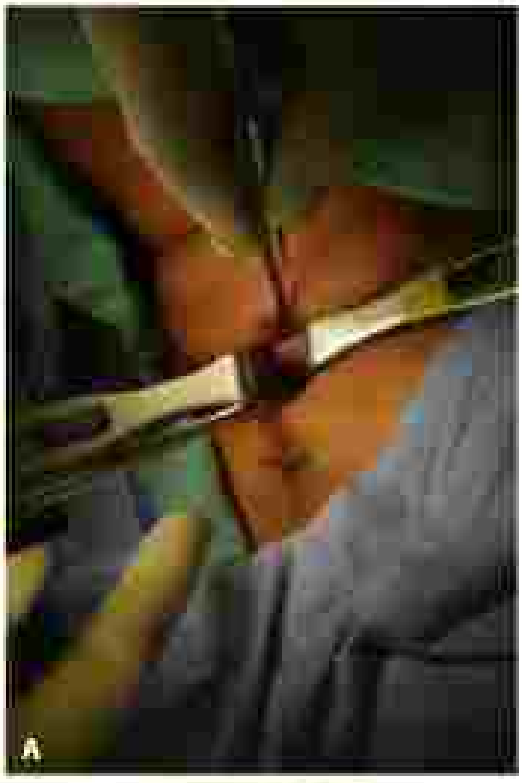


FIG. 4 After incision of the platysma, a combination of electrocautery and blunt dissection reveals the sternohyoid and sternothyroid (strap) muscles, which are retracted or divided.



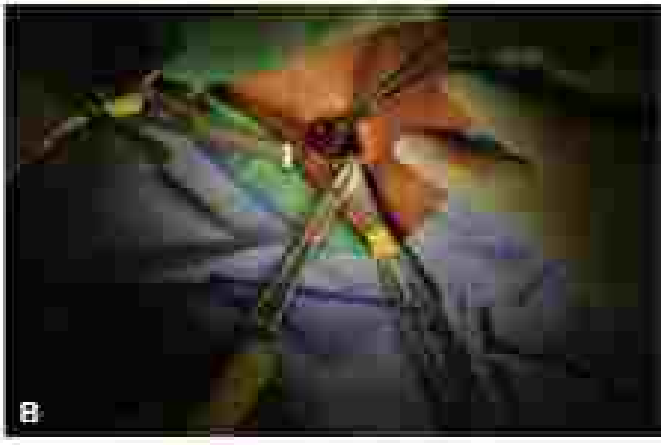


FIG. 5 (A) The thyroid isthmus is encountered, dissected off of the pretracheal fascia and (B) then divided and suture-ligated between clamps.

tracheostomy cuff is inflated, and the ventilator circuit is connected to the new tracheostomy tube. End tidal CO_2 and breath sounds are confirmed before removal of the translaryngeal tube, and 2–0 monofilament nonabsorbable monofilament sutures are used to secure the tracheostomy neck plate to the skin (Fig. 10).

Procedural Technique: Percutaneous Dilational Tracheostomy (Single-Step Dilation Technique)

Percutaneous dilational tracheostomy may be performed in either the OR or ICU settings. There are significant cost and time savings associated with performing the procedure in the ICU given that it obviates the need for OR staff and related resources. In the ICU, the optimal staff complement will include an anesthesiologist or intensivist with advanced airway and procedural sedation training to manage the existing translaryngeal tube and reintubate if necessary, and to provide bronchoscopic guidance during the initial portion of the procedure and administer anesthetics and neuromuscular blockade. An ICU or OR nurse familiar with the procedure and principles of sterile technique should also be available to assist throughout.

Informed consent is similar to that for surgical tracheostomy. The patient is positioned supine with neck extension and slight reverse Trendelenburg position. The patient's neck is shaved, and skin is prepped from nipple line to mandible and a sterile field established with towels and drapes, and a time out for safety is called that includes verification of functional flexible bronchoscopy.

The patient is preoxygenated with 100% FiO_2 and landmarks are palpated. The ideal location for percutaneous dilational tracheostomy is between the first and second or second and third tracheal rings; any higher risks injury to the cricothyroid membrane that may increase long-term incidence of stenosis, whereas lower penetration may increase risk of tracheoinnominate arterial fistula. The site is chosen primarily based on palpation of relevant landmarks including the tracheal rings themselves; bronchoscopy may provide an adjunct as well. The skin and subcutaneous tissues are infiltrated with lidocaine with epinephrine. A 1.5 cm transverse or vertical incision is made sharply in the midline of the neck over the intended site of entry, and underlying subcutaneous tissues are bluntly dissected using Kelly forceps (Fig. 11). The bronchoscope is withdrawn to the level at which it transilluminates the skin at the intended site of entry. The cuff on the endotracheal tube is deflated sufficient to allow retraction of the tube to the site. Finally, a 14 gauge introducer needle is used to puncture the trachea in the midline under bronchoscopic guidance with 10 to 15 degrees of angulation inferiorly (Fig. 12). Careful attention is paid to avoid posterior tracheal wall injury during this

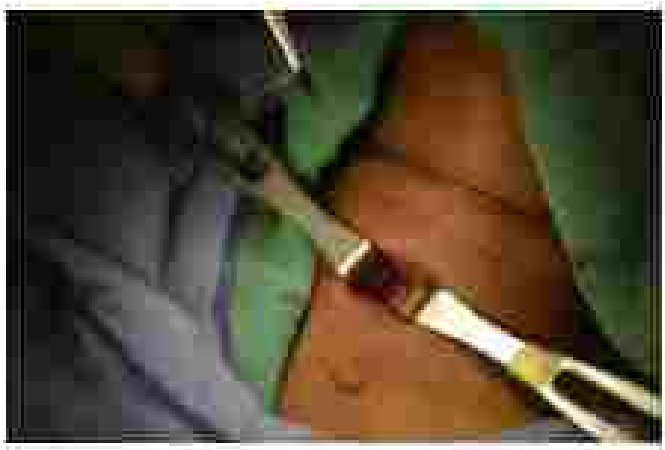


FIG. 6 The pretracheal fascia is divided to reveal the tracheal rings.

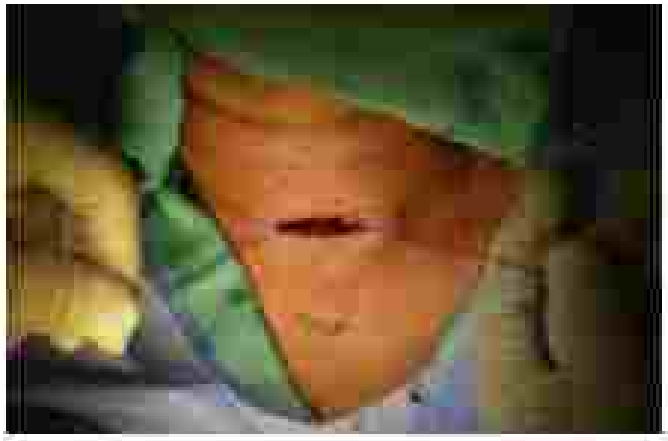


FIG. 7 Three surgeons place two tracheal stay sutures with air knots using monofilament nonabsorbable suture.

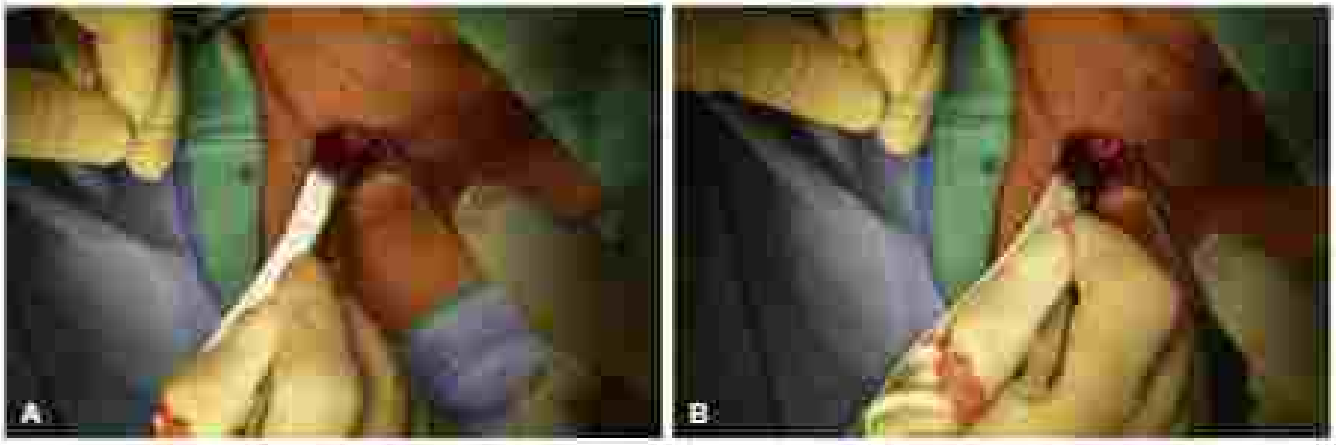


FIG. 9 Tracheotomy is performed using a No. 11 scalpel in a longitudinal fashion (A) through the second and third tracheal rings (B).

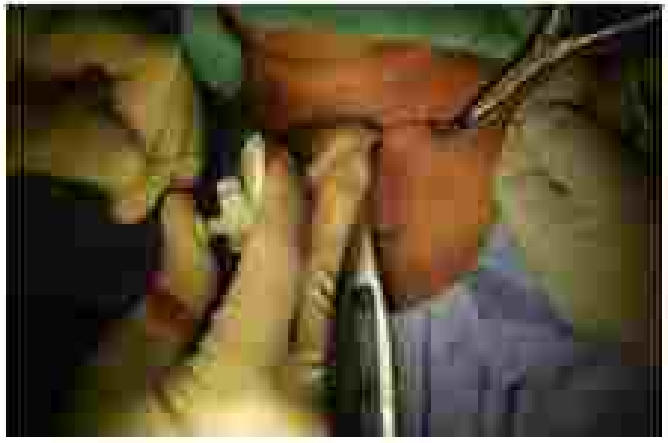


FIG. 9 After testing the balloon and deflating completely, the tracheostomy tube is inserted using a 90-degree rotation from the 9 or 3 o'clock to the final 6 o'clock position.

FIG. 11 A 1.5-cm transverse or vertical incision is made sharply and then local anesthetic with epinephrine is injected.

FIG. 14 Proper placement is confirmed with adequate capnography. Note three hand-delivered breaths before switching back to the ventilator on this waveform.

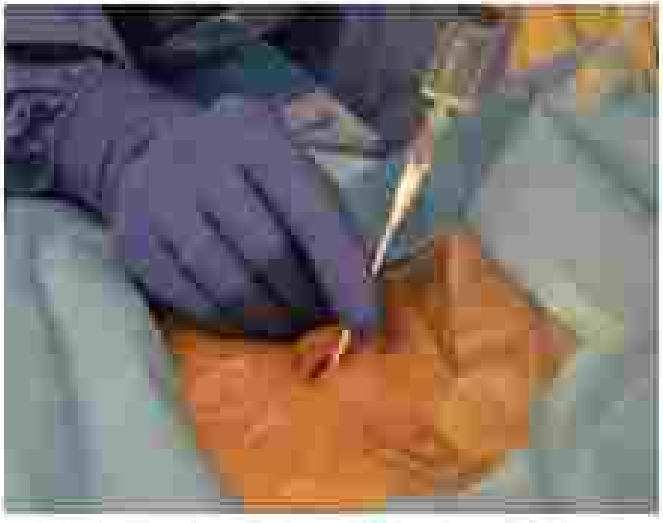


FIG. 13 The introducer needle is used with bronchoscopic guidance to puncture the trachea in the midline.

step, which can result in pneumomediastinum or tracheoesophageal fistula. Aspiration of air in conjunction with bronchoscopic guidance confirms access to the trachea, and a flexible J-tipped guidewire is threaded through the needle toward the carina (Figs. 13 and 14). The needle is removed, and an initial dilation is performed with a 14Fr introducer dilator followed by single-step dilation using the dilator provided (Figs. 15 and 16). A mark on the dilator indicates the depth of dilation required relative to the skin surface. Finally, the leading dilator surface is lubricated, a new tracheostomy tube is loaded onto the appropriately sized leading dilator, and the tracheostomy tube is

FIG. 11. The J-tipped guidewire is inserted into the trachea under bronchoscopic guidance to ensure distal direction of the wire.

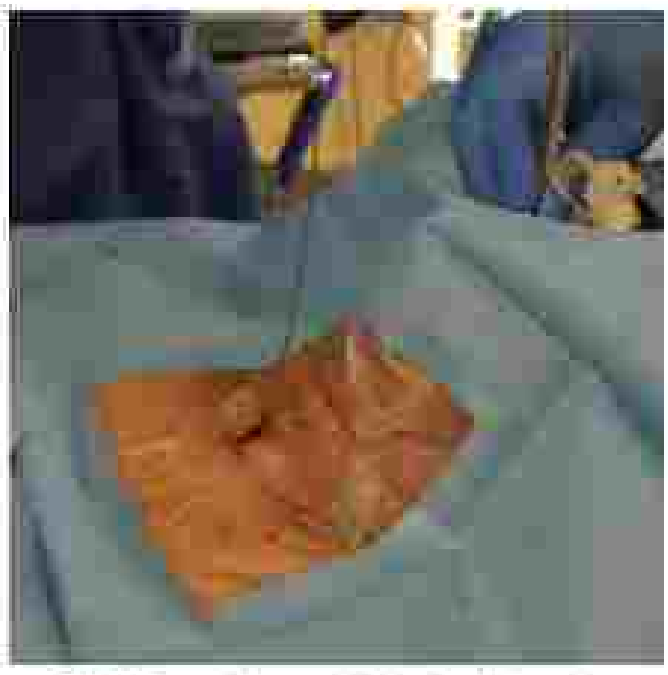


FIG. 12. The cannula is removed, leaving the guidewire in place.

introduced (Figs. 12 and 13). The leading dilator is removed, the tracheostomy cuff is inflated, and the ventilator circuit is transitioned to the new tracheostomy. Ventilation is assured via end tidal CO_2 and breath sounds before removal of the translaryngeal endotracheal tube. The neck plate of the tracheostomy is secured in place using 2-0 nonabsorbable monofilament sutures.

Of note, new tracheostomy tubes that are provided in modern percutaneous kits have a longer tapered tip and low profile cuff to avoid the gap between tube and leading dilator that previously complicated insertion. Angular tracheostomy tubes do not taper or conform to the leading dilator tip well and frequently require significant force to pass through the tracheal wall, potentially contributing to tracheal ring fracture and posterior tracheal wall injury. Therefore, tracheostomy tubes designed for percutaneous insertion should be used during this procedure.

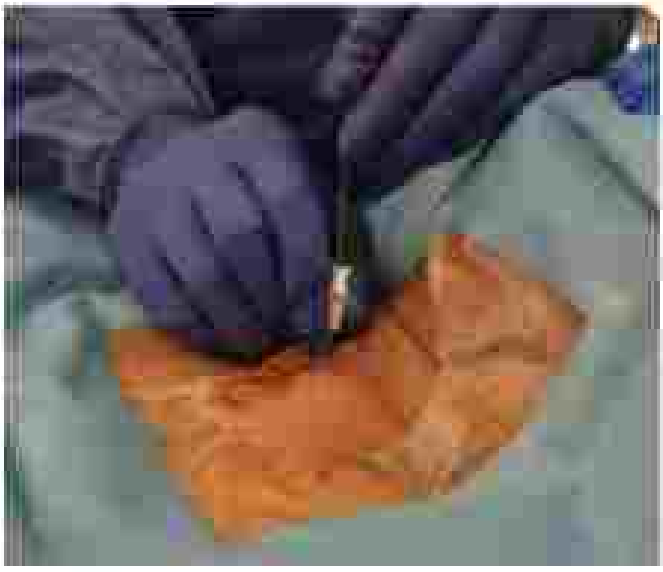


FIG. 13. The 14-gauge dilator is advanced into the trachea.

Other and Emerging Procedural Techniques

Griggs' Forceps, PercuTwist, and Ciaglia Blue Rhino

There other major techniques for percutaneous dilational tracheostomy have been described and remain in use. The Griggs forceps technique, formally described in 1991, relies on forceps that are designed to accommodate the J-tipped guidewire to guide their entry into the trachea. The forceps are then used to dilate the tracheal defect, analogous to the single-step dilator used in the Ciaglia technique, before insertion of the new tracheostomy tube. The PercuTwist technique provides dilation in a single step but is advanced by a cork screw motion into the trachea. A 2008 single-center prospective observational study suggested that the procedure may be more likely to result in posterior tracheal wall injury and longer procedural times compared with the Ciaglia Blue Rhino single-dilator technique; however, RCTs have demonstrated only equivocal differences. Finally the Ciaglia Blue Dolphin system decreases the number of steps to complete the procedure and provides theoretical benefits of purely radial tracheal dilation by combining a dilating balloon on the same cannula that loads the new tracheostomy tube. The tracheostomy introducer is threaded over a J-tipped wire as in other percutaneous tracheostomy procedures, but a balloon on the introducer is delivered into the tracheal defect and then inflated to 11 atm to provide sufficient dilation for entry of the tracheostomy tube, which is preloaded onto the introducer and advanced into intratracheal position after dilating balloon deflation. The procedure potentially improves economy of motion and reduces tracheal trauma during dilation. The technique was shown to be equivalent in outcomes to the Ciaglia Blue Rhino single-step dilation technique in a single-center RCT.

Although the different percutaneous dilational techniques have been compared in small randomized trials, it should be reiterated that differences in outcomes are equivocal, and operator experience is more important than the technique chosen.

Ultrasonography for Percutaneous Dilational Tracheostomy

Point-of-care ultrasonography (US) has become ubiquitous in ICUs over the last decade, with clearly defined roles in many bedside procedures and evaluations. However, the role of US in percutaneous dilational tracheostomy has been slower to evolve. This is likely because of the excellent safety profile of the procedure with bronchoscopy, and conservative patient selection in which inability to clearly palpate landmarks have traditionally been a contraindication to the procedure.

FIG. 16 The single-step dilator is advanced into the trachea to the limit indicated on the dilator.

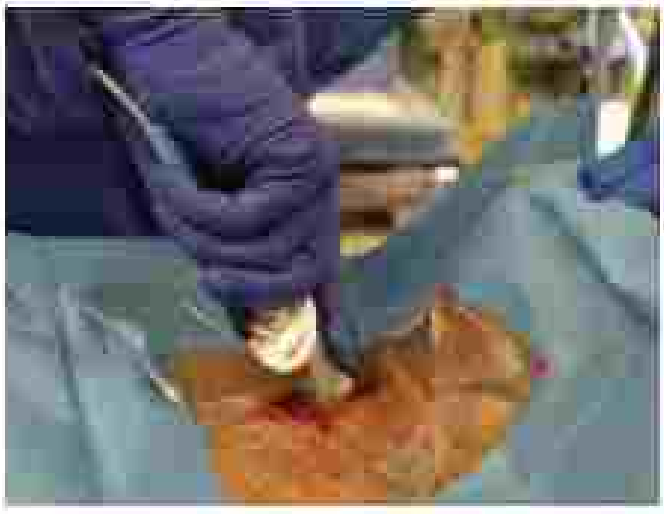


FIG. 17 The tracheostomy tube is loaded onto the appropriately sized dilator and advanced into position. End-tidal CO_2 is confirmed and fiberoptic bronchoscopy confirms tip position.

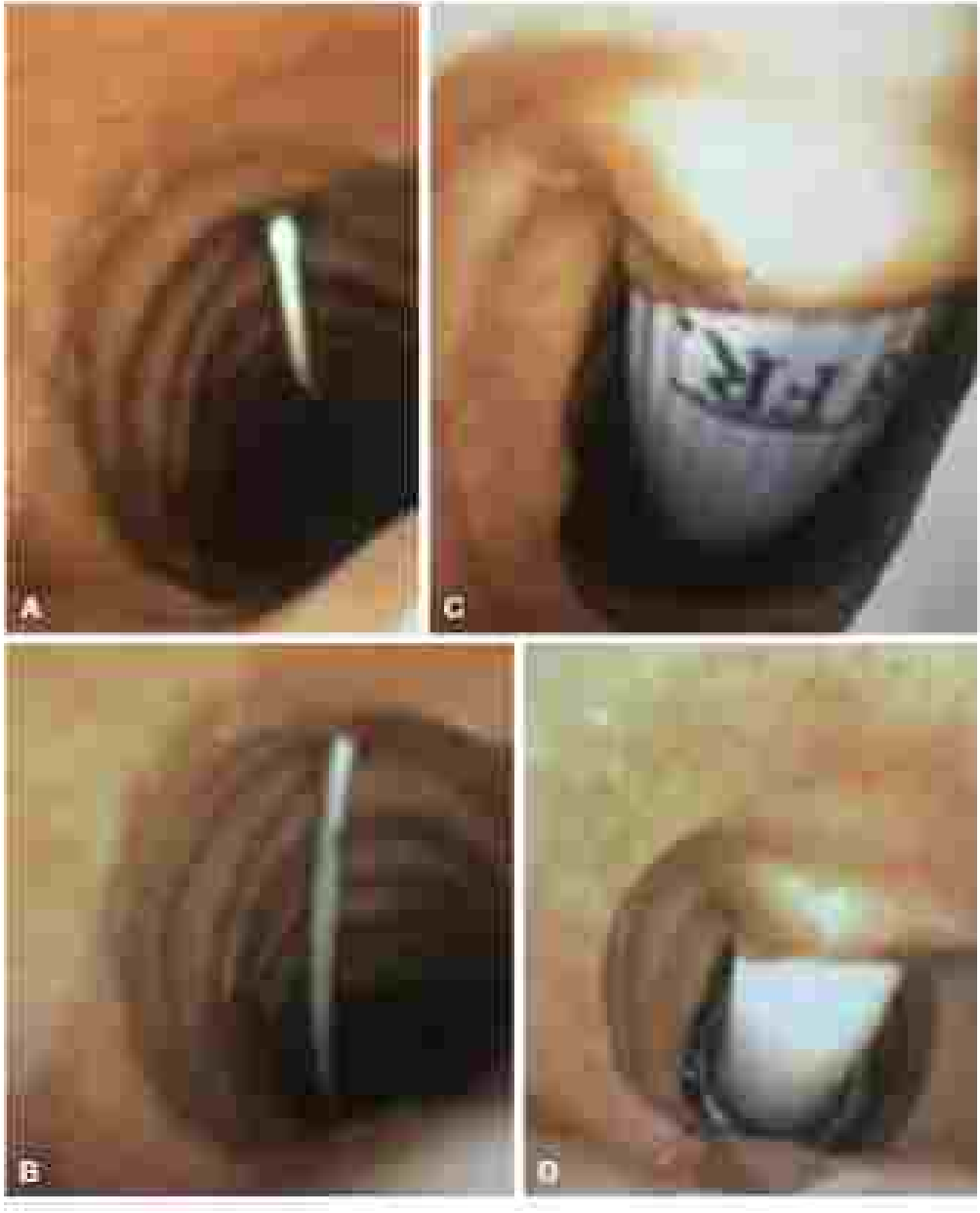


FIG. 18 Bronchoscopic view during tracheostomy. (A) Introducer needle in the midline. (B) ... are visualized in distal direction. (C) Single-step dilator. (D) Tracheostomy tube in appropriate position.

As percutaneous dilational tracheostomy becomes the procedure of choice for most patients, new adjuncts to improve the safety of the procedure among patients with suboptimal surface anatomy may be useful. One major benefit of US during percutaneous dilational tracheostomy is the ability to visualize the relative locations of the hyoid bone, tracheal cartilage, cricoid cartilage, and even the superior tracheal rings in real time. This allows selection of an appropriate skin puncture site and facilitates tracheal puncture under direct guidance. Furthermore, US may guide selection of tracheostomy tube size and identify anomalous vascular or thyroid anatomy associated with bleeding complications prior to injury.

Aided by easy access to high resolution bedside units in ICUs, the role of US in safe tracheostomy continues to evolve. In absence of RCTs demonstrating efficacy and safety of the sole guidance technique, US guidance should be considered an adjunct to bronchoscopy as it undergoes further study.

COMPLICATIONS

Complications can be divided into early and late events (Box 1). Minor early adverse events, including stoma infection and self-limited bleeding, are common. Serious complications and mortality are rare but reported. The frequency with which the procedure is performed means that clinicians should be prepared to deal with a serious complication during their career, and any physician who performs the procedure should be familiar with recognition and management of early and late complications. Pneumothorax and pneumomediastinum are rare (<1%) but important early complications. Subcutaneous emphysema (<2%) during the procedure raises concern for extratracheal cannulation. Late complications include bleeding from granulation tissue, tracheoesophageal and tracheoinnominate arterial fistulae, or accidental decannulation.

Decannulation

Accidental decannulation during or after the placement of a tracheostomy is an important cause of morbidity and mortality. Early decannulation (prior to maturation of the stoma tract, usually 5 to 7 days) should be distinguished from late decannulation, as the former is an indication for emergent translaryngeal endotracheal intubation to reassure the patient's airway. Endotracheal reintubation avoids the potential complication of malpositioning the replaced tracheostomy which can lead to bleeding or creation of a false tract with ventilation of the mediastinum or paratracheal tissues. Replacement of the tracheostomy tube through the stoma should be reserved only for those patients with a mature fistula.

BOX 1 Complications of Tracheostomy

Early Complications

- Minor or major hemorrhage
- Soft tissue ulceration or infection
- Tracheal ring fracture
- Failure to complete the procedure
- Aspiration
- Loss of airway and hypoxemia, hypercarbia
- Pneumothorax, pneumomediastinum
- Subcutaneous emphysema

Late Complications

- Tracheal stenosis
- Granuloma tissue, obstruction, hemorrhage
- Tracheomalacia
- Pneumonia
- Tracheoinnominate arterial fistula
- Tracheoesophageal fistula
- Accidental decannulation or obstruction with hypoxemia, hypercarbia
- Dysphagia
- Dysphonia

Tracheoinnominate Arterial Fistula

Fistulization between the innominate (brachiocephalic) artery and the trachea is an uncommon but feared complication of tracheostomy. Most commonly manifesting after postoperative day 7, the complication has been described as early as 48 hours after surgery. The classic presentation is a small but now perfusional bleed in the weeks after the procedure, which heralds impending massive hemorrhage. In reality, approximately 50% of cases will present with this self-limited sentinel bleed. Mortality is typically owing to hypoxemia and airway occlusion by blood long before hemorrhagic shock, and airway protection is the immediate concern in suspected cases. Tracheoinnominate fistula should be considered the most likely culprit for any perfusional hemorrhage 1 week or more postoperatively from tracheostomy, and immediate management consists of the following:

- Maximize oxygenation
- Consider urgent bronchoscopy in a stable patient to confirm the source of bleeding
- Overinflate tracheostomy cuff (may temporarily occlude source of hemorrhage) and avoid further cuff manipulation
- If unable to control hemorrhage with cuff inflation, emergent translaryngeal intubation and digital compression through stoma site
- Proceed with urgent surgical exploration.

The usual surgical management is isolation and ligation of the innominate artery in an unstable patient. Vascular interposition graft or bypass may be a consideration in a stable patient, but the priority remains avoiding further airway hemorrhage that may compromise oxygenation. Extracorporeal membrane oxygenation has also been described in the interposition of tracheoinnominate arterial fistula, but the mainstay of treatment remains rapid control of the hemorrhage and surgical intervention.

TIMING OF TRACHEOSTOMY

Historically, tracheostomy was performed after approximately 3 weeks of mechanical ventilatory support via translaryngeal endotracheal tube. The 1989 consensus statement from the American College of Chest Physicians reflects this arbitrary threshold for tracheostomy. The 1990s saw increased interest in identification of patients who would benefit from earlier tracheostomy, with the perceived benefits of tracheostomy probably inflated due to prior reliance on high-pressure, low-volume cuffed endotracheal tubes. Subsequent enthusiasm for early tracheostomy among critically ill patients may be attributed in part to a well-designed study involving three hospitals and 120 patients by Rumbak and colleagues in 2004, which demonstrated impressive reductions in mortality and ventilator-associated pneumonia. From 2004 through 2014, multiple attempts were made to address whether early (variably defined as 4 to 7 days of intubation) or delayed (typically >7 days of intubation) tracheostomy would improve a variety of outcomes for patients in the mechanically ventilated ICU population.

Italian 2010 Multicenter Study and 2013 United Kingdom TracMan Trial

The largest two randomized trials studying the timing of tracheostomy are the 2010 Italian multicenter study described by Terragni and colleagues (n = 419), and the 2013 United Kingdom TracMan trial (n = 909). In the Italian study, a mixed medical and surgical population from 12 Italian ICUs were used to comparison of early (≤ 10 days after intubation) versus late (≥ 11 to 15 days of intubation) tracheostomy.

Outcomes were ventilator-associated pneumonia, early and delayed mortality, ventilator- and ICU-free days, procedural adverse events, hospital length of stay, and successful weaning. Although ventilator- and ICU-free days were improved in the early tracheostomy group, none of the other outcomes were significantly improved, including pneumonia, overall hospital length of stay, and mortality. Similarly, the TracMan trial included a varied ICU population in the United Kingdom and compared early tracheostomy (within 4 days of intubation) versus delayed (after 10 days of intubation and mechanical ventilation). Outcomes included early and delayed mortality, antibiotic use, and sedative use per day. The trial reiterated the findings from the Italian study with no significant difference in all-cause mortality at multiple timepoints; additionally, there was no difference in antibiotic use between groups, which may be a reasonable surrogate for pneumonia. Unsurprisingly, there was a significant decrease in the amount of sedation required in the early tracheostomy group. One additional important finding from the TracMan trial was that nearly 25% of patients who were randomized to receive late tracheostomy never required the intervention, primarily due to respiratory recovery (Fig. 1F).

2013 Cochrane Library Systematic Review

A 2013 Cochrane review on the subject of early versus delayed tracheostomy among mechanically ventilated, critically ill patients included patients from eight randomized trials, including those summarized earlier (Box 1). Among the remaining six studies, only one small trial (Rumbak et al, 2012; n = 40) demonstrated any improvement in mortality in the early tracheostomy group. Interestingly however, the group's meta-analysis concluded that there was a very small but statistically significant improvement in late mortality in the early versus late tracheostomy groups (42.1% and 53.2%, respectively; $P = .02$). Earlier mortality measures were generally equivalent, and statistical heterogeneity precluded a meta-analysis of pneumonia. The authors cautioned that data were insufficient to identify any specific subgroup or patient characteristics that would make them better candidates for early tracheostomy.

With a lack of consensus and no clearly demonstrated benefit to early tracheostomy demonstrated across multiple large randomized studies, research efforts have shifted from increasing the number and power of studies to focusing on specific patient populations that may stand to benefit from earlier intervention. Bösel and colleagues' 2013 Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT) represents such an effort and was included in the Cochrane review described earlier. The patient population was restricted to those with severe stroke in the acute ICU. This small but well-controlled pilot study is an important marker in the field in that it demonstrated considerable mortality benefits in the early tracheostomy group. Based on these results, the larger, multiinstitutional SETPOINT-2 is underway to further assess the question in the neurocritical care population.

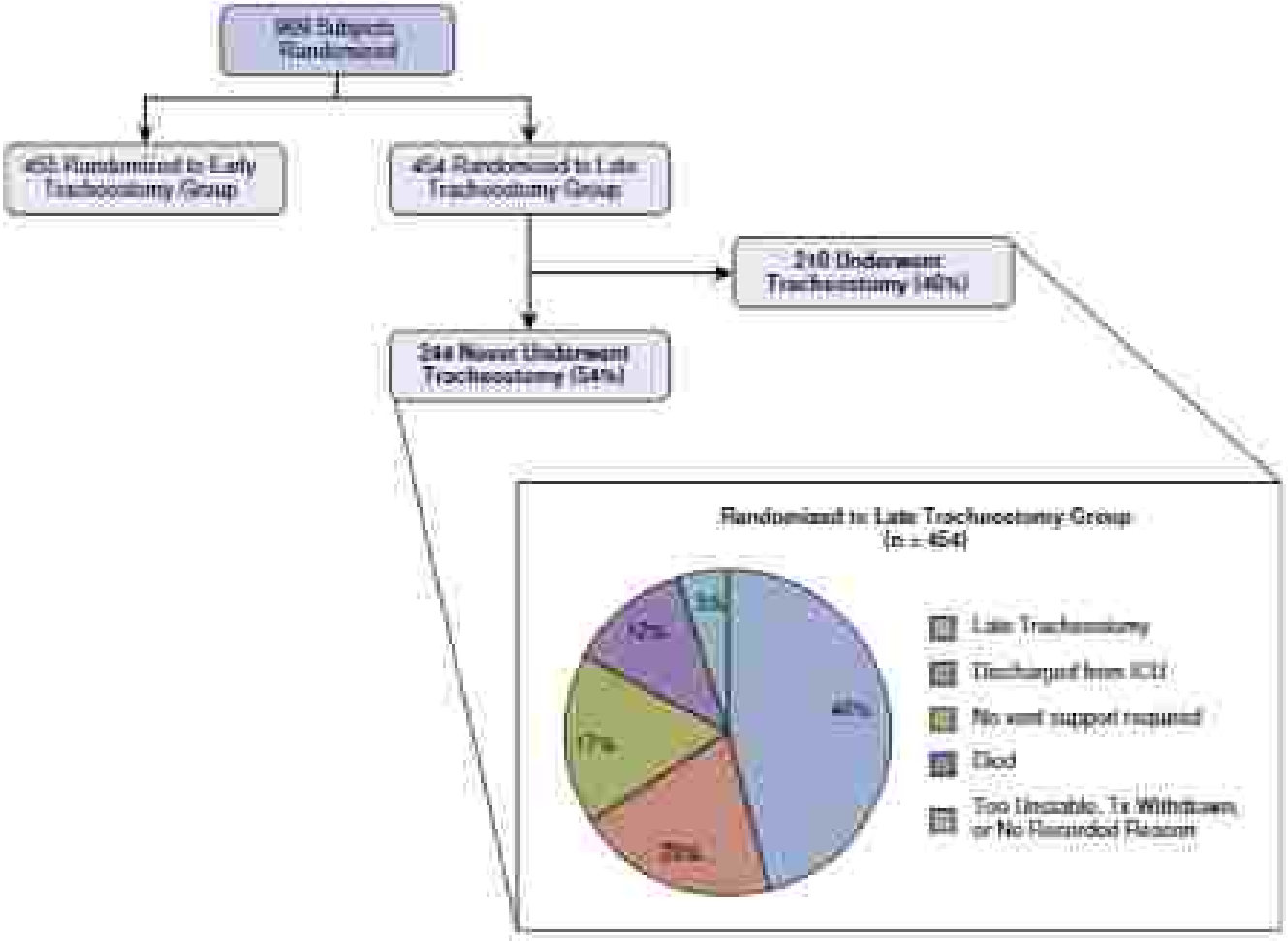


FIG. 1F Summary of late tracheostomy group in 2013 TracMan trial. More than half of the patients randomized to late tracheostomy (>10 days) never underwent the procedure, as it was no longer clinically indicated at that time. ICU, intensive care unit; Tx, treatment. (Data from Young D, Harrison DA, Cuthbertson BH, et al. For the TracMan Collaborators. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. JAMA. 2013;309(20):2121–2129.)

BOX 3 Randomized Trials Included in the Cochrane Review of Tracheostomy Timing

Barquist, 2006 (n = 68)
Rumbak, 2004 (n = 120)
Terragni, 2010 (n = 419)
Trouillet, 2011 (n = 216)
Young, 2013 (n = 909)
Zheng, 2012 (n = 119)

Griffiths RD, Griffiths RR, Saunders H, et al. Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev 2010;1:CD007271.

Synopsis and Recommendations

Given the fairly common nature of adverse events with tracheostomy, the poor ability of clinicians to determine need for prolonged mechanical ventilation potentially leading to unnecessary procedures, and the lack of durable improvements in outcome demonstrated by the largest and best-powered trials, it is prudent to wait 10 to 14 days after intubation to ensure that a patient has ongoing requirements for mechanical ventilation and will benefit from tracheostomy. However, the data are numerous and occasionally conflicting on the subject, once again highlighting the importance of clinical judgment in each patient's case.

OUTCOMES

In-hospital mortality among patients undergoing tracheostomy is approximately 2% overall. Mortality is typically associated with the patient's underlying disease process rather than with the procedure itself. In a nationally representative sample from the United States including over 100,000 tracheostomized adults, the overall perioperative complication rate was approximately 3%, including minor and relatively common complications such as stoma infection and minor hemorrhage. However, the in-hospital mortality was nearly 20%. Patients with cardiac comorbidities were at the highest risk of in-hospital death after tracheostomy, and only 0.6% of patients experienced both a complication of tracheostomy and in-hospital mortality, reflecting mortality dependence on underlying medical problems rather than the procedure itself.

Depending on the indication, tracheostomy can be a palliating or otherwise permanent procedure. However, decannulation (removal of tracheostomy tube with subsequent closure of the stoma) after resolution of precipitating respiratory failure is usually the desired outcome. Among patients with respiratory failure ultimately liberated from mechanical ventilation during ICU stay, the median time to decannulation after tracheostomy is approximately 3 weeks. Unfortunately, only approximately 30% of patients with respiratory failure requiring tracheostomy are decannulated by the time they are discharged from the hospital.

SUMMARY

Tracheostomy is a common procedure performed in the OR or the ICU that allows durable protection of the airway and a means to provide mechanical ventilation. Benefits of tracheostomy over prolonged translaryngeal endotracheal intubation include decreased use of sedatives and paralytics, which facilitates weaning and ICU discharge. However, other perceived benefits (prevention of pneumonia and cuff-related complications) have not been borne out in recent studies. For patients with normal neck anatomy and acceptable habitus, the percutaneous dilational technique is preferred for improved efficiency and a small but significant decrease in risk of minor complications. Surgical tracheostomy has nearly equivalent outcomes but is typically reserved for patients with difficult anatomy owing to its requiring surgical personnel to perform. Serious early and late complications including mortality are rare but reported, and any physician that performs the procedure should be familiar with diagnosis and treatment of its complications. Finally, the timing of tracheostomy for patients requiring mechanical ventilatory support has undergone extensive study without clear evidence of benefit for early tracheostomy. The decision on when and in whom to perform tracheostomy should be individualized to the patient, but generally should not be considered early in ventilator course without surrounding circumstances (i.e., quadriplegia) pending further research in specific patient populations.

Suggested Readings

Alansari M, Alsaati H, Al Aseri Z, et al. Use of ultrasound guidance to improve the safety of percutaneous dilational tracheostomy: a literature review. Crit Care. 2015;19:328.

Andriolo BNG, Andriolo RB, Saconato H, et al. Early versus late tracheostomy for critically ill patients. Cochrane Database of Syst Rev. 2015;1:CD007271.

Delaney C, Theurtzer N, Gardner M, et al. Percutaneous and surgical tracheostomy in critically ill adult patients: a meta-analysis. Crit Care. 2011;15(6):R264.

Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheostomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. JAMA. 2010;303(15):1483–1489.

Young D, Harrison DA, Cuthbertson BH, et al. Effect of early vs late tracheostomy on survival in patients receiving mechanical ventilation: the TracMan randomized trial. JAMA. 2013;309(20):2121–2129.

Acute Kidney Injury in the Injured and Critically Ill

Maria E. Tecca, MD, and Rasly L. Fanning, MD, FACS

Injury and critical illness can create an environment that put the kidneys and other organs at risk for hypoperfusion. This can be a result of shock itself, or the physical and medical events by which the body and physicians respond to it, such as vasoconstriction and vasopressors. In addition to being susceptible to ischemic physiologic states, the kidneys can also fall victim to injury mediated by toxins including drugs, myoglobin, medications, infectious pathogens, and oxygen free radicals.

When caring for patients in the context of renal injury, we must consider the magnitude by which function deviates from baseline. The classification of kidney injury is variable and lacking in specific, protocol-driven treatment algorithms. To help delineate the disparate elements of renal impairment and construct a framework for treatment, acute kidney injury (AKI) and acute renal failure were defined by the Acute Dialysis Qualitative Initiative (ADQI), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO).

EPIDEMIOLOGY

As many as 30% of patients that undergo surgery will develop AKI; of these, approximately 50% to 80% are preventable. It occurs often

BOX 3 Randomized Trials Included in the Cochrane Review of Tracheostomy Timing

Barquist, 2006 (n = 68)
Bösel, 2013 (n = 60)
Dunham, 1989 (n = 74)
Rumbak, 2004 (n = 120)
Terragni, 2010 (n = 419)
Trouillet, 2011 (n = 216)
Young, 2013 (n = 909)
Zheng, 2012 (n = 119)

From Andriolo BNG, Andriolo RB, Saconato H, et al. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev* 2015;1:CD007271.

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Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheostomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA*. 2010;303(15):1483–1489.

Young D, Harrison DA, Cuthbertson BH, et al. Effect of early vs late tracheostomy on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *JAMA*. 2013;309(20):2121–2129.

Acute Kidney Injury in the Injured and Critically Ill

Maria E. Tecce, MD, and Keely L. Buesing, MD, FACS

Injury and critical illness can create an environment that puts the kidneys and other organs at risk for hypoperfusion. This can be a result of shock itself, or the physical and medical events by which the body and physicians respond to it, such as vasoconstriction and vasopressors. In addition to being susceptible to ischemic physiologic states, the kidneys can also fall victim to injury mediated by toxins including drugs, myoglobin, medications, infectious pathogens, and oxygen free radicals.

When caring for patients in the context of renal injury, we must consider the magnitude by which function deviates from baseline. The classification of kidney injury is variable and lacking in specific, protocol-driven treatment algorithms. To help delineate the disparate elements of renal impairment and construct a framework for treatment, acute kidney injury (AKI) and acute renal failure were defined by the Acute Dialysis Qualitative Initiative (*ADQI*), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO).

EPIDEMIOLOGY

As many as 30% of patients that undergo surgery will develop AKI; of these, approximately 50% to 80% are preventable. It occurs often

to patients with multiple comorbidities and is associated with an increase in mortality up to 50%. Even when patients recover from AKI, their risk for eventual chronic kidney disease increases and they have significantly increased length of stay and hospital costs. Furthermore, mortality related to AKI can reach levels of 30% to 60% in developed nations and up to 90% in developing countries. When acute renal failure is considered, estimates ranging from 5% to 25% of intensive care unit (ICU) patients are afflicted, resulting in a mortality that can reach 60%. With the prevalence of AKI in our surgical patients, a thorough understanding of preventable contributing factors and a defined algorithm for diagnosis and treatment is worth consideration.

The US Renal Data System compiles an annual report that emphasizes outcomes of patients with a diagnosis of AKI during hospital admission. According to that 2013 report, up to 8.2% of patients aged ≥65 with a first hospitalization for AKI will die during their stay. Of those who survive, only 48.2% will return home on discharge, with the others being discharged to another institution (30.6%), other (7.5%), or hospice (5.8%). This dismal disposition profile of patients with a diagnosis of AKI during their first hospitalization underscores the importance of preventative measures for avoiding renal dysfunction.

CLASSIFICATION OF AKI

Glomerular filtration rate (GFR) is the gold standard marker for chronic kidney disease, but the current equations for calculating GFR (Cockcroft-Gault, Modification of Diet in Renal Disease Study, and Chronic Kidney Disease Epidemiology Collaboration) rely on serum creatinine (SCr) to be in steady state, which is often not the case in AKI. Moreover, SCr may be erroneously elevated in patients with a high percentage of lean body mass (i.e., athletes). Other parameters, such as oliguria, also have fault as measures specifically, oliguria can be a representation of normal renal tubule response to exogenous, thereby hyperconcentrating urine. Conversely, malfunctioning renal tubules can also yield adequate urine output (UO), by way of inability to properly concentrate urine. The latter scenario is of particular concern when evaluating AKI in ICU and septic patients. When taken singularly or in broad context, these parameters are demonstratively fallible. Equations for kinetic GFR calculation when SCr is fluctuating have been proposed but not validated. The lag time of SCr changes behind current kidney function makes it an imperfect surrogate marker for AKI stage. Other factors can also contribute to changes in SCr, such as reduction in creatinine production during acute illness and volume overload leading to creatinine dilution.

In 2012, the KDIGO workgroup aimed to decrease the heterogeneity of classification systems found in published work by combining elements from prior definitions of AKI (Table 1 lists the elements of the KDIGO classification system). While considering this guideline for classification of AKI (which is currently the most widely accepted iteration of a standardized definition), it should be steadfastly kept in mind that the intention of the KDIGO authors was not to "…replace or to exclude clinical judgment…" but rather "…provide a framework for the clinical diagnosis of AKI…." The diagnosis of AKI remains a complex issue, requiring astute clinical judgment.

Acute Dialysis Quality Initiative and RIFLE

The ADQI developed a method for assessing AKI via analysis of severity classes (risk, injury, and failure), and outcome states (loss and end-stage disease), a model otherwise known as RIFLE. Under this context the worst parameter: SCr or UO, is used to define the severity class, whereas time is used to distinguish the outcome state. The minimum ICU admission RIFLE status has been shown to strongly correlate with mortality, with AKI yielding an attributable mortality of 8.8%, 11.4%, and 26.3% for classes R, I, and F respectively. Conversely, those without AKI were reported to have a mortality of 5.2%.

AKIN and KDIGO

AKIN further modified RIFLE with respect to both diagnostic criteria and injury state. The AKIN AKI diagnostic criteria evaluate changes in SCr or UO over a 48-hour timeframe. An increase in SCr ≥0.3 mg/dL, increase in SCr ≥50% (baseline SCr ≥ 1.5 or more), or decrease UO (<0.5 mL/kg per hour for ≥6 hours) mark the first stage of AKI according to AKIN criteria. By using absolute and percent increase over baseline values for any given patient, AKIN aims to account for interpatient variation such as gender, amount of lean body mass, and age. To assess AKI according to the AKIN parameters using the UO guided approach, all elements that could impair UO must be excluded. Patients must only fulfill one criterion to be assigned a stage; any patient on renal replacement therapy is considered to be in stage 3.

Last, the KDIGO guidelines define patients as being in AKI if they exhibit an increase in SCr ≥0.3 mg/dL in 48 hours, increase in SCr ≥1.5 times baseline within 1 week, or UO less than 0.5 mL/kg per hour for 6 hours. Notably, KDIGO also considers a GFR <35 mL/min per 1.73 m^2 body surface area for patients under the age of 18 to be stage 3 as well.

Regardless of classification system used to define the extent of AKI, the main tenets of treatment include identifying the underlying cause and working toward resolution, mitigating risk factors, and investing in follow-up testing to ensure resolution of AKI. AKIN and KDIGO criteria are summarized in Table 2 for reference.

Biomarkers

Investigations into biomarkers that reflect tubular injury and renal stress are ongoing. Tubular injury biomarkers include neutrophil gelatinase–associated lipocalin, interleukin 18, liver-type fatty acid binding protein, and kidney injury molecule 1. Renal stress

TABLE 1 RIFLE Criteria for AKI

RIFLE Severity Class	SCr/GFR Criteria	UO Criteria	ICU AKI-Attributable Mortality
Risk	SCr × 1.5 or GFR ↓ >25%	UO <0.5 mL/kg/hr × 6 hr	8.8%
Injury	SCr × 2 or GFR ↓ >50%	UO <0.5 mL/kg/hr × 12 hr	11.4%
Failure	SCr × 3 or GFR ↓ >75% or SCr >4 mg/dL (acute ↑ ≥0.5 mg/dL)	UO <0.3 mL/kg/hr × 24 hours or anuria × 12 hours	26.3%
RIFLE Outcome States			
Loss	Persistent acute renal failure: complete loss of renal function >4 weeks		
End-stage disease	End-stage renal disease		

AKI, Acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; ICU, intensive care unit; RIFLE, risk, injury, and failure, loss, and end-stage disease; SCr, serum creatinine; UO, urine output.

TABLE 2 AKIN and KDIGO Criteria for AKI

	AKIN Criteria		KDIGO Criteria	
Stage	SCr Criteria	UO Criteria	SCr Criteria	UO Criteria
1	>0.3 mg/dL or 150%–200% of baseline	<0.5 mL/kg/hr; >6 hours	1.5–1.9 × baseline or ↑SCr ≥0.3 mg/dL	<0.5 mL/kg/hr; 6–12 hr
2	>200%–300% of baseline	<0.5 mL/kg/hr; >12 hours	2–2.9 × baseline	<0.5 mL/kg/hr; ≥12 hr
3	>300% of baseline or SCr >4 mg/dL + acute ↑ ≥0.5 mg/dL	<0.3 mL/kg/hr; ≥24 hr or anuria ≥12 hr	3 × baseline or SCr >4 mg/dL or renal replacement therapy	<0.3 mL/kg/hr; ≥24 hr or anuria ≥12 hr

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; SCr, serum creatinine; UO, urine output.

biomarkers include tissue injury metalloproteinase 2 and insulin-like growth factor binding protein 7, which are currently marketed as the Nephrocheck Test (Astute Medical) and identify patients at high risk of developing KDIGO stage 2 to 3 AKI. Neutrophil gelatinase-associated lipocalin, cystatin C, and kidney injury molecule 1 can be useful in identifying patients who may develop AKI when the disease process is still in the subclinical phase; that is, before a detectable change in UO or SCr. It is hoped that these biomarkers will eventually aid the classification of AKI into precise phenotypes that can be targeted with specific therapeutics.

PREVENTION OF AKI

The mainstay of AKI prevention is centered on fluid status maintenance. Patients who are at risk for developing AKI should be adequately fluid resuscitated in an effort to treat any component of dehydration, nephrotoxicity, or low flow state that could contribute to renal dysfunction. Plasma volume should be expanded in patients who need contrast imaging studies as their disease physiology permits. If unable to give the patient fluids, there may be some utility in administering N-acetyl cysteine; however, there is not an additive effect observed from N-acetyl cysteine when the patient can receive intravenous fluids. Other medications (such as dopamine, fenoldopam, loop diuretics, and calcium channel blockers) have not been shown to be consistently protective of renal function in ICU patients. Conversely, loop diuretics may actually hinder AKI recovery, as evidenced by a study in which significant increase in mortality and persistent renal dysfunction were found in patients who received loop diuretics (odds ratio, 1.77; 95% confidence interval, 1.14–2.76).

The AIKIII recommends avoiding hyperchloremia that can lead to metabolic acidosis in patients at risk for AKI. A study of ICU patients who were assigned to either chloride liberal or chloride restrictive groups revealed that the chloride restrictive group exhibited a decreased SCr change ($P = .02$), decreased requirement for renal replacement therapy (RRT) ($P = .06$), and decreased number of patients classified as RIFLE I and F ($P < .06$)[1]. Chloride levels should be monitored and controlled as a prophylactic measure when the potential for AKI is considered.

Much debate remains regarding the types of fluids and medications that are helpful or harmful when resuscitating and treating patients at risk for AKI while receiving ICU care. The European Society of Intensive Care Medicine released a document of conglomerate expert recommendations for renal preservation, which are summarized in Table 3. Notably, the recommendations at the 1A level exist promoting the use of specific fluids or medications.

AKI WITH SPECIAL CONSIDERATIONS

The ICU setting can present unique situations that can lead to or further complicate the development of AKI. Comorbid conditions can increase the likelihood of developing a renal complication, or underlying renal dysfunction can be exacerbated in these circumstances.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is clinically defined by an intraabdominal pressure exceeding 20 mm Hg accompanied by clinically relevant organ dysfunction such as decreased UO, reduced cardiac output as a result of impaired venous return to the right atrium leading to decreased preload, and so on. One of the clinical manifestations of elevated intraabdominal pressure is oliguria, when the kidneys succumb to the reduced vascular flow to the nephron. The amelioration of ACS is dependent upon its cause. Paracentesis may be adequate to relieve ACS caused by massive ascites, whereas more invasive surgical intervention may be necessary to treat ACS related to hemoperitoneum or abscess with accompanying intestinal ileus. Although these procedures can dispel acute decompensation and improve the overall condition of the patient, kidney dysfunction is not likely to be alleviated regardless of subsequent improvement in renal venous hypertension or arterial hypotension. This is sometimes because of persistent renal hypertension, which can be caused by edema of the kidney or a subcapsular hematoma requiring incision and drainage. When considering the care of a patient with ACS, fluid management should be strictly monitored. A "crystal fluid cap" that limited to 0 L total before ICU admission has been shown to decrease pre-ICU fluid volume by 0.8 L, intraabdominal hypertension, necessity of open abdominal intervention, and ICU length of stay. Aggressive fluid resuscitation can be harmful in the setting of ACS.

Rhabdomyolysis

Rhabdomyolysis is characterized by the systemic release of intracellular components, including heme pigment from myoglobin, after muscle necrosis. Other features include high creatine kinase (CK) levels, myoglobinuria, and myalgias. This process has nephrotoxic potential because tubules can become damaged or obstructed, and blood supply to the outer medulla can be compromised via vasoconstriction. Although a healthier patient may be able to self-regulate these disturbances, the multifactorial disease processes present in critically ill or decompensated ICU patients can be compounded, thereby precipitating AKI. Identifying patients with rhabdomyolysis who are at risk for the development of AKI is critical to treating the disease state; those with CK >15,000 to 20,000 U/L have higher risk, as do those who are hyperuricemic or acidotic.

In an effort to identify the risk of requiring RRT or death secondary to AKI in patients with rhabdomyolysis, a risk prediction score was developed. Patients scoring less than 5 had a low risk (<2.3%–3%) for death or severe complications from AKI, whereas those scoring more than 10 were found to have a high risk (>39%–41%) for complications up to and including death. The cutoff value of 6 had a negative predictive value of 87%–88%. Although promising, this study was limited by the fact that it was performed in two urban hospitals, and requires validation in more diverse settings. Results are summarized in Table 4.

Prompt recognition of hypovolemia and electrolyte abnormalities is key in treating rhabdomyolysis and preventing AKI. Appropriate fluid resuscitation should be initiated, the underlying cause should be

TABLE 3 ESICM Recommendations and Suggestions for AKI Prevention and Treatment

PVE	Recommendations	Suggestions
Fluid resuscitation for volume depletion	1C	
Prophylactic PVE with isotonic fluids in those at risk of RCN	1B	
Avoid 10% HES ≥500/0.5	1B	
Avoid gelatins and dextrans in sepsis		2C
Prophylactic PVE with crystalloids to prevent AKI by certain medications		2C
DIURETICS		
Avoid loop diuretics to prevent or ameliorate AKI	1B	
Vasopressors and Inotropes		
MAP should be maintained >60–≤65 mm Hg	1C	
Norepinephrine or dopamine (plus PVE) are first-line agents for vasodilatory shock	1C	
Avoid low-dose dopamine to protect against AKI	1A	
VASODILATORS		
Vasodilators may be useful for renal protection after resuscitation and with hemodynamic monitoring		2C
Fenoldopam may be useful in cardiovascular surgery patients at risk of AKI		2B
Avoid fenoldopam for RCN prophylaxis		1A
Theophylline to mitigate RCN risk in those who cannot undergo PVE		2C
Avoid natriuretic peptides as the protective agents against AKI in general intensive care unit patients but may be considered in cardiovascular surgery patients		2B
METABOLIC INTERVENTIONS		
Avoid routine selenium supplementation as an AKI preventive	2C	
Enteral nutrition is preferred for patients at risk of AKI		2C
Avoid N-acetyl cysteine as prophylaxis against RCN or other forms of AKI		2B

AKI, Acute kidney injury; AKIN, Acute Kidney Injury Network; ESICM, European Society of Intensive Medicine; HES, hydroxyethyl starch; MAP, mean arterial pressure; PVE, plasma volume expansion; RCN, renal cortical necrosis; SCr, serum creatinine; UO, urine output.

identified and mitigated as best able, and sequelae such as metabolic acidosis should be anticipated and promptly corrected. Although appropriately aggressive fluid resuscitation is a key component of therapy for rhabdomyolysis, care should be taken to avoid the pitfalls of ACS development.

Septic AKI

A patient with septic shock may face a myriad of complications, the most likely of which is AKI. Fluid resuscitation in the face of sepsis may induce hypernatremia in the renal vasculature; this process is unique when compared to other modalities of AKI that are influenced heavily by the patient's hemodynamic state. In contrast, sepsis-induced AKI may be mediated by toxins, inflammation, or immune responses. Renal blood flow should be carefully monitored. A multicenter randomized controlled trial found no significant difference in overall 90-day mortality between RIFLE failure class patients with early septic shock who began RRT within 12 hours of failure class AKI identification vs those who began 48 hours after identification (58% vs 54%, $P = .38$).

Impact of AKI on Outcomes

AKI has a profound impact on a patient's healing process and can lengthen ICU stay by up to 1.5 weeks. Although renal support therapies (RST) continue to improve, patients whose renal dysfunction necessitates RRT can have mortality rates as high as 60% when multisystem organ dysfunction is cautionary. Approximately 12% to 15% of patients who undergo RRT for AKI during their admission will remain on chronic RRT; this figure increases to 35% when acute on chronic kidney injury is considered.

MANAGEMENT AND RECOVERY OF AKI

Poorly controlled hypertension and diabetes mellitus are the most common etiologies of slowly developing renal failure outside of the hospital. Inpatient AKI is often precipitated by acute episodes of hypoperfusion or drug toxicity, which often occur now on a background of mild chronic renal dysfunction from the prehospital period in many of our patients.

Up to 50% of AKI may be prevented by early recognition and mitigation of risk factors; however, the basics of care for patients at risk are often neglected. Fluid balance assessment, fluid therapy to maintain renal perfusion, and regular laboratory monitoring comprise the foundation of care for patients at risk for AKI. Underlying risk factors include advanced age (defined for this purpose as >55 years), preexisting chronic renal dysfunction, prior episodes of acute kidney injury, existing comorbidities such as diabetes mellitus, congestive heart failure and sepsis, among others. Nephrotoxic medications such as aminoglycosides, nonsteroidal antiinflammatory drugs,

TABLE 4 Risk Prediction for Rhabdomyolysis-Associated Acute Kidney Injury or Mortality

Parameter	Score
Age >60–<70 years	1.5
Age >70–<80 years	2.5
Age >80 years	3
Female	1
Initial SCr 1.4–2.2 mg/dl	1.5
Initial SCr >2.2 mg/dl	3
Initial calcium <7.5 mg/dl	2
Initial CK >40,000 U/L	2
Underlying cause other than seizure, syncope, exercise, statins, or opioids	3
Initial serum phosphate 4.0–5.4 mg/dl	1.5
Initial serum phosphate >5.4 mg/dl	2
Initial serum phosphate <1.9 mg/dl	2

From McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. JAMA Intern Med 2013;173(19):1821–1828.
CK, Creatine kinase; SCr, serum creatinine.

and iodinated contrast should be avoided in at-risk patients. Because there are no specific therapies for ischemic or nephrotoxic AKI, attention to intravascular volume in high-risk patients is perhaps one of the most easily accessible interventions. Judicious restoration of intravascular volume has been shown to reduce the incidence of such cases AKI dramatically.

Several trials have attempted to uncover the effect of modalities of dialysis. The Acute Renal Failure Trial Network revealed a 45.2% day 28 dialysis dependence after 5000 intermittent dialysis events. Conversely, the randomized evaluation of normal vs augmented level renal replacement therapy trial found a lower level at day 28 dialysis dependence (13.9%) after 344 instances of intermittent dialysis. Additionally, the Sepsis Occurrence in Acutely Ill Patients Trial showed that lower fluid status per day was associated with survival.

RENAL SUPPORT THERAPY

Two broad categories of RST exist: intermittent and continuous. The term RRT has been used to describe these modalities but may obscure the context of the therapies. Rather than replacing all functionality of the kidney, these treatments make alterations to water and solute; any vascular tonic or parenchymal dysfunction is not corrected. With this understanding, it may be more suitable to consider the therapies as RST rather than RRT.

Solute clearance during RRT is achieved through diffusion, convection, or a combination of both. Small molecule removal (size <1 kDa) is best achieved through diffusion, which is based on a concentration gradient across the membrane. Convection, which is based on

TABLE 5 Modalities of RRT

Comparison of Intermittent and CRRT

Parameter	IHD	CCRT
Time per day	3 to 4 hours	24 hours
Flow rate	High	Low
Specialty nurse requirement	Yes	No
Cost	Lower	Higher
GFR	Variable	Constant
Real-time volume management	While running	Continuously
Recirculation	Higher	Lower
Use with pressors	No	Yes
Membrane clotting	Uncommon	Occasional
Intraoperative use	No	Yes
Reduced renal blood flow	Yes	No
Nutritional support volume management	More difficult	Easier

Comparison of Different RRT Modalities

Intermittent	Mechanism	Use	Continuous
Hemodialysis	Diffusion	Small particle clearance (size <1 kDa)	Continuous venovenous hemofiltration dialysis
Hemofiltration	Convection	Water and medium particle clearance (size <50 kDa)	Continuous venovenous hemofiltration
Hemodiafiltration	Both	Both	Continuous venovenous hemodiafiltration

CCRT, Continuous renal replacement therapy; IHD, intermittent hemodialysis; RRT, renal replacement therapy.

ultrafiltration, is ideal for water and molecule removal with size up to 50 kDa. The high flow process of ultrafiltration is not only useful in the setting of fluid overload, but also for drug overdose or electrolyte disturbances.

Hemodialysis uses diffusive clearance on an intermittent schedule, typically for 4 to 6 hours per session, with three to four sessions per week. Blood and solutes flow in opposite directions, creating a concentration gradient that facilitates diffusion across the semipermeable dialysis membrane. Hemofiltration is a related concept that uses hydrostatic pressure gradients to create solvent drag via convection, which in turn promotes convective clearance. During hemofiltration, no dialysis solution is used; instead, replacement fluid is used to replete the solutes that are cleared. Electrolytes and urea are filtered in the same concentration as plasma, which also limits solution to preserve the concentration gradient. Hemodiafiltration, as the name implies, uses both diffusive and convective clearance. During hemodialysis, solute clearance is increased by increasing either the blood or dialysate flow rate. In hemofiltration, increasing the ultrafiltration (or effluent) flow rate will increase solute clearance.

A middle ground exists between intermittent and continuous RRT techniques, termed prolonged intermittent RRT, of which slow low efficiency dialysis is a subtype. As the name would suggest, this type of dialysis uses a slower rate (and in turn, longer treatment time) that typically occurs over a span of 8 to 15 hours (every other day or daily). This is a gentler approach to fluid and electrolyte shifts that is tolerated better, with less side effects, by those who are more critically ill and susceptible to large swings in their hemodynamics.

The continuous RRT (CRRT) modalities are performed 24 hours per day. The continuous modalities are also better tolerated in hemodynamically unstable patients. Methods for CRRT include both venous and arterial cannulation; however, continuous arterio-venous hemofiltration is not commonly used in current practice because of the bleeding complications with arterial cannulation. The veno-venous approach accounts for the bulk of continuous RRT modalities, including continuous veno-venous hemofiltration dialysis, continuous veno-venous hemofiltration, and continuous veno-venous hemodiafiltration. These CRRT modalities apply the same concepts as described for their respective intermittent hemodialysis (IHD) counterparts in a treatment setting that can be run 24 hours per day at the bedside. This style of treatment allows for those who are hemodynamically (including those requiring pressor support) to tolerate RRT without experiencing large swings in fluid dynamics that could otherwise compromise their care. The selection of modality is influenced by the target molecule identified for clearance, similar to IHD. Notably, continuous veno-venous hemofiltration may be preferable for clearance of immunomodulators in the setting of inflammation. Additionally, a constant CFR is achieved with CRRT, allowing for specific medication dosing, as well as nutritional adjustments.

Indications

The indications for RRT for patients with AKI include severe metabolic acidosis (or other acid-base imbalances refractory to medical therapy), hyperkalemia refractory to medical therapy, drug intoxication (lithium, ethylene glycol, methanol, salicylates, theophylline, phenobarbital), volume overload, and uremia and its associated complications (pericarditis, encephalopathy, bleeding). Debate continues regarding the precise timing of initiation of RRT. Evidence shows no significant difference in overall 90 day mortality in early vs late initiation in the setting of sepsis. Other studies have shown greater impact when starting treatment at lower blood urea nitrogen and with earlier initiation in specific patient populations, including those who have undergone cardiac procedures, trauma patients, and mixed surgical/medical patients. Moreover, no significant benefit to CRRT over IHD when adjusted for illness severity (considering the limitation of CRRT as the only RRT option for pressor-dependent patients), and IHD does provide better eventual recovery of kidney function. Further analysis is necessary for develop algorithms for initiation of RRT in the critically ill, and attention should be given to ability to use IHD vs CRRT.

CONCLUSIONS

The care of a critically ill patient should go beyond treating the acute disease process at hand and encompass care that consider prevention of possible further decompensation. Kidney protective measures should be initiated, and the patient's renal status should be evaluated with RIFLE, AKIN, or KDIGO guidelines. The patient should also be monitored for the development of disease states that could hasten clinical decline, such as sepsis, rhabdomyolysis, and ACS. RRT is a useful adjunct to the care of a critically ill patient with AKI. Goals should be defined to guide the decision making process regarding which modality of RRT should be used, and consideration should be given to the possibility of maintaining the patient on RRT, so long as clinical status requiring more resource intensive CRRT are not factors (hemodynamic instability, pressor support, or limitations of fluid shifts).

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Fluids and Electrolytes

Umar Khan, MBBS, MD

Claude Bernard is quoted as saying, "The living organism does not really exist in the inflow exterior (the atmosphere if it breathes, salt or fresh water if that is its element) but in the liquid inflow interieur formed by circulating organic liquid, which surrounds and bathes all tissue elements." This concept of a condensed ecology within ourselves at the cellular level is crucial to understanding the changes pathology imparts on the critically ill. This understanding allows us to picture the disorders of water balance and salt balance that plague many surgical patients, both acutely and chronically.

TOTAL BODY WATER AND FLUID COMPARTMENTS

The "water" component of the body makes up approximately 60% of an individual's lean body weight. The body divides its water content into two major compartments (Fig. 1): the extracellular fluid compartment (ECF) and intracellular fluid compartment (ICF). These compartments are divided by a highly selective lipid bilayer, known as the cell membrane, which allows water to pass freely but not electrolytes. Specifically, the extracellular compartment maintains a relatively higher concentration of sodium, chloride, and bicarbonate, whereas the intracellular compartment stores higher concentrations of potassium and phosphate. Further, as the lean proportion of the body decreases (as in obesity), the total body water percentage also decreases.

The fluid in the various compartments and the electrolytes that reside within them are all inextricably linked and interdependent. This is defined by the concept of osmolarity (mOsm/L). Solutes dissolved in water (fluid) do not freely traverse a semipermeable membrane; they are known as osmoles. Hence, osmolarity is a measure of the concentration of osmoles in a solution. Modern laboratories are able to measure osmoles directly per weight of solution; this is known as osmolality (mOsm/kg). As can be deduced from the equation, sodium is by far the most important osmole in plasma with glucose and urea exerting their effects mainly during disease states such as diabetes and renal failure respectively:

$$P_{osm}(mOsm/kg) = 2 \times [Na^+] + [glucose]/18 + BUN/2.8$$

in which BUN indicates blood urea nitrogen. The normal osmolality of plasma ranges from 275 to 290 mOsm/kg.

Finally, plasma tonicity (also known as effective osmolality) is the parameter that determines the transcellular distribution of water. Water moves from an area of lower tonicity to an area of higher tonicity (i.e., from an area of higher water content to an area of lower content). Tonicity only takes into account the distribution of solutes that do not freely permeate the cell membrane; this lack of free distribution is what causes water to shift across cell membranes. Tonicity is differentiated from osmolality in that certain solutes are ineffective osmoles and are distributed equally across cellular membranes (such as urea). Effective osmoles, on the other hand, do not easily cross a membrane and therefore exert an osmotic pressure favoring the retention of water.

This concept is exemplified by the following physiologic scenario: Renal failure results in the retention of abnormally large concentrations of urea. This can result in an increase in osmolality (see the formula presented previously), but the tonicity is unchanged because urea is an ineffective osmole and redistributes freely across cell membranes (i.e., there are equal concentrations in both the ICF and ECF compartments). If hemodialysis is instituted, urea is rapidly removed from the ECF. This removal may be faster than urea can equilibrate across the blood brain barrier. Hence, in this scenario, urea temporarily acts as an effective osmole and imparts both increased osmolality and increased tonicity to the cerebral cells. This can result in water influx and cerebral edema, which can lead to dialysis disequilibrium syndrome.

Fluid Compartments and Regulation of Volume

Sodium homeostasis, through the regulation of urinary sodium excretion, is the primary determinant of the ECF volume. This is accomplished through several mechanisms.

In hypovolemia, the renin angiotensin aldosterone and sympathetic nervous systems (which promote renin secretion) are activated resulting in sodium retention. Conversely, atrial distention from hypervolemia results in the release of natriuretic peptides promoting sodium excretion. Severe hypovolemia that is significant enough to result in hypotension can trigger the release of antidiuretic hormone (ADH) as well. In this scenario ADH activates both V2 receptors, which increase water retention at the level of the distal tubules and collecting ducts, and V1 receptors, which result in peripheral vasoconstriction (hence the synonym vasopressin). The primary role of ADH, however, is in the regulation of plasma osmolality via osmoreceptors (rather than volume sensitive receptors that activate in severe hypovolemia). The volume of the extracellular fluid compartment is thereby regulated.

In a slightly less direct way, the extracellular sodium concentration also regulates the intracellular fluid volume. Modulation of extracellular sodium results in the alteration of plasma tonicity as described earlier, which results in the movement of water into or out of the ICF.

This interrelationship is demonstrated in the management of the acutely brain injured patient, a scenario commonly seen in many intensive care units. The administration of hypotonic intravenous fluids results in hyponatremia, with decreased plasma osmolality and tonicity (as sodium is an effective osmole). Because water moves from an area of low tonicity to an area of high tonicity, water would enter the brain causing cerebral edema and result in worsening of the traumatic insult. The administration of hypotonic fluid in the brain injured patient is, therefore, contraindicated. Conversely, the administration of hypertonic fluid (such as 3% sodium chloride) results in hypernatremia with increased plasma osmolality and tonicity. This would result in flow of water out of the brain and decrease cerebral edema; therefore, the therapeutic increase in plasma sodium levels through the administration of hypertonic saline is a common therapy for neurologic injury.

The reverse process occurs in dehydration. Instead of altered regulation of solute, dehydration results from excessive loss of water resulting in a significant total body water deficit. This will often result in a hypernatremia.

Regulation of Osmolality

As mentioned previously, the primary hormonal mechanism of regulating plasma osmolality is antidiuretic hormone. It is secreted by the posterior pituitary gland in response to very small changes in plasma osmolality as detected by the body's osmoreceptors. Hence, suppression of ADH is the primary mechanism of protection against water retention in the setting of low plasma osmolality, whereas the stimulation of thirst is the primary protective mechanism against excessive water loss (by increasing intake) in the setting of elevated plasma osmolality. ADH may also be secreted in response to large levels of volume depletion via volume sensitive receptors.

The preceding discussion engenders an understanding of normal physiology and homeostasis. The surgical intensivist will, however, care for patients suffering derangements of any number of these of regulatory mechanisms.

Syndrome of Inappropriate ADH

Syndrome of inappropriate ADH (SIADH) is a condition in which the secretion of ADH is autonomously elevated and unrelated to plasma

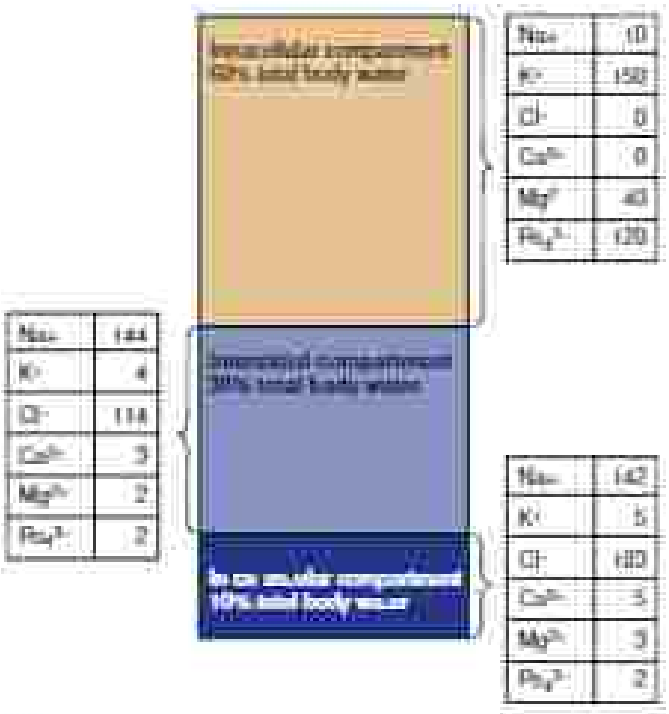

FIG. 1 Distribution and composition (mEq/L) of total body water. Ca^{2+}, calcium; Cl^-, chloride; K^+, potassium; Mg^{2+}, magnesium; Na^+, sodium; PO_4^{3-}, phosphate.

osmolality. This results in an abnormally high amount of free water retention and subsequent hyponatremia. The syndrome is frequently seen in perioperative patients and is thought to be related to pain receptor activation. It can, however, occur in a variety of other conditions including various neurologic disorders (including stroke, trauma, and hemorrhage), transsphenoidal pituitary surgery, malignancies (particularly small cell cancer of the lung), and drugs (such as carbamazepine, selective serotonin reuptake inhibitors, haloperidol, opiates, nonsteroidal antiinflammatory drugs [NSAIDs], ephedrine, amitriptyline, and cyclophosphamide). The diagnosis should be entertained in patients with hyponatremia and an appropriate antecedent history. Laboratory evaluation (Fig. 2) would demonstrate low plasma osmolality (<270 mOsm/kg) with a high urine osmolality (>100 mOsm/kg) and high urine sodium concentration (>40 mEq/L). These findings in a clinically euvolemic patient with no recent diuretic use, and no evidence of thyroid, adrenal, or pituitary insufficiency can lead to the diagnosis.

The treatment of SIADH is fluid restriction (<1 L/d) and in usually all that is needed to mediate a gradual increase in plasma sodium levels. However, the hyponatremia is severe and/or symptomatic, hypertonic saline may be required. This is particularly pertinent in patients with subarachnoid hemorrhage who develop SIADH, fluid restriction may precipitate vasospasm and ischemic insults. In this scenario, therefore, low volume 3% hypertonic saline may need to be administered to gradually raise the sodium level without predisposing to hypervolemia. Additional therapies include the use of oral salt tablets (9 g/d) and loop diuretics (to increase free water excretion).

The temptation to use isotonic saline should be avoided in all cases of SIADH because urine osmolality is usually far higher than the concentration of sodium in isotonic saline. Because sodium handling is intact, all administered sodium will be excreted; however, all the water will not be excreted since the urine is highly concentrated in the setting of high plasma ADH levels. Hence, water will be retained preferentially to sodium and will worsen the hyponatremia.

Finally, the diagnosis of SIADH should not be confused with cerebral salt wasting (CSW) syndrome. This is a similar, but much rarer disorder with similar laboratory findings but which is characterized by clinical evidence of hypovolemia.

Diabetes Insipidus

On the other end of the spectrum of osmolar dysregulation syndromes is diabetes insipidus (DI). In this disease state there is either a deficiency in the body's ability to secrete ADH (central DI) or in the ability of the distal tubules and collecting ducts to respond to the circulating ADH (nephrogenic DI). Because of the absence or inefficiency of ADH, the kidneys excrete high volumes of dilute urine; hence, DI is diagnosed (Fig. 2) in the presence of a high normal serum sodium concentration (>142 mEq/L resulting from free water loss) associated with polyuria (up to 10 L/day of dilute urine [osmolality: <200 mOsm/kg]) and an elevated plasma osmolality (>296 mOsm/kg).

Central DI can be seen after pituitary surgery or trauma, whereas the most common cause of nephrogenic DI is lithium toxicity. DDAVP (desmopressin) can help differentiate the two diseases; administration results in improvement of urine osmolality in the former, but not in the latter. The treatment of DI includes a low salt, low protein diet, diuretics, and NSAIDs supplemented by DDAVP in central DI.

SPECIFIC ELECTROLYTE DISORDERS

Sodium

Plasma sodium levels are directly affected by fluid balance. Hyponatremia results from excess water intake that is not excreted, whereas hypernatremia results from an excessive loss of free water.

Hyponatremia is defined as a sodium level less than 135 mEq/L (mild: 130–134 mEq/L; moderate: 120–129 mEq/L; severe: <120 mEq/L). True hyponatremia that is secondary to excess plasma free water retention will result in decreased plasma osmolality, due to the most common kind of hyponatremia in surgical patients and to consider hypotonic hyponatremia. There are certain conditions, however, that can result in hyponatremia without a decrease in plasma osmolality; therefore, a serum osmolality is generally the first step in the workup of hyponatremia. If the plasma is isotonic, the "hyponatremia" occurs in the context of abnormally elevated lipid or plasma protein levels. This is known as a pseudohyponatremia because the decreased sodium level is an artifact of older laboratory measurement techniques that uses the total plasma volume rather than the aqueous portion when measuring the sodium levels. If the plasma is hypertonic, this indicates the presence of a significant number of minor osmolar constituting to hyperosmolality in lieu of sodium; this can occur with, for example, severe hyperglycemia or in the presence of high levels of mannitol. These osmolar cause free water to move from the ICF to the ECF and result in a decreased plasma sodium level. In hyperglycemia, this level of sodium can be predicted for every 100 mg/dL increase in glucose levels, the plasma sodium will decrease by 2.4 mEq/L on average. This association is nonlinear and, in fact, a correction factor of 1.6 may be needed for glucose levels above 400 mg/dL. Similarly, the use of surgical irrigants such as during a transurethral resection of the prostate or bladder or hysteroscopy can lead to hyponatremia through the absorption of hypotonic water and the expansion of the ECF. In all these scenarios, treating the underlying source of the normal plasma tonicity will address the hyponatremia.

Once a true hypotonic hyponatremia is diagnosed, the volume status needs to be assessed. Patients who are overtly hypervolemic likely have an underlying disorder that results in total body water retention, but with diminished effective intravascular circulation. This can result from disease processes such as cirrhosis, congestive heart failure, nephrotic syndrome, and hypoalbuminemia. The diminished intravascular circulating volume results in the nonosmotic stimulation of ADH release leading to free water retention despite the underlying hypervolemic status. The hyponatremia is generally asymptomatic and chronic in nature precluding the need for rapid reversal in situations of mild or moderate hyponatremia. In general, the mainstay of treatment is fluid restriction.

Euvolemic hyponatremia is the most common cause of hyponatremia in the hospitalized patient. After confirmation of a true hyponatremia, the workup entails checking the urine osmolality. A

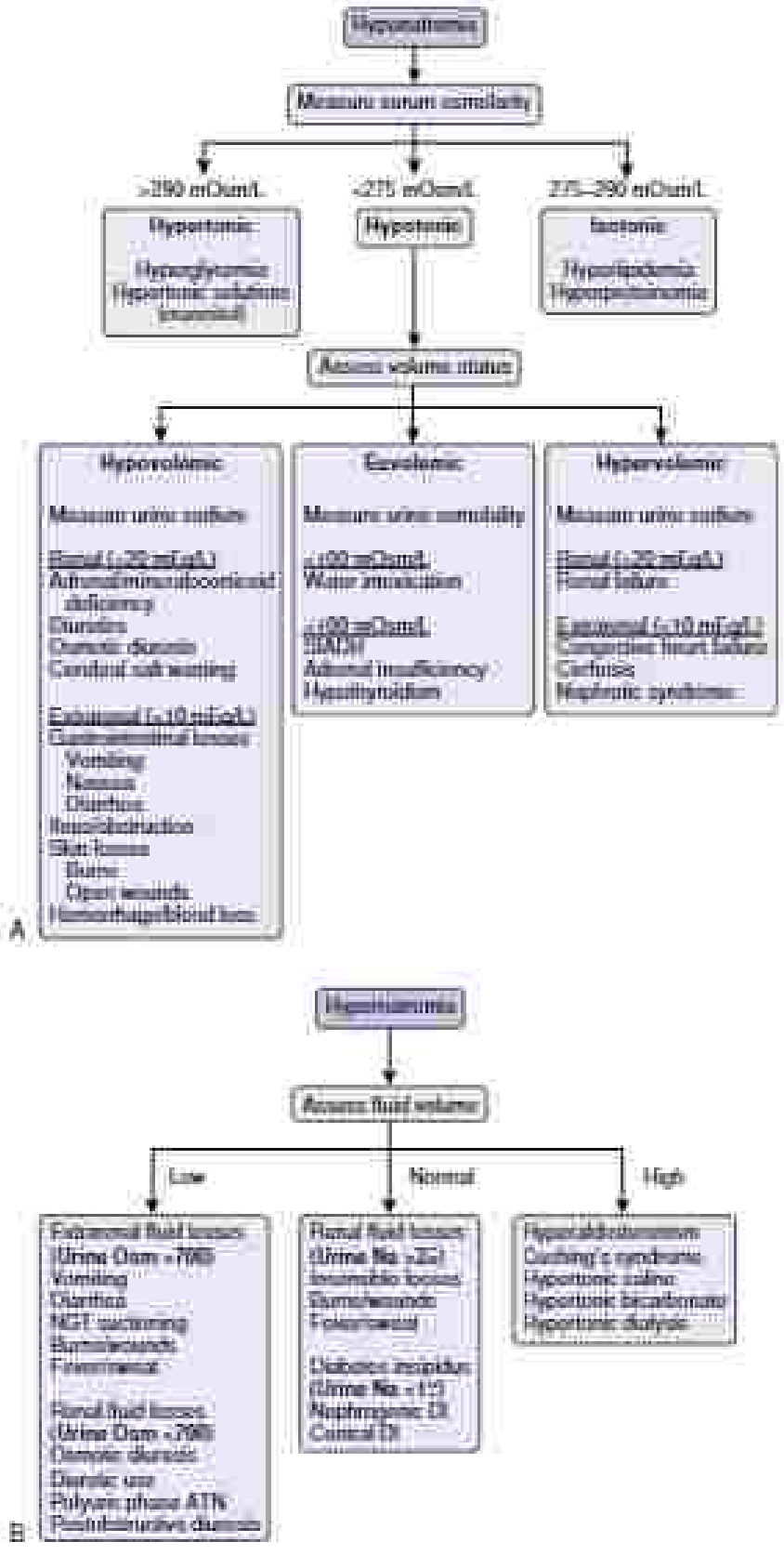

FIG. 1 (A) ... glucosemia. (B) Hyponatremia. ATN, acute tubular necrosis; DI, diabetes insipidus; Na, sodium; NCT, nasogastric tube; Or ..., osmolality; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

high urine osmolality implies the presence of SIADH and an internal homeostasis disorder (see the previous section), whereas a low urine osmolality suggests excessive exogenous intake (water intoxication).

Hypovolemic hyponatremia is the most common cause of hyponatremia in the postoperative state and can be seen in conditions of high fluid loss such as through the gastrointestinal (GI) tract, fluid sequestration (third spacing), or from hemorrhage. Again, the volume loss results in a nonosmotic stimulation of ADH release and the retention of free water resulting in hyponatremia and concentrated urine with a low sodium concentration (<10 mEq/L). Primary renal losses can lead to a similar clinical condition except with a more elevated urine sodium level (>20 mEq/L). Finally, large volume sodium depletion can occur in the CSW. This syndrome can occur in the setting of brain injury and results in the active excretion of sodium with high levels in the urine (>40 mEq/L). In contrast to SIADH, fluid restriction will compound the hyponatremia because there is an underlying hypovolemia in CSW. Volume and salt replacement, such as with isotonic intravenous fluids, is therefore the mainstay of treatment.

An important consideration in the management of hyponatremia is the rate of correction. Patients with chronic hyponatremia are at much higher risk for central pontine myelinolysis than those who develop hyponatremia acutely (within 48 hours). In the former situations, a slow correction of the hyponatremia should be considered (0.25–0.5 mEq/L per hour). Correction that is too rapid can predispose to the development of central pontine myelinolysis, which generally occurs 2 to 6 days after the sodium correction. Symptoms include dysarthria, paresis, seizure, lethargy, and coma among others. Symptoms tend to be irreversible. Severely ill critical patients may experience locked-in syndrome, in which patients are awake but unable to communicate except through eye movements. In acute hyponatremia, a faster correction (1–2 mEq/L per hour) is safe and can be accomplished through the infusion of 3% hypertonic saline.

Hypernatremia is defined as a sodium level greater than 145 mEq/L (moderate, 146–159 mEq/L; severe, ≥160 mEq/L). Clinical signs include restlessness and insomnia but can progress to lethargy and coma at extremely high sodium levels. Similar to hyponatremia, hypernatremia can occur in all variations of intravascular volume.

In the surgical patient, hypovolemic hypernatremia is the most common scenario and is secondary to unreplaced water loss. This can be secondary to GI losses such as nasogastric suctioning, vomiting and diarrhea; renal losses such as with diuretic use or with multiple, large open wounds (e.g., burns) resulting in evaporative losses. A key differentiating factor is that renal losses will have elevated urine sodium loss (>20 mEq/L) compared with decreased urine excretion in other etiologies.

Euvolemic hypernatremia most commonly develops in the context of DI (see the previous section). Hypervolemic hypernatremia is usually iatrogenic and related to large volume administration of isotonic or hypertonic saline. Mineralocorticoid or glucocorticoid excess may also cause similar findings (Conn's and Cushing's syndrome, respectively).

Irrespective of the volume status of the patient, however, all patients of hypernatremia have a free water deficit; therefore, the treatment of hypernatremia revolves around the administration of hypotonic fluid and may be supplemented with diuretics in hypervolemic states. To accomplish this, the free water deficit should be calculated and can be done with the following formula:

$$\text{Free water deficit} = \frac{[\text{Na}^+]_{\text{measured}} - 140}{140} \times \text{total body water}$$

In general, half the calculated water deficit is replaced in the first 24 hours and the remaining half over the next 24 hours. The choice of fluid used to correct the hypernatremia depends on any other ongoing electrolyte abnormalities and the underlying etiology. In general, hypernatremia is treated with the administration of hypotonic fluid (oral or intravenous) such as 0.45% saline or 5% water; however, if the hypernatremia is associated with hypovolemia (i.e., both fluid and salt lost) additional solute may be required such as with the administration of more isotonic solutions such as 0.9% normal saline or balanced crystalloids. A further consideration is the rate of correction: acute hypernatremia (within 48 hours) is generally safe to correct rapidly (1–2 mEq/L per hour for example), but rapidly correcting hypernatremia that is more chronic can lead to cerebral edema. Hence, chronic hypernatremia should not be corrected at a rate faster than 0.5 mEq/L per hour.

Chloride

Chloride is the second most abundant electrolyte in the ECF. Its primary roles are in its contribution to osmolality as well as muscular function, GI and pulmonary function, as well as urine concentration by the kidney.

The primary method of chloride homeostasis is via excretion through the kidney and its range is maintained between 95 and 105 mEq/L. Hyperchloremia is generally seen in situations of dehydration where it is paired with a hypernatremia such as with large volume diarrhea. These situations entail the development of a normal anion gap metabolic acidosis (i.e., high loss of bicarbonate and retention of chloride). Biliary and pancreatic fistulas are other important causes. Iatrogenic hyperchloremia is common secondary to the large volume administration of acidic isotonic fluid such as 0.9% normal saline, which has a much higher concentration of chloride (154 mEq/L) compared with plasma (~110 mEq/L). Consequently, a rise in chloride leads to a drop in serum bicarbonate and a hyperchloremic metabolic acidosis.

Conversely, hypochloremia is generally associated with a metabolic alkalosis and may be physiologic as in physiologic chloriduria where renal excretion of chloride is increased in exchange of bicarbonate reabsorption as a compensatory response in the setting respiratory acidosis. Primary hypochloremia is usually secondary to GI losses such as congenital chloride diarrhea, nasogastric suctioning, and high ileostomy output, which preferentially lose high volumes of chloride. In these scenarios, the fluid lost may also have a relatively low bicarbonate content relative to the ECF. The water loss leads to contraction of the ECF with a relatively stable bicarbonate concentration and a contraction alkalosis. Uncontrolled renal losses, such as with diuretic therapy or renal failure, can also contribute to a hypochloremic metabolic alkalosis.

Potassium

Unlike sodium and chloride, potassium is primarily an intracellular cation. Potassium is the primary determinant of the resting membrane potential across the cell membranes of most cells and that is why alterations can lead to dysrhythmias and cardiac abnormalities. Its homeostasis is maintained primarily through renal excretion.

Hypokalemia is a common condition particularly in the postoperative state. It is defined as a serum potassium value of less than 3.5 mEq/L. Hypokalemia can occur through GI losses, renal losses, alkalosis, the administration of insulin, as well as others (Table 1). Patients complain of nonspecific symptoms such as fatigue and weakness, and hypokalemia can predispose to intestinal ileus. Severe hypokalemia can lead to electrocardiogram changes such as T wave flattening.

In addition, most of the causes of hypokalemia also predispose to hypomagnesemia. These patients are likely to be refractory to replacement of potassium alone without treating the hypomagnesemia as well; hence, magnesium levels should be checked and replaced in all hypokalemic patients. Potassium can be replaced orally or intravenously. The latter is generally considered in patients with more severe hypokalemia and should be administered in a monitored setting due to the risk of arrhythmias.

Oral repletion of potassium is a frequent necessity for surgical services. The healthcare provider should be cognizant of not administering a high potassium load through the GI tract all at once because it can lead to nausea and vomiting. Potassium is, therefore, generally repleted over 4 to 6 divided doses (Table 2); in all confirmed or

TABLE 1 Causes of Abnormal Potassium Levels

Hypokalemia	Hyperkalemia
EXTRARENAL LOSSES	**EXTRARENAL CAUSES**
• Diarrhea • Malabsorption • VIPoma • ZE syndrome • Villous adenoma	• Pseudohyperkalemia • Metabolic acidosis • Succinylcholine • Beta 2 adrenergic antagonists • Digoxin • Rhabdomyolysis • Tumor lysis syndrome • Ethanol or methanol • Salt shock • Insulin deficiency
INTRACELLULAR POTASSIUM SHIFT	**RENAL ETIOLOGIES**
• Metabolic alkalosis • Beta 2 adrenergic agonists • Theophylline • Caffeine • Hypothyroidism	• Renal failure • Mineralocorticoid deficiency (low-degree hyporeninemia, Addison's disease, ACE inhibitors, ARBs, NSAIDs)
RENAL LOSSES	• Mineralocorticoid resistance (spironolactone, amiloride/trimterene, cyclosporine, tacrolimus)
• Diuretics (loop, thiazide, and osmotic agents) • Other medications (amphotericin B, cisplatin, foscarnet, aminoglycosides) • Hypercalcemia/renal (Conn's syndrome, Cushing's syndrome, dehydration) • Magnesium deficiency • Defective tubules	

ACE, Angiotensin converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal antiinflammatory drugs; ZE, Zollinger Ellison.

TABLE 2 Example of Electrolyte Replacement Protocol[a]

Serum Level (mg/dL)	Replacement Dose
POTASSIUM[b]	
3.5–3.9	40 mEq KCl PO/IV
3.0–3.2	60 mEq KCl PO/IV
2.6–2.8	80 mEq KCl IV
<2.6	100 mEq IV
MAGNESIUM[c]	
1.6–1.9	4 g $MgSO_4$ IV or 250 mg MgO PO × 2 doses[d]
1.0–1.5	6 g $MgSO_4$ IV
<1.0	8 g $MgSO_4$ IV
PHOSPHORUS[e]	
2–2.5	20 mmol Na Phos or K Phos (provides ~20 mEq K^+)
1.6–1.9	30 mmol Na Phos or K Phos (provides ~44 mEq K^+)
<1.6	40 mmol Na Phos or K Phos (provides ~60 mEq K^+)
CALCIUM[f,g]	
3.5–3.9	2 g IV Ca gluconate
3.0–3.4	4 g IV Ca gluconate
<2.9	6 g IV Ca gluconate

[a]Excludes patients on dialysis or with creatinine clearance <20 mL/min.
[b]IV KCl infusion rate should not exceed 10 mEq/hr through peripheral line or 40 mEq/hr using central line and continuous cardiac monitoring.
[c]IV $MgSO_4$ infusion rate should not exceed 2 g/hr.
[d]Oral magnesium replacement should be avoided in patients with poor oral tolerance or GI disturbance.
[e]For simultaneous K+ replacement, subtract the amount given with K Phos and give remainder as KCl.
[f]Normal calcium, 3 mg/dL = 0.25 mmol/L.
[g]IV Ca gluconate infusion rate should not exceed 2 g/hr; for CaCl, give one-third dose using central line and continuous cardiac monitoring.
CaCl, Calcium chloride; Ca gluconate, calcium gluconate; GI, gastrointestinal; IV, intravenous; K^+, potassium; KCl, potassium chloride; K Phos, potassium phosphate; Mg+, magnesium oxide; $MgSO_4$, magnesium sulfate; Na Phos, sodium phosphate; PO, per oral(ly).

hypokalemia, the renal function must be evaluated. Aggressive replacement may be inappropriate in patients with renal insufficiency as they have a reduced capacity for potassium excretion.

Hyperkalemia is defined as a potassium level exceeding 5.5 mEq/L. A frequent cause of an elevated laboratory value of serum potassium is due to hemolysis of the specimens. The serum potassium should be repeated in these cases. The etiology of hyperkalemia can be from a variety of sources and includes mineralocorticoid deficiency, renal failure, ischemia reperfusion injury, and the use of succinylcholine in certain clinical conditions such as burns or major trauma.

True hyperkalemia will result in muscle weakness and cardiac conduction abnormalities. This usually occurs with severe hyperkalemia (>7.8 mEq/L) or lesser elevations that occur acutely. Cardiac abnormalities include peaked T waves and shortened QT intervals. Symptomatic hyperkalemia, hyperkalemia of more than 6.5 mEq/L, and/or hyperkalemia in the presence of renal impairment or other sources of ongoing potassium absorption are considered hyperkalemic emergencies. In these scenarios the management of hyperkalemia should be implemented in two paradigms:

1. Rapidly acting therapies that mobilize potassium back into the cells.
2. Therapies that remove potassium from the body.

In hyperkalemic emergencies rapidly acting therapies should be implemented. This includes the administration of IV calcium (e.g., 1000 mg of intravenous calcium gluconate over 30 to 60 minutes) to antagonize the effects of potassium on the cell membranes and to provide a membrane stabilizing effect. In addition, 10 U of intravenous insulin should be administered be administered to mobilize potassium into the cells. To prevent hypoglycemia, dextrose may be administered in addition to the insulin (e.g., 50 mL of 50% dextrose solution).

It should be emphasized that the aforementioned therapies are temporizing measures and do nothing to alter the total body potassium content. To truly decrease the body's potassium levels other therapies will need to be instituted. These therapies include the administration of diuretics, gastrointestinal cation exchangers, and the use of hemodialysis.

The administration of loop diuretics can lead to a kaliuresis and decrease the body's potassium levels. This is particularly helpful in cases of preserved renal function; however, most patients with refractory hyperkalemia will have some element of renal dysfunction. In these patients, loop diuretics should not be used in isolation.

The use of sodium polystyrene sulfonate has historically been frequently cited as a therapy to remove potassium through the GI tract, but studies have shown that complications are frequent and include intestinal necrosis. Sodium polystyrene sulfonate should therefore only be used as a last resort. Other cation exchangers, such as patiromer, may be used instead.

The mainstay of therapy for hyperkalemia is hemodialysis and should be instituted as soon as possible. Other therapies may not be necessary if dialysis and vascular access are immediately available.

The administration of beta 2 adrenergic agonists and sodium bicarbonate may be considered as supplements to the therapies discussed previously.

Magnesium

Magnesium is also an electrolyte the majority of which resides in the ICF. Hypomagnesemia is defined as a serum level of <1.8 mg/dL and is common in surgical patients with GI losses, diuretic, or those with poor oral intake. Symptoms include seizure, seizures, and dysrhythmias. Repletion can be done orally or parenterally, however, oral repletion should be used with caution as diarrhea can sometimes be precipitated. Furthermore, rapid repletion of serum levels may inhibit renal reabsorption of magnesium; therefore, severe hypomagnesemia should be managed with more prolonged infusion (e.g. 12 hours). Conversely, magnesium administered to short ureate dysrhythmias (e.g., torsades de pointes) should be infused rapidly.

Hypermagnesemia occurs with serum levels greater than 2.8 mg/dL. Symptoms include decreased deep tendon reflexes, lethargy, and cardiac conduction abnormalities. Because of the efficiency with which the kidneys clear magnesium, hypermagnesemia is an uncommon entity. It generally occurs in renal insufficiency or in the context of a large magnesium load. In the setting of normal renal function, loop diuretics may be used to help clear the hypermagnesemia. In addition, patients with renal insufficiency may need hemodialysis. Symptomatic hypermagnesemia should be interpreted with the administration of intravenous calcium to counteract magnesium's effects in precipitating abnormal cardiac conduction and its effects on the neurologic system.

Calcium

Calcium is the most abundant electrolyte in the body but mostly exists in a mineralized state in the skeletal system. The normal range of total serum calcium is 8.5 to 10.5 mg/dL, and the normal range of the active, ionized form of calcium is 4.65 to 5.25 mg/dL. This ionized portion constitutes approximately 45% of the plasma calcium. The rest is bound to albumin (40%) or complexed to anions such as phosphate and citrate (15%). The consequence of this is that serum albumin concentration has a direct correlation to the measured total calcium concentration, a decrease in albumin of 1 g/dL leads to a measured decrease of 0.8 mEq/L of serum calcium (therefore requiring correction of any laboratory measurements of total calcium). Calcium homeostasis is accomplished via the hormones parathyroid hormone (PTH), vitamin D (calcitriol), and calcitonin (Fig. 1).

1. PTH is secreted by the parathyroid glands in response to hypocalcemia. This leads to an increase in calcium levels (via stimulation of osteoclasts and kidney reabsorption) and a decrease in phosphate levels (via excretion by the kidneys). The increased phosphate excretion allows the liberated calcium to remain in the plasma as the active, ionized form.
2. PTH also stimulates the production of vitamin D in the kidneys, which further stimulates the reabsorption of calcium from the gastrointestinal tract and kidney. Vitamin D also stimulates bone resorption and remodeling.
3. Calcitonin is produced by the parafollicular cells of the thyroid gland and serves to decrease calcium levels by inhibiting bone resorption.

Hypocalcemia occurs if the plasma calcium level falls below 8.4 mEq/L (or an ionized calcium of <4.5 mEq/L). Classic symptoms of hypocalcemia include perioral numbness and tingling, twitching of the facial muscles on tapping the facial nerve in the region of the parotid gland (Chvostek's sign), and carpopedal spasm at the level of the hand and forearm precipitated by ischemia, such as by the application of a blood pressure cuff on the ipsilateral arm (Trousseau's sign). Electrocardiogram findings include a prolonged QT interval and arrhythmias. Hypocalcemia is often seen after thyroid and parathyroid surgery, severe acute pancreatitis, vitamin D deficiency, hyperphosphatemia, hypomagnesemia, and malnutrition. In the critically ill population, hypocalcemia develops frequently and is likely a consequence of suppressed PTH and vitamin D production, as well as end organ resistance to the actions of PTH likely secondary to decreased magnesium levels and the effects of inflammatory cytokines. Large volume blood transfusion can also predispose to hypocalcemia because the citrate used as an anticoagulant acts as a calcium chelator (the total calcium is therefore detected as normal but in effect the level of ionized calcium is low). Hypocalcemia should be treated if the levels fall below a total calcium of 7 mEq/L (ionized calcium <3 mEq/L), or if symptoms develop. This repletion is frequently through the intravenous route in the form of calcium gluconate or calcium chloride. The latter formulation has three times the elemental calcium of the former; it can rapidly reverse dysfunction but infusions

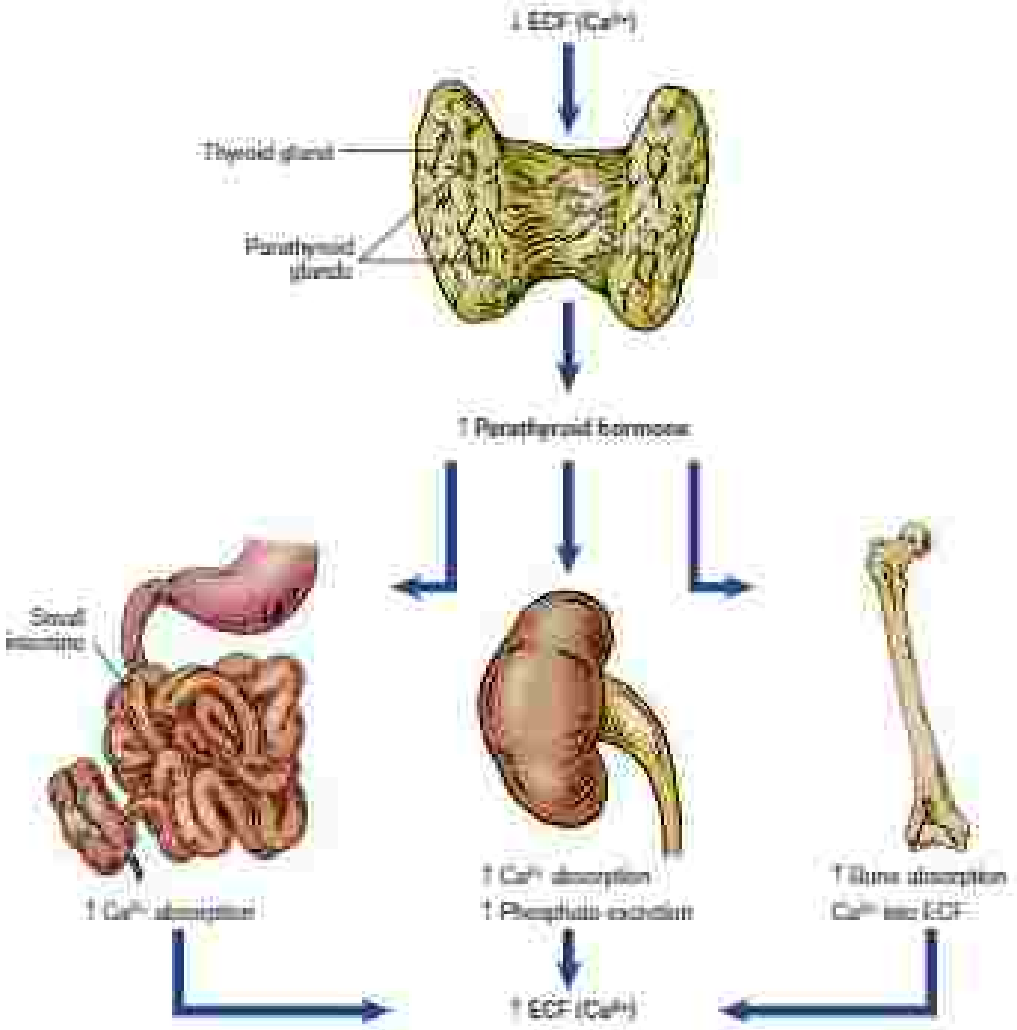

FIG. 3. Calcium homeostasis. Ca^{2+}, Calcium; ECF, extracellular fluid.

need to be through central venous catheters and in a monitored setting. Oral calcium carbonate or calcium gluconate can be used in chronic or milder forms of hypocalcemia.

Hypercalcemia is defined as a total calcium level above 10.6 mEq/L (>5.6 mEq/L ionized calcium) and is represented by a classic constellation of symptoms (and an oft repeated mnemonic): myalgias and arthralgias ("painful bones"), the development of "kidney stones," nausea, vomiting ("abdominal groans"), lethargy, and altered mental status ("psychic moans"). Hypercalcemic crisis can occur with levels over 14 mEq/L. The most common cause of hypercalcemia in nonhospitalized patients is hyperparathyroidism, whereas it is malignancies (such as breast, lung, and multiple myeloma) that cause hypercalcemia most frequently in hospitalized patients. Other causes include immobilization, familial hypocalciuric hypercalcemia, thiazide diuretics, and medications such as vitamin A and lithium. Treatment should be instituted for severe elevations (>14 mEq/L) or if symptoms are present, including the following.

1. Isotonic saline to correct any fluid losses related to hypercalcemia-induced urinary salt wasting and vomiting. An initial rate may need to be as high as 300 to 500 mL/hr until adjustments can take place to maintain a urine output of 100 to 150 mL/hr.
2. Intramuscular or subcutaneous calcitonin should be administered concurrently at a starting dose of 4 IU/kg every 6 to 12 hours. This allows for increased urinary excretion and decreased bone breakdown.
3. Finally, bisphosphonates, such as pamidronate, should also be administered. Bisphosphonates interfere with osteoclast-mediated bone resorption. Although the administration of bisphosphonates is the most potent treatment, their peak effect does not occur until 2 to 4 days after administration; therefore, combination therapy with saline and calcitonin (which reduces calcium levels more rapidly) is the mainstay of treatment.

Phosphorus

Similar to calcium, the majority of phosphorus is also contained in the bone and is also regulated by PTH and vitamin D. Hypophosphatemia occurs if the phosphorus level falls below 2.5 mg/dL and is seen frequently in the postoperative setting especially after hepatic resections. If severe, deficiencies can lead to heart and respiratory failure. Refeeding syndrome is also an important and common cause of hypophosphatemia in the critically ill and malnourished. Other causes include the administration of diuretic medications, intestinal malabsorption, vitamin D deficiency, and hyperparathyroidism. Repletion can occur via the oral or parenteral route. Hyperphosphatemia can occur after parathyroid or thyroid surgery, the symptoms are usually related to the concomitant hypocalcemia. In the acute setting this is treated with volume expansion. Chronic hyperphosphatemia, however, is seen commonly in renal failure and can be treated with phosphate binders.

SUMMARY

The preceding discussion should impart to the reader the importance of the fluid milieu of the human body, whether the intracellular or the extracellular components, and the salts that are dissolved within it. Successful recognition and management of these complex problems requires a patient and systematic evaluation while recognizing the pitfalls of performing electrolyte abnormalities that may be appropriate physiologic responses or chronic derangements.

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ACID-BASE PROBLEMS

Ana M. Velez-Rawsthorne, MD, and Marko Baker, MD, FACS

The human body's tightly regulated pH of 7.35 to 7.45 is vital to maintaining homeostasis for a variety of physiologic functions including oxygen transport, cardiac electrophysiology, neurotransmission, enzymatic activity, and drug metabolism, among others. Different stressors, including trauma, surgical intervention, and critical illness, can precipitate acid-base disturbances that may result as a direct consequence of these inciting events or as a result of preexisting comorbid conditions.

Different theories exist to explain acid-base physiology, the most prominent of which is the traditional model. Alternative methods of acid-base analysis such as Stewart's physicochemical model exist and are beyond the scope of this summary. In clinical practice, one theory has not been shown to be superior to the other and both are limited as they describe the state of a biologic solution at the moment of analysis. The traditional model is based on the initial Lowry's theory, which characterizes acids as hydrogen ion (H^+) donors and bases as H^+ acceptors. This is based on the notion that any change to concentration of H^+ in the body results in a compensatory response to restore the pH into normal range. As determined by the Henderson-Hasselbalch equation, the traditional model uses measured concentrations of plasma carbon dioxide (CO_2) and bicarbonate (HCO_3^-) to determine the pH of blood. This equation is shown below where pK is the acid dissociation constant, 0.03 is the solubility constant of CO_2 in the blood, and $PaCO_2$ is the partial pressure of carbon dioxide in the arterial blood.

$$pH = pK + \log_{10}[HCO_3^-/0.03\,(PaCO_2)]$$

ACID-BASE HOMEOSTASIS

The narrow pH range of body fluids is maintained despite the normal acid loads produced as a byproduct of metabolism. To maintain this stable plasma acid-base balance, endogenous acid load is efficiently neutralized by a combination of mechanisms that vary temporally and can be used to help determine the acuity of the disorder present. These include extracellular and intracellular buffer systems (which act in minutes), changes in alveolar ventilation (which occurs in hours), and renal excretion (which takes days). When acid-base disturbances are present, existing physiologic adaptations are better at combating acidosis than alkalosis.

Buffer Systems

Proteins and phosphates are the main intracellular buffers, whereas hemoglobin is the main buffer within red blood cells, with histidine moieties acting as H^+ binding sites. The bicarbonate-carbonic acid system is the most prominent extracellular buffer, whereas plasma proteins such as albumin and inorganic phosphates contribute to a lesser extent. Bone, although not an acute buffer, can absorb H^+ in exchange for sodium (Na^+) and potassium (K^+), and releases calcium, HCO_3^-, carbonate, and phosphates.

Respiratory System

In patients with normal gas exchange, CO_2 diffuses quickly and is cleared via compensatory changes to alveolar ventilation in response to pH changes sensed in the carotid body and by medullary chemoreceptors. This leads to rapid changes in $PaCO_2$.

Renal System

The proximal tubule modulates both H^+ excretion and reabsorbs 85% of the filtered HCO_3^-. Additionally, the distal tubule functions to excrete H^+, either in exchange for Na^+, or in combination with ammonia as ammonium chloride (NH_4Cl).

DISORDERS OF ACID-BASE METABOLISM

Acid-base disorders occur when there is a lack of balance between the production of acids and bases and the body's ability to compensate. This may be due either to a rapid rate of production or a defect in the physiologic compensatory mechanisms. These disturbances are markers of an underlying disease process. Correction of abnormalities should occur while simultaneously searching for inciting causes.

Acidemia is defined as a plasma pH less than 7.35, and alkalemia is defined as a plasma pH greater than 7.45. These definitions are a reflection of the serum pH, not necessarily a reflection of the acid-base disorders that collectively may or may not lead to pH alterations. Acidosis is defined as any process that lowers the pH (increases H^+) and alkalosis any process that increases the pH (decreases H^+). Acid-base disorders can develop as a result of metabolic or respiratory alterations. Additionally, multiple acid-base disorders can exist at one time and can be uncovered by examining the expected and observed compensatory changes in $PaCO_2$ and HCO_3^- responses. It is important to note that "compensatory" responses to the primary acid-base disturbance occur in the same direction and are only partially corrective. For example, in metabolic acidosis the serum HCO_3^- level decreases with a physiologic decrease in the $PaCO_2$ through increased minute ventilation. Estimates of physiologic responses are depicted in Table 1. If compensation is greater or less than predicted, that is, the $PaCO_2$ or HCO_3^- is not within the range predicted by the formula, it is important to evaluate for a mixed acid-base disorder.

Physiologic Effects of Acidosis and Alkalosis

Acidosis, acidosis has physiologic benefits, such as enhanced peripheral oxygen delivery by decreased binding of oxygen to hemoglobin and catecholamine and aldosterone stimulation augmenting cardiac

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The human body's tightly regulated pH of 7.35 to 7.45 is vital to maintaining homeostasis for a variety of physiologic functions including oxygen transport, cardiac electrophysiology, neurotransmission, enzymatic activity, and drug metabolism, among others. Different stressors, including trauma, surgical intervention, and critical illness, can precipitate acid-base disturbances that may result as a direct consequence of these inciting events or as a result of preexisting comorbid conditions.

Different theories exist to explain acid-base physiology, the most prominent of which is the traditional model. Alternative methods of acid-base analysis such as Stewart's physicochemical model exist and are beyond the scope of this summary. In clinical practice, one theory has not been shown to be superior to the other and both are limited as they describe the state of a biologic solution at the moment of analysis. The traditional model is based on Brønsted and Lowry's theory, which characterizes acids as hydrogen ion (H^+) donors and bases as H^+ acceptors. This is based on the notion that any change to concentration of H^+ in the body results in a compensatory response to restore the pH into normal range. As determined by the Henderson-Hasselbalch equation, the traditional model uses measured concentrations of plasma carbon dioxide (CO_2) and bicarbonate (HCO_3^-) to determine the pH of blood. This equation is shown below where pK is the acid dissociation constant, 0.03 is the solubility constant of CO_2 in the blood, and $PaCO_2$ is the partial pressure of carbon dioxide in the arterial blood.

$$pH = pK + \log_{10}[HCO_3^-/0.03\,(PaCO_2)]$$

ACID-BASE HOMEOSTASIS

The narrow pH range of body fluids is maintained despite the normal acid loads produced as a byproduct of metabolism. To maintain this stable plasma acid-base balance, endogenous acid load is efficiently neutralized by a combination of mechanisms that vary temporally and can be used to help determine the acuity of the disorder present. These include extracellular and intracellular buffer systems (which act in minutes), changes in alveolar ventilation (which occurs in hours), and renal excretion (which takes days). When acid-base disturbances are present, existing physiologic adaptations are better at combating acidosis than alkalosis.

Buffer Systems

Proteins and phosphates are the main intracellular buffers, whereas hemoglobin is the main buffer within red blood cells, with histidine moieties acting as H^+ binding sites. The bicarbonate-carbonic acid system is the most prominent extracellular buffer, whereas plasma proteins such as albumin and inorganic phosphates contribute to a lesser extent. Bone, although not an acute buffer, can absorb H^+ in exchange for sodium (Na^+) and potassium (K^+), and releases calcium, HCO_3^-, carbonate, and phosphates.

Respiratory System

In patients with normal gas exchange, CO_2 diffuses quickly and is cleared via compensatory changes to alveolar ventilation in response to pH changes sensed in the carotid body and by medullary chemoreceptors. This leads to rapid changes in $PaCO_2$.

Renal System

The proximal tubule modulates both H^+ secretion and reuptake 85% of the filtered HCO_3^-. Additionally, the distal tubule functions to excrete H^+, either in exchange for Na^+, or in combination with ammonia as ammonium chloride (NH_4Cl).

DISORDERS OF ACID-BASE METABOLISM

Acid-base disorders occur when there is a lack of balance between the production of acids and bases and the body's ability to compensate. This may be due either to a rapid rate of production or a defect in the physiologic compensatory mechanisms. These disturbances are markers of an underlying disease process. Correction of abnormalities should occur while simultaneously searching for inciting causes.

Acidemia is defined as a plasma pH less than 7.35, and alkalemia is defined as a plasma pH greater than 7.45. These definitions are a reflection of the serum pH, not necessarily a reflection of the acid-base disorders that collectively may or may not lead to pH alterations. Acidosis is defined as any process that lowers the pH (increases H^+) and alkalosis any process that increases the pH (decreases H^+). Acid-base disorders can develop as a result of metabolic or respiratory alterations. Additionally, multiple acid-base disorders can exist at one time and can be uncovered by examining the expected and observed compensatory changes in $PaCO_2$ and HCO_3^- responses. It is important to note that "compensatory" responses to the primary acid-base disturbance occur in the same direction and are only partially corrective. For example, in metabolic acidosis the serum HCO_3^- level decreases with a physiologic decrease in the $PaCO_2$ through increased minute ventilation. Formulas of physiologic responses are depicted in Table 1. If compensation is greater or less than predicted, that is, the $PaCO_2$ or HCO_3^- is not within the range predicted by the formula, it is important to evaluate for a mixed acid-base disorder.

Physiologic Effects of Acidosis and Alkalosis

Acutely, acidosis has physiologic benefits, such as enhanced peripheral oxygen delivery by decreased binding of oxygen to hemoglobin and catecholamine and aldosterone stimulation augmenting cardiac

TABLE 1 Expected Compensation for Primary Acid-Base Disturbance

Metabolic acidosis	$PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$
Metabolic alkalosis	$PaCO_2 = (0.7 \times [HCO_3^-]) + 40 \pm 2$
Acute respiratory acidosis	$\uparrow HCO_3^- = \Delta PaCO_2/10$
Acute respiratory alkalosis	$\downarrow HCO_3^- = 2\ (\Delta PaCO_2/10)$
Chronic respiratory acidosis	$\uparrow HCO_3^- = 4\ (\Delta PaCO_2/10)$
Chronic respiratory alkalosis	$\downarrow HCO_3^- = 5\ (\Delta PaCO_2/10)$

$\Delta PaCO_2$ is calculated from the normal value of 40.
HCO_3^-, Bicarbonate; $PaCO_2$, partial pressure of carbon dioxide.

output. At the pH decreases below 7.2, however, deleterious effects such as decreased cardiac inotropy, hyperkalemia-induced cardiac conduction deficits, and central venous vasoconstriction may occur. Neurologic effects are manifested by decreased sensorium, which may progress to coma, and cerebral vasodilation that in turn results in increased intracranial pressure.

Clinical manifestations of alkalosis are subtle. Acute metabolic consequences are most commonly related to associated electrolyte derangements and neurologic effects. Increased pH results in hypokalemia, hypophosphatemia, and hypocalcemia resulting from increased uptake of K^+ and phosphate into cells, and increased binding of calcium to albumin. This can lead to cardiac and neuromuscular effects such as altered coronary blood flow and arrhythmias, increased neuromuscular excitability, presenting as paresthesias and muscle cramps, can progress to encephalopathy and seizures. Additionally, oxygen delivery is diminished as a result of increased binding of oxygen to hemoglobin.

APPROACH TO ACID-BASE DISTURBANCES: BLOOD GAS INTERPRETATION

When these disorders occur in the perioperative period, it is imperative to have a rapid and accurate clinical approach to developing a diagnostic and therapeutic plan that optimizes the patient's outcome. The blood gas sample is the test most commonly used to evaluate acid-base physiology at the bedside. The pH, arterial partial pressure of oxygen, and $PaCO_2$ are measured directly. The derived components include arterial oxygen saturation, HCO_3^- (using the Henderson-Hasselbalch equation), and the base excess (BE). Normal values in both arterial and venous samples can be seen in Table 2.

Systematic blood gas interpretation typically proceeds in the following order (Fig. 1):

1. The pH value provides the first and most representative estimate of the severity of the acid-base disorder, with acidosis at a pH less than 7.35 and alkalosis at a pH greater than 7.45.
2. In primary metabolic disorders, the pH and pCO_2 values are displaced in the same direction, with change in opposite directions indicating a primary respiratory disorder. If there is compensation, the change in pH may still occur though in a less pronounced form.
3. HCO_3^- is reduced in metabolic acidosis and as a compensatory mechanism in chronic respiratory alkalosis. It is increased in metabolic alkalosis and in chronic respiratory acidosis.
4. BE is the amount of acid measured in mmol/L required to titrate 1 L of blood to a pH of 7.4 at 37°C; normal values are between −3 and 3. A positive BE indicates lack of acid and thus a component of metabolic alkalosis. A negative BE indicates excess acid with a contributing metabolic acidosis; therefore, BE reflects the pure metabolic component of the acid-base disorder.

TABLE 2 Normal Blood Gas Values

	Arterial	Venous
pH	7.40 ± 0.04	7.38 ± 0.04
$PaCO_2$ (mHg/L)	40 ± 4	46 ± 4
HCO_3^- (mEq/L)	24 ± 2	26 ± 2

HCO_3^-, Bicarbonate; $PaCO_2$, partial pressure of carbon dioxide.

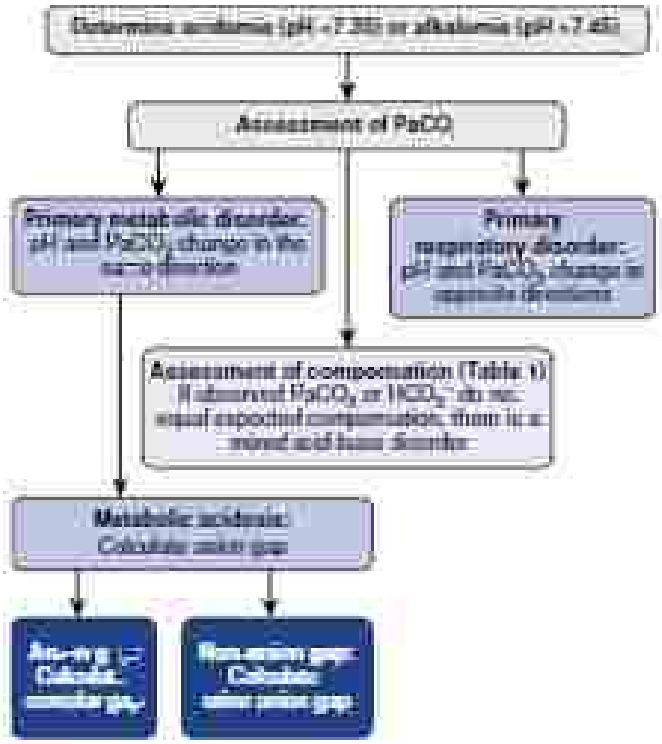

FIG. 1 Systemic approach to interpreting arterial blood gas. HCO_3^-, Serum bicarbonate; $PaCO_2$, partial pressure of carbon dioxide.

5. PO_2 levels provide an evaluation of pulmonary function and in cases of respiratory alkalosis, changes in PO_2 indicate whether the primary stimulus is hypoxemia or another cause.
6. Compensatory changes in mixed disorders can be diagnosed based on differences between expected and observed levels of pCO_2 and HCO_3^- (Table 1). The pH can change in the same direction (mixed disorders in the same direction) or remain neutral (mixed acidosis and alkalosis).

Although arterial blood gas analysis is the gold standard for determining the metabolic milieu in a critically ill patient, arterial samples may be difficult to obtain and may not provide significant additional information compared to venous blood gas (VBG) samples that would lead to diagnostic or therapeutic changes. Studies have shown acceptable correlation of VBG and arterial blood gas samples in noncritically ill patients. Arterial partial pressure of oxygen has significant variability and is typically 35 mm Hg lower than arterial in central venous samples. Central VBG samples offer the additional benefit of providing an assessment of global oxygen consumption by measuring central venous oxygen saturation.

ANION GAP METABOLIC ACIDOSIS

In the perioperative period, the most frequently encountered acid-base disturbance is metabolic acidosis, which occurs when the

plasma HCO_3^- to less than 22 mEq/L. The differential diagnosis depends on the presence or absence of an anion gap (AG). The AG represents unmeasured serum anions such as albumin, phosphates, sulfates, and lactate that are not typically quantified in routine laboratory measurements. The AG is calculated by subtracting the measured serum anions (chloride [Cl$^-$] and [HCO_3^-]) from the cations (Na^+ and K^+), though K^+ has such a low concentration in the serum that is generally omitted from the equation. The normal range for AG is 8 to 16, though this may vary as each institution reports its own expected normal.

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

The utility of the anion gap depends on normal circulating levels of albumin, which is also a weak acid. As most critically ill patients are hypoalbuminemic, the AG is lower than expected. To correct for this discrepancy the following equation can be used:

Corrected AG = AG + 2.5 × (4.5 − Serum albumin concentration [g/dL])

The AG may be used to determine the etiology of the metabolic disturbance, with an increased AG indicating accumulation of acids. The *MUDPILES* mnemonic is commonly used to define the differential diagnosis of AG metabolic acidosis, with the most common causes being lactic acidosis, ketoacidosis, and renal insufficiency (Box 1). In patients with an AG metabolic acidosis not explained by common causes and when toxic ingestion is suspected, the osmolar gap (OG) should also be calculated. The OG is the difference between the measured and calculated plasma osmolarity. An elevated OG indicates the presence of osmotically active substances in the plasma, such as ingested agents like methanol or ethylene glycol. The normal OG is less than 10 mOsm/kg and can be determined with the equation, where BUN is blood urea nitrogen.

OG = Measured plasma osmolarity − Calculated plasma osmolarity

$$\text{Calculated plasma osmolarity} = 2[Na^+] + \left(\frac{\text{glucose (mg/dL)}}{18}\right) + \left(\frac{\text{BUN (mg/dL)}}{2.8}\right)$$

Lactic Acidosis

Lactic acidosis occurs when lactate levels exceed 5 mmol/L, with a pH less than 7.35 and an increased AG. It accounts for approximately one-half of all AG metabolic acidoses in the critically ill surgical patient. Lactate has important therapeutic and prognostic implications and has been shown to correlate with outcome in patients in hemorrhagic and septic shock. Lactic acidosis results from tissue hypoxia and anaerobic metabolism resulting in lactate production at a rate that exceeds its clearance. This may be due to sepsis, shock (hypovolemic and cardiogenic), trauma, or severe heart failure; however, not all causes of lactic acidosis are associated with tissue hypoxia, such as seizures, underlying liver disease and poisoning with salicylates, cyanide, and toxic alcohols. Certain medications such as epinephrine, metformin, and linezolid may also cause lactic acidosis.

BOX 1 Anion Gap Metabolic Acidosis: MUDPILES

- Methanol, metformin, muscle injury (rhabdomyolysis)
- Uremia (renal failure), unoccupied (oxidative phosphorylation (cyanide)
- Diabetic ketoacidosis
- Propofol infusion syndrome, paraldehyde, propylene glycol (gastrointestinal, lorazepam)
- Isoniazid
- Lactic acidosis
- Ethanol, ethylene glycol (antifreeze)
- Salicylates, short gut (D lactate with bacterial overgrowth)

Although the majority of lactate is cleared by the liver, up to 20% is eliminated renally. Persistent lactate elevation may result from deficiency of pyruvate dehydrogenase or thiamine, a cofactor of pyruvate dehydrogenase, the enzyme responsible for lactate breakdown. Treatment of lactic acidosis is directed at identifying and treating the cause of this derangement and restoring tissue perfusion. Additionally, appropriate fluid resuscitation and optimization of oxygen delivery are vital. Sequential monitoring of serum lactate levels with arterial or venous samples is a useful therapeutic marker of appropriate resuscitation. Lactate levels should be correlated with the BE and failure to correct these values should prompt the consideration of an ongoing source of shock, including an unidentified injury or source of sepsis. Attempts to counteract the acidosis with exogenous administration of HCO_3^- without addressing the cause of tissue hypoxia will be unsuccessful and may in fact result in a superimposed respiratory acidosis due to the additional CO_2 load that is generated from HCO_3^- metabolism. In patients with maximal respiratory compensation and ventilatory hyperventilation this imbalance can result in worsening acidosis. Other buffers that have a lower CO_2 load such as Carbicarb and sodium acetate may be used when available. Generally speaking, administration of buffers has a limited role in the management of metabolic acidosis. In cases when the pH falls below 7.2 with associated instability, the HCO_3^- deficit may be calculated using the following equation:

HCO_3^- Deficit (mEq/L) = 0.6 × weight (kg) × (15 − plasma HCO_3^- [mEq/L])

This equation partially corrects the HCO_3^- deficit to a concentration of 15 mEq/L, with further correction being unnecessary.

NORMAL ANION GAP METABOLIC ACIDOSIS

A metabolic acidosis with a normal AG results from the loss of plasma HCO_3^- with a compensatory increase in Cl$^-$ reabsorption by the kidneys or from a net gain of Cl$^-$. The differential diagnosis can therefore be divided based on history, with the most common surgical causes being iatrogenic dilutional acidosis from intravenous saline infusion, gastrointestinal losses resulting in decreased body HCO_3^-, or renal failure with diminished H^+ excretion (Box 2).

Rapid administration of normal saline is the most common iatrogenic cause of a normal AG metabolic acidosis. Normal saline has a 1:1 Na^+ to Cl$^-$ ratio, whereas plasma has a ratio of 140:100, which decreases with rapid saline infusions, resulting in a relative increase in Cl$^-$ concentration with new body HCO_3^- losses to maintain electroneutrality. Insufficient urinary excretion of excess Cl$^-$ as ammonium chloride and decreased renal HCO_3^- reabsorption induced by hyperchloremia results in a metabolic acidosis. Evidence suggests that iatrogenic hyperchloremic acidosis results in important adverse clinical effects, with increased rates of renal dysfunction and use of dialysis noted in critically ill patients treated with normal saline compared with balanced crystalloid solutions.

BOX 2 Normal Anion Gap Metabolic Acidosis

Iatrogenic
- Rapid administration of normal saline
- Total parenteral nutrition with insufficient acetate

Kidneys
- Renal tubular acidosis
- Carbonic anhydrase inhibitors
- Spironolactone
- Ureteral diversion

Gastrointestinal tract
- Diarrhea
- Duodenal, biliary, or pancreatic diversion

Normal AG metabolic acidosis as a consequence of renal dysfunction or gastrointestinal (GI) losses can be clinically distinguished using urine pH and urine anion gap calculation using the following formula:

$$\text{Urine anion gap} = \text{urine } (Na^+ + K^+) - Cl^-$$

Renal causes of normal AG metabolic acidosis, such as renal tubular acidosis, result in a net increase in acid resulting from either impaired HCO_3^- absorption in the proximal kidney or inability to secrete H^+ as ammonium in the distal kidney. The urinary pH will be alkaline, usually greater than 5.5, and the urine AG will be positive as a result of increased urinary ammonium.

GI loss of HCO_3^-–rich fluid, commonly resulting from diarrhea, fistulas, and GI diversions, can result in a normal AG metabolic acidosis as a result of disproportionate loss of Na^+ compared to Cl^-. Normal kidneys compensate by increasing H^+ excretion and HCO_3^- regeneration; therefore, the urinary pH is low, usually less than 5, and the urine AG is negative.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs when the plasma $[HCO_3^-]$ exceeds 26 mEq/L and is the most common acid-base disturbance encountered in hospitalized patients. Because normal kidneys are very efficient at excreting HCO_3^-, this typically occurs when there is both an increase in alkali and impaired excretion of HCO_3^-. The differential diagnosis in a patient with this disturbance can be broadly distinguished by whether there is ongoing H^+ loss, either from the GI tract or the kidneys, or exogenous administration of HCO_3^- or bicarbonate precursor, as can occur from citrate in stored blood, acetate in parenteral nutrition, or sodium lactate in Ringer's solution.

In surgical patients, metabolic alkalosis frequently develops as a result of H^+ loss, as can occur with vomiting or nasogastric drainage, or from excess HCO_3^- regeneration as a result of diuretic therapy. In these situations, hypovolemia stimulates aldosterone secretion that in turn stimulates renal excretion of both H^+ and K^+ in exchange for Na^+. This results in reabsorption of Na^+, Cl^-, and HCO_3^-, and K^+ loss. Additionally, hypochloremia, which develops from gastric losses, prevents HCO_3^- excretion by inhibiting renal Cl^-/HCO_3^- exchange. The overall effect leads to the classic hypochloremic, hypokalemic metabolic alkalosis with paradoxical aciduria.

Metabolic alkalosis can occur less commonly as a result of hormonal mechanisms, such as mineralocorticoid excess, which results in a chronic state of Cl^- loss. To distinguish the cause of the disorder, urine Cl^- measurement can be used. A urine Cl^- concentration less than 25 mmol/L is suggestive of acute Cl^- loss, which can be effectively replaced, and thus is chloride responsive. Chloride-responsive metabolic alkalosis is commonly seen in surgical patients and can be treated with intravenous normal saline and potassium supplementation. Formulas for calculating estimated Cl^- deficit and replacement volume of saline needed are available. A urine Cl^- concentration greater than 40 mmol/L is indicative of a hormonal mechanism causing ongoing Cl^- loss, which would be resistant to chloride administration. In this case the supportive treatment includes administration of carbonic anhydrase inhibitors (i.e., acetazolamide) or hydrochloric acid infusion in severe cases while the underlying cause is treated.

RESPIRATORY ACIDOSIS

Respiratory acidosis develops when the $PaCO_2$ exceeds 40 mm Hg, and can be a result of pulmonary or extrapulmonary pathologies that cause inadequate CO_2 elimination by the lungs relative to the rate of CO_2 produced by cellular metabolism. Acute respiratory acidosis can result from depression of the central respiratory center, which may be due to cerebral disease (stroke, trauma) or drugs (narcotics, sedatives). It may also develop from neuromuscular impairment, as can be seen with residual paralysis after general anesthesia, as well as with hypophosphatemia or hypokalemia, or from airway obstruction related to acute exacerbation of obstructive lung disease. Chronic respiratory acidosis is caused by existing neuromuscular disease, chest wall disease such as kyphoscoliosis, or chronic obstructive pulmonary disease. If mechanical ventilation is being used, the minute ventilation rate should be adjusted to reach the desired $PaCO_2$ levels. In patients with chronic respiratory acidosis, caution should be used to not overcorrect CO_2 levels to normal values as this can result in difficulty weaning from the ventilator as well as cerebral ischemia from vasoconstriction. Associated hypoxemia is common in patients with acute respiratory acidosis. In a patient breathing room air, $PaCO_2$ cannot exceed 80 mm Hg before severe, life-threatening hypoxemia develops. Prompt assisted ventilation is vital and treatment should be directed toward the underlying cause.

Central respiratory depression resulting from medications may be addressed with administration of reversal agents such as naloxone or flumazenil, whereas bronchodilators are used in the treatment of airway obstruction. In patients with unaltered sensorium and ability to protect the airway, noninvasive ventilatory support may be a useful adjunct. Mechanical support should be considered in unstable patients, those with deterioration in central nervous system function, recent upper GI surgery, and patients exhibiting signs of respiratory muscle fatigue.

RESPIRATORY ALKALOSIS

Respiratory alkalosis develops when $PaCO_2$ is less than 40 mm Hg, occurring when alveolar ventilation exceeds the rate necessary to eliminate CO_2 produced by cellular metabolism. Acute respiratory alkalosis can result from stimulation of the central respiratory center from pain, fever, central nervous system lesions, and salicylate toxicity. Hyperventilation can also be stimulated by pulmonary receptors in patients with primary pulmonary disorders such as pneumonia, pulmonary edema, or pulmonary embolism. Chronic respiratory alkalosis may be seen in pregnancy, hyperthyroidism, and liver failure.

Severe alkalemia is uncommon in patients with respiratory alkalosis; however, this acid-base derangement should alert the clinician to search for an underlying disorder. In patients who are mechanically ventilated, changes in respiratory rate, tidal volume, or pain/sedation regimen can correct alkalosis that develops from hyperventilation.

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Catheter Sepsis in the Intensive Care Unit

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Central venous catheters (CVCs) have become one of the most essential tools for caring for critically ill patients. Despite their utility, use of CVCs is not without risk. One of the most common, and expensive, complications of CVC use is development of central line–associated bloodstream infection (CLABSI). According to estimates by the Centers for Disease Control and Prevention (CDC) in 2009, there were 18,000 CLABSIs in hospitals across the United States. These infections are considered the costliest healthcare acquired infection (HAI) with an estimated per infection cost of $45,000 due to increased length of stay, additional critical care needs, and prolonged expensive antibiotic treatment. CLABSIs can also be deadly and are associated with a mortality of up to 15%. Because of the significant impact on patients, and the reasoning that most CLABSIs can be prevented, the CDC deemed CLABSI a "never event" in 2008 eliminating reimbursement. This incentivized the healthcare industry to aggressively develop and institute preventative measures, which resulted in significant reductions in the incidence of CLABSI across the United States, effectively saving thousands of lives.

As part of these efforts, the CDC has outlined standardized definitions for infections involving CVCs. A CLABSI is most often used for surveillance. It is a clinical diagnosis requiring laboratory confirmation of a bloodstream infection arising in a patient with a CVC in place for at least 48 hours before the onset of infection and is not caused by an infection at another site. Catheter related bloodstream infection (CRBSI), however, requires a culture positive catheter tip or a differential time to positivity of blood cultures that identify the catheter as the source of the infection, ruling out other sources of the bacteremia/fungemia (Table 1). Evidence based clinical practice guidelines, published in 2009 and 2011 by the Infectious Disease Society of America (IDSA), concisely outline the prevention, diagnosis, and management of catheter related infections and provide the framework for this discussion.

DIAGNOSIS

Index of Suspicion

The presence of CLABSI should be considered in patients with CVCs in place who exhibit derangements in temperature, either fever or hypothermia, without other apparent cause. Manifestations of systemic signs of infection such as hypotension, tachycardia, tachypnea, evidence of decreased perfusion, or altered mental status should raise the index of suspicion for sepsis or septic shock and prompt treatment should follow standard guidelines.

Investigation

When a patient is suspected of having a bloodstream infection, the catheter site should be examined for erythema, discharge, pain, and catheter integrity. Blood cultures should be collected followed by prompt administration of empiric antibiotic treatment. Two blood samples are drawn from a peripheral vein, preferably by a phlebotomy team, as this has been shown to reduce contamination of the culture and reduce the rate of obtaining false positive results. If peripheral samples cannot be obtained, samples may be obtained from the catheter, preferably one set from each lumen. However, it should be noted that contamination of blood cultures taken from catheters are common. Ideally, cultures are sent prior to infusion of antimicrobial therapy, but should not delay antibiotic administration, particularly in the setting of sepsis and septic shock as delay significantly increases morbidity and mortality. If the suspicion for CRBSI is high, removal of the CVC is advised as soon as safe to do so and the tip should be sent for culture. It should also be noted that random culturing and/or surveillance of patients not suspected of having a bloodstream infection is not recommended. Contamination of the blood culture by normal skin flora can lead to excessive false positive results and inappropriate treatment, placing the patient at risk for complications and adding undue cost and length of stay (Fig. 1).

Diagnosis

Definitive diagnosis of CRBSI can be determined in two ways. The first requires that the same organism grow from at least one peripheral blood culture and from the tip of the CVC. Alternatively, one sample from a peripheral vein and one obtained from a catheter hub can meet CRBSI criteria by quantitative blood cultures or differential time to positivity (DTP) blood sample analysis. Quantitative blood cultures are considered the most accurate method. If the colony counts sampled from the catheter are three orders of magnitude greater than those sampled from the periphery with the same organism, the findings are considered diagnostic for CRBSI. DTP blood sample analysis is performed by continuously monitoring blood culture samples for microbial growth. A greater inoculum of bacteria will require a shorter incubation period. When microbial growth in a catheter sample is identified greater than 2 hours before growth is identified in the peripheral samples the source of the infection is considered the catheter and is consistent with diagnosis of a CRBSI. The DTP method has shown similar accuracy when compared to quantitative blood cultures in the critical care population. An approach to diagnosing CVC infections is located in (Fig. 1).

INFECTION PREVENTION

Insertion and Maintenance Bundles

There are four mechanisms by which CVC can become infected and cause a CLABSI: skin colonization, intraluminal or hub contamination, secondary hematogenous seeding from a bloodstream infection, and contamination of infusate (Fig. 2). Over the last 15 years, utilization of evidence based catheter care bundles has reduced rates of CLABSI by more than 70%. The bases of these bundles are rooted in the recommendations from the Joint Commission and IDSA clinical practice guidelines and includes healthcare personnel education and knowledge assessments regarding the proper procedures for insertion and maintenance of CVCs. These bundles can be broken into two major categories, those interventions associated with the insertion of new catheters and those associated with the maintenance of existing lines. Recent recommendations in the literature advocate for inclusion of additional practices or materials, use of commercially prepared insertion kits, and limiting the number of overall attempts at a particular access site to be added to the bundles (Tables 2 and 3).

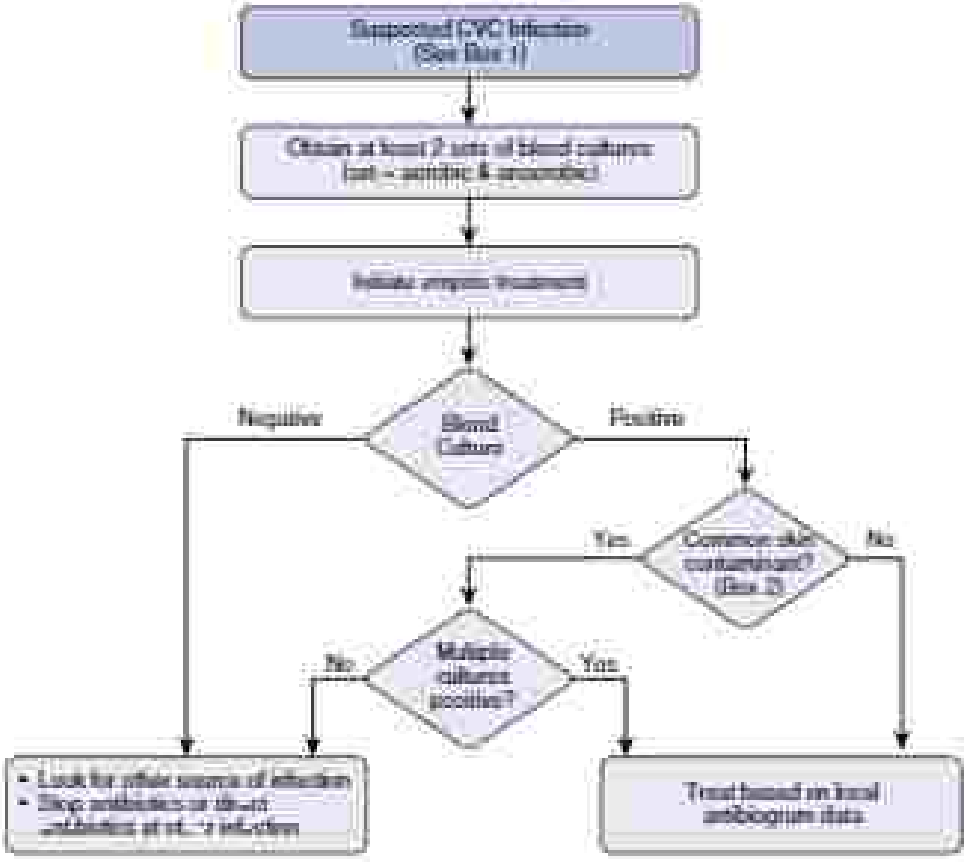
Patient Preparation

As with every patient encounter, proper hand hygiene practices should be employed immediately before and after patient contact. Use of full barrier precautions, including sterile gowns, gloves, and full patient sterile draping. Always wear eye protection, hat, and mask to protect from splashes. The Joint Commission also recommends using a 2% chlorhexidine gluconate in 70% isopropyl alcohol solution to prep the skin, allowing it to dry for at least 30 seconds. If the patient is sensitive and/or allergic to chlorhexidine, povidone iodine prep is the alternate prep of choice. Maintain aseptic sterile technique throughout the procedure. Using checklists and performing a

TABLE 1 Definitions of CLABSI and CRBSI

Central line–associated bloodstream infection (CLABSI)	Laboratory-confirmed bloodstream infection that arises in a patient with a CVC that was in use within 48 hours before the onset of bloodstream infection
Catheter-related bloodstream infection (CRBSI)	Clinical signs of sepsis and positive peripheral blood culture in the absence of an alternate source other than CVC with one of the following: Positive semiquantitative (>15 CFU) or quantitative (>10^3 CFU) culture from a catheter segment with the same organisms isolated peripherally Simultaneous quantitative blood cultures with a ratio of ≥3:1 (CVC vs peripheral) Time to culture positivity difference >2 hours between CVC cultures and peripheral cultures

CFU, Colony-forming units; CVC, central venous catheter.
Modified from the Centers for Disease Control and Prevention: https://www.cdc.gov/hai/bsi/bsi.html.



Box 1: Clinical features increasing suspicion for central catheter infection

Any one of the following, in the absence of signs/symptoms of another source of infection:
- Fever (high) / hypothermia
  - Children > adult: >38.3°C (101°F)
  - Infants < 3 months: >38°C (100.4°F)
- [illegible]
- Tachycardia
- Hypotension
- Altered perfusion (capillary refill >2 seconds)
- Vasoactive support
- Altered mental status
- Chills
- Erythema, tenderness, or purulent discharge at/near the central line site
- CVC malfunction with another source of infection as above

Box 2: Common skin contaminants*

- Aerococcus species
- Bacillus species
- Coagulase-negative staphylococci
- Cutibacterium
- Enterococcus species
- Propionibacterium
- Viridans group streptococci

*A single positive culture can be a true pathogen in cases in which [illegible]

FIG. 1 Approach to diagnosis of central venous (CVC) catheter infections.

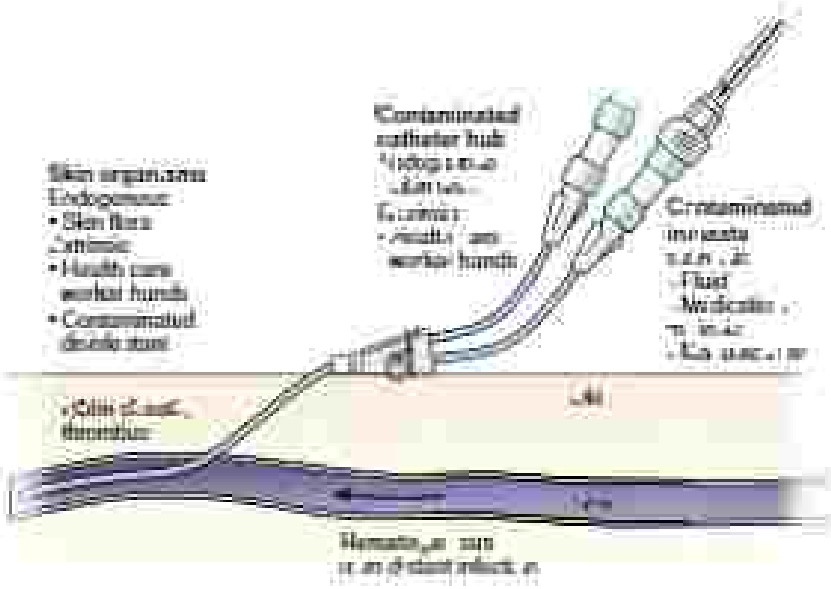


FIGURE [illegible]

TABLE 2 Central Venous Catheter Insertion Bundle

Insertion Bundle Elements	Recommendations
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

[illegible]
[illegible]

TABLE 3 Central Venous Catheter (CVC) Maintenance Bundle

Maintenance Bundle Elements	Recommendations
Daily review of line necessity	Remove unnecessary CVCs promptly
Require accurate documentation	Document CVC location, date of insertion, indwelling duration, date of removal, and any associated complications
Hand hygiene	Perform proper hand hygiene immediately before and after manipulation of the IV system
Catheter injection ports	Cover open lumens (such as catheter hubs, stopcocks, or injection ports) with sterile end caps or needleless connectors Caps should not be changed more frequently than every 72 hours
Maintain catheter site dressing	Change gauze dressing every 2 days, clear dressings every 7 days (and more frequently if soiled, damp, or loose)
Catheter access manipulation	Use aseptic technique for all line access episodes
IV infusion set maintenance	Adhere to institutional evidence-based best practice guidelines
Infusate preparation	Use aseptic technique in preparation and transportation of infusate according to institutional standards
Infusate administration	Prioritize infusions requiring central venous access Minimize use of CVC for infusions not requiring central venous access when possible
Educate personnel	Standardize and mandate routine hands-on and competency-based education for all practitioners involved with CVC placement and maintenance

CVC, central venous catheter; IV, intravenous.
Modified from [illegible] [illegible]

tions set can help to reduce errors and ensure adherence to your local hospital CVC placement guidelines.

Catheter Selection

The more lumens a catheter has and the longer it is in place, the more likely it is going to get infected. Selecting a catheter with the minimum number of lumens required to fulfill its purpose can reduce the infectious risk. If a catheter is not needed, removal is the best way to prevent infection. In situations where a line is expected to be needed for a prolonged duration, use of antimicrobial impregnated catheters can reduce the risk of infection. Antimicrobial impregnated catheters have been extensively studied, and results of these studies to administrators, but do indicate benefits for patients whose catheter is expected to remain in place for more than 7 days. A meta-analysis of chlorhexidine silver sulfadiazine or minocycline rifampin impregnated catheters demonstrated a reduction in the absolute risk of CLABSI and CVC infections, but failed to demonstrate improvement in clinically diagnosed sepsis or mortality.

Peripherally Inserted Central Catheters

Placement of peripherally inserted central catheter (PICC) lines in the neonatal care unit (NICU) has been an ongoing topic of debate. Currently, PICC lines are widely used for patients requiring intermediate and long-term access in outpatient and inpatient settings. Use of these lines in outpatient and not critically ill patients has shown exceptionally low infection rate profile approximately 0.4 infections per 1000 catheter days. Prospective studies have shown, however, that PICC lines used in high-risk hospitalized patients have a comparable rate of CLABSI similar when compared to conventional CVCs (approximately 2 to 5 infections per 1000 catheter days). There have been few [illegible] reporting PICC lines to CVCs associated complications with PICC lines compared to CVCs include high rates of line thrombosis, more challenging blood draws, and increased rate of deep venous thrombosis. It is imperative to utilize PICC lines with caution in patients with renal failure. Preservation of upper extremity veins is required for potential future arteriovenous fistula or arteriovenous graft creation. Salt-laden steroids is also concerning long-term complication in renal failure patients as it can interfere with the creation, function, and durability of arteriovenous fistula.

Indwelling Port and Tunneled Lines

Insertion of indwelling subcutaneous infusion ports and tunneled hemodialysis lines in acutely ill patients is generally avoided, as is accessing ports and tunneled lines already in place at the time of admission. There is an increased risk of CLABSI with repeated use and often patient's acuity is prohibitive for placement, or replacement, of these more invasive lines. If no other suitable intravenous (IV) access is available in an emergent setting, use of indwelling ports and tunneled lines may be required and can be lifesaving. Securing another venous access site should be prioritized according to the patient's condition. The indwelling port/tunneled line should only be used until another infusion access site is secured.

Insertion Site Selection

Several considerations should be kept in mind when selecting a CVC insertion site. Patient condition, practitioner experience, equipment availability, insertion technique, plan for catheter use, intended duration, and infection risk should be weighed. Additional patient factors such as bleeding risk and ability to tolerate complications of line placement must also be considered. Recent studies have demonstrated that the subclavian vein catheterization is associated with the lowest risk of CLABSI (0.9%) compared with femoral (4.7%) or internal jugular (1.9%) catheterization. The authors postulated potential explanations for this observation include a longer subcutaneous course before vein entry, the area with lowest bacterial line burden, and the location with the least dressing disruptions. Conversely, immediate mechanical complication of a pneumothorax is greatest with subclavian vein catheterization, as is the risk of subclavian vein stenosis. The subclavian vein should be avoided if possible in patients with advanced kidney disease and/or who will require long-term hemodialysis as subclavian vein stenosis can interfere with function, ing and durability of upper extremity arteriovenous dialysis fistula.

Dressings

Scheduled maintenance of catheter dressings has reduced the rate of CLABSIs. Several commercially available dressings impregnated with chlorhexidine gluconate are available, and meta-analysis have shown moderate evidence of reduction in both frequency of CRBSI and reduce catheter tip colonization compared with standard dressings. Additionally, the frequency of dressing changes has been shown to affect the rate of infection. The data now supports changing unruffled adherent dressings every 7 days with immediate change of any soiled or leaking dressings.

Catheter Access/Manipulation

Use of CVCs for intermittent intravenous medication administration creates the opportunity for translocation of bacteria. The data are clear that when lines are accessed, proper hand hygiene should be performed before manipulation of the IV system. The connectors should also be scrubbed with disinfecting solutions. Less clear is the precise technique, local duration of scrubbing, and optimal type of disinfectant solutions employed to minimize infection rates.

Intravenous Infusion Tubing Sets

Special consideration should be given to replacing sets immediately after administration of blood products and within 4 hours following administration of infusates that enhance microbial growth, such as fat emulsions and parenteral nutrition.

Connector caps

Open lumens (catheter hubs or stopcocks) should be kept covered when not in use by injection ports, sterile end caps, or needleless connectors. Recently engineered caps impregnated with disinfectant solutions designed to remain on the IV connector in between episodic and require scrubbing before initiation of infusion, administration of medications, or blood draws. This new technology has been studied in a variety of settings from the ICU to oncology units.

Retrospective data indicated that disinfection caps significantly reduce the CLABSI rates from 1.6 infections per 1000 catheter days to 0.6 per 1000 catheter days. Large investigation and prospective studies need to be done in order to ascertain clearer guidelines.

Antimicrobial Locks

The practice of instilling antimicrobial solution in catheters between line uses, to be removed just before the next time the line is used, is commonly termed an antimicrobial "lock." This strategy is often recommended in the outpatient and oncology settings to reduce the incidence of line infections, but this strategy has not been well studied in the acute inpatient setting. Close adherence to line manufacturer inserts is imperative as not all catheters are compatible with the commonly used antimicrobial solutions. Some catheters may degrade with the use of certain types of agents causing erosion, brittleness, and breakage. Additionally, not all catheters have been tested for compatibility with available antimicrobial solutions.

Routine Replacement

Catheter infection risk is directly related to the indwelling duration, and the daily infection rate is considered a constant. Studies have examined the historical practice of routine replacement of central lines. Although the practice was able to decrease the number of infections per any individual catheter, routine CVC changes did not reduce number of infections per catheter day or reduce patient risk. Therefore, routine replacement of CVCs to prevent CLABSI is not supported in the literature and is not recommended.

Sample CVC Insertion Checklist

Patient's Name: _____

Medical Record Number: _____

Date of Insertion: _____

Site of insertion:
☐ Right ☐ Left ☐ IJ ☐ Subclavian ☐ Femoral

Pre-Procedure time out
☐ [illegible]
☐ [illegible]
☐ [illegible]

Pre[illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]

[illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]

[illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]
☐ [illegible]

FIG. 3 Sample central venous catheter insertion checklist. CVC, Central venous catheter; IJ, internal jugular; [illegible]

Process Standardization

Reducing variability in practice can help reduce human error. The Joint Commission recommends insertion bundles include ongoing education about CLABSI prevention, creation of CVC carts that contain all necessary supplies, with checklists to improve adherence to evidence-based practices. Hands-on training of personnel is usually considered most effective. Retention is enhanced when follow-up education is provided at regular intervals. Bedside personnel should be empowered to stop nonemergent procedures when the bundles are not being followed. Proper documentation, including date and name provider performing the procedure, and catheter tip number is recommended. Providing feedback on CLABSI and CRBSI rates can be useful in investigating the cause of negative trends, which can help educate personnel how to and improve adherence to evidence-based guidelines to create and maintain a culture of infection prevention. (An example of an insertion checklist is provided in Fig. 3.)

Preventative Removal

The best way to prevent CLABSIs/CRBSIs is to not have a CVC in place. Daily review for the ability to remove the CVC should be performed and prompt removal of CVC should be done when appropriate. Safe removal practices must be followed to prevent introduction of air emboli and excessive bleeding. Details of removal should be

documented in the medical record including the date, location of the CVC, and identification of the provider.

MANAGEMENT

Antimicrobial Selection

Several professional organizations and institutions have published on management strategies of CRBSI. The most common CRBSIs are caused by *Staphylococcus aureus*, coagulase negative staphylococci, Enterococcus, gram negative bacilli, and *Candida*. Empiric antibiotic treatment regimens should be prescribed based on local antibiograms, with consideration of specific patient factors, such as immunosuppression and ability to remove and/or replace the line. Antimicrobial therapy should be tailored to the organism once culture results are obtained. For complicated or unique situations, such as multidrug resistant organisms or inability to remove CVC access, providers may require alterations to selection and duration of antimicrobials.

Central venous Catheter removal versus Line Salvage

Ideally, all short-term catheters should be removed from patients with CRBSI, if possible. The IDSA guidelines also recommend removal of long-term indwelling catheters and ports from patients with severe sepsis, suppurative thrombophlebitis, or endocarditis secondary to CRBSI. CRBSIs with *S. aureus*, *Candida* sp, pregnant, lung, or myelodysplastic are particularly challenging to treat and usually necessitate the removal of indwelling catheters. There are some cases, however, where line salvage may be attempted. In these cases, antibiotic lock therapy should be used for catheter salvage. If this is not an available modality of treatment, then the systemic antibiotics should be administered through the colonized catheter. If catheter salvage is attempted, surveillance cultures should be taken every 24 hours until negative. If the bloodstream infection persists despite 72 hours of antimicrobial therapy to which the infecting microbes are susceptible, then the CVC should be removed.

SUMMARY

Bloodstream infections from CVCs remain a costly problem with significant morbidity and mortality. Aggressive preventative measures have greatly reduced the incidence of CLABSIs/CRBSIs, yet they persist to be a common clinical problem in the ICU environment. Prevention remains the most critical intervention. Early diagnosis, catheter removal, and timely initiation of appropriate antimicrobial agent tailored to culture results and local antibiograms are the foundation for management.

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SEPTIC RESPONSE AND MANAGEMENT

Charles A. Adams ..., M... ...an... ...ole, ... C... ...S, FCCM

Sepsis, a serious, life-threatening condition affecting nearly every organ system in the body, is due to dysregulation of the host's immune inflammatory response to infection. Each year 1.7 million Americans develop sepsis, resulting in nearly 270,000 deaths, one-third of all hospital deaths are due to sepsis. Clearly, sepsis is a public health problem that consumes significant healthcare expenditures in addition to lives. The Surviving Sepsis Campaign, an international effort to raise awareness of the problem and promote evidence-based therapies in a "sepsis bundle" has done a great deal to focus attention and resources on the condition. It is somewhat ironic that the larger medical community has finally embraced many of the basic tenets of managing this condition that surgeons have been practicing for nearly a century.

ABCDE PRINCIPLES

The basic principles of treating sepsis center on its early recognition, eradication of the origin of sepsis, restoration of an effective circulating volume and timely administration of appropriate antibiotics. One of the greatest challenges of treating sepsis is identifying the septic patient, thus it is imperative that clinicians maintain a high index of suspicion that a deteriorating patient may be exhibiting early signs of sepsis. A detailed and thorough history and physical examination should be undertaken to identify a point of infection. Laboratory assessments and radiologic imaging studies can narrow the differential and home in on the correct diagnosis. If an infected focus is identified, concerted efforts to contain or eradicate it should ensue. The act of eliminating the cause of sepsis is termed "source control" and surgeons have been performing this activity for centuries. The inability to obtain source control prolongs the course of sepsis and generally portends a worse outcome than those patients in whom prompt source control is achieved. Studies looking at the effect of source control on sepsis related mortality have found that it is more important than compliance with all other components of the sepsis bundle establishing its prime importance in the management of sepsis.

SOURCE CONTROL

Source control has many components and may include the excision or removal of infected tissue, organs, or foreign bodies. The simplest examples of source control include removal of infected intravenous or urinary catheters. Other implanted devices such as orthopedic hardware or prosthetic meshes are not as easily removed but extensive surgery to remove these devices is often required in cases of severe or life-threatening sepsis. Infected organs that are amenable to surgical extirpation such as the gallbladder, appendix, or sigmoid colon should be removed if they are the *de* cause sepsis. Abscesses should be drained, whereas those in the pleural or peritoneal spaces are

documented in the medical record including the date, location of the CVC, and identification of the provider.

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SEPTIC RESPONSE AND MANAGEMENT

Charles A. Adams Jr, MD, and William G. Cioffi, MD

Sepsis, a serious, life-threatening condition affecting nearly every organ system in the body, is due to dysregulation of the host's immune inflammatory response to infection. Each year, 1.7 million Americans develop sepsis, resulting in nearly 270,000 deaths; one-third of all hospital deaths are due to sepsis. Clearly, sepsis is a public health problem that consumes significant healthcare expenditures in addition to lives. The Surviving Sepsis Campaign, an international effort to raise awareness of the problem and promote evidence-based therapies in a "sepsis bundle" has done a great deal to focus attention and resources on this condition. It is somewhat ironic that the larger medical community has finally embraced many of the basic tenets of managing this condition that surgeons have been practicing for nearly a century.

BASIC PRINCIPLES

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SOURCE CONTROL

Source control has many components and may include the excision or removal of infected tissue, organs, or foreign bodies. The simplest examples of source control include removal of infected intravenous or urinary catheters. Other implanted devices such as orthopedic hardware or prosthetic meshes are not so easily removed but extensive surgery to remove these devices is often required in cases of severe or life-threatening sepsis. Infected organs that are amenable to surgical extirpation such as the gallbladder, appendix, or sigmoid colon should be removed if they are the *de* cause sepsis. Abscesses should be drained, whereas those in the pleural or peritoneal spaces are

BOX 1 Red Flag Signs and Symptoms of Necrotizing Soft Tissue Infections

- Hypotension
- Altered mental status
- Pain out of proportion to physical examination
- Rapidly progressing erythema
- Dusky skin color
- Hyperthermia or hypothermia
- Bullae
- Skin necrosis
- Cutaneous anesthesia
- Tachycardia

[illegible] Clin Infect Dis. 2007;45:63–68.

often drained percutaneously. Organ space infections, such as liver abscesses, can be percutaneously drained but it may not be desirable to approach all abscesses in this fashion. Lung abscess are best drained through internal bronchoscopic efforts rather than percutaneous methods to avoid bronchopleural fistulae.

When achieving source control, it is paradoxical that the sicker the patient is, the more aggressive and definitive the attempts at source control must be. Soft tissue infections such as necrotizing fasciitis or necrotizing cellulitis need to be debrided such that all infected and compromised tissue is removed (Box 1). This often requires removal of some healthy uninfected tissue just beyond the area of obvious infection to completely contain the infection, akin to how firefighters contain brush fires. Tentative or limited resection typically allow these infections to continue to spread through adjacent tissue and ultimately results in greater tissue loss than would have occurred had the initial operation been definitive. Inadequate debridement that fails to achieve source control is associated with worse outcomes. In extreme cases in which the soft tissue infection extends into the muscle compartment causing myonecrosis, amputation of infected limbs may be necessary. Similarly, patients in septic shock resulting from *Clostridium difficile* infections require a total abdominal colectomy because limited resections, which fail to achieve source control, frequently result in the patient's demise. A long rectal stump following colectomy may perpetuate sepsis and should be avoided. Vancomycin enemas are a helpful adjunct in very severe cases of *C. difficile* even after surgery. Interestingly, infections where definitive source control cannot be achieved, such as ventilator associated pneumonia or meningitis, usually exhibit a more protracted and prolonged course of sepsis and are often associated with further complications. The benefit of prompt source control cannot be overstated, a recent study revealed that in patients with peritonitis and septic shock, time to operation was an independent predictor of mortality.

DIAGNOSIS

The diagnosis of sepsis can be exceedingly difficult if the source of sepsis is not readily apparent. Various scoring system and clinical decision tools have been proposed to aid in the diagnosis of sepsis however no gold standard exists. The systemic inflammatory response syndrome (SIRS) was initially proposed as an early marker of a patient manifesting septic physiology (Table 1). The concept was that there was an orderly progression from SIRS to severe sepsis to septic shock; however, this continuum has been disproven. In fact, most intensive care unit (ICU) patients meet SIRS criteria on unit admission and many ward patients exhibit two or three criteria at some point during their hospital stay as well, indicating that SIRS criteria are overly sensitive but not very specific for diagnosing sepsis. Although SIRS has fallen out of favor as an indicator of sepsis because most believe it is overly sensitive, a very large retrospective study showed that up to 12% of septic patients had less than two SIRS criteria. This study illustrates the limited ability of SIRS criteria to diagnose sepsis as well as the tremendous genetic variability of response to systemic infections.

TABLE 1 Systemic Inflammatory Response Syndrome Criteria

Temperature	<36°C or >38°C
Heart rate	>90 beats/min
Respiratory rate	>20 breaths/min or partial pressure of carbon dioxide <32 mm Hg
White blood cell	>12,000 cells/mm^3 <4000 cells/mm^3, >10% bands

Two or more need to be present for diagnosis; presence of SIRS in infection may require sepsis.

From [illegible] Bell RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–1655.

BOX 2 Six Parameters Composing the National Early Warning System for Sepsis

- Respiratory rate
- Oxygen saturation
- Temperature
- Systolic blood pressure
- Pulse rate
- Level of consciousness/confusion

From Kyriacos RM, Mitchell R, et al. Clinical early warning scores in emergency department triage may allow earlier identification of patients with severe sepsis and septic shock: a retrospective observational study. Emerg Med J. 2014; 31:55–61.

The Third International Consensus Definitions for Sepsis and Septic Shock (aka Sepsis 3) proposed the quick Sequential Sepsis related Organ Failure Assessment (qSOFA) as a rapid and simple bedside tool to help diagnose sepsis. The components of this score comprise hypotension, tachypnea, and altered mental status; derangements in any two of the three should prompt consideration of sepsis. Criticisms of the qSOFA stem from the fact that the patient must manifest end organ damage before the tool suggests the diagnosis of sepsis, thus, the sensitivity of qSOFA may be too low and overreliance on this instrument may expose patients to increased mortality due to delays in diagnosis and treatment. Novel early warning scores for sepsis such as the National Early Warning Score or Modified Early Warning Score consider six clinical parameters that aim to identify patients at risk for deterioration; however, these scores have not yet been validated (Box 2). It is likely that no scoring system, combination of biomarkers, or other clinical decision tool will emerge as the benchmark for diagnosing sepsis because of genetic heterogeneity and the variability of individual manifestations of whole body immune inflammatory activation.

The importance of a detailed and thorough history and physical when encountering a patient who may be septic cannot be overstated, but this process may be adversely affected by sepsis itself. Of all the organ systems impacted by sepsis none is more important than the central nervous system (CNS). The sensitivity of the CNS to dysfunction in sepsis is why nearly every sepsis diagnostic tool or scoring system considers alterations in sensorium or level of consciousness as one of the indicators of sepsis. Septic encephalopathy, a global CNS dysfunction in response to systemic infection, is a common manifestation with an incidence between 30% and 70%. The etiology of this

dysfunction is not well elucidated, but it is thought to be due to the body's inflammatory response to systemic infection. ...ghere there are localizing signs, imaging studies are exceedingly low yield and are not routinely indicated in workup septic encephalopathy. Previously, septic encephalopathy was thought to be transient and reversible; however, emerging data suggest that there may be lifelong neurocognitive deficits in survivors of sepsis. This long-term prolonged CNS dysfunction is one of the central features of postintensive care syndrome (PICS). It appears that PICS may be more common following ICU discharge for sepsis compared with poly trauma or other causes of critical illness. There are no therapies or interventions to treat septic encephalopathy other than supportive care, so its prevention through the timely diagnosis and treatment of sepsis is the best option. Similarly, efforts to avoid ICU delirium appear to be the best intervention to prevent PICS. The interplay between delirium and encephalopathy is complex and not well understood but both likely contribute to PICS. A bundle of ICU based efforts known as the ABCDEF (Assess and treat pain, awakening and spontaneous breathing trials, Choice of drugs, Delirium assessment, Early mobility, and Family engagement) bundle appears to be a very effective strategy to prevent delirium and PICS and decrease overall ICU mortality (Table 2).

As with the CNS, the heart is also sensitive to dysfunction in sepsis, particularly in cases of septic shock. The initial response of the cardiovascular system to systemic infection is to increase cardiac output through tachycardia. This typically results in a hyperdynamic state but as the sepsis progresses, 20% to 50% of patients will manifest sepsis related myocardial dysfunction. Circulating cytokines and other inflammatory mediators promote capillary leak and loss of intravascular fluid into the interstitium, sometimes referred to as the third space. Myocardial dysfunction is compounded by the loss of preload and cardiac output falls due to decreased stroke volume. One of the mainstays of therapy for septic patients is the administration of intravenous crystalloid to restore an effective circulating volume. Nearly two decades ago, a landmark trial showed that aggressive fluid administration to achieve predetermined endpoints of resuscitation within 6 hours in patients with severe sepsis or septic shock yielded lower mortality than standard therapy.

The results of this breakthrough study have had far reaching effects on the management of septic patients and have rendered the resuscitation of septic patients more uniform. Subsequent prospective trials have failed to show a benefit of additional intravenous fluid resuscitation following an effective resuscitation. The interpretation of this finding should not be that fluid administration is not beneficial in sepsis, as previously shown, but rather that the standard of care in managing septic shock now universally includes early and aggressive fluid resuscitation and that supra physiologic resuscitation is not helpful. Three decades ago, a similar finding was observed when surgical patients who were resuscitated and exhibited supra normal parameters had better outcomes compared with those with standard parameters. The survival benefit of supra normal resuscitation was lost when compared with surgical patients who were adequately resuscitated before randomization to an indicated supra physiologic group. Considering these two seminal papers, the goals of resuscitation in septic patients ought to be to administer enough fluid to restore tissue and organ perfusion, while avoiding overresuscitation.

FLUID RESUSCITATION

The definition of adequate fluid resuscitation has always been controversial and despite a myriad of surrogate endpoints, there is no ideal marker or endpoint of resuscitation in sepsis. It is important that clinicians remember this because overreliance on any one single sign is likely to lead to more adverse outcomes than good. Central venous pressure (CVP) has had varying degrees of popularity over the years as a marker of resuscitation. Early sepsis guidelines suggested that patients be resuscitated to a CVP of 8 to 12 mm Hg; however, CVP does not correlate with responsiveness to fluid administration. CVP has limited ability to estimate cardiac preload or left ventricular end diastolic pressure but may help in differentiating certain types of shock states; a high CVP is observed in cardiogenic shock, whereas a low CVP is observed in hypovolemic shock. It must be remembered that CVP is not precise enough to fine tune the amount of fluid to administer to a septic patient. Similarly, elevated lactic acid is found as both an indicator of sepsis and lactate clearance is proposed to be a marker of adequate fluid administration. The kinetics of lactic acid metabolism are variable based on patient genetics, muscle mass, and microcirculation and may be dramatically affected by certain medications. Overreliance on lactic acid determination is likely to result in excess fluid administration, particularly if the lactic acid is due to other causes besides anaerobic tissue metabolism as is seen in so called type B lactic acidosis. Lactate clearance has been extensively studied in sepsis and the preponderance of data suggests that those patients who clear their lactic acidosis will have lower mortality than those who do not clear there is some utility in trending this parameter.

Although sepsis guidelines do not include any recommendations for pulmonary artery catheter (PAC) use in the management of septic patients, it still has an important role in care of the septic patient. The PAC measures cardiac output, systemic and pulmonary vascular resistance, and mixed venous oxygen saturation and facilitates calculation of oxygen delivery and consumption. Of all the measurements and parameters that can be determined from PAC, none is more useful that the mixed venous saturation (S_vO_2). $S-O_2$, the oxygen saturation of the sum of all the venous return to the body, is a global indicator of oxygen delivery and consumption. If the S_vO_2 is above 60%, it can be assumed that all vascular beds are receiving adequate oxygen (and blood flow) but, as with all measurements, there are pitfalls to relying on a single number. S_vO_2 is susceptible to sampling errors and may be falsely elevated in some medical conditions where an arteriovenous shunt exists, such as portal hypertension or in those patients with a hemodialysis fistula. In addition to the morbidity of central access and the catheter itself, PAC use is associated with higher complications, thus its routine use in sepsis is not recommended. Rather

TABLE 2 ICU Liberation: ABCDEF Bundle

Symptoms: Pain, Agitation, Delirium Guidelines	Monitoring Tools	Core ABCDEF Bundle
Pain	Critical Care Pain Observation Tool Numeric Rating Scale Behavioral Pain Scale	A: Assess, prevent, and manage pain B: Both spontaneous awakening trials (SAT) and spontaneous breathing trials C: Choice of analgesia and sedation D: Delirium: assess, prevent, and manage E: Early mobility and exercise F: Family engagement and empowerment
Agitation	Richmond Agitation Sedation Scale Sedation Agitation Scale (SAS)	
Delirium	Confusion Assessment Method for the Intensive Care Unit Intensive Care Delirium Screening Checklist	

Modified from Ely EW. Tear down the ICU bundle: science and philosophy of how ICU liberation saves patients and staffers. Crit Care Med. 2017;45(12):321–330.

iterations of the sepsis guidelines recommended monitoring of the mixed venous saturation of blood obtained from the superior vena cava ($ScvO_2$) to guide resuscitation of the septic patient. Although some of the morbidity of having a catheter residing inside the patient's heart was avoided, $ScvO_2$ monitoring is associated with many of the same pitfalls that were seen with SvO_2 monitoring. SvO_2 or $ScvO_2$, if available, can aid in the decision to transfuse a septic patient, especially in cases where cardiac output is fixed however restrictive transfusion practices are generally safe in septic patients. A transfusion "trigger" of 7 mg/dL is reasonable.

Systolic cardiac failure is less common in sepsis than diastolic dysfunction but to extreme cases, the heart will manifest both forms of cardiac failure. This biventricular type of infection induced cardiac failure is termed septic cardiomyopathy. Patients with septic cardiomyopathy typically exhibit severely diminished cardiac contractility and a low cardiac output. This type of cardiac failure does not respond to additional fluid administration; these patients require inotropic support to boost their cardiac output. This population typically requires a PAC to guide management. Dobutamine is the most commonly used agent to increase cardiac contractility but it can worsen hypotension via its vasodilatory effect on certain vascular beds. Epinephrine, a second line agent, can augment both cardiac output and blood pressure, but it is arrhythmogenic and can wreak havoc on glucose metabolism. The preferred vasoactive agent in septic shock is norepinephrine because it greatly increases vascular tone and blood pressure as well as increases cardiac output through its inotropic effects. Dopamine should not be used and is associated with higher mortality than norepinephrine in the treatment of septic cardiomyopathy. Patients with hypotension refractory to norepinephrine benefit from treatment with the nonadrenergic agent vasopressin, which increases vascular tone and blood pressure but has no effect on cardiac output or contractility. Interestingly, during a recent shortage of norepinephrine, sepsis mortality was noted to rise in large national databases when phenylephrine was substituted, thus this agent should not be used in the management of septic shock.

CURRENT RECOMMENDATIONS

Current recommendations are to administer 20 mL/kg of balanced crystalloid (e.g., lactated Ringer's) to septic patients exhibiting hypotension and/or increased serum lactate, over 3 hours, which is about 2 L of fluid for an average 70 kg patient. Classic biomarkers such as urinary output, heart rate, blood pressure, and skin perfusion should be continually assessed and monitored for responsiveness to fluid administration and can roughly guide resuscitation. There are conflicting data about the risks and benefits of colloids in the resuscitation of septic patients. Albumin is costly and does not have a mortality benefit or improved organ function when compared to crystalloid resuscitation. Allogenic hydroxyethyl starches, a relatively small molecule, and passes freely from the vasculature into the interstitium in septic patients. This fact is in direct opposition to the often cited dictum that albumin is a large molecule that tends to stay in blood vessels and as such is falsely believed to be a superior resuscitation fluid. The use of hydroxyethyl starches in septic patients is associate with the need for renal replacement therapy and should not be used in the resuscitation of septic patients.

Current sepsis guidelines have moved away from static measurements of serum lactate or global markers of perfusion and now consider fluid responsiveness in identifying those patients requiring further resuscitation. Passively raising a patient's legs 45 degrees by raising the lower half of the hospital bed such that the legs are above the heart is a simple bedside test that can guide fluid resuscitation. Patients who exhibit an increase in systolic blood pressure within 60 seconds of the maneuver are very likely to benefit from additional fluid administration; however, this test can be invalid if the patient has elevated intraabdominal pressures, ascites, etc. Mechanically ventilated patients exhibiting a varying baseline on their arterial tracing are likely intravascularly depleted. As the ventilator cycles, intrathoracic pressure rises, and cardiac preload falls with a resultant narrowing of the pulse pressure. Many bedside monitors are now able to detect and calculate this pulse pressure variation (PPV). Patients with a PPV of 12% or more will benefit from additional intravenous fluid while those with a PPV less than 8% are likely euvolemic. A PPV between 8% and 12% is indeterminate and cannot accurately guide fluid administration.

Bedside echocardiography performed by intensivists is rapidly becoming the modality of choice to help guide fluid resuscitation in septic and critically ill patients. As with PPV, variation in the diameter of the inferior or superior vena cavae during the respiratory cycle can identify those patients who are likely hypovolemic. Patients with small contracted cardiac ventricles require further fluid resuscitation and papillary appearance or "kissing ventricles" strongly indicates that the patient will be fluid responsive. Like PPV, stroke volume variation is another indicator that can guide resuscitation and patients with a stroke volume variation of 12% or more are very likely to be fluid responsive. Narrowing of the outflow tract during systole implies left ventricular underfilling and can also guide fluid management. It is best if several echocardiographic findings are considered and a global picture is constructed indicating the patient's volume status and likelihood of responding to additional fluid rather than fixating on any one single echocardiographic parameter. Although echocardiography is an excellent bedside tool to help guide the resuscitation of septic patients, it has not yet been validated as the gold standard to govern volume resuscitation to sepsis.

Cardiac System

The cardiac system is affected several ways to sepsis and it is not uncommon for a septic patient to manifest elevations to troponin in the bloodstream. Elaboration of troponin from the myocardium is a sign of inflammation rather than a marker of coronary atherosclerosis disease and the treatment of this damage should be to obtain timely source control, begin fluid resuscitation and antibiotic therapy. It is inappropriate to delay either the source control to focus on the troponin elevation and cardiology consultations introduce delays in definitive therapy. Even significant sepsis related cardiac failure will resolve in a few days if the basic directives of sepsis management are observed and long term cardiac dysfunction is not common. Troponin elevation during sepsis is a true biomarker of sepsis related injury and the degree of elevation appears to directly correlate with mortality in sepsis.

As with troponin elevations, atrial fibrillation (AF) is another common finding in sepsis. The most likely explanation for AF in septic patients is that it is due to the presence of multiple inflammatory mediators that makeup septic response. The incidence of AF rises as patients are treated with fluid and vasoactive substances to achieve higher mean arterial pressures (MAPs) rather than lower MAPs. Nearly one in five patients with sepsis will manifest AF and its incidence appears to be higher in those patients with preexisting cardiac comorbidities. Analogous to troponin leaks, the development of AF in sepsis portends a higher mortality. β blocker therapy in the treatment of sepsis related AF confers a survival benefit, but this does not appear to be the case with other rate or rhythm controlling agents such as calcium channel blockers or antidysrhythmics. Amiodarone is preferred over β blockers for AF in patients with a compromised or failing left ventricle. It is likely that some of β blocker's survival benefit is derived from widespread antiinflammatory protective effects and that the survival benefit is not solely derived from its effects on the cardiovascular system. Unlike nonsepsis related AF, anticoagulation to prevent stroke is associated with increased bleeding events. Although evidence to guide clinicians is limited, it appears that the increased bleeding complications of anticoagulation in sepsis outweighs it benefits, particularly in those patients with incisions, drainages, and other surgical interventions.

Lungs

Unlike the heart, the lungs are both a frequent home of sepsis, but as well as a target of the inflammatory products of sepsis. The initial

response of the pulmonary system to sepsis is to increase respiratory rate promoting a respiratory alkalosis to compensate for worsening metabolic acidosis. Ironically this increase in work of breathing contributes to metabolic acidosis as well because ischemic respiratory muscles elaborate lactic acid. Capillary leak and fluid resuscitation increase lung water and alveolar congestion, which hinders oxygen diffusion far more than that of carbon dioxide, resulting in hypoxemia. Respiratory collapse is common in sepsis so early intubation and mechanical ventilation should be done electively rather than in response to respiratory arrest. Bicarbonate causes adrenal vasoconstriction through a direct inhibition of one of the hydroxylases necessary for the creation of cortisol thus other induction agents such as midazolam or ketamine are preferred. Ventilator management should follow the lung protective strategy initially outlined by the Acute Respiratory Distress Syndrome (ARDS) Network consortium. Tidal volumes should be targeted at 6 mL/kg of ideal body weight and respiratory acidosis is tolerated if the patient's pH is 7.2 or greater. This ventilator strategy is termed lung protective or open lung ventilation and aims to minimize volutrauma in patients with ARDS and sepsis related respiratory failure. Similarly, positive end expiratory pressure (PEEP) should be increased to raise mean airway pressure and further limit stretching of the alveoli. The increase in mean airway pressure also improves oxygenation through opening of partially filled alveoli in a process termed recruitment. Inspired fractions of oxygen above 60% are associated with oxygen toxicity and further lung damage, so increased PEEP may also improve oxygenation while limiting toxicity. Lung recruitment improves as PEEP is increased but so do adverse hemodynamic effects, so ventilator management must be tailored to balance the optimization of these two criteria in septic patients. Hypovolemic patients are particularly sensitive to the negative hemodynamic effects of increased PEEP, so it is advisable to allow fluid resuscitation to occur before making significant increases in PEEP.

Patients with severe ARDS may benefit from several additional measures such as prone positioning, advanced ventilator modes, neuromuscular blockade and in severe cases, extra corporeal membrane oxygenation (ECMO). Prone positioning is labor intensive and exposes the patient to complications such as pressure ulcers, dislodgement of medical devices, and limits physical examination, but it can dramatically improve oxygenation in patients with refractory hypoxemia. Several studies have shown that prone positioning confers a mortality benefit when compared to supine ventilation in patients with life threatening ARDS. In extreme cases, patients may be placed into prone position even if they have an open abdomen, but it is prudent to reinforce the temporary abdominal dressing in these patients. Patients failing conventional ventilator management may benefit from advanced modes such as airway pressure release ventilation, jet ventilation, and inverse pressure control ventilation. Patients with profound ventilator dyssynchrony or poor pulmonary compliance with hypoxemia should be paralyzed with neuromuscular blockers (NMBs). NMBs have conferred a mortality benefit in patients with ARDS, but only if the degree of hypoxemia is severe and life threatening. NMB has an added benefit of maximizing oxygen delivery to the brain and vital organs, whereas oxygen consumption by skeletal muscle is minimized; however, NMB use is associated with ICU myopathies and muscle atrophy. ECMO is emerging as an effective rescue strategy for life threatening ARDS and many patient conditions that were formerly believed to be a contraindication to this modality have been disproven. ECMO can accomplish the gas exchange that failing lungs cannot as well as provide cardiovascular support while allowing the lungs to rest and recover from the toxic effects of high pressures, volumes, and required oxygenation.

Kidneys

Perhaps no organ system is more adversely affected in sepsis than are the kidneys since nearly half of septic patients will exhibit acute kidney injury (AKI). AKI increases septic mortality by six to eight times and leads to chronic kidney disease in survivors. Even minor AKI negatively affects survival in sepsis and can have lifelong adverse effects. Sepsis impairs renal perfusion at both the macroscopic and microscopic levels, and septic patients who are normotensive may still develop AKI. As with other organ systems, circulating toxins, oxidative products, cytokines, and other inflammatory mediators that are part of the septic milieu adversely affecting the renal system. The action of these circulating factors can be compounded by hypoperfusion of the kidney; thus, effective fluid resuscitation and management is critical to reducing sepsis-related AKI. The ideal MAP to reduce the occurrence of AKI has not been determined. As previously noted, lactated Ringer's is the preferred fluid because normal saline resuscitation yields higher rates of AKI. Again, the goal should be to restore an effective circulating volume without overresuscitating. - some fluid has detrimental effects on many organ systems, especially the lungs, and in the late stage of sepsis, positive fluid balance contributes to excess mortality. For patients who require renal replacement therapy, there is no clear cut directive governing the type or timing of this therapy despite a multitude of clinical trials. Continuous renal replacement therapy is the practical choice for patients unable to tolerate the negative hemodynamic effects of standard hemodialysis but there appears to be no benefit to early, preemptive continuous renal replacement therapy.

Liver, Pancreas

Unlike the kidneys, sepsis induced liver failure is a rare complication, and its appearance is typically a preterminal event. The liver is intimately involved in the body's response to sepsis and performs a whole host of critically important activities ranging from phagocytosis and clearance of bacteria from the bloodstream, production of countless crucial proteins, regulation of iron metabolism to modulation of the host's inflammatory response. Patients with preexisting liver dysfunction are particularly vulnerable to sepsis that is borne out by the fact that nearly one third of cirrhotic patients will require hospitalization for bacterial infections. Like the liver, outright pancreatic failure is a very uncommon finding in septic patients, however most septic patients will manifest some degree of pancreatic dysfunction. Elevations in serum amylase and lipase are common as are some disturbances in the exocrine function of the pancreas. Digestive insufficiency can adversely affect patient's nutritional status and can lead to malabsorption of fat soluble vitamins resulting in clinical deficiency syndromes, especially in long term ICU patients. Stools should be examined for signs of fat malabsorption and if suspected, replacement therapy with enteral pancreatic enzymes is an effective treatment. While pancreatic endocrine function is minimally affected by sepsis, dysregulation of glucose metabolism is exceedingly common.

The gut has been described as the "motor" of multiple system organ failure, highlighting its importance as both a cause of sepsis as well as a target for sepsis-induced failure. The bowel lymphoid tissue is the largest aggregate of immune cells in the human body and is necessary since the gut is home to more than 100 trillion bacteria known as the microbiome. Although previously thought to be innocuous, the microbiome is being implicated in a wide range of pathologic conditions and is a very active area of investigation. As with the lung, the gut may be the site of a septic focus as well as negatively affected by sepsis from a remote location resulting in an ileus. In the absence of an ileus, the gut ought to be used, several benefits of enteral over parenteral nutrition have been described. Critically ill patients can be tube fed into the stomach and the utility of checking gastric residuals has been disproven, but clinicians must remain vigilant for feeding intolerance. It remains controversial whether transpyloric feedings are safer than gastric feeding, but massive aspiration is far likely and postpyloric feeding is avoided with the transpyloric route. Vasopressors are a relative contraindication to enteral nutrition, however, the threshold for withholding feedings has not been established. In practical terms, patients with escalating requirements for vasopressor support or those requiring a second vasopressor or

lactate should not be enterally fed. Patients who are intolerant of enteral nutrition or in those that cannot have their needs met enterally ought to receive parenteral nutrition and prolonged periods of starvation must be avoided in critically ill patients.

Glucose Control

Like many other forms of organ dysregulation, sepsis induced hyperglycemia is both a marker of disease severity as well as a mediator of further injury. Cytokines, cortisol, catecholamines, and other inflammatory agents cause alterations in the hormonal control of insulin as well as engender a state of peripheral insulin resistance. Although there have been few studies specifically looking at glucose targets in sepsis, there have been several major clinical trials aiming to identify the optimal blood glucose level in critically ill patients. After many iterations, it appears that the ideal glucose value in ICU patients lies between 140 and 180 mg/dL, and the trigger for glucose management should commence at 180 mg/dL. Hyperglycemia is to be avoided because this has been shown several times to be an independent risk factor for death in critically ill patients. Patients with preexisting diabetes are at several fold increased risk of sepsis but surprisingly are not at increased risk for death when admitted to the ICU with sepsis, and those with poor premorbid glucose control have even lower death rates, yielding a "diabetes paradox." This contradiction only applies to ICU patients because diabetic patients admitted to other levels of care in the hospital have worse outcomes than those without diabetes.

One of the greatest controversies in the management of critically ill patients centers around the role of the adrenal glands and corticosteroids in patients with shock. After several conflicting large clinical trials, the current recommendation is that patients requiring vasopressors for blood pressure support ought to be given 200 mg of hydrocortisone in divided doses. There is no need for adrenal stimulation studies or for coadministration of pure mineralocorticoid agent such as fludrocortisone. Interestingly, pure glucocorticoid agents such as dexamethasone appear to treat relative adrenal insufficiency despite a lack of any mineralocorticoid activity; however, this drug is not used to treat adrenal insufficiency. "Stress dose" steroids do not need to be weaned and should be discontinued once the patient is adequately resuscitated and vasopressors are no longer required to maintain MAP. Steroids shorten the time that patients require vasopressors, which has practical benefits, but they do not confer a mortality benefit. Steroid therapy can worsen sepsis induced hyperglycemia and many patients will require exogenous insulin to keep their blood glucose in the desired range. Conversely, despite their well established immunosuppressive actions, stress dose steroids are not associated with increases in infectious complications.

Immune System

The complexity of the immune system and its alterations and dysregulation in response to sepsis is profoundly intricate and is why there is not a single approved medication to reduce mortality in sepsis despite the performance of well over 100 large clinical sepsis trials. Every single component of the humoral and tissue immune systems is altered in response to sepsis and these changes generally follow a similar pattern. Initial immune activation is typically followed by a period of hyperinflammation, resolution to homeostasis, or immune suppression but any one of the conditions may predominate at any given time. In some ways, obtaining source control diminishes the trigger that sets off the immune inflammatory cascade. Complementary to this is the timely administration of appropriate antibiotics directed against the most likely pathogens. Clinical studies have repeatedly shown that the longer the interval is between the onset of sepsis to dosing of appropriate antibiotics, the worse the outcomes. A retrospective review of the Surviving Sepsis database found that in-hospital septic mortality increased for every hour that antibiotic therapy was delayed beginning 2 hours after patients were diagnosed with sepsis. This rise in mortality increased up to a 1.5 times the odds ratio of death when antibiotic therapy was delayed by 6 hours. Much like failure to obtain prompt source control, delays to administering antibiotics to a septic patient contributes to excess mortality.

Antibiotic Selection

Similarly, choosing the wrong empiric antibiotic usually increases the mortality of sepsis by a factor of two to five times. It is imperative that clinicians select antibiotics based on the most likely bacteria for each given septic focus and consider local resistance patterns and patient comorbidities. Blood and other cultures should be obtained at the start of therapy, but antibiotics should never be withheld in that cultures can be drawn. It may be necessary to use more than one agent if the most likely microbes causing sepsis cannot be treated with monotherapy. The possibility that the septic response is due to infections caused by yeast or viruses should not be overlooked, particularly in patients taking immune modulating agents for inflammatory conditions or immunosuppression following transplantation.

Considering the mortality of delayed or inappropriate antibiotic selection in the treatment of sepsis, clinicians must resist the urge to use overly broad antibiotics or powerful last line agents. Doing so will lead to opportunistic infections, antibiotic resistant infections, and further complications. Accordingly, antibiotic therapy ought to tailor based on culture results as these become available, typically in 2 or 3 days, and the broad spectrum empiric antibiotics switched to the narrowest possible agent. This process is known as antibiotic deescalation and it minimizes antibiotic resistance, opportunistic infections, and waste of resources. The duration of antibiotic therapy ought to be limited based on available evidence in the literature and there is no role for long courses of broad spectrum "empiric" antibiotics even for the sickest patients. Patients with pertonsitis who achieve source control can be treated with a 4 day duration of antibiotics based on clinical data. Similarly, ventilator associated pneumonia can be treated with 8 days of therapy for all bacterial infections except those caused by the Enterobacteriaceae family.

Occasionally a patient will manifest ongoing sepsis for several days despite negative culture data and no obvious source. This conundrum is particularly vexing if the patient is elderly or has serious medical comorbidities. In this situation, all antibiotics should be stopped, and new cultures obtained from blood and other likely sites of infection. An exhaustive physical examination should be performed, and computed tomography scanning is usually required to assess for occult infections in the peritoneal and/or thoracic cavities. Surgeons must be humble and should consider that the source of sepsis may be a complication of their surgical intervention. If a septic source is identified, vigorous efforts to achieve source control should be undertaken and reoperative surgery is often necessary. Although stopping antibiotics in someone with ongoing sepsis seems risky, another way of looking at this is that the patient is not responding to the antibiotics that he or she is receiving so stopping them can do no further harm.

SUMMARY

Sepsis remains a challenging and costly problem for society, and surgeons continue to play a central role in its therapy. The diagnosis of sepsis remains difficult because of its variable presentation, so it is mandatory that clinicians have a high index of suspicion that a deteriorating patient could be septic. Overreliance on septic clinical parameters, biomarkers, or laboratory value is likely to lead to complications and higher mortality. Therapeutic interventions and management strategies need to be continually reevaluated because what seems like an effective or beneficial therapy is often found to be untrue when rigorously studied. Sepsis mortality has fallen as the principles of source control, fluid resuscitation, and timely antibiotics have become widely embraced and surgeons need to stay involved in this process if the best outcomes are to be achieved.

Suggested Readings

Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.

Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371(15):1381–1391.

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Multiple Organ Dysfunction and Failure

Mitchell Ryan Levitt, MD, PhD and Arthur Vanessa Vaughn, MD

Critically ill patients are complex and require a systematic approach to ensure excellent care. They are often managed by thinking about each system in turn so that all of their maladies are considered and appropriately treated. Unfortunately, despite a physician's best efforts, patients may deteriorate to the point that multiple organs are dysfunctional and heading toward failure. When this occurs, the acuity and complexity of these patients escalate and considerable attention to the details of each system is paramount.

After a short history of the term multiple organ failure (MOF), this chapter will briefly discuss the end-organ dysfunction and failure often encountered in each organ system in critically ill surgical patients. Appropriate grading systems for the organ systems and patients as a whole will be discussed, as well as a few special populations that deserve mention. Finally, the importance of when to consider end of life and palliative care is included.

History

The term *multiple organ failure* was first coined by Arthur Baue in 1975. In the years following, numerous attempts have been made to ascribe an etiology and pathophysiology to this entity while recognizing that each organ system may suffer some dysfunction without being in frank failure. Organ dysfunction that occurs short of failure has now been termed multiorgan dysfunction syndrome (MODS). Decades of research have ensued in an effort to effectively treat and reverse MODS before it becomes MOF, and many advances have been made. Aside from correcting the underlying etiology, however, there has been no single treatment strategy that can be used to cure all patients. Moreover, salvage therapies are lacking for severe MODS that progresses to MOF.

Dysfunction and Failure by Organ System

Neurologic

The neurologic function of critically ill patients is often abnormal and can be affected by numerous factors. Mental status change is a common early sign of MODS and shock; however, delirium, stroke, traumatic brain injury, and exposure to sedative medications also cause altered mental status and should remain on the differential.

When a patient's mental status deteriorates, a prompt workup should occur to determine the underlying cause and the change should not be attributed to medications alone. Effects of medications on mental status, while important to consider, should essentially be a diagnosis of exclusion. The earliest and most often used assessment of global neurologic function in the initial evaluation is the Glasgow Coma Score (GCS; Table 1). Patients with a GCS of 8 or less have a mental status change significant to prevent them from protecting their airway and intubation should be considered. Further, GCS is included as part of the Sequential Organ Failure Assessment (SOFA) score (Table 2) and the Marshall MOD Score (Table 3), since on the SOFA and quick SOFA scores appear in the section on scoring systems) and thus is essential in evaluating a newly critically ill patient.

Pain control is also a parameter used to assess neurologic dysfunction. Patients with seemingly increased or out of proportion pain should be assessed for an underlying etiology. The addition of the pain could be one of the many causes of MODS or MOF (i.e., abscess, sepsis, bowel perforation, and bleeding). If these underlying etiologies have been ruled out, a multimodal pain regimen should be implemented that adequately controls pain while limiting the risk of delirium. More recently, intensive care units (ICUs) have adopted pain, agitation, and delirium protocols to help better treat these conditions in a more real time way using bedside nursing assessment to drive management. Pain services should be used for patients requiring increasing pain medications, and neuraxial blockade should be considered if appropriate.

There is evidence that ICU patients may have brain dysfunction and depression that lingers beyond their recovery. It is well recognized that to prevent changes in consciousness and reduce delirium in the ICU, we should strive to maintain sleep-wake cycles, reduce sedation as much as is possible in mechanically ventilated patients (by providing sedation vacations), avoid benzodiazepines, and be aggressive with physical therapy and daily mobilization.

The ultimate central nervous system dysfunction or failure is brain death. Brain death can be thought as from any of the causes mentioned previously if they ultimately result in global ischemia of the brain and subsequently the absence of blood flow to the brain. This typically occurs as a result of increased intracranial pressure such that it decreases cerebral perfusion pressure to the point that the brain completely dies. Once this happens, the damage is irreversible. The legal declaration of brain death varies from state to state, but typically requires at least two examinations by two providers with an interval observation period. In addition, to be declared brain dead, metabolic causes of brain dysfunction must be excluded. These include being normothermic, having a negative toxicology screen, normal electrolytes, and normal acid base status.

Cardiovascular

Dysfunction of the cardiovascular system, in the form of hypotension and shock, is perhaps the most frequent cause of ICU admission. Cardiovascular abnormalities can have numerous causes and in the noncardiac surgical patient, is often a secondary result from a different primary disease, for example sepsis. Cardiac complications from surgery do occur and cardiovascular collapse can be due to postoperative myocardial infarction, submassive or massive pulmonary

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Mitchell Ryan Ladd, MD, PhD, and Arthur Jason Vaughn, MD

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Table 1 Glasgow Coma Scale

Component	Score
EYE OPENING	
Spontaneously	4
To voice	3
To pain	2
No response	1
VERBAL	
Oriented	5
Disoriented	4
Inappropriate	3
Incomprehensible sounds	2
No response	1
MOTOR	
Following commands	6
Localizing to pain	5
Withdrawing to pain	4
Abnormal flexion	3
Abnormal extension	2
No response	1

embolism, or atrial fibrillation. Distinguishing the cause of cardiovascular collapse is important because the physiology surrounding cardiovascular dysfunction will dictate its treatment. Bedside and formal echocardiography may be helpful in determining the cause of cardiovascular dysfunction if the diagnosis is unclear. Echocardiography may also be helpful in tracking the adequacy of resuscitation both by evaluating the ventricular function, assessing valvular abnormalities, atrial filling, and fullness of the inferior vena cava.

In the setting of distributive shock (e.g., sepsis, anaphylaxis) there is vasodilation, capillary leak, and resulting hypotension. In hypovolemic/hemorrhagic shock, there is vasoconstriction in an attempt to preserve blood pressure, however, because of the low blood volume, hypotension persists. Cardiogenic shock is due to injury to the heart itself and results in pump dysfunction or failure, that then leads to poor blood distribution to end organs resulting in vasoconstriction, cold extremities, and ultimately hypotension resulting from inadequate pumping. Obstructive shock causes a central cardiac outflow obstruction that results in hypotension. Neurogenic shock results in vasodilation, reduced preload, and frequently bradycardia all of which work together to cause hypotension. Different types of shock are treated with different algorithms, it is important to recognize the type of shock a patient has and treat accordingly.

Cardiovascular dysfunction sets off a cascade of injury to other organ systems because of inadequate perfusion. It is therefore imperative to support the cardiovascular system, regardless of the cause of dysfunction, to prevent further injury to end organs. This is often done with a combination of fluid resuscitation and vasopressors depending on the type of shock present. In general, these interventions are targeted to maintain a mean arterial pressure (MAP) of 65 and lactate less than 2 mmol/L to ensure adequate end organ perfusion. Details of management for each of type of shock can be

TABLE 2 Sequential Organ Failure Assessment (SOFA) Score

Organ System	0	1	2	3	4
Respiratory: PaO_2/FiO_2	>400	<400	<300	<200 with ventilator support	<100 with ventilator support
Cardiovascular: hypotension (mm Hg)	MAP >70 No pressors	MAP <70 No pressors	Dopamine <5	Dopamine >5 or epinephrine <0.1 or norepinephrine <0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Hepatic: bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.4	5.5–11.9	>12.0
Coagulation: platelet count ($\times 10^3$/mm^3)	>150	<150	<100	<50	<20
Neurologic: GCS	15	13–14	10–12	6–9	<6
Renal: creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or Urine <500	>5.0 or Urine <200

Vasopressor doses in μg/kg/min.
FiO_2, Fraction of inspired oxygen; GCS, Glasgow Coma Scale score; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

TABLE 3 Marshall Multiple Organ Dysfunction Score

Organ system	0	1	2	3	4
Respiratory: PaO_2/FiO_2	>300	226–300	151–225	76–150	≤75
Cardiovascular: HR × CVP/MAP	<90	10.1–15	15.1–20	20.1–30	>30
Hepatic: bilirubin (mg/dL)	<1.2	1.2–3.5	3.5–7.0	7.0–14	>14
Hematologic: platelet count ($\times 10^3$/mm^3)	>120	81–120	51–80	21–50	≤20
Neurologic: GCS	15	13–14	10–12	7–9	≤6
Renal: creatinine (mg/dL)	<1.4	1.4–2.4	2.5–4.9	5.0–9.7	>9.7

C, F, Central venous pressure; FiO_2, fraction of inspired oxygen; GCS, Glasgow Coma scale score; HR, heart rate; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

found elsewhere in this text but will be reviewed briefly here. Distributive shock, which is most commonly associated with sepsis, is treated using Surviving Sepsis principles with aggressive fluid resuscitation (typically 30 mL/kg in bolus form over the first 3 hours), antibiotics (which should be given within an hour of the first episode of hypotension), and source control. If MAPs are still not adequate, norepinephrine should be used as the vasopressor of choice. On occasion, vasopressin can be added for extra support, but this does not change overall mortality. In the case of anaphylactic shock, epinephrine should be administered. The treatment of hypovolemic/hemorrhagic shock should consist of fluid/blood resuscitation combined with controlling the source of blood or fluid loss. In addition, vasopressors can be added if necessary and typically norepinephrine or phenylephrine are used. Cardiogenic shock requires inotropic support and epinephrine is usually the best first line agent for this; however, dobutamine is also used frequently and can be added as a second line agent (note that supporting heart failure is in fact more nuanced than this depending on whether failure is systolic, diastolic, left or right sided, but this is discussed elsewhere in this text). Intra-aortic balloon pumps and transvenous pacing may also be necessary with extracorporeal membrane oxygenation as another potential salvage option. Obstructive shock is most commonly from a large pulmonary embolus and this should be treated with tissue plasminogen activator, anticoagulation, or pulmonary thromboembolectomy depending on the severity of the situation and presence or absence of contraindications to tissue plasminogen activator or anticoagulation. Neurogenic shock is treated with large volumes of intravenous fluids to fill the venous system and augmented with phenylephrine to help maintain MAP. If neurogenic shock is associated with severe bradycardia, dopamine may be preferred over phenylephrine to improve chronotropy while simultaneously providing alpha 1 stimulation. If untreated, the final common pathway for cardiovascular dysfunction and collapse is cardiac arrest.

Pulmonary

Inadequate gas exchange and pulmonary failure are a mainstay of critical illness. MODS, and MOF. In general, the pulmonary failure of MODS in the ICU manifests as the acute respiratory distress syndrome (ARDS). ARDS can result from direct or indirect lung injury. Direct lung injury is as it sounds with an insult to the lungs such as pneumonia, aspiration, smoke inhalation injury, or traumatic lung injury. Indirect lung injury is when inflammation or a nonpulmonary insult results in ARDS such as sepsis, hemorrhage/hypovolemia (often from a combination of inflammation and aggressive fluid resuscitation), transfusion related lung injury, or severe pancreatitis. Both categories of lung injury are common in the surgical ICU.

The pathophysiology of ARDS involves poor oxygen exchange across the alveolar membrane. The initial effect of ARDS is atelectasis and ventilation perfusion mismatch. This is quickly followed by neutrophil activation and sequestration in the lungs where they degranulate, releasing inflammatory molecules. This results in a capillary leak and increased fluid and edema of the alveoli preventing oxygen diffusion. As the process continues, inflammation leads to fibrosis further worsening oxygen exchange and so called hyaline membrane disease can develop. If severe enough, patients with ARDS will die of failure to oxygenate. Due to the initial exudative stage of diffuse alveolar damage and lasts 7 to 10 days. If patients survive this stage, they may progress through the fibroproliferative stage and ultimately the fibrotic stage.

The Berlin criteria have been developed to aid in the diagnosis of ARDS. For the diagnosis, all of the following criteria must be present: respiratory symptoms started within 1 week of inciting insult, bilateral opacities must be present on radiograph or computed tomography, the respiratory failure must not be fully explained by cardiac disease or fluid overload, and a moderate impairment of oxygenation must be present (i.e., at least a minimum partial pressure of oxygen/fraction of inspired oxygen ratio of less than or equal to 300 mm Hg when on positive end expiratory pressure or continuous positive airway pressure of 5 cm H_2O).

Patients with ARDS require respiratory support that minimizes volutrauma/barotrauma to the lungs and worsening of the lung disease using the guidelines well published by the ARDSNet group. The principles of ARDSNet ventilation include low tidal volumes (6 mL/kg of predicted body weight), permissive hypercapnia, and maintaining a plateau pressure of 30 cm H_2O or less with the oxygenation goal of partial pressure of oxygen 55 to 80 or blood oxygen saturation 88% to 95% and pH goal of ~ 30 to 7.45. Overresuscitation should be avoided to prevent further worsening of oxygenation. If ARDSNet strategy of ventilation does not provide enough oxygenation, appropriate patients may be placed in prone position and/or given a paralytic to improve survival. If done, these maneuvers should not be delayed because benefit is improved with earlier initiation. Other modes of ventilation may be attempted such as airway pressure release ventilation, bilevel, or in some settings, high frequency oscillatory ventilation as salvage therapies. Inhaled nitric oxide is also used on occasion to improve oxygenation, but with no proven survival benefit. Finally, patients that continue to have respiratory failure, extracorporeal membrane oxygenation may be necessary to provide adequate oxygen, prevent further barotrauma, and to allow the lungs to heal.

Renal

Acute kidney injury (AKI) is common to the surgical patient and the ICU. It is estimated that AKI affects 2% to 18% of all hospital inpatients and 20% to 57% of ICU admissions. Of the cases of AKI, 30% to 40% occur in the perioperative setting. There are numerous causes of AKI such as prolonged hypotension (from hypovolemia, heart failure, etc.), sepsis/inflammation (one of the most common causes in the ICU setting), exposure to nephrotoxic drugs/toxins (including iodinated contrast), microangiopathic hemolytic anemias, or vasculitis. AKI carries with it a significant increase in perioperative mortality, with some studies suggesting 30 day mortality as high as 34% compared with 1.0% in those without AKI.

The definition of AKI has been murky, but consensus definitions have been in place now since 2004; however, there are currently three different criteria for defining AKI: the risk, injury, failure, and stage renal disease (or RIFLE criteria), the criteria put forth by the Acute Kidney Injury Network (or AKIN criteria), and the Kidney Disease: Improving Global Outcomes Foundation (or KDIGO) criteria. They have similarities and overlap in their definitions (Table *). The RIFLE criteria evaluate urine output and relative changes in serum creatinine, the AKIN criteria are similar but allow for absolute changes in serum creatinine to define injury, and the KDIGO criteria combine the RIFLE and AKIN criteria but add an allowance for short term changes in 48 hours and for those that occur over a longer time course (i.e., 7 days). Numerous biomarkers have been investigated to help identify AKI early, but to date none of them have the sensitivity nor specificity to be useful clinically.

AKI has traditionally been categorized as having one of three broad causes: pre renal, intrinsic kidney injury, and postrenal. In reality, AKI is often multifactorial and a patient can be suffering from more than one of the basic pathophysiologic mechanisms (i.e., prolonged pre- or postrenal injury can result in intrinsic injury). In addition, one should think about intrinsic renal injury by the region of the kidney affected: damage to the renal vasculature from emboli or vasculitides, damage to the renal interstitium from allergic reactions or infection, or damage to the renal tubules resulting from inflammation from toxins such as contrast, antibiotics, myoglobin, or hemoglobin.

The perioperative patient has many factors that put them at risk for AKI. First, there are numerous comorbidities that have been recognized as increasing the risk of AKI: obesity, chronic kidney disease, diabetes, cardiovascular disease, liver disease, chronic obstructive pulmonary disease, smoking, chronic steroid use, and cancer. In addition, the type (e.g., cardiac, transplant) and urgency of surgery being performed can increase the risk. Intraoperative factors also play

TABLE 4 RIFLE, AKIN, and KDIGO Classifications of Renal Failure

Stage	↑Serum Creatinine	Urine Output
RIFLE CLASSIFICATION OF RENAL FAILURE		
R: Risk for renal injury	Baseline Cr × 1.5 Decrease GFR >25%	<0.5 mL/kg/hr × 6 hr
I: Injury to kidney	Baseline Cr × 2 Decrease GFR >50%	<0.5 mL/kg/hr × 12 hr
F: Renal failure	Baseline Cr × 3 Cr >4 mg/dL with increase ≥0.0 mg/dL Decrease GFR >75%	<0.3 mL/kg/hr × 24 hr Anuria × 12 hr
L: Loss of renal function	Persistent renal failure Loss of renal function >4 weeks	
E: ESRD	Renal failure >3 months	
ACUTE KIDNEY INJURY NETWORK (AKIN) CLASSIFICATION OF AKI		
1	Baseline Cr × 1.5–2 Increase >0.3 mg/dL in 48 hr	<0.5 mL/kg/hr × 6 hr
2	Baseline Cr × 2–3	<0.5 mL/kg/hr × 12 hr
3	Baseline Cr × 3 Cr >4 mg/dL with acute increase 0.5 mg/dL Renal replacement therapy	<0.3 mL/kg/hr × 24 hr Anuria × 12 hr
KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES (KDIGO) STAGING OF AKI		
1	Baseline × 1.5–1.9 Increase >0.3 mg/dL	<0.5 mL/kg/hr for 6–12 hr
2	Baseline × 2–2.9	<0.5 mL/kg/hr for >12 hr
3	Baseline × 3 Increase >4 mg/dL Initiation of renal replacement therapy <18 years old, decreased GFR <35 mL/min per 1.73 m²	<0.3 mL/kg/hr for 24 hr Anuria >12 hr

AKI, Acute kidney injury; Cr, creatinine; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

a role. In particular, hypovolemia, hypotension (from hypovolemia or decreased systemic vascular resistance from anesthetic), increased intraabdominal pressure, or direct injury to the kidneys themselves. The use of nonbalanced fluids (normal saline) can result in hyperchloremia, which is associated with perioperative AKI. Interestingly, intraoperative urine output does not correlate well to risk for AKI at least for elective surgeries. This is likely because the fluid administered during anesthesia has reduced distribution and clearance from the vascular space and thus intraoperative oliguria may not accurately reflect the actual fluid status of the patient. To reduce a patient's risk of postoperative AKI, one must consider all possible risk factors, modify those that can be changed preoperatively, minimize the intraoperative risk of developing AKI by maintaining an intraoperative MAP of ≥65 mm Hg or greater with the use of fluids and vasopressors when necessary, and avoiding nephrotoxic drugs when able.

The primary treatment for AKI, once it has started, is to fix its underlying cause (fluid resuscitate the patient, treat sepsis, improve cardiac output, and avoid nephrotoxic drugs as examples) along with supportive care, assuming the patient has not progressed to kidney failure requiring renal replacement therapy. If kidney failure does occur, then renal replacement therapy should be initiated if indicated (i.e., volume overload, acidosis, electrolyte disturbances, hyperkalemia, hyperuremia in particular). In the ICU setting, this is commonly done via hemofiltration using continuous venovenous hemodialysis because it results in fewer swings in blood pressure. However, once a patient is stabilized, intermittent hemodialysis can also be performed.

Gastrointestinal

Gastrointestinal (GI) dysfunction and failure occur in ICU patients as a result of either direct injury or indirect injury secondary to hypoperfusion. Once injury occurs, there can be loss in the normal gut flora and barrier, causing translocation of gut bacteria and bacterial products into the lymphatics and bloodstream causing severe inflammation. GI dysfunction can be difficult to diagnose and there are a wide variety of definitions of it in the literature. More recently a consensus definition of four grades of acute gastrointestinal injury (AGI) has been developed by the Working Group on Abdominal Problems of the European Society of Intensive Care Medicine. These definitions were developed for research purposes and have not yet been well validated in the clinical setting.

In general, the new consensus definitions of AGI involve diagnosis by clinical symptoms with the assistance of radiologic studies (i.e., abdominal radiographs and computed tomography scans). There are no good nor validated biomarkers or blood tests (such as creatinine for kidney function) that can define, quantify, or help follow AGI. AGI grade I represents being at risk for injury and involves still limiting symptoms such as postoperative nausea/vomiting, mild diarrhea, and abdominal distention. AGI grade II is GI dysfunction that requires interventions, consists of severe or several less severe symptoms, and which does not cause deterioration of the patient's general medical condition. Examples of dysfunction in this category include gastroparesis, having large gastric residual volumes (typically considered to be more than 250 mL), thus, severe diarrhea requiring electrolyte correction,

grade I: intraabdominal hypertension (intraabdominal pressure of 12–15), or visible blood in gastric contents or stool. ACS grade III represents GI failure, defined as symptoms that persist or progress despite interventions or that is part of worsening MODS. Symptoms in ACS grade III include all those of grade II, which worsen despite intervention and also include persistent abdominal signs. Finally, ACS grade IV is GI failure that is life threatening. Examples of grade IV would include necrotic bowel, GI bleeding causing hemorrhagic shock, Ogilvie's syndrome, and abdominal compartment syndrome.

Management of ACS depends on the symptoms and should be approached systematically. In general, enteral nutrition should be used to feed the gut and at least trophic feeds (typically agreed on to be 20 mL/hr of feeds) should be attempted in patients as long as they do not have ACS grade IV and they are able to tolerate it. Trophic feeds help maintain gut barrier function and prevent the abnormal translocation of enteric bacteria into the lymphatics and bloodstream and thus systemic infection. When possible, prevention of ACS should be the goal, accomplished by minimizing narcotics and sedatives, early mobilization, early enteral nutrition, and early institution of a bowel regimen; however, many of these interventions may be difficult to achieve in an ICU patient.

Hepatic

Although the liver can initiate MODS, especially in the setting of acute liver failure or acute on chronic liver failure, it is frequently secondarily involved. Hepatic dysfunction as a part of MODS has two phenotypes: acute sudden failure, termed shock liver, or a more insidious dysfunction that presents as mild hyperbilirubinemia with or without cholestasis and normal liver function. In shock liver, the first abnormality observed is a marked elevation in transaminases, followed by hyperbilirubinemia, and, last, a loss of synthetic function represented by an increase in international normalized ratio, hypoglycemia, and hyperammonemia. The second form of hepatic dysfunction typically resolves if MODS resolves. Treatment of hepatic dysfunction, in addition to treating the underlying cause of MODS, is supportive care of the liver while avoiding hepatotoxins that might worsen the injury. In addition, patients should receive adequate nutrition and have their encephalopathy (if present) closely managed.

When shock liver is severe, the inflammatory mediators from the Kupffer cells of the liver spill over into the systemic circulation and can greatly affect and damage other organ systems. In addition to synthetic dysfunction in their failure causing a coagulopathy, patients may also have trouble clearing lactate and an already nutritional hypoglycemia and hyperammonemia. Inflammation from the liver can affect the brain causing encephalopathy from hyperammonemia and cerebral edema from inflammation in microglial cells and glutamine accumulation in astrocytes. Not surprisingly, if hepatic failure or dysfunction is the initial insult, it can also cause ARDS, AKI, shock, and, as previously mentioned, MODS with MOF.

Endocrine/Metabolic

Critical illness, surgical, and traumatic insults all result in a wide variety of endocrine and subsequently metabolic disturbances. Both the central nervous system and the innate immune system are involved in recognizing and responding to threats of homeostasis (i.e., injury/infection), with the central nervous system being responsible for perceiving and responding to macroscopic threats and the innate immune system responsible for recognizing microscopic threats (e.g., pathogens). The responses to injury that ensue affect the hypothalamic–pituitary–adrenal axis, glucose metabolism, and the hypothalamic–pituitary–thyroid axis. Each of these will be discussed briefly in turn.

Adrenal insufficiency is a common problem in the ICU. The initial response of the hypothalamic–pituitary–adrenal axis to critical illness is to increase cortisol secretion usually in proportion to the injury sustained. As inflammation continues, this system is exhausted and relative adrenal insufficiency may develop. Cortisol is important because it maintains the vascular reactivity to catecholamines. Historically, adrenocorticotropic hormone stimulation tests were performed to assess for adrenal insufficiency and to determine who should be treated with exogenous steroids. This has fallen out of favor, and now steroids are recommended only for those patients that do not respond appropriately to adequate resuscitation with fluids and the appropriate vasopressors. In these cases, hydrocortisone is administered at no more than 300 mg/d in divided doses. The adrenal gland is also responsible for the secretion of vasopressin (also known as ADH). Vasopressin acts on numerous receptors to increase vascular vasoconstriction, to increase water reabsorption, and it even acts centrally in the anterior pituitary to stimulate the release of adrenocorticotropic hormone; thus, vasopressin has effects on cortisol secretion. After initial injury, vasopressin levels rise rapidly, but then also fall rapidly. Vasopressin levels are not routinely measured because a majority of it is bound to platelets and it has a short half-life. Although vasopressin is not recommended as a first-line vasopressor agent, it can be added (as described previously) in low doses if normal MAPs are not achievable after adequate fluid resuscitation and other vasopressors maximized. When vasopressin is added, it is typically only in a dose of 0.02 to 0.04 U/min.

Critical illness causes a hypermetabolic state because of a surge of catecholamines, cortisol, glucagon, and growth hormone. The release of these substances results in insulin resistance, hepatic gluconeogenesis, muscle catabolism, and hyperglycemia. Uncontrolled hyperglycemia is known to cause numerous increased risks and complications in the critically ill such as increased risk of infection, neurologic outcomes, and increase in mortality. Potential mechanisms for worsening outcomes in hyperglycemic patients include effects on the host response such as reduced chemotaxis, phagocytosis, increased inflammatory cytokines, increased oxygen free radicals, prothrombotic effects, and dysregulation in the production of endothelial nitric oxide production. Thus, glucose should be monitored and controlled within a reasonable range. Current recommendations suggest a permissive hyperglycemia with a glucose target range of 140 mg/dL to 180 mg/dL to prevent excessive hyperglycemia while avoiding life-threatening hypoglycemia.

Thyroid abnormalities are common in critical illness and are often referred to as sick euthyroid syndrome or nonthyroidal illness syndrome. The decrease in thyroid hormone is mediated primarily by inflammatory cytokines and is thought to be a protective mechanism to increase resistance to stressors by reducing cellular metabolism. Sick euthyroid syndrome begins with a decrease in T_3 as a result of decreased conversion of T_4 to T_3. This is followed by a subsequent decrease in T_4 and thyroid binding globulin. These abnormalities typically correct once the critical illness is resolved and no specific treatment is needed and should not be implemented. If a patient is found to have sick euthyroid syndrome, they may benefit from repeat thyroid testing once they are well to ensure they do not have baseline thyroid dysfunction.

Immunohematologic/Disseminated Intravascular Coagulation

Anemia is common in the ICU, with estimates that 30% to 50% of ICU patients receive red blood cell transfusions. Anemia in the ICU occurs via mechanisms associated with anemia of inflammation or chronic disease. There are three main abnormalities associated with the host response that result in anemia: dysregulation of iron homeostasis, impaired proliferation of erythroid progenitor cells, and decreased erythropoietin response. Numerous clinical trials have evaluated whether a liberal or restrictive transfusion strategy should be used in the ICU with the overwhelming evidence supporting a restrictive transfusion strategy (i.e., only transfusing patients with blood if their hemoglobin is less than 7 g/dL, or less than 8 g/dL if the patient has an acute coronary syndrome). The exception to these transfusion thresholds is the bleeding patient who should receive blood as necessary; however, once bleeding is controlled, a restrictive transfusion strategy should be maintained. In addition, these transfusion triggers should not be used blindly, but should be considered in concert with the clinical parameters of the patient and with

regard to their overall tissue oxygenation. Anemia in the ICU can be exacerbated by phlebotomy and so all strategies to reduce anemia in the ICU should also be used. These include decreasing phlebotomy, using low volume blood sample tubes, using as few blood conservation devices that reinfuse waste blood, and using cell salvage during surgical procedures when possible.

Thrombocytopenia is generally defined as a platelet count less than 150,000/μL, although more recently it has been graded into mild, moderate, and severe thrombocytopenia corresponding to platelet counts of 100,000 to 149,000/μL; 50,000 to 99,000/μL, and less than 50,000/μL. Thrombocytopenia can have numerous etiologies such as heparin induced, drug induced, autoimmune disease, sepsis, disseminated intravascular coagulation (DIC), consumption (from trauma or cardiopulmonary bypass), or mechanical circulatory devices such as intraaortic balloon pump. The most common causes in the ICU are sepsis, DIC, consumption, and mechanical circulatory support devices. Exact transfusion thresholds for platelets have not been as well studied as for red blood cells, but general guidelines exist and depend on the risk of bleeding. In patients with ongoing bleeding, platelet counts should be kept above 50,000/μL. If the bleeding is intracranial or a neurosurgical intervention is being planned, the goal should be 100,000/μL. Otherwise, without bleeding or planned intervention, a platelet transfusion threshold of 10,000/μL is recommended. Other recommendations include the following thresholds: greater than 10,000 to 20,000/μL for central venous catheter placement, greater than 50,000/μL for laparotomy or chest tube placement, and greater than 20,000/μL for lumbar puncture.

Coagulopathy is also common in the critically ill and like anemia and thrombocytopenia has the same numerous potential causes. In addition, liver failure can result in decreased synthesis of coagulation factors and administration of anticoagulant medications can alter the clotting cascade. Despite this, there are specific indications for transfusion of plasma and almost all relate to active bleeding. Thus, in those patients that have massive hemorrhage, fresh frozen plasma (FFP) should be given. In addition, those that have warfarin induced coagulopathy and active bleeding or are in need of a surgical procedure, FFP should be administered. Other indications for FFP administration include liver disease with active bleeding, DIC with active bleeding, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome during the initial treatment phase and with plasmapheresis, and in cases of acquired deficiencies of a single coagulation factor for which the appropriate factor replacements are not available or are ineffective. In general, in a bleeding patient or a patient needing a procedure, the international normalized ratio goal of FFP transfusion should be less than 1.5. Patients may require other blood products (such as individual factors or cryoprecipitate) depending on the coagulation abnormality present. Recently, the thromboelastogram has emerged as an excellent tool to monitor and guide treatment of coagulation abnormalities. However, these considerations are discussed in detail elsewhere in this text and are outside the scope of this chapter.

Sepsis and MODS are known after the innate and adaptive immune responses and their changes can persist after the acute phase of MODS has resolved. These long-term changes cause ongoing chronic inflammation and immune suppression that put patients at risk for recurrent, secondary, and nosocomial infections resulting in risk of death even months after patients have recovered from their initial illness. Much work on understanding these cellular mechanisms and how to treat them is still required.

GRADING SYSTEMS OF ORGAN DYSFUNCTION

Organ dysfunction in the ICU patient can be categorized by the deranged physiologic system that requires intervention or by the degree and extent of intervention necessary (i.e. mechanical ventilation, renal replacement therapy, cardiovascular support). Numerous grading systems and scales exist to characterize and grade the severity of MODS based on the following systems: respiratory, cardiovascular, renal, hepatic, neurologic, and hematologic. The most recent and most commonly used assessment is called the Sequential Organ Failure Assessment (SOFA) score, which was described by J.L. Vincent and colleagues in 1996 (Table 2). The SOFA score assigns a value of 0 to 4 in six system categories with the higher score indicating a worse derangement. A shorter form of the SOFA score, called the quick SOFA or qSOFA for simpler bedside evaluation of potentially septic patients, has been developed. In this score, only three criteria are evaluated as being present or absent with a point assigned for each one that is present. The criteria are GCS less than 15, respiratory rate greater than or equal to 22, and systolic blood pressure less than or equal to 100 mm Hg. If two of these criteria are met, patients are thought to be at high risk for organ dysfunction and they should be thoroughly worked up, closely monitored, and a full SOFA score should be performed. The Marshall MODS score was developed in 1995 and assigns a score of 0 to 4 in six organ systems as well (Table 3). With both of these scoring systems, the risk of ICU death increases as the severity of organ dysfunction and number of failing organs increases.

The Acute Physiology and Chronic Health Evaluation II score was developed in 1985 by Knaus et al. to evaluate severity of illness by assigning scores to 12 physiologic parameters and including age and previous health status. The parameters include: temperature, MAP, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood cell count, GCS, age, and chronic health status. The score ranges from 0 to 71, with higher scores predicting a higher mortality rate.

MODS generally develops within 48 hours of an inciting event. Subtle neurologic disturbances are noted first, followed by acute dysmutic respiratory and cardiac dysfunction. Generally, hepatic, gastrointestinal, and renal dysfunction develop at a slightly later time during the disease course.

SPECIAL POPULATIONS

Pregnant Patients

With the rise in maternal mortality, it is only natural that pregnant women are frequenting ICUs. It is estimated that 1 in 329 deliveries will be admitted to the ICU in the United States. Changes in maternal physiology, fetal considerations, and medical emergencies related to pregnancy pose complications to critical care practitioners. With the increase in maternal mortality, ICUs must become adept to critical care obstetric issues.

The most common reason for ICU admissions in the United States includes hypertensive disorders of pregnancy (preeclampsia, eclampsia, and hemolysis, elevated liver enzyme, low platelet [HELLP] syndrome), followed by obstetric hemorrhage, and sepsis. During pregnancy, the maternal physiology can change significantly. By the mid second trimester, there is an increase of 50% in intravascular volume leading to an increase in cardiac output facilitated by a decrease in systemic vascular resistance. These changes are thought to aid the perfusion of the growing placenta and fetus. The increase in volume results in an increase in glomerular filtration and physiologic anemia with a standard hemoglobin of 10 to 11 g/dL.

Pulmonary physiology also significantly changes. Although there is a marginal increase in inspiratory capacity, the growing uterus causes marked decrease in the expiratory reserve volume and functional reserve capacity. These changes can place pregnant women at risk for progression of severe disease in pulmonary infections (i.e., pneumonia and influenza).

Hypertensive Diseases of Pregnancy and the ICU

Preeclampsia affects 2% to 5% of all pregnancies in the United States and is described as new onset hypertension and proteinuria usually occurring in the third trimester of pregnancy (Table 4). In general, many women with a hypertensive disorder of pregnancy are not admitted to the ICU because obstetric providers feel comfortable

TABLE 5 Diagnostic Criteria for Preeclampsia, HELLP Syndrome, and Eclampsia

Preeclampsia	Blood pressure Nonsevere: SBP >140 mmHg or DBP >90 mmHg after 20 weeks Severe: SBP >160 mmHg or DBP >90 mmHg after 20 weeks	Proteinuria Protein >300 mg/24 hr urine collection Protein/creatinine ratio >0.3 Dipstick reading of 1+ (only if other methods not available)
	In the absence of proteinuria, new-onset hypertension with new onset of any of the following: Platelet count <100,000/μL Serum creatinine >1.1 mg/dL or doubling of serum creatinine concentrations Elevated blood concentration of liver transaminases twice normal Pulmonary edema Cerebral or visual symptoms	
Eclampsia	Presence of new-onset grand mal seizure in a woman with preeclampsia	
HELLP syndrome	Platelets <100,000/μL, elevated liver transaminases twice normal, and signs of hemolysis (elevated lactate dehydrogenase or indirect bilirubin)	

caring for women in labor and delivery wards. However, ICU practitioners should become familiar with the most severe forms of hypertensive diseases of pregnancy (i.e., HELLP syndrome and eclampsia). The organ damage specific to these diseases can involve severe liver injury from subcapsular hematoma, intracranial hemorrhage from severe ranges of blood pressures, kidney failure, and hematologic abnormalities including DIC.

HELLP syndrome affects 0.1% to 0.2% of all pregnancies in the United States and is on the spectrum of hypertensive disorders of pregnancy. Women with HELLP syndrome are generally diagnosed based on laboratory parameters (Table 6). Women with HELLP syndrome have a higher maternal mortality and mortality secondary to DIC and hepatic rupture. Therefore, women with rising aspartate aminotransferase and alanine aminotransferase with dropping hemoglobin should be evaluated for a subcapsular hematoma by either sonography or computed tomography. Because of the high morbidity of disease, women are usually urgently delivered, and magnesium sulfate is given to women with both preeclampsia and HELLP syndrome for eclampsia prophylaxis. The regimen for eclampsia is 4 g intravenously over 20 minutes, then 2 g intravenously hourly while intrapartum and 24 hours after delivery.

Monitoring for magnesium toxicity is usually done by physical examination, which includes deep tendon reflexes, mental status, and urine output to ensure adequate clearance. Magnesium levels can be monitored as well, and the goal level is 4 to 7 g/dL. If eclamptic seizure occurs, a redose of magnesium sulfate of 4 to 6 grams intravenously can be given on top of the continuous infusion. In the setting of eclamptic seizures, magnesium sulfate is superior to other forms of seizure prophylaxis (i.e., benzodiazepines and phenytoin). In the setting of magnesium toxicity, which can result in lethargy (levels >8 g/dL) and cardiac arrest (levels >10 g/dL), calcium chloride 1 g intravenously or calcium gluconate 3 g intravenously should be administered. Although HELLP syndrome is highly morbid, it is by definition limited to pregnancy and should resolve within 72 hours after delivery.

In the event maternal improvement does not occur, ICU staff should consider alternative diseases. Differential diagnosis should include atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and other autoimmune disease such as systemic lupus erythematosus. These diseases may be quiescent throughout life and may be newly triggered by pregnancy.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is an incredibly rare, morbid disorder characterized by quickly progressive liver failure. Although AFLP affects 1 to 10,000 pregnancies, maternal mortality from this process can be as high as 5% to 9%, so a tertiary care center. Women with AFLP have liver abnormalities but usually to the most severe form. In AFLP, both aspartate aminotransferase and alanine aminotransferase usually are above 500 IU/L and can often be above 1000 IU/L. There are also other signs of liver failure including unexplained hypoglycemia, acidosis, an elevated direct bilirubin and altered mental status from hyperammonemia. Upon imaging, the liver shows steatosis.

Commonly, women with AFLP have coagulopathy and DIC and pose a high transfusion risk. Women with AFLP should be at centers with an efficient blood bank at time for delivery for risk of massive transfusion. Although patients with AFLP can progress to complete liver failure with renal injury, the disease is usually limited to pregnancy and after delivery patients tend to have full liver recovery within 1 week. Supportive measures such as transfusion for bleeding and DIC, mechanical ventilation for respiratory failure, extensive glucose supplementation, and ammonia-clearing agents are warranted during the recovery. For patients who have liver recovery, neither transplant nor biopsy is warranted; however, if recovery is not seen, these options should be considered to rule out other forms of failure. Because of the rarity of the disease, other forms of liver failure should be considered in reproductive age women as well. Aminoglycoside toxicity, drug induced from other medications, infections, newly diagnosed HIV, and hepatitis to name a few.

Obese Patients in the Critical Care Unit

Obesity continues to be a huge medical problem in the United States. Obesity is associated with cardiovascular disease, coronary artery disease, and diabetes as well as increased health care cost. Although obesity can cause increased complications, superobese patients (body mass index >50) may pose different challenges to critical care practitioners. Patients with superobesity and obesity are more likely to have longer length of stays in the ICU when compared with nonobese patients. They are also more likely to need noninvasive ventilation and succumb to pulmonary disease.

Postoperatively, superobesity carries risk of higher perioperative morbidity including infections, which include sepsis, septic shock, and urinary tract infections. Patients with superobesity are also more likely to have prolonged ventilatory days, unplanned or emergent intubations, renal insufficiency, and pulmonary embolism. Dosing of weight-based medications such as antibiotics and anticoagulation also pose a problem and put these patients at risk for critical illness secondary to subtherapeutic levels.

PALLIATIVE CARE AND ETHICS

In a culture of medicine that focuses on curing disease, palliative care remains an underused service in many institutions. Patients with terminable or incurable preexisting conditions are at most risk of disease-causing MODS like sepsis. The most common preexisting condition associated with palliative care is metastatic cancer; however, critical care providers should be aware the scope of palliative care can

be used in severe heart failure, pulmonary hypertension, as well as end-stage pulmonary disease.

Palliative care consultation is also not just for presenting conditions. In cases with intractable septic shock, irreparable bleeding, or organ failure without the ability to transplant, palliative care should be considered. A multidisciplinary team of the primary surgeon, intensivist, the patient or family, as well as a provider well versed in palliative medicine should discuss and determine what is "success" for these patients. Palliative care should be considered and integrated early in a diagnosis of serious illness to help facilitate treatment and patient goals.

Despite being advocated by the World Health Organization, many patients do not have palliative care initiated until the final days of life. This is likely secondary to the negative stigma that palliative care focuses on death, dying, and hopelessness. Palliative medicine is rooted in symptom control, pain management, and improved quality of life.

In patients undergoing end-of-life care, it is important for clinicians to discern what is futile in their treatment. Futile interventions are those that simply cannot accomplish the intended physiologic goal, and clinicians should not provide futile interventions. In clinical settings where there is concern for futile treatment, ethics committees should be consulted if available.

SUMMARY

This chapter attempted to provide an overview of multiple organ dysfunction that is often seen in the ICU and to describe each organ in turn. MOF is the final common pathway for many ICU patients and especially those that develop severe MODS that is not expeditiously corrected. We have described commonly used grading systems to help discern the severity of the organ dysfunction. These grading systems can be helpful in gauging the severity of and in some cases the predicted mortality for patients with MOD. We have also described select special patient populations that are increasingly encountered in the ICU. Finally, we have emphasized the importance of involving palliative care early in the course of patients that experience MODS and MOF and in necessary cases, ethics consultants when the ICU practitioner has reached the point that they deem further curative intent care to be futile.

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Antibiotics for Critically Ill Patients

Kelly A. Ervin, MSc and David J. Milia, MD

Infection remains a significant source of morbidity and mortality in the intensive care unit (ICU). As in polytrauma, acute myocardial infarction, and stroke, early identification and appropriate management of sepsis reduces mortality and improves outcomes. Although initiatives such as the Surviving Sepsis Campaign have been shown to improve outcomes, the most fundamental tenet in the management of the septic patient is source control. In surgical patients, procedural interventions are the mainstay for achieving source control in the appropriate clinical setting. To accompany this, proper antibiotic choice and duration can augment surgical control through local and systemic effects (Tables 1 and 2).

APPROACH TO ANTIBIOTIC USE IN THE CRITICALLY ILL

Sepsis in the surgical patient continues to be a challenge for surgical intensivists. Early identification of septic patients, timely implementation of therapies, and identifying the source of infection are

be used in severe heart failure, pulmonary hypertension, as well as end-stage pulmonary disease.

Palliative care consultation is also not just for processing conditions. In cases with intractable septic shock, unstoppable bleeding, or organ failure without the ability to transplant, palliative care should be considered. A multidisciplinary team of the primary surgeon, intensivist, the patient or family as well as a provider well versed in palliative medicine should discuss and determine what to "maximize" for these patients. Palliative care should be considered and integrated early to a diagnosis of serious illness to help facilitate treatment and patient goals.

Despite being advocated by the World Health Organization, many patients do not have palliative care initiated until the final days of life. This is likely secondary to the negative stigma that palliative care focuses on death, dying, and hopelessness. Palliative medicine is rooted in symptom control, pain management, and improved quality of life.

In patients undergoing end-of-life care, it is important for clinicians to discern what is futile to their treatment. Futile interventions are those that simply cannot accomplish the intended physiologic goal, and clinicians should not provide futile interventions. In clinical settings where there is concern for futile treatment, ethics committees should be consulted if available.

SUMMARY

This chapter attempted to provide an overview of multiple organ dysfunction that is often seen in the ICU and to describe each organ in turn. MOF is the final common pathway for many ICU patients and especially those that develop severe MODS that is not expeditiously corrected. We have described commonly used grading systems to help discern the severity of the organ dysfunction. These grading systems can be helpful in gauging the severity of and in some cases the predicted mortality for patients with MOD. We have also described select special patient populations that are increasingly encountered in the ICU. Finally, we have emphasized the importance of involving palliative care early in the course of patients that experience MODS and MOF and in necessary cases, ethics consultants when the ICU practitioner has reached the point that they deem further curative interventions cant to be futile.

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ANTIBIOTICS FOR CRITICALLY ILL PATIENTS

Kelly A. Boyle, MD, and David J. Milia, MD

Infection remains a significant source of morbidity and mortality in the intensive care unit (ICU). As in polytrauma, acute myocardial infarction, and stroke, early identification and appropriate management of sepsis reduces mortality and improves outcomes. Although initiatives such as the Surviving Sepsis Campaign have been shown to improve outcomes, the most fundamental tenet in the management of the septic patient is source control. In surgical patients, procedural interventions are the mainstay for achieving source control in the appropriate clinical setting. To accompany this, proper antibiotic choice and duration can augment surgical control through local and systemic effects (Tables 1 and 2).

APPROACH TO ANTIBIOTIC USE IN THE CRITICALLY ILL

Sepsis in the surgical patient continues to be a challenge for surgical intensivists. Early identification of septic patients, timely implementation of therapies, and identifying the source of infection are

TABLE 1 Antibiotic Classes and Agents Clinically Important in the Critically Ill: β-Lactam Antibiotics

β-Lactam antibiotics	Attach to penicillin-binding proteins in the cell membrane, interfering with peptide chain cross-linkages in the bacterial cell wall peptidoglycan, leading to cell lysis	
Groups	**Examples**	**Comments**
PENICILLINS		
Natural penicillins	Penicillin G	Very effective against *Streptococcus* spp., nonresistant *Enterococcus faecalis*, and *Clostridium perfringens*
Penicillinase-resistant penicillins	Oxacillin Nafcillin	Very effective against MSSA and *Streptococcus* spp.
Aminopenicillins	Ampicillin Ampicillin-sulbactam	Active against *Streptococcus* spp., MSSA, *E. faecalis*; variable activity against VRE Adding BLI extends activity against gram-negative bacilli and *Bacteroides fragilis* *Pseudomonas* is resistant …sobacterial cell resistance is rising; coverage is variable and unreliable
Ureidopenicillins	Piperacillin-tazobactam	Broad-spectrum activity including against *Pseudomonas* and anaerobes
CEPHALOSPORINS		
First generation	Cefazolin	• Active against MSSA, *Streptococcus* spp., *E. coli*, *Klebsiella*, *Proteus mirabilis*
Second generation	Cefuroxime	• Increased aerobic gram-negative activity, including against *Haemophilus* or *Moraxella*
Second generation (cephamycins)	Cefoxitin Cefotetan	• Extended activity against *B. fragilis*; resistance increasing • Methylthiotetrazole side chain inhibits vitamin K activation, resulting in rise in international normalized ratio
Third generation	Ceftriaxone Ceftazidime Cefotaxime	• Increased spectrum of activity against aerobic gram-negative bacilli • Vulnerable to inactivation by extended-spectrum β-lactamases and AmpC cephalosporinases
Third generation, antipseudomonal	Ceftazidime Cefoperazone-sulbactam Cefepime-tazobactam	• Active against *Pseudomonas*, less active against *Staphylococcus* • Adding BLI extends activity against resistant aerobic gram-negative bacilli
Fourth generation	Cefepime	• Very effective against aerobic gram-negative bacilli, including *Pseudomonas* • Able to avoid destruction by β-lactamases by rapid penetration through the cell wall • Maintains activity against *Staphylococcus* and *Streptococcus*
Fifth generation	Ceftaroline	• Broad-spectrum activity, including against MRSA and aerobic gram-negative bacilli • Inactive against *Pseudomonas*
OTHER β-LACTAMS		
Carbapenems	Ertapenem	• Broad-spectrum activity against gram-positive cocci, gram-negative bacilli, and anaerobes; readily penetrate cell membranes of gram-negative bacilli, have high affinity for penicillin-binding proteins, and are resistant to hydrolysis by β-lactamases • Ertapenem is not active against *Pseudomonas* or *Enterococcus*
AP carbapenems	Imipenem-cilastatin Doripenem Meropenem	• Seizure risk is greater than with other β-lactam antibiotics • Active against *Pseudomonas* • Doripenem is indicated for complicated intra-abdominal infections and urinary tract infections but not for pneumonia
Monobactam	Aztreonam	• Active against aerobic gram-negative bacilli, including *Pseudomonas*

BLI, β-lactamase inhibitor; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

essential to sepsis management. The practice of indiscriminate procalcitonin and initiation of broad-spectrum empiric antibiotics on all patients is falling out of favor. Instead, surgical intensivists should be taking a good history and performing a thorough physical examination to guide necessary laboratory tests, imaging studies, or interventions. Once potential sources are identified, directed culturing allows for tailored therapy. Depending on the site of infection and the clinical status of the patient, empiric antibiotics may be beneficial while cultures are pending or other interventions are being arranged. In addition to treating the infections that prompted admission to the ICU, the surgical intensivist will have to juggle the many complications that can arise in critically ill patients. Many of these complications are healthcare-associated infections related to indwelling devices, including ventilator-associated pneumonia, central line–associated bloodstream infection, catheter-associated urinary tract infection, and surgical site infection. It is imperative that every practitioner faced with the decision to start antibiotics appreciate this responsibility with good clinical stewardship. This means starting

TABLE 2 Antibiotic Classes and Agents Clinically Important in the Critically Ill: Non–β-Lactam Antibiotics

Group	Examples	Comments
Glycolipopeptides	Vancomycin Telavancin Oritavancin Dalbavancin	• Disrupts bacterial cell wall synthesis by impairing peptidoglycan synthesis • Active against gram positive cocci, including MRSA • Daptomycin and oritavancin active against VRE • Oral vancomycin effective against *Clostridium difficile* • Oritavancin and dalbavancin have very long half lives, allowing single dosing (oritavancin) or weekly × 2 dosing (dalbavancin) • Daptomycin is inactivated by surfactant, not used for pneumonia; also associated with myopathy; statins should be stopped; check CPK weekly
Polymyxins	Polymyxin B Colistin (polymyxin E)	• Cationic polypeptides that act as detergents to disrupt the bacterial cell membrane • Active against Enterobacteriaceae, *Acinetobacter*, *Pseudomonas*, and *Stenotrophomonas* • Cause significant renal toxicity
Aminoglycosides	Gentamicin Tobramycin Amikacin	• Inhibit bacterial protein synthesis by binding irreversibly to the 30S ribosomal subunit • Active against gram negative bacilli, including *Pseudomonas* (gentamicin less so than tobramycin or amikacin) • Synergistic activity with penicillins and vancomycin against *Enterococcus* and *Staphylococcus* • Exhibit concentration dependent activity and a significant postantibiotic effect • Significant incidence of renal toxicity and ototoxicity (auditory and vestibular) • Once daily dosing improves effectiveness and reduces toxicity • Limiting usage to 5 days reduces toxicity
Tetracyclines	Doxycycline Minocycline	• Inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit • Active against *Staphylococcus*, including MRSA; variable activity against VRE and *Streptococcus*
Glycylcyclines	Tigecycline	• Broad spectrum agent active against gram positive cocci (MRSA and VRE), gram negative bacilli, and anaerobes • Inactive against *Pseudomonas* • US Food and Drug Administration black box warning; should not be used as first-line therapy
Macrolides, ketolides, azalides, chloramphenicol	Erythromycin Clarithromycin Azithromycin Telithromycin Clindamycin Chloramphenicol	• Inhibit bacterial protein synthesis by reversibly binding to 50S ribosomal subunit at overlapping sites; use of 2 or more of these classes results in antagonism • Variable activity against MSSA and *Streptococcus* spp.; active against atypical bacterial • Telithromycin only active against *C. difficile* • Azithromycin and clarithromycin active against *Haemophilus influenzae* • Active against *Staphylococcus* and *Streptococcus*; 90% to 95% of *Bacteroides fragilis* • Potentially additive to clostridial and streptococcal gangrene for its ability to inhibit toxin production • Active against *Staphylococcus* (MRSA), *Streptococcus*, *E. coli*, *Klebsiella*, *H. influenzae*, anaerobes • Variable activity against VRE • Limited use because of bone marrow suppression and rare aplastic anemia
Streptogramins	Quinupristin–dalfopristin	• Inhibits bacterial protein synthesis by binding to 50S ribosomal subunit • Active against gram positive cocci, including MRSA and VRE • Inactive against *Enterococcus faecalis* • Causes severe arthralgia, myalgia, and phlebitis; infuse through central line
Oxazolidinones	Linezolid Tedizolid	• Inhibit bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit • Active against gram positive cocci including MRSA and VRE; resistance to linezolid can develop • High bioavailability; oral is as effective as intravenous • Bone marrow suppression with thrombocytopenia may occur after 10 days of treatment with linezolid; reversible after cessation • Tedizolid indicated for acute bacterial skin and skin structure infections for 6 days • Weak monoamine oxidase inhibitors; 1%–3% incidence of serotonin syndrome when given with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors • Long term use associated with reversible optic neuropathy and irreversible peripheral neuropathy

Continued

TABLE 2 Antibiotic Classes and Agents Clinically Important in the Critically Ill: Non–β-Lactam Antibiotics—cont'd

Groups	Examples	Comments
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin	• Inhibit DNA gyrase and topoisomerase IV • Active against broad spectrum of nonresistant gram-positive cocci and gram-negative bacilli, including *Pseudomonas* (not moxifloxacin) • Moxifloxacin active against 85% of *B. fragilis*, but does not cover urine and cannot treat UTIs • Concentration dependent antibacterial effect • High bioavailability, oral to an effective IV • Not approved for children <16 years, associated with joint and tendon injuries
Nitroimidazoles	Metronidazole	• Chemically reduced in the bacterial cell and disrupts the DNA helix, causing strand breakage • Active against *Bacteroides* and *Clostridium*, *Peptostreptococcus* • Often combined with cephalosporins and fluoroquinolones for intraabdominal infections • One of the main therapies for *C. difficile* colitis • Disulfiram-like reaction occurs with alcohol consumption • Not tolerated long term, associated with bone marrow suppression
Rifamycins	Rifampin	• Inhibits DNA dependent RNA polymerase • Active against MRSA and VRE • Always used in combination with other agents, may reduce development of resistance • Has many drug interactions and may be hepatotoxic
Sulfonamides	TMP/SMX	• SMX inhibits dihydropteroate synthase, TMP inhibits dihydrofolate reductase: 2 steps in bacterial folate pathway • Active against MSSA, MRSA, coagulase negative *Staphylococcus*, *Stenotrophomonas*, *Burkholderia*, *Serratia* • Inactive against *Enterococcus* (despite in vitro sensitivity)
Other	Nitrofurantoin	• Inhibits bacterial enzymes, leading to cell death • Active against VRE, *E. coli*, *Klebsiella* • Oral antibiotic, used in urinary tract infection • Macrocrystal form causes less nausea • Do not use if creatinine clearance <60 mL/min

CPK, Creatine phosphokinase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; TMP/SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant *Enterococcus*.

appropriate broad spectrum antibiotics with the discipline to narrow the spectrum when culture data results and the clinical situation allows. Evolving evidence from contemporary clinical trials should guide duration of use. Used in conjunction with adequate source control and management of alterations in physiology, this approach will yield optimal outcomes for both the patient and the healthcare system as a whole.

PATHOGENS ENCOUNTERED IN CRITICALLY ILL PATIENTS

Historically, patients admitted to the ICU from the community or early in a hospital stay were more likely to have the wild type spectrum of pathogens, including gram positive cocci and gram negative bacilli. Nosocomial infections were associated with higher rates of multidrug resistance; however, healthcare- and community acquired infections are no longer entirely distinct. The basis for this is multifactorial and includes enhanced virulence, increased antibiotic resistance, and increased transmissibility as healthcare associated infections spread to community contacts.

Community-Acquired Pathogens

Among gram positive cocci, *Staphylococcus* and *Streptococcus* are common causes of skin and skin structure infections. Methicillin susceptible *Staphylococcus aureus* (MSSA) is very sensitive to the penicillinase-resistant penicillins, oxacillin and nafcillin, and to cefazolin, a first-generation cephalosporin. Methicillin resistant *S. aureus* (MRSA) has traditionally been classified into healthcare associated (HA MRSA) and community associated; however, this distinction is becoming less clear as patients who develop MRSA colonization in one realm can develop manifestations of infection in another.

Community acquired methicillin resistant *S. aureus* (CA MRSA) is genetically distinct from HA MRSA. CA MRSA strains are classified by USA300 and USA400 clonal groups, and this smaller genetic package is thought to explain why CA MRSA is less resistant than HA MRSA. Patients with CA MRSA tend to be younger and healthier, may live in crowded conditions, or may be athletes. CA MRSA is more prevalent in intravenous drug abusers and in children younger than 2 years of age, usually presenting as cutaneous abscesses or boils. Most strains of CA MRSA are susceptible to clindamycin, trimethoprim-sulfamethoxazole (TMP/SMX), or a tetracycline and are usually resistant to macrolides and fluoroquinolones.

β Hemolytic *Streptococci*, groups A, B, C, and G, are responsible for many cases of cellulitis. Group A *Streptococcus pyogenes* can be the causative agent of streptococcal necrotizing skin and soft tissue infections. These organisms may be virulent but are susceptible to penicillin G, cefazolin, or ceftriaxone. Gram negative bacilli and anaerobes causing intraabdominal infections in the community are usually susceptible to cephalosporins with metronidazole and

to extended-spectrum penicillins with a β-lactamase inhibitor. A notable exception is *Escherichia coli*, which is commonly resistant to ampicillin/sulbactam. For this reason, ampicillin/sulbactam no longer is recommended as initial empiric therapy for intra-abdominal infections.

NOSOCOMIAL PATHOGENS

Gram-positive cocci in the hospitalized or other healthcare-associated patient include HA-MRSA, methicillin-resistant *Staphylococcus epidermidis*, and vancomycin-resistant *Enterococcus* (VRE). HA-MRSA is endemic in hospitals and healthcare facilities worldwide. Methicillin-resistant *S. epidermidis* and other coagulase-negative *Staphylococci* are common skin flora and frequently infect implanted devices such as central venous catheters. VRE overgrowth results from the selective pressure from broad-spectrum antibiotic therapy. VRE contains plasmids that confer resistance, and the VanA plasmid has been transferred to MRSA, conferring vancomycin resistance.

Clinically important members of the Enterobacteriaceae family include *E. coli*, *Klebsiella pneumoniae*, *Proteus* species, *Enterobacter* species, *Serratia* species, and *Citrobacter* species. Other important gram-negative rods are *Pseudomonas* species, *Acinetobacter* species, and *Stenotrophomonas* species. Many of these organisms have developed resistance by producing extended-spectrum β-lactamases, which hydrolyze penicillins and cephalosporins. AmpC β-lactamase hydrolyzes first-, second-, and third-generation cephalosporins. Carbapenemases that hydrolyze penicillins, cephalosporins, and carbapenems, but not aztreonam (a monobactam), are also now being observed. Some of these organisms contain plasmids that confer aminoglycoside resistance. *Clostridium difficile* can be infected not by broad-spectrum antibiotic therapy, especially by fluoroquinolones.

Multidrug resistance is a worrying problem, especially among these pathogens: *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. The Infectious Diseases Society of America launched the 10 × '20 Initiative in 2010 to encourage greater research and development of antibiotic therapies to combat these organisms, with the goal of developing 10 new antibiotics by 2020. Since 2010, the US Food and Drug Administration has approved eight new antibiotics: ceftaroline, fidaxomicin, bedaquiline, dalbavancin, telavancin, oritavancin, ceftolozane–tazobactam, and ceftazidime–avibactam.

COMMON CONDITIONS

The following is a review of common conditions encountered in surgical ICUs, and treatment descriptions are based on general recommendations. Antimicrobial flora and resistance patterns can vary considerably between regions, and antimicrobial selection should be tailored based on institutional pathogram resistance patterns.

Pneumonia

Background

Postoperative pulmonary complications are a major cause of morbidity and mortality. Pneumonia is the third most common postoperative infection and may account for 15% to 20% of all nosocomial infections. Several factors increase the risk of developing postoperative pulmonary complications, including emergency surgery, age older than 65 years, surgery lasting longer than 3 hours, heart failure, and chronic obstructive lung disease. Many of these risk factors are unmodifiable. Although the pathogenesis of postoperative pneumonia is multifactorial, endotracheal intubation is a primary risk factor. The intubated population is at high risk for colonization of the airway and aspiration of contaminated gastrointestinal tract secretions. Hosts face an opportunity to modify risk factors, and considerable effort has been invested in ICU prevention bundles as a means of mitigating ventilator-associated pneumonia (VAP). Specific strategies include head-of-bed elevation, proper circuit maintenance, reduced sedation levels, and comprehensive oral care. Like most devices, removal of endotracheal tubes as early as clinically possible allows patients to cough and expel secretions aiding in reducing the development of pneumonia. For nonintubated patients, similar techniques can be applied, but also include early mobility and incentive spirometry. New concepts suggest focusing on perioperative interventions as well, including decreasing oral bacterial load with oral cleansing and nutritional systems paired with an oral antiseptic pre- and postoperatively.

Treatment

Empiric therapy for hospital-acquired pneumonia (HAP) and VAP should include agents with activity against *S. aureus* (20%–30% of VAP isolates), *P. aeruginosa* (10%–20% of VAP isolates), and enteric gram-negative bacilli (20%–40% of VAP isolates). The choice of a specific regimen for empiric therapy should be based on knowledge of the individual patient's risk factors for multidrug resistance and prior microbiology data. Early-onset pneumonia, in which there is low risk for multidrug-resistant organisms, can be treated with ceftriaxone, a fluoroquinolone, ampicillin/sulbactam, or ertapenem. Late-onset pneumonia, in which multidrug-resistant organisms are likely, need to be treated more aggressively with empiric combination therapy to minimize the chance of coverage gaps and to decrease mortality. Cefepime, piperacillin–tazobactam, or meropenem should be combined with either a fluoroquinolone or an aminoglycoside. If MRSA is also a risk, vancomycin or linezolid should be added. Many hospitals perform surveillance screening for MRSA, especially in ICU settings, to determine necessity of MRSA coverage. Negative MRSA surveillance studies need to be interpreted within the context of local prevalence of MRSA. Once culture and sensitivity results are available, the antibiotic regimen should be refined further. *Acinetobacter* species is found in approximately 5% to 10% of VAP isolates; ampicillin/sulbactam, a carbapenem, or a polymyxin may be necessary for treatment. Inhaled aminoglycosides or colistin may play a role in difficult-to-treat pneumonias, but the results of trials are not conclusive.

Catheter-Associated Urinary Tract Infections

Background

Catheter-associated urinary tract infection (CAUTI) is among the most common nosocomial infections worldwide. Urinary catheterization is a common practice in critically ill patients (>90% of ICU patients in some series) for the purposes of bladder drainage and accurate urinary output monitoring. Age, female sex, length of ICU stay, duration of catheterization, and obesity have all been shown to be independently associated with an increased risk of CAUTI. Preventive measures focus on sterile insertion technique, the use of unobstructed closed drainage systems, early removal, and the avoidance of catheter manipulation. There are novel devices on the market with antimicrobial-impregnated materials for urinary catheters; however, infections still occur with these devices and ultimate reductions in CAUTI remain unclear.

Treatment

Uncomplicated urinary tract infections are usually susceptible to TMP/SMX. Nitrofurantoin is effective against VRE and *E. coli* but should not be used in end-stage renal failure. Ciprofloxacin and levofloxacin are also effective agents and concentrate well in the urine. CAUTIs, however, are complicated and are often polymicrobial. If CAUTI is suspected, the indwelling catheter should be removed if possible. If an indwelling catheter has been in place for more than 2 weeks at the onset of CAUTI and is still indicated, the catheter should be replaced. Ideally, antimicrobial selection should be based on the culture results when available. Empiric therapy is warranted, however, for patients with signs of systemic toxicity. Common organisms include *Enterobacteriaceae*, *Pseudomonas* species, and *Enterococcus* species. As such, ampicillin and gentamicin, piperacillin–tazobactam, a carbapenem, or a fluoroquinolone may be used. If the risk of

Enterococcus is low, cefazolin, ceftriaxone, cefuroxime, cefotaxime, ceftazidime, cefepime are appropriate choices. Deescalation or change of antibiotic should be based on culture and sensitivity results.

Surgical Site Infections

Background

Surgical site infections (SSIs) are one of the most common complications affecting surgical patients. The frequency of SSI is closely related to the category of the operation (clean, clean-contaminated, contaminated, and dirty), with clean and low risk operations having the lowest incidence, and contaminated cases having higher infection rates. Should an infection arise at the surgical site, the classification is differentiated by the depth of the process:

- *Superficial:* Skin and subcutaneous tissue
- *Deep:* Deep soft tissues of the incision (fascia and muscle layer)
- *Organ/space:* Any part of the body deeper than the fascia or muscle layer that was opened or manipulated during the operative procedure

SSIs rarely occur during the first 48 hours after surgery. SSIs occurring during this time frame are almost always the result of *S. pyogenes* or *Clostridium* species. In general, SSIs usually require an additional procedure to ensure proper source control, and antibiotic therapy should only be used as an adjunct.

Treatment

Clinical practice guidelines exist to aid selection of appropriate antimicrobial prophylaxis for most surgical cases. The standardized approach offers the most effective use of antimicrobial agents for the prevention of SSIs based on current clinical evidence. In general, the prophylactic antibiotic targets the flora that may be present in the anatomy that is to be exposed. In the perioperative setting, antibiotic choice for SSI follows a similar mindset. An SSI from a clean case would likely target skin flora. Mild infections that require only oral therapy can be treated with cephalexin or dicloxacillin. If there is concern for MRSA, TMP/SMX, clindamycin, minocycline, or doxycycline can be used. More severe skin infections can be treated with cefazolin or vancomycin for MRSA. Daptomycin, telavancin, ceftaroline, linezolid, or tedizolid also may be used.

SSIs after clean-contaminated, contaminated, or dirty cases involving the gastrointestinal or genitourinary tract may be caused by skin flora and/or gram negatives and anaerobes. Antimicrobial options with action against aerobic gram negative bacilli and *Bacteroides fragilis* include ceftazidime, ceftazidime avibactam, ceftolozane tazobactam, cefepime, or a fluoroquinolone with metronidazole. Piperacillin tazobactam and antipseudomonal carbapenems can be used as single agents. Vancomycin or linezolid should be used if MRSA is likely. If cultures can be obtained, antibiotics should be deescalated or changed based on the results of culture and sensitivity.

Vascular Access Device–Related Infections

Background

Vascular access for the purposes of monitoring, fluid resuscitation, nutrition, and medication administration is often necessary in critically ill patients; however, up to 80,000 central venous catheter–related bloodstream infections occur in ICUs every year. Risk of bloodstream infection varies according to the intravascular device, the insertion site, experience of individual placing the catheter, frequency the catheter is accessed, and duration the catheter remains in place. Regardless of the device, standardized insertion and device maintenance bundles aimed at infection prevention should be used. These strategies generally involve proper hand hygiene, skin antisepsis, full barrier precautions at insertion, proper catheter site maintenance, and removal of the device as early as the clinical situation allows.

Treatment

Most catheter-associated infections are caused by skin flora, namely, *S. aureus* and *S. epidermidis*. Once a local infection or bacteremia is diagnosed, the catheter should be removed if possible. Vancomycin is recommended for empiric therapy in settings with a high prevalence of MRSA. If there is concern for aerobic gram negative bacilli, as in immunocompromised or burn patients, then cefepime, piperacillin tazobactam, or an antipseudomonal carbapenem should be added. Femoral catheters, catheters used for total parenteral nutrition, and catheters in immunocompromised patients may be infected with *Candida*, in which case an echinocandin should be added. Fluconazole could be considered in select patients without recent azole exposure or with low risk of *Candida krusei* or *Candida glabrata* infection. As always, deescalation is appropriate once culture and sensitivity results are available.

Abdominal Sepsis

Gastrointestinal Tract

Complicated intraabdominal infections remain a common problem, with a wide range of severity and resulting morbidity and mortality. After initial intravenous fluid resuscitation and stabilization, source control and antimicrobial therapy remain the mainstays of treatment.

Treatment

Antimicrobial regimens for intraabdominal infections should have activity against typical gram negative Enterobacteriaceae, gram positive cocci, and anaerobes. Infections of mild to moderate severity, including perforated appendicitis and diverticulitis in which there is no physiologic impairment, can be treated with first-, second-, or third-generation cephalosporins or fluoroquinolones with metronidazole. Appropriate single agents include cefoxitin, moxifloxacin, ertapenem, and tigecycline. Ampicillin/sulbactam should not be used as empiric therapy because of the high rate of resistance of *E. coli*. In patients who have undergone adequate source control, outcomes after shorter duration antibiotic therapy (4 days) are equivalent to those after a longer course of antibiotics (8 days). Severe infections with physiologic compromise should be treated with cefotaxime, ceftazidime avibactam, ceftolozane tazobactam, cefepime, or a fluoroquinolone with metronidazole. Piperacillin tazobactam and antipseudomonal carbapenems are appropriate single agents. Consider adding an aminoglycoside when there is a high rate of resistant *Pseudomonas* and extended-spectrum β-lactamase–producing Enterobacteriaceae in hospitalized patients. If MRSA is considered, add vancomycin or linezolid to the regimen. Deescalation or change in antibiotic therapy is warranted based on culture and sensitivity reports. Of note, *B. fragilis* may not grow but should be expected and treated.

Infections of the Biliary Tree

Biliary tree infections can arise primarily from ductal structures (cholangitis) or secondarily from stasis with or without obstructive causes (acute cholecystitis, acalculous cholecystitis, cholelithiasis). The mainstay of treatment is still adequate source control or appropriate drainage and effective antibiotic therapy.

Treatment

Cholecystitis is inflammatory in etiology and not always infectious; however, in patients undergoing cholecystectomy for acute cholecystitis, antimicrobial therapy may be added in the perioperative setting. Cholecystitis of mild to moderate severity can be treated with a first-, second-, or third-generation cephalosporin. Antibiotics should be discontinued within 24 hours if operation unless there is evidence of infection outside the wall of the gallbladder. More severe infections, including those in patients with biliary obstruction, biliary stent, malignancy, recent hospitalization, or in immunocompromised hosts are more likely to be drug-resistant or anaerobic. Piperacillin tazobactam and carbapenems are effective against gram negative aerobes and

ll, fogle. Fluoroquinolones, cefepime, cefotaxime (cefotaxime, and ceftriaxone with or without metronidazole.

C. Difficile Colitis

C. difficile is the most common cause of healthcare-associated infection in adults in the United States. Importantly, community-acquired C. difficile infection (CDI) is on the rise. There is a wide spectrum of disease, ranging from mild diarrhea to fulminant colitis, multiple organ failure, and death. Best methods for diagnosis remain controversial, but new guidelines suggest that physicians should only test patients with new onset and unexplained diarrhea involving three or more unformed stools in 24 hours. Given the significant burden on morbidity and mortality in surgical patients, a multidisciplinary approach is paramount, including early recognition, strict hand hygiene, contact precautions, evidence-based treatment strategies, and antibiotic stewardship to combat this potentially fatal pathogen.

Treatment

Resistance to current treatments and increase in treatment failure have presented clinical challenges and compelled changes to practice. Oral metronidazole used to be the mainstay of treatment of C. difficile colitis; however, new guidelines recommend oral vancomycin or fidaxomicin for an initial episode of CDI, which demonstrate higher cure rates than metronidazole. If impairment of the gastrointestinal tract is present, such as ileus or bowel discontinuity, and oral vancomycin would not reach the colon effectively, vancomycin enemas should be considered. Intravenous metronidazole should be administered with oral or rectal vancomycin if ileus is present. Recurrence is often treated with vancomycin as a tapered and pulsed regimen. Fecal microbiota transplantation should be used to treat patients with two or more recurrences of CDI, along with individuals who did not respond to traditional antibiotic treatment. Evidence for probiotics is mixed, and overall there are insufficient data to recommend probiotics for prevention of CDI. If surgical management is necessary for severely ill patients with fulminant CDI or megacolon, perform a subtotal colectomy with preservation of the rectum. An alternative approach is to create a diverting loop ileostomy, perform intraoperative colonic lavage, followed by antegrade vancomycin instillations postoperatively.

Necrotizing Soft Tissue Infections

Necrotizing skin and soft tissue infections (SSTIs) differ from milder, superficial infections by clinical presentation, operative management, and treatment strategies. Aggressive infections often mainly lead to necrosis of one or more layers of the skin, subcutaneous tissues, fascia, or muscle. These infections are potentially devastating because of the risk of major tissue destruction and death. The initial skin lesion may be innocuous, but as it progresses, there is local cellulitis, edema, pain, and possible gangrene that may be accompanied by systemic toxicity and septic shock. When suspected, early antibiotic therapy resuscitation, and surgical debridement should be sought immediately.

Treatment

Surgical intervention is the primary therapy for necrotizing SSTIs, but antimicrobial therapy should be administered until further debridement is no longer necessary, the patient has improved clinically, and fever has been absent for 48 to 72 hours. Because necrotizing SSTIs may be monomicrobial or polymicrobial, empiric antibiotic therapy should be broad spectrum initially, including MRSA coverage. Vancomycin, linezolid, or daptomycin may be continued with (1) piperacillin-tazobactam, (2) a carbapenem (imipenem-cilastatin, meropenem, and ertapenem), (3) fourth-generation (cefepime) or fifth-generation (ceftaroline) cephalosporins plus metronidazole, or (4) a fluoroquinolone plus metronidazole. Clindamycin or linezolid are often added because they suppress the streptococcal toxin and cytokine production responsible for toxic shock syndrome.

As culture results become available, deescalation of antibiotics is appropriate. If clostridial or group A streptococcal gangrene is identified, high-dose penicillin G with clindamycin is effective. Staphylococcal infections may be treated with vancomycin or daptomycin with clindamycin (for toxin inhibition). Alternatively, linezolid can be used as a single agent as it offers MRSA coverage and inhibits toxin production. Known MSSA infections can be treated with oxacillin or nafcillin with clindamycin.

Fungal Infections

Infection due to Candida species is largely a condition associated with medical progress and ranges from superficial mucosal infections to invasive disease associated with candidemia and metastatic organ involvement. Candidemia is associated with up to 47% attributable mortality. There are at least 15 distinct Candida species that cause human disease, but more than 90% of invasive disease is caused by the 5 most common pathogens: C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. Candida species may be causative agents in catheter infections, especially if the catheter is used for total parenteral nutrition. Early removal of the contaminated central venous catheter is associated with better outcomes. Candida peritonitis may complicate a perforated viscus. Candida rarely causes pneumonia or empyema unless the patient is immunocompromised. Aspergillus may infect burn wounds and can be found as pulmonary "fungus balls." Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. Preferred empiric therapy for suspected candidiasis in immunogenic patients in the ICU is an echinocandin. Fluconazole is acceptable for patients with documented C. albicans and no recent azole exposure. C. krusei and C. glabrata are resistant to fluconazole and should be treated with an echinocandin or voriconazole. Voriconazole is also effective for Aspergillus. Recommended duration of empiric therapy for suspected invasive candidiasis in these patients who improve is 2 weeks, the same as for documented candidemia. For patients with no clinical response to empiric antifungal therapy at 4 to 5 days and no evidence of invasive candidiasis based on laboratory results, strongly consider stopping antifungal therapy.

Suggested Readings

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Endocrine Changes in Critical Illness

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Critical illness results in changes in whole body homeostasis, largely affecting the release of mediators affecting serum cortisol levels as part of the stress response. Alterations in acute critical illness include increased serum catecholamine levels, cortisol levels, insulin insensitivity, and changes in thyroid hormone levels. Both the hypothalamic pituitary adrenal (HPA) and the hypothalamic pituitary thyroid (HPT) axes are affected resulting in multiple endocrine changes. Given that these endocrine changes have been postulated to be adaptive responses to stress, it is controversial whether interventions to restore these axes to their normal state are necessary or beneficial. This chapter reviews the changes in endocrine function resulting from critical illness and the evidence for interventions to address these changes.

ADRENAL INSUFFICIENCY

Acute stress and critical illness activate the HPA axis, resulting in release of corticotropin releasing hormone and arginine vasopressin from the hypothalamus that stimulate the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). In turn, ACTH activates the adrenal cortex to synthesize and release glucocorticoids, mainly cortisol, into the circulation. Regulation of the HPA axis occurs through a feedback loop. Elevated circulating cortisol levels provide negative feedback to suppress corticotropic releasing hormone and ACTH production (Fig. 1). Cortisol acts on the adrenal medulla to stimulate secretion of epinephrine and norepinephrine, resulting in the fight or flight response to stress and acute illness. Increased cortisol levels result in metabolic, cardiovascular, and immune effects. Cortisol mobilizes glucose for utilization by the brain and heart by increasing liver gluconeogenesis and decreasing glucose uptake by muscle and other tissues; improves hemodynamics by maintaining the responsiveness of vascular smooth muscle to catecholamines; inhibits the inflammatory response to injury; and suppresses the immune response.

It was previously thought that elevated cortisol levels seen during acute illness were due to stress induced activation of the HPA axis. On further investigation, ACTH was found to be unexpectedly low in critically ill patients. This relationship was deemed the ACTH-cortisol dissociation. There is now good evidence that elevated cortisol found in cases of severe and chronic critical illness is mediated outside of the HPA axis. There are several mechanisms that may explain this finding. Systemic inflammatory cytokines tumor necrosis factor α and interleukin-6 may independently stimulate cortisol production and are found to correlate positively with cortisol levels in critically ill patients. Increased sensitivity of the adrenals is unlikely, given that critically ill patients show a decreased response to corticotropin stimulation tests. Additionally, suppressed levels of cortisol metabolizing enzymes could explain reduced cortisol clearance. During critical illness, cortisol metabolizing enzymes such as A-ring reductases in the liver and 11β HSD2 in the kidneys are suppressed. Bile acids are known competitive inhibitors of both 11β-HSD2 and A-ring reductase, and cholestasis is often seen in critically ill surgical patients.

The concept of an inadequate response of the HPA axis and systemic cortisol resistance seen during stress has been termed *relative adrenal insufficiency* or *critical illness related corticosteroid insufficiency*. Symptoms and signs of adrenal insufficiency are often vague and nonspecific, such as weakness and fatigue, anorexia, nausea, and vomiting, abdominal pain, fever, and tachycardia. In critically ill patients, consideration for adrenal insufficiency should be triggered by the presence of hemodynamic instability refractory to adequate fluid resuscitation and vasopressor administration. Unfortunately, there are neither accurate diagnostic criteria nor strong evidence to guide indications for treatment of relative adrenal insufficiency. Measurement of total cortisol is problematic in that there is lack of uniformity in the accuracy of the tests; measurement of total serum cortisol levels does not reflect free, biologically active cortisol levels; and there is variability in the hourly secretion of cortisol. In addition, the synthetic ACTH stimulation test is unhelpful in making the diagnosis. In a large, multicenter randomized trial of glucocorticoids in septic shock, the results of this test did not predict responsiveness to glucocorticoid treatment. Other tests that have been considered include stimulation with low dose synthetic ACTH, at 1 μg, and measurement of salivary cortisol; however, neither of these tests has been extensively studied in critically ill patients.

The utility of treating septic shock with corticosteroids (either glucocorticoids or mineralocorticoids) remains controversial. Historically, two randomized, controlled trials, Corticosteroid Therapy of Septic Shock, reported contradictory mortality benefit with supplemental corticosteroids in septic shock. Similarly, two subsequent, large scale, multicenter trials—Activated Protein C and Corticosteroids for Human Septic Shock and Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock—reported conflicting mortality benefit under similar clinical scenarios. Each of these studies reported accelerated shock reversal in the treatment groups, however (Table 1). Meta analyses from 2018 report an mortality benefit at 28 or 90 days with corticosteroid treatment in septic shock. There is low-quality evidence that there is faster shock reversal, faster wean from the ventilator, and shorter intensive care unit (ICU) length of stay. Tapering corticosteroids after resuscitation of hemodynamic status was previously recommended. New data suggest tapering after treatment for septic shock is not necessary and may be harmful.

Adjuncts to hydrocortisone may be beneficial in patients with septic shock. Vitamin C, which is acutely depleted in sepsis, reduces organ injury and improves survival in experimental models. The combination of vitamin C, corticosteroids, and thiamine may act synergistically in and in sepsis survival. In 2017, Marik et al. published a small, retrospective before-and-after study evaluating the addition of intravenous vitamin C and thiamine to hydrocortisone in patients with septic shock. Although there were numerous limitations to this study, the authors found the treatment group to have rapid reversal of shock physiology, no patient progressed to multi organ damage resulting from sepsis, and there was a significant decrease in hospital mortality from 40.4% in the control group to 8.5% within the treatment group. There are multiple randomized trials under way aiming to validate these results.

HYPERGLYCEMIA

Impaired glycemic regulation and insulin resistance are often seen in critical illness. Under normal physiologic conditions, blood glucose is maintained by a balance of pancreatic secretion of insulin and glucagon, hepatic gluconeogenesis, and peripheral glucose uptake. Glucose is transported across cellular membranes by carrier mediated facilitated transport by five glucose transporter isoforms (GLUT 1–5). Three of the isoforms, GLUT 1, GLUT 2, and GLUT 4, are important regulators of glucose uptake. GLUT 1 is found in many tissues and is responsible for basal glucose uptake. GLUT 2 mediates uptake and release of glucose by hepatocytes and regulation of glucose stimulated insulin secretion in the pancreas. GLUT 2 allows the liver to be permeable to glucose, ensuring that glucose transport is not rate limiting for hepatic glucose uptake.

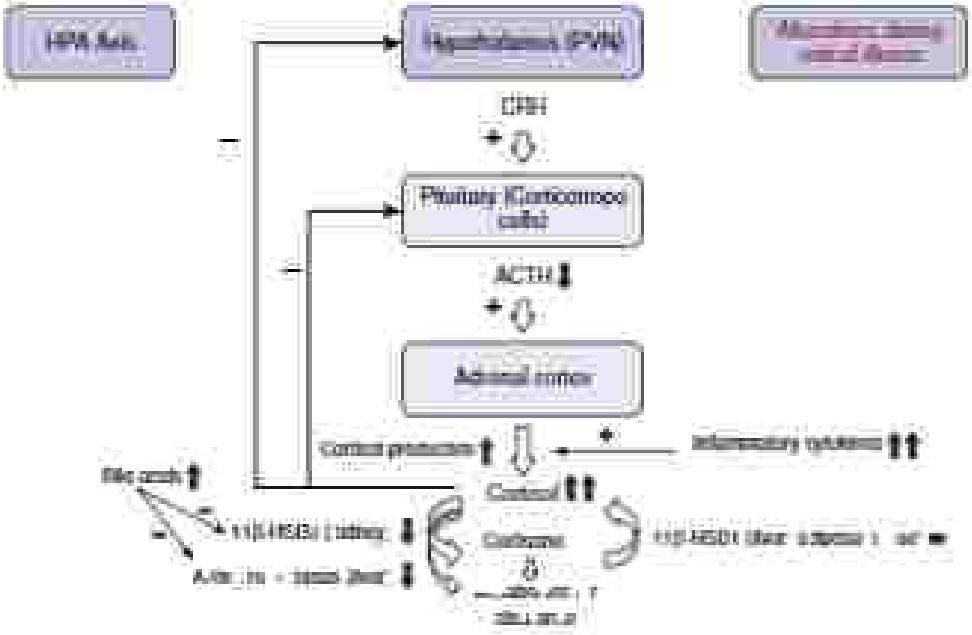

FIG. 1. Simplified overview of the regulation of the hypothalamic-pituitary-adrenal axis and cortisol production during critical illness. ↑, increase; plasma concentrations; ↓, decrease; plasma concentrations; +, stimulation; −, inhibition; ACTH, adrenocorticotropic hormone; PVN, paraventricular nucleus. (Modified from Pickkers P, Jansen J, Lorente JA, et al. Stress hormones and the immune response in acute renal failure. Kidney Int. 2004;66(2):770–776.)

Glucose stimulates insulin release by facilitated transport via GLUT 2, expressed on the surface of pancreatic beta cells. Insulin has potent antiinflammatory effects, although the exact mechanism of this in critical illness is not clear. One potential mechanism is insulin-mediated release of nitric oxide from the endothelium. Nitric oxide downregulates the expression of endothelial cell adhesion molecules and pro-inflammatory cytokines.

Marked insulin resistance and glucose dysregulation are frequently features of sepsis and critical illness. During sepsis, insulin-induced tyrosine phosphorylation of insulin receptor substrate 1 and subsequent activation of phosphoinositide 3 kinase is impaired, resulting in defective GLUT 4 receptor translocation, diminished glucose uptake, insulin resistance in skeletal muscle, and hepatic insulin resistance (Fig. 2). This dysfunctional glycemic regulation in critical illness, termed stress hyperglycemia, results in increased energy expenditure, changes in substrate utilization, and negative nitrogen balance (Fig. 3). Stress hyperglycemia improves with resolution of the underlying insult.

Multiple studies published over the past two decades have reported an association between uncontrolled stress hyperglycemia in hospitalized patients and poor clinical outcomes such as increased surgical site and healthcare acquired infections. Hyperglycemia contributes to a decrease in postoperative neutrophil phagocytic activity and decreases the oxidative burst of leukocytes, which may contribute to post operative infection susceptibility. Critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate than patients who are normoglycemic. In 2001, a landmark single-center randomized trial, the Leuven trial, reported that tight glycemic control with an insulin infusion to target glucose levels of 80 to 110 mg/dL resulted in improved outcomes as compared to conventional control to target levels of 180 to 200 mg/dL. The most significant benefit of tight glycemic control was a reduction in mortality resulting from multiple organ failure in septic patients. Other benefits included decreases in bloodstream infections, acute renal failure requiring dialysis or hemofiltration, median number of red blood cell transfusions, and critical illness polyneuropathy. Although tight glycemic control with intensive insulin therapy was widely adopted, its benefit has not been substantiated in subsequent trials. Furthermore, in 2009, a multicenter randomized trial, the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation trial, demonstrated increased mortality in patients receiving tight glycemic control. Severe hypoglycemia (blood glucose <40 mg/dL) was reported in 6.8% of patients receiving intensive glycemic control vs 0.5% in patients receiving conventional glycemic control. No significant difference between the two groups was noted in terms of median number of days in the ICU, number of days on mechanical ventilation, need for renal replacement therapy, or number of days in the hospital. Multiple explanations have been offered for the differences between these studies, both with regards to biological mechanisms and clinical trial methodology. In particular, the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation trial had less risk of bias and more generalizability given its heterogeneous patient population and pragmatic trial design.

Although current glycemic targets are debated, several societies have advanced recommendations based on best available evidence. Across societies, the recommended glucose target range for critically ill patients is less than 180 to 200 mg/dL. In addition, the Society of Critical Care Medicine convened a task force regarding recommendations for insulin infusion therapy for management of hyperglycemia in critically ill patients. Despite the very low quality of evidence, they recommend initiation of insulin therapy at a blood glucose of 150 mg/dL and maintenance of glucose levels below 180 mg/dL. Optimally, glycemic targets must be achievable with low rates of hypoglycemia (<70 mg/dL) given the association between hypoglycemia and increased mortality. Therefore, individual intensive care units need to carefully evaluate their insulin protocols and monitoring processes to ensure reasonable rates of hyper- and hypoglycemia. Furthermore, patients on insulin infusions should be transitioned off using basal and bolus insulin rather than sliding scale insulin regimens. Basal-bolus insulin regimens based on long acting insulin (i.e., glargine) have been associated with improved glycemic control and reduced surgical site infections in noncritically ill surgery patients.

Additional strategies are under investigation in terms of their impact on glycemic control and clinical outcomes. Glucose-insulin therapy, whereby high glucose and high insulin infusions are simultaneously administered, has metabolic and immune effects that theoretically could improve outcomes. It has been evaluated in multiple randomized trials in cardiac surgery, but the results are mixed, and it is not currently recommended for routine use. Nutritional strategies for improving glycemic control such as diabetic formulas (i.e., low in carbohydrates and high in monounsaturated fatty acids), hypocaloric feeds, and glutamine supplementation have been studied as well. Although diabetic formulas and glutamine show promise in terms of intermediate outcomes such as rates of hyperglycemia and

TABLE 1 Select Randomized, Controlled Trials Investigating Mortality Benefit With Corticosteroid Treatment for Septic Shock

Trial	N	Inclusion Criteria	Treatment[a]	Shock Resolution	28-Day Mortality			Other Results	Conclusion
					Control (%)	Treatment (%)	OR or RR		
Cor Ins (CRIT, Annane et al)	299	Septic shock with hypotension resistant to >1 hr vasopressors and fluid resuscitation	Hydrocortisone + fludrocortisone, 7 days, no taper	Vasopressor withdrawal, median 7 days vs 9 days	61	55	Adjusted OR: 0.65 (95% CI: 0.32–1.07)	Effects enhanced in nonresponders to corticotropin stimulation test	↓ 28-day mortality ↓ Duration of vasopressor administration
CORTICUS (2008, Sprung et al)	499	Septic shock with hypotension resistant to >1 hr vasopressors and fluid resuscitation	Hydrocortisone, 5 days, 6 day taper	Reversal of shock, median 3.3 days vs 3.8 days	32	34	RR: 1.09 (95% CI: 0.84–1.41)		– 28-day mortality ↓ Duration of shock physiology
APROCCHSS (2018, Annane et al)	1241	Septic shock <24 hr and hypotension resistant to >1 hr vasopressors and fluid resuscitation >2 dysfunctional organ systems	Hydrocortisone + fludrocortisone, 7 days, no taper	In 28 days after randomization, organ failure free; mean 14 days vs 12 days	35.7	38.9	RR: 0.87 (95% CI: 0.75–1.01)	Primary outcome: 90 day mortality 43% vs 49% (RR, 0.88; 95% CI: 0.78–0.99)	↓ 90 days, ICU discharge, hospital discharge mortality ↓ Duration of vasopressor use ↓ Duration of mechanical ventilation use ↓ Duration of shock physiology
ADRENAL (2018, Venkatesh et al)	3658	Septic shock and hypotension resistant to >1 hr vasopressors and fluid resuscitation Mechanical ventilation	Hydrocortisone continuous infusion, 7 days, no taper	Resolution of shock, median 3 days vs 4 days	23.4	22.3	OR: 0.89 (95% CI: 0.76–1.03)	Primary outcome: 90-day mortality no difference	– 90 day mortality ↓ Duration of shock physiology ↓ Blood transfusion ↓ Time to ICU discharge

[a]Hydrocortisone given in 50-mg intravenous bolus every 6 hr; the ADRENAL study used a continuous infusion of 200 mg daily. Fludrocortisone 50 µg was given by mouth daily. – Not specified; ADRENAL, Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock; APROCCHSS, Activated Protein C and Corticosteroids for Human Septic Shock; CI, confidence interval; CORTICUS, Corticosteroid Therapy of Septic Shock; ICU, intensive care unit; OR, odds ratio; RR, risk ratio.

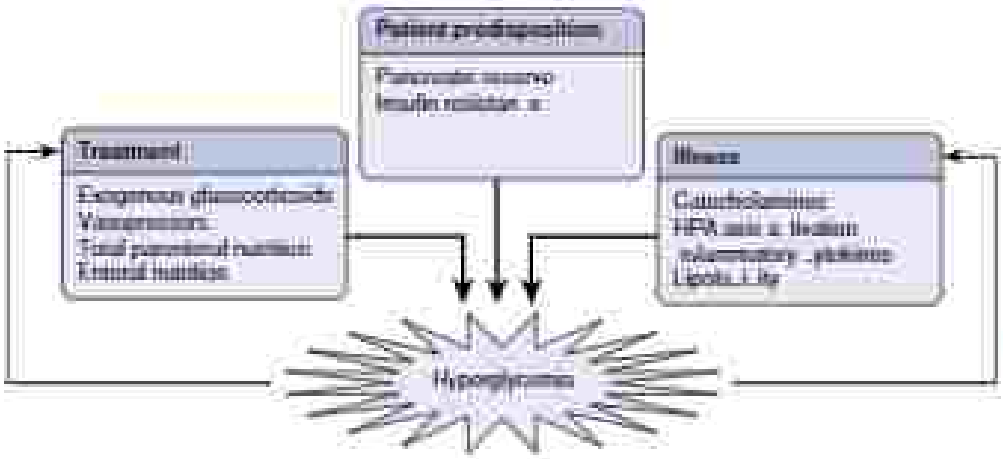

FIG. 2 Multifactorial causes of hospital-related hyperglycemia. (From Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798-1807.)

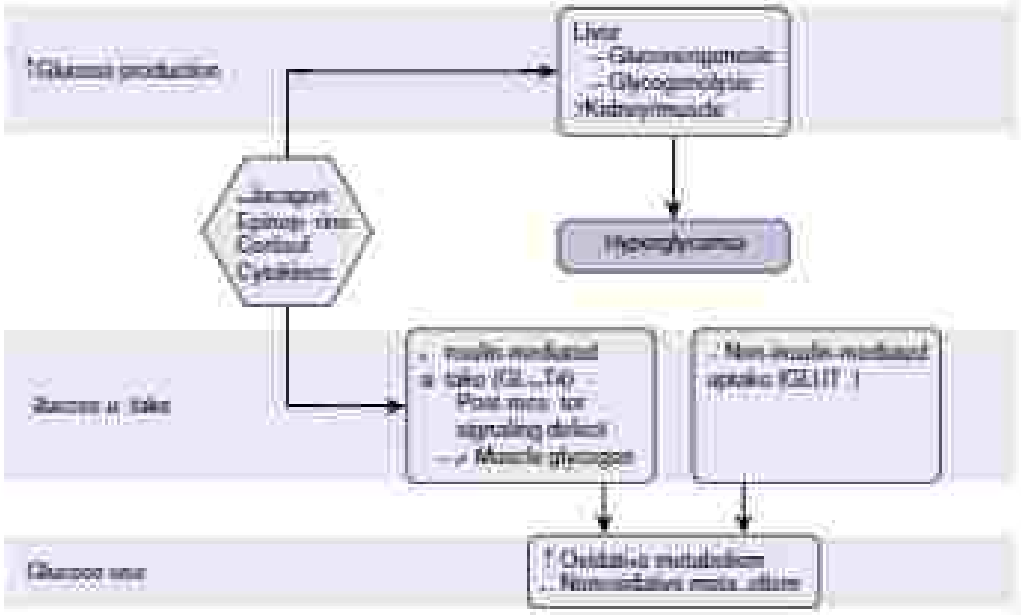

FIG. 3 Glucose metabolism in acute hyperglycemia. (From Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798-1807.)

hyperglycemia, some of these therapies have been demonstrated to improve clinical outcomes. Improved strategies for delivering insulin therapy such as use of short acting insulin infusions, continuous glucose monitoring in the inpatient and intensive care setting, and development of closed loop control systems are also promising, although further study is needed.

THYROIDAL DYSFUNCTION

The HPT axis modulates the neuroendocrine response in both healthy and critically ill patients. Abnormalities in thyroid hormone concentrations without evidence of coexisting thyroid or pituitary gland disease are commonly seen in a wide variety of illnesses including septic shock, myocardial infarction, burn injury, acute trauma, and major surgery. In healthy patients, serum levels of thyroid hormones are regulated through a feedback loop. Neurons in the paraventricular nucleus of the hypothalamus synthesize thyrotropin-releasing hormone, which in turn stimulates the anterior pituitary gland to synthesize and release thyroid-stimulating hormone (TSH) or thyrotropin in a diurnal and pulsatile manner. Binding of TSH to receptors on thyroid follicular cells results in the release of thyroid hormones into the circulation: 90% as tetraiodothyronine (thyroxine [T_4]) and 10% as triiodothyronine (T_3). Free thyroid hormone composes less than 1% of total circulating T_4 and T_3; the rest are bound to thyroxine-binding globulin, transthyretin, and albumin in that order. Once taken up by the target tissues, T_4, which acts as the prohormone, is acted upon by deiodinases 1, 2, and 3 (D1, D2, and D3). Depending upon the location of the iodine that is removed, T_4 can either be converted to its active form, T_3, or to an inactive form, reverse T_3 (rT_3). Serum thyroid hormone provide negative feedback to the hypothalamus and pituitary gland, which regulate TSH secretion (Fig. 4).

Critical illness is associated with profound changes of the neuroendocrine axis including abnormalities in thyroid hormone concentrations. Changes in thyroid hormone levels differ from those seen in primary and secondary thyroid disorders and are referred to by several interchangeable names: euthyroid sick syndrome, low T_3 syndrome, and nonthyroidal illness syndrome (NTIS). These changes include low plasma concentrations of T_3, low or normal plasma concentrations of T_4, or elevated plasma rT_3 in the presence of normal TSH. NTIS has specific measurable changes in thyroid hormone parameters in addition to having alterations in both the central regulation of the thyroid axis and in the peripheral conversion of thyroid hormone at the tissue level.

In acute critical illness, total and free T_3 levels decrease rapidly, whereas plasma concentrations of rT_3 rise within a few hours of

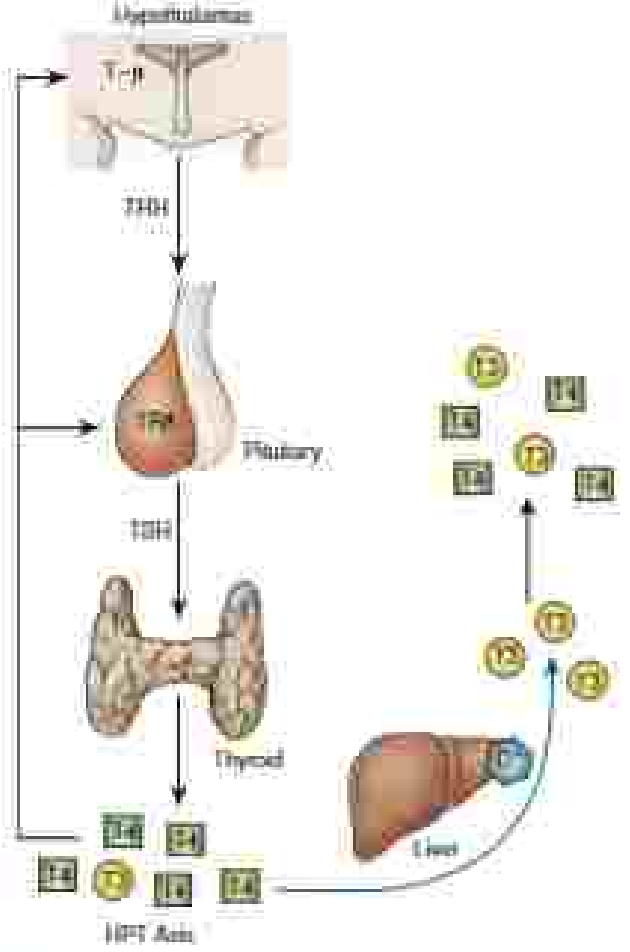

FIG. 1 posthumous pituitary-thyroid axis. D1, Deiodinase 1; T_3, thyroid hormone receptor β; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_4, thyroxine. *From Araujo JA, Fonseca JJ, Moreira CA. Thyroid hormone metabolism in skeletal muscle-brain and adult brain neurotransmission. Endocr Rev. 2021;42(1):1–15.*

the fasting event. An acute alteration in the peripheral conversion of T_4 occurs because of decreased D1 activity and an increased D3 activity, thereby contributing to decreased conversion to T_3. Meyer et al. found no statistical difference between T_3 and free T_4 levels on admission compared to values obtained at 2 days and at discharge from ICU in critically ill patients. Notably, free T_4 levels significantly decreased in nonsurvivors and increased in survivors. Meyer et al. further showed that median T_3 levels on ICU admission were lower in septic patients as compared to those with a systemic inflammatory response syndrome. The lowest T_3 levels were found in patients with septic shock. The mechanism of the acute decrease in T_3 has not been completely elucidated; however, decreases in plasma concentrations of thyroid hormone binding proteins and albumin, in addition to inhibition of hormone binding, transport, and metabolism by elevated levels of free fatty acids and bilirubin, are important mediators of T_4 to T_3 conversion in acute illness.

In prolonged critical illness, T_3 levels remain low and rT_3 levels remain elevated. Total and free T_4 levels decline. TSH secretion dampens and loses its diurnal rhythm. Factors responsible for hypothalamic suppression during prolonged critical illness are not clear. A local increase in D2 activity in the hypothalamus may elevate local thyroid hormone levels, altering the set point for feedback inhibition. Additionally, unlike to acute injury, peripheral tissues in the prolonged phase of critical illness adapt by increasing thyroid hormone transporters, activating local thyroid hormone, and increasing gene expression of active receptors. For example, the majority of T_3 is produced by peripheral 5′-deiodination of T_4 to T_3 in organs such as muscle, liver, and kidney. This conversion is done by the enzyme 5′-monodeiodinase, which has decreased enzymatic activity when calorie intake is low and in fatal illness. T_3 is also inhibited by high concentrations of serum cortisol, free fatty acids, cytokines (such as interferon α, nuclear factor κB, and interleukin 6), and medications including amiodarone and propranolol. Furthermore, patients with critical illness often have circulating substances such as inflammatory mediators that inhibit T_4 binding to proteins, which results in a reduction in total serum T_4 concentrations and low serum free T_4 levels. The reduced circulating T_3 levels in sick patients may be due in part to a decreased peripheral T_4 deiodination by D1 or D2, or both.

Because of the changes that occur in the HPT axis, newly diagnosing primary thyroid disorders in acute illness is controversial. Both primary hypothyroidism and NTIS can result in elevated TSH levels. Although a normal TSH rules out primary hypothyroidism in healthy patients, TSH may be low in patients with primary hypothyroidism and NTIS. Furthermore, drugs may contribute to a paradoxically low TSH level. Primary hypothyroidism is usually accompanied by decreased T_3 and T_4 levels, which can also be seen in patients with prolonged critical illness or during recovery from NTIS. A high serum T_3 to T_4 ratio, a low serum rT_3, and a low thyroid hormone binding ratio may be more supportive of primary hypothyroidism; but the diagnostic accuracy of these tests is limited. Longitudinal follow-up with repeated testing after recovery from critical illness is necessary to confirm the diagnosis. Primary hyperthyroidism should be considered in patients with elevated serum T_3 and T_4 levels, given the rarity of this finding due to critical illness.

The management of thyroid dysfunction in the setting of known or suspected underlying disease is different from that for NTIS. If a patient is known to have preexisting primary hypothyroidism, the previous dose of thyroid replacement medication is continued. If a patient has myxedema coma, treatment is comprised of thyroid hormone replacement, treatment of the underlying condition, and supportive care such as passive rewarming, vasopressor therapy, and antibiotics as indicated. Intravenous glucocorticoids are recommended because of the possibility of concomitant adrenal insufficiency. If a patient has thyroid storm, treatment includes thionamides such as either propylthiouracil or methimazole followed by iodine administration. Hyperadrenergic symptoms can be treated with β-blockers, and glucocorticoids should be administered if adrenal insufficiency is suspected.

The question of whether NTIS warrants treatment is controversial. To date, there is no convincing evidence that treatment of NTIS is either needed or beneficial. Thyroid hormones have been evaluated in several small, underpowered trials in heterogeneous patient populations. For example, in a study of severely burned patients given daily T_3, no beneficial or detrimental effect was noted; however, improved myocardial function and the need for reduced amounts of vasopressor have been observed with T_3 infusion in adults undergoing coronary artery bypass surgery. Although there may be subgroups of patients for whom short-term benefits may exist such as heart failure patients, there are no outcome data demonstrating clear benefit in terms of long-term morbidity and mortality. Initial studies by Van den Berghe et al. in patients with severe NTIS showed that combination of TSH, growth hormone releasing hormone, and growth hormone releasing peptide 2 reduces protein catabolism by restoring physiologic hormone levels. However, the lack of association of low T_3/free T_4 in this study fails to lend evidence to the potential usefulness of thyroid hormone treatment in critically ill patients. Surrogate outcomes such as circulating thyroid hormone levels and markers of metabolism were improved, but there was no impact on morbidity or mortality.

Treatment of NTIS with thyroid hormones is fraught with challenges. First, thyroid hormone doses that are required for normalization of serum levels may result in high tissue levels. Second, pharmacologic doses of thyroid hormones can suppress the HPT

axis, resulting in utilization and depletion of thyroid reserves. Last, thyroid hormone treatment must be monitored closely as simultaneous recovery from NTIS may result in overtreatment and acute hyperthyroidism.

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Nutrition Therapy in the Critically Ill Surgical Patient

Kimberly Joseph, MD, and Krishnan Sriram, MD, FCCM, FACS(C), FACS

Nutrition therapy, the preferred term, is not adequately emphasized in medical school curricula or even in residency and fellowship programs. With the abundance of information physicians are forced to absorb, nutrition therapy is often given low priority; however, in critically ill patients, nutrition therapy becomes all the more important because of significant changes in physiology and metabolism that accompany such illness. Concepts regarding critical care nutrition have evolved during the past few decades, with new information and controversies emerging with each passing year. There continue to be fundamental differences between guidelines published by various societies from different parts of the world. There is also significant evidence that nutrition therapy for surgical patients must be approached differently than therapy for medical patients. This chapter attempts to provide the reader with a practical approach to the nutritional care of the critically ill surgical patient.

Defining Malnutrition/ Nutrition Risk

Defining malnutrition has been a dilemma for several decades. No definitions or characterizations have been durable in terms of

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Defining Malnutrition/ Nutrition Risk

Defining malnutrition has been a dilemma for several decades. No definitions or characterizations have been durable in terms of

universal and cost-effective applicability. Earlier definitions have been based on the World Health Organization's recommendations, which were in turn based on epidemiologic data and heavily relied on a patient's weight and anthropometric measurements. What used to be called nutritional laboratory markers, such as serum protein levels (transferrin, prealbumin) have been shown to be of limited value in hospitalized patients, hence are no longer widely recommended. As they reflect inflammation (and are inversely proportional to the level of serum pro-inflammatory markers such as C-reactive protein), they must be considered in the overall context of a patient's status with regards to inflammation rather than as nutrition markers per se. Similarly, although inflammation-based definitions for malnutrition have been explored, assaying highly specific biomarkers is expensive and not cost-effective.

To this end, several major societies joined forces to simplify the definitions, based more on subjective clinical assessment by a trained clinician. A diagnosis of malnutrition may be made if the patient has two or more of the following criteria:

- Insufficient energy intake
- Weight loss
- Loss of muscle mass
- Loss of subcutaneous fat
- Localized or generalized fluid accumulation
- Decreased functional status

It is highly likely that most critically ill perioperative surgical patients will fulfill two or more of these criteria; however, even this definition may not always capture acute onset disease-related malnutrition. Also, the presence of these criteria may not be immediately evident on presentation. Certain subsets of surgical patients may be considered to have some degree of disease-related malnutrition and should thus be considered candidates for early nutrition therapy, regardless of whether they satisfy the criteria listed at the time of presentation. Such patient populations include but are not limited to severely injured polytrauma patients, burn patients meeting criteria for resuscitation, patients with traumatic brain injury, and patients with major soft tissue and other infections.

It is worth specific mention of overweight and obese patients as a subpopulation; nutrition therapy for overweight/obese surgical patients is often delayed owing to a misperception on the part of clinicians regarding such patients' nutritional status. There is a persistent myth that overweight/obese patients cannot be malnourished; however, clinicians must remember that protein catabolism occurs at alarming rates in critically ill patients, with daily losses of up to 700 g of lean body mass, leading to sarcopenia. Overweight/obese patients experience the same losses; using the definitions and criteria mentioned previously, most overweight/obese critically ill patients will experience loss of muscle mass and localized/generalized fluid accumulation, as well as possible disease-related acute inflammation. Losses of this latter cannot be specifically measured. In light of this, it is vitally important that critically ill overweight/obese patients receive aggressive nutrition therapy.

Aside from definitions of and criteria for malnutrition, there are templates for assessing "nutrition risk" that clinicians may also find useful. One such template is the Nutrition Risk in the Critically Ill score, developed by Heyland et al., which incorporates illness severity parameters (Acute Physiologic Assessment and Chronic Health Evaluation score, Sequential Organ Failure Assessment) as well as an assessment of comorbidities, age, time to intensive care unit (ICU) admission, and interleukin-6 measurements. Scoring modifications were made for circumstances in which interleukin-6 measurements were not available. The complementary use of nutrition risk scoring tools along with the definitions/criteria for malnutrition mentioned previously may be useful for practitioners in making decisions regarding the initiation of nutrition therapy.

Finally, not all ICU patients are candidates for specialized nutrition therapy. Patients who are in the ICU for short periods and/or who can tolerate unrestricted oral intake early in their stay will likely be at low risk from a nutritional standpoint.

EVALUATION OF NUTRITION REQUIREMENTS IN THE CRITICALLY ILL SURGICAL PATIENT

Currently, the only recommended method to objectively evaluate the nutrition/energy requirements for critically ill patients is the use of indirect calorimetry. Aside from the expense involved, this methodology may be difficult to use in surgical patients, who often require frequent interventions that might preclude obtaining steady-state measurements. Predictive equations have fallen out of favor because of questions regarding their accuracy and reliability. There has been much interest recently in the use of imaging techniques to assess sarcopenia. These include bedside ultrasound of thigh musculature as well as computed tomography imaging of the lumbar/psoas musculature. At present, though, there are no universally accepted standards. For these and other reasons, a simple weight-based equation recommending 25 to 30 kcal/kg per day energy provision is considered applicable for most critically ill patients as a starting point.

The preponderance of current literature emphasizes the importance of adequate protein intake to attenuate muscle breakdown, hence the recent interest in optimizing perioperative protein intake and the availability of such enteral products. Protein intake has traditionally been recommended in ranges of 1.2 to 2 g/kg per day for these patients; however, more recent data suggest that provision of up to 2.5 g/kg per day is safe and may be more effective. For obese patients, guidelines suggest using a weight-based energy provision of 11 to 14 kcal/kg of *actual* body weight per day for patients with body mass index (BMI) of 30 to 50, and 22 to 25 kcal/kg *ideal* body weight per day for patients with BMI greater than 50. Protein intake for obese patients should consist of 2 g/kg ideal body weight per day for patients with BMI of 30 to 40, and up to 2.5 g/kg ideal body weight per day for patients with a BMI 40 or greater. These measures are important to minimize muscle wasting.

Micronutrients (vitamins and trace elements) have ubiquitous functions in the body and are critical for all enzyme functions. Wound healing is affected by deficiencies of several micronutrients, notably zinc, copper, vitamin A, vitamin C, among others. The micronutrients known to affect cardiac function include vitamin D, vitamin B$_1$ (thiamine), selenium, and copper. Preoperative measurement and correction are indicated only when a deficiency is suspected on clinical grounds. Polypharmacy, history of excessive alcohol intake, being elderly, and obesity are conditions where micronutrient deficiencies may go unsuspected. Thiamine deficiency, common in patients with history of excessive alcohol intake, may result in unexplained lactic acidosis and mental changes.

Refeeding syndrome occurs if nutrition therapy, parenteral or enteral, is administered to severely malnourished patients and advanced too rapidly, sometimes leading to death. Clinical features include fluid balance abnormalities, disturbances in glucose metabolism, hypophosphatemia, hypomagnesemia, hypokalemia, and thiamine deficiency. In addition, selenium deficiency may occur with its known effects on the myocardium, causing cardiomyopathy. Hypophosphatemia may contribute to failed weaning attempts, in addition to its effect on the oxygen dissociation curve. Surgeons should maintain a high index of suspicion to detect and intervene in patients suspected to have refeeding syndrome. In patients at risk, nutrition therapy is initiated at very slow rates of 10 kcal/kg per day and advanced while electrolyte levels are being normalized.

IMPORTANCE OF PROTEIN

As noted, the provision of adequate protein to critically ill patients is considered vitally important to attenuate muscle breakdown and wasting. Critically ill patients have a hypo-aminoacidemia that is characterized by a state of increased amino acid uptake in tissues experiencing rapid protein turnover (e.g., liver, bone marrow, splanchnic organs, immunologically active tissues); this is limited by the maximum rate of amino acid release from muscle and results in a

enteral protein deficiency. The provision of normal dietary amounts of protein is inadequate to meet these requirements, hence the recommendations for higher levels of protein provision in critical illness. The recommended amounts of protein to be administered have varied for different disease states and by different guideline-producing entities, however. In a 2012 systematic review, Heyland and Stapleton noted a number of difficulties with the then current recommendations, which included the simple issue of what type of weight was being used in different studies to make weight-based recommendations. They also noted that, even with the then current recommendations, many of the studies only achieved protein delivery in the range of 0.8 to 0.9 g/kg per day irrespective of the weight type used. Although these primary recommendations are for additional research, they felt comfortable concluding that protein substrate provision in the range of 1 to 2.5 g/kg/d normal body weight was safe and probably more effective relative to lower ranges. A more recent analysis by Kochanda et al. looked at the history of protein provision to hospitalized patients as well as newer methods to evaluate protein requirements. Some of these techniques may not be easily available to the majority of clinicians as yet.

Clinicians should therefore concentrate on practical methods to try to ensure adequate protein delivery. These may include the following:

- Rather than aiming for the minimum in the general recommended ranges, aim for a goal of 2.0 g/kg per day protein substrate provision in most patients. In severely obese patients (even when being provided with fewer overall calories), the goal may be as high as 2.5 g/kg per day; in burn patients, it may be higher.
- Consider the addition of modular protein supplements to meet the goals.
- Consider a volume-based approach (discussed later in the chapter) in cases in which it is anticipated that there will be frequent interruption of nutrition therapy.

The importance of protein provision cannot be overstated, even in situations in which overall calorie delivery must be altered, practitioners should maintain their focus on adequate protein delivery.

BENEFITS OF EARLY ENTERAL NUTRITION

For at least three decades, it has been accepted that enteral nutrition (EN) provides benefits to critically ill and injured patients. Surgical stress and the stress of major trauma/burns results in local release of inflammatory cytokines as well as counter-regulatory hormones (e.g., adrenocorticotropic hormone and cortisol). If that inflammation overwhelms the local or systemic environment, it can result in hypercatabolism, characterized by accelerated protein breakdown in skeletal muscle and clinical wasting. Alterations in gut lymphatic tissue in such circumstances also predispose to reduced immune competence. Multiple investigators have demonstrated that even small amounts of EN ("trophic feeding") results in preservation of tight junctions, microvilli height, and epithelial/mucosal surface area, thereby decreasing bacterial translocation. Conversely, delays in providing EN have been associated with gut mucosal atrophy as well as with impaired carbohydrate absorption, higher rates of pneumonia and other nosocomial complications, increased ventilator days, and longer lengths of stay. In a 2018 meta-analysis designed specifically to determine if EN provided within 24 hours was superior to other forms of nutrition, the authors concluded that there was no benefit to early EN. Even in this study, a priori subgroup analyses of trials in trauma and burn patients and of patients with secondary pancreatitis demonstrated a mortality benefit with early EN. This again emphasizes that surgical patients may have different requirements for and responses to EN than their medical counterparts.

Controversy persists regarding how trophic feeding/permissive underfeeding compares with full caloric EN therapy in terms of outcomes. Several recent studies suggest that there is no difference in patient outcomes between the two strategies. The NeMIT trial, for example, examined provision of 60% to 65% of nonprotein calories versus more than 70% calories with full protein provision and found no differences in near-term outcomes. It remains to be seen if these results can be widely replicated. Additionally, other studies have provided evidence that patients who accumulate significant caloric deficits over the course of their hospital stay have worse outcomes. It remains unclear how long it is safe to underfeed a patient. Underfeeding may also reduce the insulin response, limiting the ability of insulin to exert its beneficial anabolic effects. Additional research is needed to better clarify the role of permissive underfeeding.

As a general rule, critically ill surgical patients should receive early EN that is increased to estimated goal rates when feasible. If permissive underfeeding is used, practitioners should still focus on adequate protein delivery from the time of initiation of nutrition therapy. Frequent evaluations should be undertaken to determine when it might be safe to increase EN to appropriate estimated goal rates. This is necessary to avoid cumulative caloric deficits.

PREOPERATIVE NUTRITION THERAPY AND PREHABILITATION

Although the bulk of this chapter focuses on the critically ill surgical patient, it is worth understanding the needs of patients requiring elective major surgery as these patients may end up in the ICU. All patients scheduled for elective major surgical procedures, involving the gastrointestinal (GI) tract or otherwise, should be evaluated by a nutritionist at least 7 to 10 days before the planned procedure. Systems must be developed in hospitals requiring this crucial step in identifying patients who are risk for malnutrition or are actually malnourished. This is as important as clearance by a cardiologist or preoperative evaluation by an anesthesiologist. Preoperative nutritional evaluation and intervention forms an integral part of the Enhanced Recovery after Surgery protocols and pathways.

As part of these protocols, patients identified as being malnourished or at high nutritional risk are provided oral nutritional supplements using any standard complete balanced EN product. Literature supports providing approximately 500 mL of the liquid or reconstituted formula consumed over the course of 24 hours in divided doses per the patient's tolerance. Meta-analyses of such studies have shown that any standard enteral formulation can be used (vs specifically immune-enhancing products). Benefits of such interventions include shorter length of hospital stay and decreased infectious complications.

Preoperative nutritional evaluation is also an excellent opportunity to detect and correct drug-nutrient interactions, especially in elderly patients and obese individuals. Micronutrient deficiencies resulting from pharmaceuticals may go undetected if not suspected and treated appropriately prior to elective procedures. Various commonly used medications (e.g., diuretics, proton pump inhibitors, metformin) variably produce deficiencies of zinc, vitamin C, vitamin B_{12}, folate, and electrolytes, including magnesium.

INTRAOPERATIVE CONSIDERATIONS

Attention to maintain optimal and electrolyte levels continues during the operative procedure. The liberal use of epidural anesthesia is encouraged for its known benefits during the actual surgical procedure and for pain management during the postoperative period. Dependence on systemic narcotics is minimized, thereby decreasing postoperative nausea and vomiting and increasing tolerance to early resumption of oral or enteral feeding. It is prudent to consider GI access to facilitate early initiation or resumption of enteral feeding. Depending on the clinical situation, preemptive access may include a soft bore nasoenteral tube with the tip positioned in the stomach or jejunum or a formal gastrostomy or jejunostomy. The majority of patients can be successfully managed with intraoperative feeding, with prophylactic postfeeding only for patients deemed to be at high risk for aspiration. By obtaining GI feeding access during the operative

procedure itself, parenteral nutrition (PN) at a later time may be avoided. It is tempting for clinicians to trust their ability to predict when their patient will be able to resume oral nutrition and forego the placement of feeding access in the operating room. However, it should be remembered that it is usually far easier to remove temporary feeding access on discovery that it is not needed than it is to place it postoperatively if it turns out it is needed.

POSTOPERATIVE AND ICU CONSIDERATIONS

One of the challenges facing clinicians in the ICU and the postoperative period is determining how to monitor the success of nutrition therapy. Unlike other pharmacotherapies, nutrition therapy usually does not result in an obvious short-term effect. Other than indirect calorimetry, there are no reliable objective methods to assess energy needs. Measurements of acute phase proteins, while they may be useful to help evaluate changes in a patient's inflammatory state, do not specifically address nutritional status. Clinicians are largely reliant on their initial assessment of the patient's admission nutrition status and nutrition risk to determine parameters for provision of therapy.

A barrier that clinicians often encounter in the ICU when trying to deliver nutrition therapy is the frequent, temporary cessation of EN therapy as the patient leaves the unit for tests, procedures, and/or operations. One option that may lessen the consequences of these interruptions is to provide volume-based rather than rate-based therapy. As proposed by McClave and colleagues, the total volume goal of enteral nutrition for a 24-hour period is calculated; if the infusion is interrupted, it is increased above the baseline rate once resumed in such a way as to make up for the lost period. For example, if it is known that a patient is returning to the operating room at a specific time, the EN infusion rate may be increased to account for the estimated lost time. By doing so, the patient's cumulative caloric deficit is reduced. Multiple studies have demonstrated an association between reduction of caloric deficit and improved outcomes in critically ill patients. To accomplish this, however, a truly multidisciplinary approach must be employed; all the members of the team must be educated as to the importance of EN therapy and specifically of the potential consequences of interruption. Protocols must be developed that are easy for team members to follow (e.g., the Enhanced Protein Therapy Promotes via the Enteral Route in Critically Ill Patients protocol or the CAN WE FEED researchers). Collaboration with anesthesiologists can be explored to reduce EN cessation before planned operations.

Another reason that EN is interrupted is because clinicians may believe that the patient is not tolerating the EN because there are no bowel sounds, no stool production, and/or no flatus. Enteral formulations are specifically designed for easy absorption in the small intestine. The presence of bowel sounds or passage of flatus is not necessary to either initiate or continue EN. Clinicians should monitor for signs of ileus; however, postoperative ileus is more likely to be a function of immobility and/or opioid and sedative medications rather than appropriate administration of EN. If anything, EN is associated with an improvement in GI motility and mucosal integrity; this is true even in the presence of an anastomosis. GI and colonic anastomoses actually heal better when enteral feeding is sustained, even if the site of feeding is proximal to the anastomosis. The common reluctance of surgeons to use this as an excuse to delay initiation of EN is not supported by the literature. An exception is procedures involving the esophagus where it is customary to obtain contrast studies before initiating oral or tube feeding; however, even in such cases, placement of a more distal jejunal feeding access may obviate the need for delay.

There is persistent controversy regarding whether EN should be initiated in patients who are hemodynamically abnormal or are on vasopressor support. Patients who are on stable, "low" levels of vasopressor support may safely receive EN. This must be evaluated by the clinician with awareness that if such issues have led to a significant delay in EN initiation or resumption the patient may have accumulated a significant caloric deficit.

There are patients who demonstrate true EN intolerance. Should this persist for more than 5 to 7 days, consideration must be given to initiating PN; however, there are strategies that may be used in advance of this. If a gastric ileus is present, prokinetics such as metoclopramide or erythromycin may be useful; however, gastric residual volumes have not been shown to correlate with EN tolerance, and their routine measurement is no longer recommended. Placement of a postpyloric feeding access may be considered in patients who are considered at high risk for gastric feeding intolerance, since this may be difficult to predict a priori, consideration should be given to placement of a nasojejunal duodenal or jejunal tube intraoperatively in patients who are undergoing open abdominal surgery (as mentioned previously). Alternatively, there are many described methods for bedside postpyloric tube placement; endoscopic or radiologic placement may also be considered.

CONCEPTS AND CONTROVERSIES REGARDING IMMUNONUTRITION

The terminology in the area of immune-modulating nutrition can be confusing. Immune-modulating, immune-enhancing, and/or immunonutrition are terms used synonymously. Moreover, although there have been numerous studies done in this area, the results have often been contradictory, partly from differences in formulations used and populations studied. When discussing immunonutrition, clinicians are generally concerned with the following nutrients: arginine, omega-3 polyunsaturated fatty acids, nucleotides, glutamine, and antioxidants.

Arginine

There has been some concern that administering arginine-containing nutrition therapy may be harmful in septic patients. The Surviving Sepsis guidelines as well as the most recent American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) guidelines for nutrition in adult critically ill patients, published in 2016, recommend specifically against arginine-containing immunomodulating formulas in sepsis. These recommendations are based on a potential concern that inducible nitric oxide synthase, a metabolite of arginine, would cause harmful vasodilatation in this patient population, particularly medical patients who are septic. However, there is literature support for arginine supplementation for surgical ICU patients (pre- and postoperatively) as well as patients with severe trauma and traumatic brain injury. The suggested dose is 15 to 30 g/day. The literature also suggests that using arginine in combination with fish oil in surgical patients may deliver the best outcomes in terms of reducing nosocomial infections and decreasing length of stay.

Omega-3 Polyunsaturated Fatty Acids/Fish Oil

These nutrients are believed to exert their positive effect by competing with arachidonic acid for cyclooxygenase and 5-lipooxygenase binding sites, resulting in a reduction of the 2-series of prostaglandins and the 4-series of leukotrienes and thereby a reduction in the inflammatory response. Initial studies in the late 1990s suggested a beneficial role for the use of docosahexaenoic acid and eicosapentaenoic acid in patients with acute respiratory distress syndrome (ARDS); subsequent investigations have not been able to demonstrate this effect, and the ASPEN/SCCM guidelines recommend against their routine use in medical ICU patients and patients with ARDS. However, there is enough literature supporting their use in surgical ICU patients, usually in combination with other immune-modulating nutrients, to allow for a positive recommendation in this population. There is also evidence that these products may be beneficial in traumatic brain injury.

Nucleotides

The use of nucleotides in combination with arginine and/or fish oil is recommended for critically ill surgical ICU and trauma patients.

There is some suggestion in recent investigations that nucleotides may have a beneficial impact on the gut microbiome.

Antioxidants

The literature regarding the use of antioxidants, such as ascorbic acid, zinc, and selenium (along with other micronutrients) has been inconsistent. Although most enteral and parenteral formulations include these elements in recommended daily doses, there is not sufficient evidence to suggest that enhanced dosing is beneficial.

Glutamine

Studies in the late 1980s/early 1990s suggested that enteral glutamine was an essential component of immune enhancing regimens administered to trauma and burn patients, as well as patients undergoing major upper GI surgery. Subsequent studies failed to demonstrate a clear benefit of enteral glutamine, and some studies implied that it was possibly harmful. Investigations into the use of parenteral glutamine have also not demonstrated clear benefit despite the consistency of delivery (relative to the enteral route). Current recommendations are for the use of glutamine supplemented immunonutrition only in patients with traumatic brain injury and perioperative surgical trauma patients in the ICU, however, it should be noted that some researchers feel that the glutamine question remains unanswered. A recent meta-analysis by Chen and colleagues noted that patients in surgical ICUs did appear to benefit from glutamine supplementation.

Clinicians must consider the available literature, existing recommendations, as well as their own clinical judgment when deciding to use immunonutrition in their patients; however, there is sufficient evidence to suggest that critically ill surgical patient populations, more so than their medical ICU counterparts, are likely to derive benefit from such regimens.

PARENTERAL NUTRITION

PN has a limited role in the preoperative preparation of malnourished surgical patients; however, when initiated, it facilitates correction of electrolyte, vitamin, and trace element deficiencies. The duration of PN is generally not extended for more than 10 to 15 days. There are no reliable laboratory tests to identify an endpoint. Weight gain from PN is mostly gain of fat, not only in the usual sites of fat stores, but also in the muscle itself.

It is prudent to minimize the use of PN during the intraoperative period especially for complex and extended procedures. This avoids the need for close monitoring and management of glucose levels during the procedure. In order to avoid wastage of PN infusates, close coordination between the pharmacy, ICU, and operating room staff is needed.

During the postoperative period, all attempts are made to optimize timely initiation of EN and advancement to goal as early as the patient's condition permits. A time limit of 3 to 5 days to achieve this goal is reasonable. When it is obvious that EN cannot be depended on as the sole route of nutrition therapy, PN should be initiated either to supplement or replace EN. Cumulative protein and calorie deficits appear to correlate with postoperative and ICU mortality and morbidity. PN may be administered as a central venous formula or mixed with higher fat content (to decrease osmolality) for peripheral vein use.

Earlier initiation of PN can be justified in conditions such as high output fistulas or ongoing bowel obstruction where resumption of EN is clearly not possible. Ileus, the definition of which is vague, is not an absolute contraindication to initiate trophic EN. Guidelines also support early initiation of PN, either total or supplemental, in patients who are severely malnourished or are at risk of malnutrition. The difficulty is defining such patients clinically because laboratory tests do not have either a positive or negative predictive value. It is suggested that surgeons should have a low threshold to initiate PN based on sound clinical judgment to minimize the adverse effects of protein and calorie insufficiency. The use of newer fat emulsions, not based on soy, derived omega 6 fatty acids, is encouraged if available.

DISEASE/CONDITION-SPECIFIC NUTRITION THERAPY

Trauma

Severely injured trauma patients benefit from early EN with an emphasis on protein delivery; traditional recommendations have been 1.2 to 2 g/kg per day, but more recent recommendations suggest up to 2.5 g/kg per day are likely safe. This is also one of the patient populations for which immunonutrition formulas (with arginine and fish oil) are recommended. Severely injured trauma patients often require frequent visits to the operating room, making achieving goal EN challenging; volume based feeding should be strongly considered in such cases. EN should begin as soon as the patient is hemodynamically normal. Nutrition therapy should not be delayed out of concern for anastomoses or an open abdomen. Even in patients undergoing damage control procedures, the literature suggests that early EN does not result in delays in abdominal closure rates.

Burns

ASPEN/SCCM guidelines recommend that burned patients requiring resuscitation receive early EN with protein goals of 1.5 to 2 g/kg per day. American Burn Association recommendations have been higher, up to 3 g/kg per day. Some studies have recommended that nasoduodenal/jejunal nutrition be implemented as early as 4 to 6 hours post burn. Pharmacologic therapy with recombinant human growth hormone, insulin like growth factor, propranolol, and oxandrolone have also been suggested by some authors to mitigate the profound catabolic insult sustained by severely burned patients.

Traumatic Brain Injury

Patients with traumatic brain injury (TBI) suffer from significant catabolic stress following their injuries. Both the Brain Trauma Foundation Guidelines and the ASPEN/SCCM guidelines recommend early EN in TBI. Although there is some evidence that transpyloric feeding is associated with fewer incidences of late pneumonia, the majority of TBI patients can tolerate continuous gastric feeding when appropriate ventilator bundle protocols are adhered to. Recently there has been interest in the effect of omega 3 fatty acids in TBI; there is some evidence that they may be immunomodulator as well as neuroprotective. The ASPEN/SCCM guidelines recommend an arginine enhanced, immune modulating formula or supplementation of a standard formula with eicosapentaenoic acid/docosahexaenoic acid for TBI patients.

Pancreatitis

Current practice guidelines encourage enteral or oral feeding for acute pancreatitis include those classified as "severe" and with complications such as pancreatic ascites or abscess. A patient centric approach is appropriate. The concept of resting the gut or pancreas in acute pancreatitis is no longer valid. In patients who are mechanically ventilated, nasogastric feeding may be initiated, with transition to intrajejunal feeding only for specific situations of intolerance. A regular polymeric formula is used with peptide based formulas as a backup.

Open Abdomen

An open abdomen is not a contraindication for EN, either gastric or jejunal. Attention should be paid to fluid balance and loss of protein through the abdominal wall defect. An additional 30 to 40 g/day of protein is generally needed. Enterocutaneous fistulas do not

TABLE 1 New ICD-10 Codes for Malnutrition and Related Clinical Conditions

ICD-10 Code	Diagnosis
E43	Unspecified PCM
E44.0	Moderate PCM
E44.1	Mild PCM
E46	Unspecified PCM
E64	Sequelae of PCM
M62.84	Sarcopenia
M62.5	Muscle wasting and atrophy

From Centers for Medicare & Medicaid Services. ICD-10-CM codes associated with malnutrition. https://www.cms.gov/Medicare/Coding/ICD10/index.html. ICD, International Classification of Diseases; PCM, protein calorie malnutrition.

preclude the use of EN unless the fistula is high output or electrolyte abnormalities are exacerbated by the additional volume supplied with EN. Supplemental PN may be used as needed.

Postoperative Patients on Ventilator Support Longer Than 48 Hours

The SCCM guidelines, based on high-quality evidence, recommend that either trophic or full EN support should be administered for patients with ARDS expected to have a duration of mechanical ventilation of 72 hours or longer. This should be initiated as soon as possible, but no later than 48 hours after ICU admission. PN should be considered only after 7 to 10 days of serious attempts to optimize EN.

Postoperative Patients Who Can Tolerate Oral Nutrition

Postoperative patients who are breathing spontaneously and have adequate mental status may be offered a regular or modified solid food diet, with appropriate consistency, depending on ability to swallow. Recent guidelines based on expert consensus indicate that, postoperatively, clear liquids are not required as the first meal. Should a clinician feel he or she must use clear liquids, there are commercial options that contain appropriate protein, but emphasis should be placed on resuming solid food as soon as feasible. In ICU patients, there is no consistent evidence that sodium intake is correlated with blood pressure or need for inotropes.

TEAM APPROACH

As has been observed in several areas in medicine, a team approach is crucial for successful implementation of guidelines and acceptance of newer practice patterns. This applies as well to the delivery of appropriate nutrition therapy. Surgical intensivists, surgeons, anesthesiologists, nurses, dietitians/clinical nutritionists, and all members of the patient's care team must buy in to the importance of nutrition therapy, and protocols must be put in place to make the process easy to understand and implement. The patient's family (and the patient, if possible) should also be involved in the decision-making process to optimize understanding and achievement of goals of care. Additionally, institution administration may require education on the importance regulatory bodies place on the assessment of malnutrition and appropriate coding (Table 1). Implementation of nutrition therapy protocols, particularly if they are new to the clinical setting or institution, may be slow. They may have to be done in stages to accomplish the culture change that might be needed to make aggressive and appropriate nutrition therapy the norm. Some suggestions include the following:

- Offer ongoing educational opportunities to all staff about nutrition therapy in critical illness using a multimedia approach: social media, in-person journal clubs, and so forth. If credit can be obtained for these offerings, some staff may take advantage of them.
- Begin early education of the nursing staff and actively seek their input when considering new protocols. Make sure that any protocols that require nursing involvement are truly nurse driven. This may require alteration of published protocols to meet local ICU or institution needs.
- Involve dietitians in the planning and implementation of new protocols as well as in the education of other staff, including medical staff. Advocate with administration for adequate dietitian staff in critical care areas to ensure patients are assessed and monitored appropriately (coding and reimbursement standards may be useful in justifying this).
- Include the patient and/or family early in discussions about the nutrition therapy plan.

When implementing a new protocol, it may help to be willing to start with a portion(s) of the protocol that all can agree on to get started, with the plan for additional implementation over time.

CONCLUSIONS AND FUTURE TRENDS

As nutrition therapy continues to evolve, it will be all the more important for practitioners to keep up to date on new developments in assessment and therapy. Exciting ideas have already been put forth regarding the importance of the gut microbiome and the potential use of probiotics in its manipulation to achieve benefit. Newer assessment techniques may become widely accessible, allowing for a more accurate nutrition therapy plan based on patient-specific information. A relatively newly described phenomenon, the persistent inflammation, immunosuppression, and catabolism syndrome (or PICS, not to be confused with post-intensive care syndrome using the same acronym), has brought attention to the subgroup of patients who have indolent, chronic inflammation. Being able to predict the development of this syndrome and apply nutrition therapy early may prevent functional losses after a long ICU and even late mortality. Some principles, however, such as the importance of adequate protein delivery, the benefits of early EN, and a comprehensive multidisciplinary approach to nutrition therapy have stood the test of time and should comprise the mainstay of all practitioners' approach to the nutrition care of critically ill surgical patients.

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Terence O'Keeffe, MD, FACS, FCCM

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There has been a significant swing in resuscitation practices over the past decade away from the use of crystalloids in critically ill patients in favor of blood and blood products. This has been especially true for patients suffering traumatic injuries. The net effect has been a decrease in the incidence of dilutional coagulopathy, which has historically been one of more common causes of coagulopathy. In one study of more than 8000 patients in the German Trauma Registry from 2017, coagulopathy was present in up to 50% of patients who received 3 L of fluid or more. There is also increasing evidence that perioperative resuscitation with excess crystalloid solutions is detrimental to postoperative recovery in terms of morbidity, but given

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TABLE 1 Congenital and Acquired Causes of Coagulopathy

Type of Coagulation Disorder	Effect on Clotting	Notes
CONGENITAL		
Hemophilia A	Increased bleeding	1 in 10,000; mostly males
Hemophilia B	Increased bleeding	1 in 34,000; mostly males
Antithrombin II deficiency	Hypercoagulability	1 in 2000; increased VTE risk
Antiphospholipid syndrome/lupus anticoagulants	Hypercoagulability	2–8 in 100; increased VTE risk in some patients
Von Willebrand factor disease	Increased bleeding	Usually mild; no spontaneous bleeding
Protein C deficiency	Hypercoagulability	2–5 in 1000; increased VTE risk
Protein S deficiency	Hypercoagulability	1 in 700; increased VTE risk; often asymptomatic
Factor V Leiden	Increased bleeding	Rare; affects 5 per million
Congenital fibrinogen deficiency	Increased bleeding	Rare; affects 1–2 per million
Congenital prothrombin deficiency (factor II)	Increased bleeding	Rare; symptoms include easy bruising, epistaxis
Congenital factor deficiencies—VII, X, XIII	Increased bleeding	Rare; symptoms include easy bruising, epistaxis, joint bleeding
ACQUIRED		
Medication induced	Increased bleeding and/or prothrombotic	See Table 6 for specific drugs
Traumatic brain injury	Increased bleeding	Possibly because of release of brain thromboplastin
Obstetric emergencies	Increased bleeding	Dilutional coagulopathy from blood loss or DIC
Sepsis/bacteremia	Increased bleeding and/or prothrombotic	Proinflammatory cytokines cause activation of clotting cascade; DIC also present
Pancreatitis	Increased bleeding and/or prothrombotic	Proinflammatory cytokines activate clotting cascade and platelets; also DIC
Burns	Increased bleeding	Dilutional coagulopathy from resuscitation; DIC
Disseminated intravascular coagulation	Increased bleeding	Multiple precipitating conditions
Hepatic disease	Increased bleeding	Prolonged PT
Renal disease	Increased bleeding	Platelet dysfunction from chronic uremia
Vitamin K deficiency	Increased bleeding	Most common in infants; in adults related to chronic conditions or medications

DIC, Disseminated intravascular coagulation; PT, prothrombin time; VTE, venous thromboembolism.

the lack of a more suitable substitute fluid for patients who suffer significant fluid shifts (e.g., burns, major abdominal surgery), these solutions are still the mainstay of therapy. It is therefore important to follow the volumes of fluid given and monitor coagulation parameters to detect impending changes early, and correct these where necessary.

Along with this move away from crystalloid resuscitation has been the explosion in massive transfusion protocols that were initially developed for trauma patients but have also been used in the bleeding nontrauma patient (e.g., obstetric hemorrhage, massive gastrointestinal bleeding). Close attention to red blood cell to fresh frozen plasma ratios and early transfusion of platelets attempts to mimic whole blood transfusions (also becoming used much more frequently) in critically ill trauma patients. When effectively performed, these massive transfusions will effectively negate any dilutional effects of multiple blood product transfusions and can reduce any catch up or need for top up transfusions after bleeding control has been achieved. Massive transfusion protocols will be dealt with in more detail in the chapter on coagulation in the trauma patient.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a syndrome that is a manifestation of an underlying systemic disorder affecting the coagulation system, simultaneously resulting in procoagulant activation, fibrinolytic activation, and consumptive coagulopathy that results in microvascular thrombi deposition in various organs thereby leading to organ dysfunction and possibly death. Patients with this condition will present with low and/or decreasing platelet counts, prolonged tests of coagulation, low levels of coagulation factors and inhibitors in the plasma, and increased d-dimer and/or fibrin degradation products. Clinically it presents with hemorrhage (although 5%–10% of cases may demonstrate only microthrombi) and in the overt form it is highly lethal, with mortality rates as high as 40%, depending on the underlying condition.

There are a multitude of disease processes that can trigger this condition, but it is most commonly the result of sepsis, although it can be caused by trauma, pancreatitis, transfusion reactions, malignancy, obstetric complications, and severe toxic reactions. Diagnosis is confirmed using either the Japanese Association for Acute

TABLE 2 Blood Tests of Clotting

Name of Blood Test	Measures	Comments
PT	Extrinsic pathway of coagulation	Useful in liver disease, warfarin effect, vitamin K deficiency
PTT	Intrinsic pathway of coagulation	Mostly used to measure efficacy of heparin infusions
INR	Standardized test of PT for patients on warfarin	Often used incorrectly as a measure of coagulopathy
Platelet count	Absolute platelet count	Does not measure platelet activity (e.g., if on medications)
Fibrinogen level	Levels of plasma fibrinogen	Can be useful if other tests are normal in the face of continued bleeding
D-dimer	Degradation product of fibrin	Used in diagnosing PE and also DIC
Fibrin split products	Degradation products of fibrin	Used in diagnosing DIC
Thrombin time	Bleeding disorders, in evaluating levels and function of fibrinogen	Superseded by functional fibrinogen assay
ACT	High doses of heparin therapy	Mostly used during cardiopulmonary bypass or cardiac device anticoagulation
Bleeding time	Mostly platelet function	Rarely used
TEG	All facets of coagulation	See discussion in chapter
Platelet function tests	Platelet function (after aspirin or postmedication)	Not often used routinely, controversial
Factor assay	Specific factors associated with a condition	Often used to investigate clotting protein deficiencies
Reptilase test	Conversion of fibrinogen to fibrin	Used when heparin is present, as reptilase is insensitive to it

ACT, Activated whole blood clotting time; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PE, pulmonary embolism; PT, prothrombin time; PTT, partial thromboplastin time; TEG, thromboelastography.

Modified DIC criteria or the International Society on Hemostasis and Thrombosis overt DIC scoring criteria (Table 2). These score on the platelet count, prothrombin time, and presence of fibrin degradation products to make the diagnosis, the only major difference between the two being that the heparin score uses the presence of systemic inflammatory response syndrome criteria as opposed to absolute fibrin levels. They have been validated prospectively as both an aid to the diagnosis of DIC, as well as being useful in predicting multiple organ dysfunction syndrome and 28-day mortality. These scores can be used to differentiate DIC from other conditions that exhibit thrombocytopenia and prolonged prothrombin times, such as chronic liver disease.

Treatment of DIC is focused on the underlying clinical disorder while supporting the patient's coagulopathy. Platelet transfusion may be necessary if the platelet count falls significantly, although this may be allowed to drop as low as 20,000 × 10^9/L if the patient is not bleeding. Platelet transfusions to keep the count above 50,000 × 10^9/L will be necessary in cases of active hemorrhage. Other blood products may be required, but these should be directed by blood testing (e.g., giving cryoprecipitate to correct fibrinogen levels). Fresh frozen plasma (FFP) may be necessary in patients with excessively prolonged clotting tests. Heparin appears to be of benefit in patients with DIC resulting from certain specific conditions such as metastasized malignancies, purpura fulminans, and major vascular abnormalities. It also appears effective in the treatment of thromboembolic complications in patients with low grade sustained DIC; however, in patients with hemorrhagic complications resulting from DIC, the use of heparin can have deleterious effects. Other treatments for DIC such as antithrombin, thrombomodulin or activated protein C (no longer commercially available) remain controversial, with no clear indications for their use, although the latter two are used to treat DIC in Japan. In severe cases of DIC, early consultation with a hematologist is prudent to help manage specific factor deficiencies.

Hepatic Dysfunction

The majority of the proteins involved in the coagulation cascade are synthesized in the liver; therefore, it should not be surprising that liver disease can have a drastic effect on the body's clotting. This occurs by a number of mechanisms: decreased synthesis of these proteins leading to an increase in prothrombin time; thrombocytopenia; dysfibrinogenemia from failure to remove sialic acid from fibrinogen; reduction in absorption of lipid soluble vitamins to cholestasis; liver disease leading to low production of factors II, VII, IX, and X; and reduced metabolization of these pharmagens activator. In patients with chronic liver disease, however, the increase in PT is tempered by a reduction in the body's anticoagulants, leading to a relative balance between the anticoagulant and coagulant pathways. In the absence of any signs of hemorrhage, prolongation of the PT do not require specific treatment, although vitamin K supplementation should be considered early in these patients.

Homeostasis Disruption

Other features of homeostasis disruption can also contribute to coagulation issues as platelets start to become increasingly less effective once the temperature drops below 35°C. Below 33°C, synthesis of clotting enzymes and plasminogen activator inhibitors is impaired, thus ensuring a normal core body temperature is a critical aspect of treating coagulopathy. Enzymatic function of the clotting cascade is impaired in cases of significant acidosis (pH <7.25) and calcium is an essential cofactor for many of these enzymes, and attention also needs to be paid to hypocalcemia, especially in patients receiving large volumes of blood products (e.g., massive transfusions).

B PLATELET DISORDERS

Thrombocytopenia

This is one of the commonest coagulation problems in critically ill patients with an incidence of around 35% to 41% in patients admitted

to an intensive care unit, when defined as a platelet count of less than $150{,}000 \times 10^3/mm^3$. Severe thrombocytopenia with a platelet count less than $50{,}000 \times 10^3/mm^3$, occurs approximately 5% to 20% of the time. This thrombocytopenia is usually multifactorial and can likely be considered as a marker of severity, with a decreased platelet count responsible for an approximate twofold increase in mortality.

The most common causes of thrombocytopenia in the critically ill patients are presented in Table 3. These include hemodilution, pseudo-thrombocytopenia, increased consumption, increased destruction, decreased production, and increased sequestration. The effective function of platelets is critical to the body's response to bleeding as they form the initial plug at the site of injury even before the deposition of fibrin and thrombin cross linking (Fig. 1). Defects in either platelet function or platelet numbers can have devastating effects on the ability of the body to properly form clots and effectively stop hemorrhage from vessels.

There is often a natural drop in a patient's platelet count following major surgery. There is typically a nadir in the count approximately 2 to 3 days after surgery, with a recovery at days 3 to 4 depending on the exact surgery performed (abdominal surgery has less of a drop and recovers sooner than cardiac surgery, for example). This correlates with the increased production of platelets to compensate for those lost during the surgical procedure by the body's megakaryocytes, and thus early thrombocytopenia can be more reflective of the magnitude of trauma or blood loss initially. As a corollary to this, an absent rise or blunted response after the first four days is strongly associated with prolonged ICU stay and mortality, with thrombocytopenia present at day 14 or an absent increase over baseline predictive of at least a doubling in mortality.

The recognition of the critical function of platelets in the clotting process leads many clinicians to be wary of performing surgery or procedures in the thrombocytopenic patient; therefore in Table 4, I have outlined the generally accepted triggers for platelet transfusion under various circumstances. Platelets also form an important part of massive transfusion protocols, which has been covered separately in a different section on trauma patients.

TABLE 3 Thromboelastography-Directed Resuscitation Guidelines

TEG Parameters	Blood Product Transfusion
ACT >120	PRBCs and plasma
Reaction time >10 min	PRBCs and plasma
K >2.5 min	Cryoprecipitate/fibrinogen/plasma
Alpha angle <55	Cryoprecipitate/fibrinogen/plasma
MA <55	Platelets/cryoprecipitate/fibrinogen
LY30 >3%	Tranexamic acid

Data from Arnaud of surgery 2010 based on experience with 1074 consecutive trauma patients using TEG as point of care test.
ACT, Activated clotting time; K, interval between reaction time and fixed value of clot firmness; MA, maximum amplitude; LY30, degree of clot lysis at 30 min; PRBC, packed red blood cells; TEG, thromboelastography.

Heparin-Induced Thrombocytopenia

One of the more feared causes of thrombocytopenia is related to heparin use, and as its consequences can be very severe it warrants a more detailed and separate review here. Heparin induced thrombocytopenia (HIT) is a specific complication of heparin therapy that can appear in either one of two distinct forms; type 1 HIT is a non-immune disorder that results from the direct effect of heparin on platelet activation and develops within the first 48 hours from heparin exposure. The thrombocytopenia from type 1 HIT is thought to be due to platelet aggregation but will resolve with continued heparin therapy.

In general, the term HIT refers to type 2 HIT, which is an immune mediated prothrombotic disorder caused by antibodies to complexes of platelet factor 4 and heparin that subsequently cause platelet activation. This occurs 4 to 10 days after exposure to heparin and can lead to venous or arterial thrombotic complications that have been associated with amputations and death. The overall risk of HIT is thought to be approximately 0.2% in all heparin exposed patients, although the incidence may be as high as 5% to patients undergoing cardiac or orthopedic procedures or with prolonged heparin exposure. Interestingly, white race and male sex seem to confer less risk, with concomitant less risk for thrombosis. Unfractionated heparin confers a higher risk than low molecular weight heparin in surgical patients, and it can occur after systemic heparin flushes or even related to heparin coated catheters.

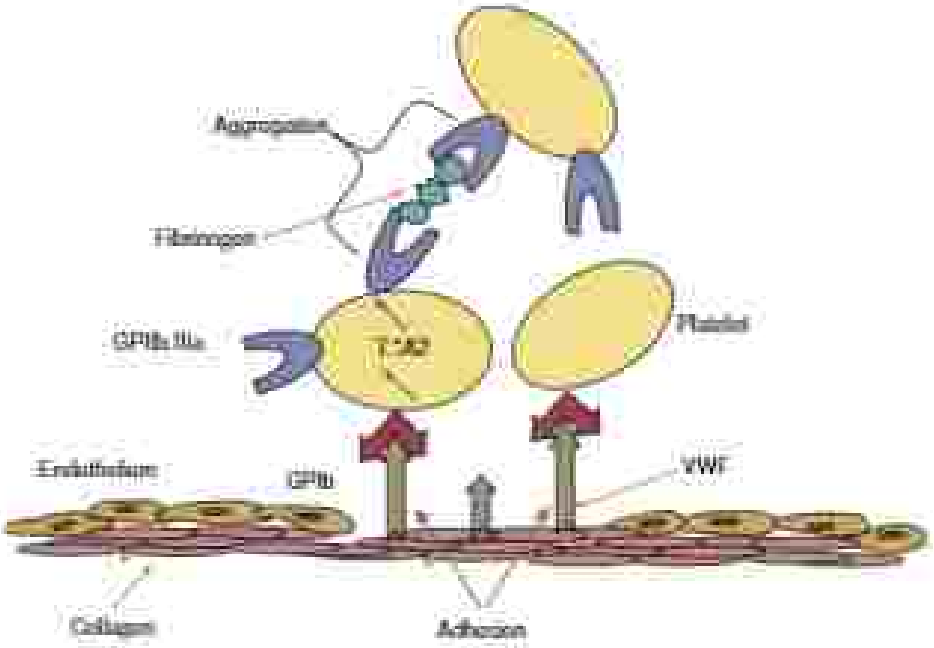

FIG. 1 Platelet functions. vWF, von Willebrand factor.

HIT should be suspected in any patient exposed to heparin who suffers a drop in platelet count below 50% of baseline. Clinical findings in true type 2 HIT may include skin lesions at heparin injection sites or acute systemic reactions including fever or chills after administration of an intravenous bolus of heparin. Venous thrombosis is the most common thrombotic complication of HIT although arterial thrombosis may also occur. Patients with HIT have a 40 fold higher risk of thrombosis than in subjects without HIT, with an absolute risk of thrombosis of 25% to 50% (and fatal thrombosis of as high as 9%–30%).

Diagnosis of HIT is based on a combination of clinical findings, thrombocytopenia characteristics, timing of the platelet drop, and laboratory studies of HIT antibodies. The Warkentin score or 4T score is used as a clinical pretest screening tool to guide in the diagnosis of HIT, and can help guide the clinician to evaluate whether further testing is required (Table 5). For patients with an intermediate or high probability score, a heparin/platelet factor 4 enzyme linked immunosorbent assay test is recommended. This widely available immunoassay has high sensitivity but low specificity in the diagnosis of HIT and depending on local laboratory facilities may take 1 to 3 days to be reported. In cases of patients with conflicting test results and Warkentin scores, a serotonin release assay may be used to confirm the diagnosis, this being a functional study often considered to be the gold standard for identification, but not widely used because of cost and being technically demanding to perform. Definitive diagnosis can be challenging in some patients, particularly in the absence of clinical thrombosis, and there are continued data to suggest that over treatment for this condition is common in the surgical population.

Treatment of HIT obviously starts with the elimination of exposure to all heparin products, including heparin flushes of any indwelling catheters. Heparin-bonded catheters need to be removed. These are prudent measures to adopt even while waiting for confirmatory laboratory testing in patients with a high pretest probability of HIT. In patients still requiring anticoagulation (the vast majority of patients), alternative agents include fondaparinux, which can be given subcutaneously, and parenteral direct thrombin inhibitors such as argatroban, bivalirudin, or oral agents such as dabigatran, apixaban or rivaroxaban. In practice, the exact agent used will depend on whether the patient has normal renal and hepatic function, as well as what is available on the hospital formulary. Anticoagulation should be continued for at least 4 weeks, and up to 3 months if thrombosis has occurred, with the patient transitioned to warfarin or a direct oral anticoagulant once stable and with a normal platelet count (>150,000 × 10^9/mm^3).

TABLE 4 Transfusion Triggers for Platelets

Condition	Desired Platelet Count
Stable hematology/oncology patient	>10,000
Complicated hematology/oncology patient	>20,000
Minor surgery/procedure	25,000–50,000
Major surgery/procedure	>50,000
Neurosurgery	>100,000
Acquired platelet dysfunction (e.g., medications, uremia)	Unknown if transfusion is effective
Congenital platelet dysfunction (e.g., von Willebrand factor, Glanzmann's thrombasthenia)	Unknown

Renal Dysfunction

Kidney disease leading to elevated urea can affect platelet function significantly by decreased production of thromboxane, alterations in platelet granules, as well as associated anemia and dysfunction of von Willebrand factor. The net effect is weaker formation of the initial platelet plug, and increases in bleeding, sometimes even spontaneously. Dialysis can be effective in restoring some of the function to platelets, as can desmopressin. The difficulty is in diagnosing platelet dysfunction in the face of a normal platelet count because many of the platelet function tests are not routinely available.

CLINICAL RELEVANCE OF COAGULOPATHY

The focus on coagulopathy has direct clinical relevance; abnormalities in platelet counts, coagulation defects or the presence of products of fibrin degradation are all independently associated with increased mortality and in hospital complications rates. In trauma patients, for example, coagulopathy is associated with approximately a threefold increased risk of death. Although it is clear that much of this coagulopathy is caused by the underlying disease processes, it is harder to ascertain whether treatment can actually impact morbidity or

TABLE 5 Estimating the Pretest Probability of HIT: The 4Ts

Category	2	1	0
Thrombocytopenia	>50% platelet fall and platelet nadir ≥20	Platelet count fall by 30%–50% or nadir 10–19	Platelet count fall by <30% or nadir <10
Timing of onset of platelet fall (or other sequelae of HIT)	Clear onset days 5–10 or platelet fall <day 1 with recent heparin in past 30 days	Consistent with days 5–10 fall, but not clear, onset after day 10, or fall <day 1 with recent heparin (past 31–100 days)	Platelet count fall <day 4 without recent exposure
Thrombosis or other sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (not proved)	None
Other cause(s) of platelet fall	None evident	Possible	Definite
Points (0, 1, or 2 for each of 4 categories; maximum possible score = 8)			

Pretest probability score: 6–8 indicates high; 4–5, intermediate; and 0–3, low.
HIT, heparin-induced thrombocytopenia.

TABLE 6 Anticoagulants and Reversal Agents

Therapeutic Agent	Target	Comments
FFP	Warfarin Hepatic coagulopathy Traumatic coagulopathy	Rapid reversal for warfarin INR of FFP unit is 1.3–1.4 Risk of TRALI
Cryoprecipitate	Low fibrinogen levels	Stored frozen, requires preparation time
Platelets	Clopidogrel, prasugrel, aspirin	Risk of new platelets being inhibited by drug still present
Prothrombin complex concentrates Kcentra, Beriplex	Warfarin + Rivaroxaban/apixaban/edoxaban	Rapid reversal, needs vitamin K in addition for warfarin
Factor VIIa	Warfarin Dabigatran Rivaroxaban	Rapid reversal, needs vitamin K in addition for warfarin Acute trauma coagulopathy
FEIBA (anti-inhibitor coagulant complex)	Direct thrombin inhibitors Anti-factor Xa inhibitors Dabigatran	Activated PCC Factors II, VIIa, IX, X
Protamine	Heparin, dalteparin, enoxaparin	Risk for hypotension, anaphylaxis
Desmopressin (DDAVP)	Uremic platelet dysfunction + Clopidogrel, prasugrel	Rapid onset Lasts 6–8 hours Unclear if effective for drugs
Vitamin K	Warfarin Vitamin K deficiency	Relatively slow onset IV or PO equivalent at 24 hours
Aminocaproic acid	Hyperfibrinolysis	Often used post-cardiac bypass, decreases blood loss
Tranexamic acid	Hyperfibrinolysis	Used in trauma patients (CRASH-2 study) and post-cardiac bypass
Pradaxa (idarucizumab)	Dabigatran (Pradaxa)	Direct thrombin inhibitor antidote, antibody fragment
Andexanet	Rivaroxaban Apixaban Edoxaban	Factor Xa inhibitor antidote, awaiting final FDA clearance in 2018

FDA, US Food and Drug Administration; *FFP*, fresh frozen plasma; *INR*, international normalized ratio; *IV*, intravenous; *PCC*, prothrombin complex concentrate; *PO*, by mouth; *TRALI*, transfusion related acute lung injury.

mortality. In patients with critical illness, it is therefore important to test for and track any coagulopathy, at least initially, because of both its prognostic significance and to treat any specific problems that could arise as a result (e.g., thrombocytopenia) in a patient with an intracranial hemorrhage.

TESTS OF COAGULOPATHY

The vast majority of the blood tests currently available in the clinic can do not tell the complete picture when it comes to coagulopathy, especially because by the time that they are available the actual clotting milieu in the patient at the bedside may have already changed, particularly if the patient is undergoing significant resuscitative efforts with intravenous fluids or blood products. The most commonly used test to evaluate for possible coagulopathy, international normalized ratio (INR), was primarily developed to evaluate the effect of warfarin on the coagulation cascade; however, it has become the de facto surrogate of coagulopathy in critically ill patients, including trauma. The turnaround time in most laboratories for this test is 30 to 40 minutes, which places some serious limitations on its utility in many clinical scenarios. Although some point-of-care tests have been introduced (e.g., the i-STAT handheld device), their reliability for coagulation testing remains in doubt. Table 6 lists the most commonly ordered coagulation blood tests, and what they measure, whereas Table 7 shows how they are disordered in common disease processes.

Thromboelastography (TEG) testing has become increasingly used over the past decade in critically ill patients in assess multiple different aspects of coagulation including platelet function and fibrinolysis and may hold promise in developing better ways to evaluate and treat coagulopathy, particularly in the acute setting. I will deal with this test separately because each requires more detailed discussion due to the complexity of interpreting its results.

TEG or Viscoelastic Testing

Conventional tests of coagulopathy have significant limitations in accurately assessing the hemostatic profile and truly predicting bleeding risk in critically ill patients, especially considering that coagulation changes are often a dynamic phenomenon rather than a static one, with stages of hypercoagulability, hypocoagulability, and fibrinolysis. Viscoelastic testing has the ability to evaluate thrombosis and lysis simultaneously, and thus give a more complete picture of the coagulation profile of the patient. Although the PT is limited to the extrinsic clotting system (factors VIIa, Xa, and IIa) and partial thromboplastin time is limited to intrinsic clotting reactions (factors XIIa, XIa, IXa, and IIa), TEG allows assessment of the whole process from initiation of coagulation to fibrinolysis and clot degradation. Additionally, conventional assays (PT, INR) are performed in the laboratory under optimal temperature and pH so they fail to take into account the in vivo effects of hypothermia and acidosis on coagulation cascade. In contrast, viscoelastic tests are performed on whole blood samples that take into account the complex interactions between different blood cells and their biochemical characteristics, assessing blood hemostatic profile in real time at the bedside.

TABLE 7 Common Laboratory Findings for Disease Processes

Condition	Platelet Count	PT	PTT	Fibrinogen Level	D-Dimer	TEG Findings
DIC	Decreased	Prolonged	Prolonged	Decreased	Increased	Hypercoagulable then hypocoagulable
Dilution	Decreased	Prolonged	Prolonged	Decreased	Decreased	R prolonged
Vitamin K deficiency	Unaffected	Prolonged	Normal or prolonged	Unaffected	Unaffected	R, K prolonged MA decreased
Warfarin use	Unaffected	Prolonged	Normal or prolonged	Unaffected	Unaffected	R, K prolonged MA decreased
Aspirin use	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	K prolonged MA decreased
Apixaban use	Unaffected	Prolonged	Prolonged	Unaffected	Unaffected	R, K prolonged
Rivaroxaban use	Unaffected	Prolonged	Prolonged	Unaffected	Unaffected	R, K prolonged with higher doses
Dabigatran use	Unaffected	Prolonged	Prolonged	Decreased	Unaffected	R, K prolonged
Hyperfibrinolysis	Unaffected	Prolonged	Prolonged	Decreased	Very high	MA decreased LY30 increased
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	R prolonged
Liver failure Early End-stage	Unaffected Decreased	Prolonged Prolonged	Unaffected Prolonged	Unaffected Decreased	Unaffected Increased	R, K prolonged MA decreased

Note: in the case of the direct oral anticoagulants, these laboratory findings do not correlate well to the degree of anticoagulation, but may be present in patients exposed to these agents.
K, interval between reaction time and fixed value of clot firmness; MA, maximum amplitude; R, reaction time.

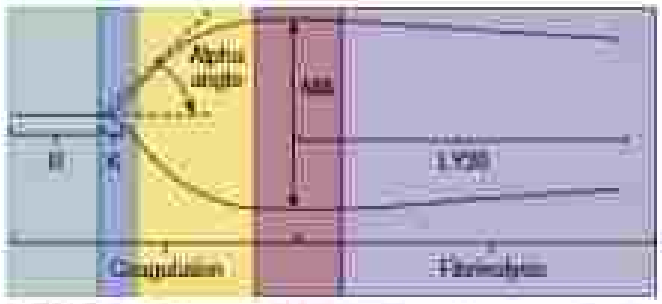

FIG. 2 Tracing of the resting blood clot. *K*, interval between reaction time and fixed value of clot firmness; MA, maximum amplitude; R, reaction time.

TEG results are presented as a combination of a graphic representation (Fig. 2) of complete timeline of the evolving blood clot generated via a transducer, which detects resistance to motion of interposition placed in rotating blood sample, as well as certain specific values related to this graph. The reaction time or *r* value (TEG activated clotting time in rTEG) represents the time taken for first measurable clot formation and is a reflection of enzymatic clotting activation. *k* value is the interval measured from the *r* to fixed value of clot firmness or the point that the amplitude of tracing reaches 20 mm; this reflects thrombin's ability to cleave soluble fibrinogen into insoluble fibrin strands. The *α* angle is the angle between the tangent line drawn from the base horizontal line to beginning of the cross-linking process, measured in degrees and primarily reflects speed at which fibrin builds up and crosslinking takes place. The maximum amplitude measures the end result of maximal platelet and fibrin interaction, reflecting the ultimate clot strength. The final reading of the tracing is LY30, the degree of clot lysis at 30 minutes of the tracing. Above normal value is indicative of hyperfibrinolysis. In addition, the TEG can measure (G), a log derivation of the maximum amplitude, representing the clot strength using dynes/cm, suggested to be the best measure of clot strength because it reflects both the enzymatic and the platelet components of hemostasis. The computer generated tracing reflects component deficits if any to coagulation proteins, platelets, fibrinogen, or fibrinolysis.

The unique ability of TEG to assess the component specific functionality of clotting blood provides the clinician with specific advantages to guiding goal directed therapy with increased accuracy compared with conventional tests of coagulation. In addition, with improvements in medical information, the TEG tracing can be observed in real time at the bedside, decreasing the time taken for potentially serious coagulation defects to be treated.

TEG and Platelet Mapping

One of the advantages to using TEG to assess platelet function is that the cells will be activated and demonstrate all of their functions to hemostasis (thrombin generation, clot formation, clot retraction, and lysis). The whole TEG assay measures the ultimate clot strength as maximum amplitude, which is 80% dependent on platelet function and 20% on fibrin activity. Whole blood TEG platelet mapping, in contrast, is a modification of the original TEG system using a focused technique to assess the independent contribution of platelets in clot formation by measuring the reactivity of the platelet activators arachidonic acid (AA) and adenosine diphosphate (ADP).

Whole blood TEG was developed to assess antiplatelet therapy most commonly in patients undergoing cardiac surgery with preoperative initiation of ADP to predict the development of microvascular bleeding in patients on aspirin or clopidogrel. The assay measures maximum hemostatic activity and the effect of therapy with aspirin (AA addition) or thienopyridines (ADP additive) is evaluated by comparing the TEG kaolin activated test curves with the AA or ADP stimulated TEG curves (Fig. 3). Although it may have a role in cardiac surgery, clinical applications so far seem limited by its inability to predict platelet or other blood component transfusions.

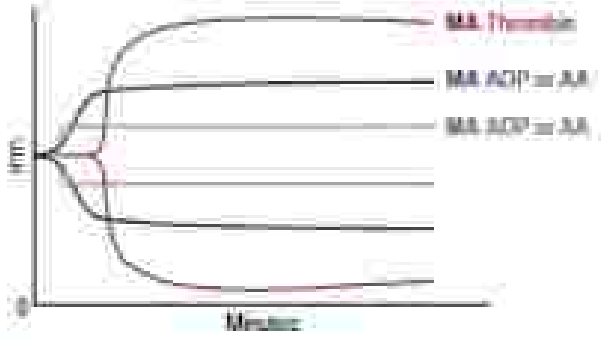

FIG. 3 Comparison of thromboelastography (kaolin activated) trace curves with arachidonic acid or ADP stimulated TEG curves. AA, Arachidonic acid; ADP, adenosine diphosphate; MA, maximum amplitude activity.

Platelet Function Tests

The absolute platelet count remains a poor marker for platelet effectiveness, and there has been an explosion of different platelet assays over recent years, from the various types of thromboelastography, aggregometry, and tests of function under shear stress.

Traditionally, the bleeding time was the first test used to measure true platelet effectiveness, and it assesses the platelet ability to develop a hemostatic plug by recording the time that the platelets take to occlude an in vivo skin wound for stopping the hemorrhage. Given how the test is performed, it is impractical to perform in all but the most stable of settings and has been generally abandoned clinically resulting from a lack of accuracy and difficulties with standardization.

Point of care testing devices have now become available that can measure platelet function by a number of different techniques. Whole blood aggregometry assesses the increase in impedance generated by aggregation of platelets to those already fixed on electrodes in the machine. This has been most useful in assessing the degree of platelet inhibition caused by medications (e.g., aspirin, clopidogrel), although it has been reported to help identify patients at risk of post-operative bleeding after cardiac surgery.

Other systems use a combination of aggregometry and optical detection, either detecting hemoconcentration caused by ADP to achieve clot/thrombus contraction, or simply assessing turbidity as fibrinogen attaches to activated platelets in the reaction chamber. These tests have been used to evaluate platelet granule dysfunction and verification of the platelet inhibitory effects of platelet antagonists. To date, despite multiple different systems having been developed (which are not discussed in detail here), little has been shown to have significant advantage in the clinical arena and to be robust as to accurately assess platelet function.

Platelet dysfunction should be considered in patients with normal blood test but continued evidence of bleeding, especially if there is a history of prior bleeding episodes without a clear precipitant, or in patients on antiplatelet medications.

Bleeding Disorders in Which Blood Tests Are Negative

The most common cause for unexplained bleeding when conventional blood tests are normal is platelet dysfunction, and frequently the reason for this is medication induced with antiplatelet drugs such as aspirin, clopidogrel, and prasugrel. Given the increased use of antiplatelet agents in general and the aging of the population, this should be strongly considered in all patients, especially if no medication history is available. Additionally, in patients with renal disease, uremia is a known factor affecting platelet function (which can be reversed to a certain extent by dialysis or administering desmopressin), whereas in patients with liver disease, the thrombocytopenia associated with cirrhosis seems to also come with a degree of platelet dysfunction.

Hypofibrinolysis is a rare but serious cause of bleeding and will usually only be demonstrated on TEG testing. Apart from its relationship with the acute coagulopathy of trauma (dealt with elsewhere in this book), it can also be associated with liver diseases and some advanced malignancies such as prostate cancer. Antifibrinolytic lysine derivatives such as tranexamic acid and aminocaproic acid are considered the medications of choice for hyperfibrinolytic bleeding.

Late diagnosis of inherited bleeding disorders, although very uncommon, may be a reason for unexplained bleeding and conditions such as hemophilias, von Willebrand's disease, and other platelet function disorders. Even more rarely some of the inherited disorders can actually develop in adult life, related to disorders of the immune system, such as autoantibodies or myelodysplastic syndromes.

PROCEDURES IN COAGULOPATHIC PATIENTS

Despite concerns regarding performing invasive procedures on patients with coagulopathy or low platelet counts, there is very little consensus on which procedures are safe to perform or what levels of clotting function are necessary to mitigate risk. There are even fewer data on whether transfusion of factors or platelets can mitigate the risk of complications. Based on a number of retrospective studies, it appears that in critically ill patients undergoing an invasive procedure, PT or INR values do not appear to be predictive of the risk of bleeding, likely because these tests only measure part of the clotting cascade. Unfortunately, despite this, in clinical scenarios, it seems that INR is the most universally used coagulation test used to decision making. A level somewhere between 1.4 and 1.6 seems to be acceptable for most neurosurgeons placing an intracranial pressure monitoring device for example or for anesthesiologists for epidural placement (although the most current American Society for Regional Anesthesia recommendations do not state a specific target number). Less invasive procedures such as central line or arterial line placement may be performed with higher INRs, particularly if they are placed in locations where pressure can be applied in the case of an unsuccessful attempt. There is little to no evidence of effectiveness for the prophylactic use of FFP before procedures, and this practice is not currently recommended.

Similarly, when looking at prophylactic platelet transfusion, there are few data to guide the physician, although clinical practice guidelines from the American Association of Blood Banks have suggested a platelet transfusion trigger of $20,000 \times 10^9$/L for central venous catheter placement, $50,000 \times 10^9$/L for lumbar puncture, and the same trigger for patients having major elective surgery (Table 4); however, these were all weak recommendations based on low-quality evidence. There are retrospective studies in trauma patients that suggest that patients with severe traumatic brain injury should have their platelet count maintained above $100,000 \times 10^9$/L, but this remains controversial, without good data to suggest that correcting this thrombocytopenia by platelet transfusion will improve outcomes.

ANTICOAGULANT MEDICATIONS

The most common reason for a coagulopathy in the twenty-first century is medication induced, that is, anticoagulant medications used to treat a chronic medical condition such as coronary artery disease, valvular heart disease, or atrial fibrillation (AF). Between 2.7 and 6.1 million Americans currently suffer from AF, and it is anticipated that 1 in every 4 people will develop AF in his or her lifetime. This incidence is expected to increase as the population increases. There has been a concomitant increase in the use of anticoagulant medications over the last decade including an explosion in the use of novel anticoagulants, as well as increased use of antiplatelet agents, leading to ever increasing numbers of patients having some form of acquired coagulation defect.

Table 5 lists the currently available anticoagulant agents, where they exert their effects, half-life, and clearance as well as any currently

TABLE 8 Clearance of Anticoagulants

Anticoagulant	Target	Half-life	Clearance	Comments
Unfractionated heparin	Xa and thrombin inhibition	≈1–90 min	Cellular and kidney	Can be used IV or SQ Reversed by protamine
Low-molecular-weight heparin	As above, but mainly Xa inhibition	3–7 hr	Kidney	Only given SQ Only ≈8% reversed by protamine
Fondaparinux	Indirect Xa inhibition	15–17 hr	Kidney	No specific antidote Consider PCC, aPCC, or Andexxa
Aspirin	Platelet cyclooxygenase inhibition	20–40 min Antiplatelet effects last 5–10 days	Liver	Risk of exogenous platelets being inhibited if drug still present
Antiplatelet agents, clopidogrel, prasugrel, ticagrelor	Platelet $P2Y_{12}$ antagonists	6–15 hr	Liver	Risk of exogenous platelets being inhibited after transfusion if drug still present
Warfarin	Vitamin K–dependent clotting factors (II, VII, IX, X, protein C and S)	20–60 hr	Liver	Reversal with vitamin K, prothrombin complex concentrates, or FFP depending on urgency
Dabigatran	Direct thrombin inhibition (IIa)	11–22 hr	80% via kidney	Antidote is idarucizumab (Praxbind), PCC or aPCC if not available
Rivaroxaban Apixaban Edoxaban	Direct Xa inhibition	4–12 hr 9–14 hr 10–14 hr	Liver and kidney	Antidote is andexanet alpha (Andexxa), PCC or aPCC if not available
Bivalirudin	Direct thrombin inhibition	20–40 min	80% plasma 20% kidney	No specific antidote
Argatroban	Direct thrombin inhibition	30–40 min	Liver	No specific antidote

aPCC, Activated prothrombin complex concentrate; FFP, fresh frozen plasma; IV, intravenous; PCC, prothrombin complex concentrate; PO, by mouth; SQ, subcutaneous.

recommended reversal agents or therapy, when available. The newer agents known as the novel or direct anticoagulants have been extremely challenging because specific reversal agents did not exist when they were first introduced. Nonspecific reversal agents, such as prothrombin complex concentrate, were the only available options for a number of years; however, idarucizumab, an antidote for dabigatran, became available in 2015. Idarucizumab is a recombinant immunoprotein that has high affinity for the dabigatran molecule and can effectively neutralize the anticoagulant effect of this drug. Although idarucizumab is effective at mitigating the underlying coagulopathy induced by dabigatran, it does not promote clot formation. Direct comparisons between the two strategies are currently lacking, but in theory, idarucizumab may have fewer thromboembolic complications than prothrombin complex concentrate; however, concerns remain about delays in the achievement of hemostasis seen in clinical trials evaluating idarucizumab. Unfortunately, the cost of reversal is more than 10 times the cost of a month's supply of the medication. In 2018, a recombinant, modified human factor Xa decoy molecule called andexanet alpha (Andexxa) was approved by the US Food and Drug Administration as a reversal agent for the anticoagulant effect of factor Xa inhibitors such as rivaroxaban and apixaban. Andexanet alpha binds to factor Xa inhibition, effectively reversing their anticoagulant effects; however, its half-life of 2 hours is much shorter than the anticoagulants being reversed, particularly in the setting of acute kidney injury. In addition, it suffers the same problem of expense, with a single dose for reversal estimated to be approximately $55,000.

Careful attention should be paid to use of anticoagulant medications in the face of hepatic or renal impairment. As Table 8 demonstrates, the vast majority of these drugs are cleared by one of these two routes; therefore, in the patient who has labile creatinine clearance or is going into hepatic failure, significant forethought should be given to the exact choice of drug. Additionally, there are many drug-drug interactions that can play havoc with the metabolism of warfarin, which is a difficult enough drug to dose correctly at the best of times. Other medications can have similar problems, and it has been estimated that around 20% of patients ingest herbal medications at the same time as anticoagulants, and up to 10% of these are at risk for herb-drug interactions. Clinicians need to be cognizant of these interactions, especially where new medications have been started in the hospital and the patient is then readmitted back to home anticoagulation.

Therapeutic Agents to Treat Coagulopathy

Table 9 lists the commonly used therapeutic agents for treatment of coagulopathy; however, in many patients the coagulation defect is not limited to just one part of the pathway and may treatment with more than one product (e.g., dilutional coagulopathy may require plasma, platelets, AND cryoprecipitate infusions), and warfarin reversal will require both prothrombin complex concentrates and/or FFP, in addition to vitamin K to prevent rebound INR increases. Administration of coagulation tests again may not correspond to clinically relevant bleeding risk, and the agents listed should be used in conjunction with clinical judgment rather than being based purely on a specific number, with treatment individualized to the specific coagulation defect and risk of hemorrhage.

TABLE 9 Commonly Used Therapeutic Agents for Treatment of Coagulopathy

Therapeutic Agent	Uses	Notes
FFP	General coagulopathy Warfarin effect reversal	Rapid reversal for warfarin INR of FFP itself is 1.3–1.4 Risk of TRALI
Platelets	Thrombocytopenia Reversal of drug effects	Vital part of an MTP Function difficult to measure
Cryoprecipitate	Low fibrinogen levels	Stored frozen, requires preparation time
Fibrinogen concentrate	Low fibrinogen levels	Data for efficacy in postsurgical patients
Prothrombin complex concentrates (e.g., Kcentra, Profilnine)	General coagulopathy Warfarin effect reversal Novel anticoagulant reversal	Increasingly used in trauma Rapid reversal, needs vitamin K in addition for warfarin
Factor VIIa	Traumatic coagulopathy Anticoagulant reversal	Less often used in trauma Possible use in reversal of novel anticoagulant agents
Tranexamic acid	Hyperfibrinolysis	Trauma patients Cardiac surgical patients
Desmopressin (DDAVP)	Uremic platelet dysfunction ↑ Clopidogrel, Prasugrel	Rapid onset, lasts 6–8 hr Questionable efficacy for medications
Vitamin K	Warfarin effect reversal Vitamin K deficiency	Relatively slow onset IV vs PO equivalent at 24 hr
Aminocaproic acid	Hyperfibrinolysis	Often used in cardiac surgery to decrease blood loss
Platelets	Thrombocytopenia Reverse antiplatelet effects	Risk of new platelets being inhibited by drug still present

FFP, fresh frozen plasma; *INR*, international normalized ratio; *IV*, intravenous; *MTP*, massive transfusion protocol; *PCC*, prothrombin complex concentrate; *PO*, oral; *TRALI*, transfusion-related acute lung injury.

Suggested Readings

Cushman M, Lim W, Zakai NA. Clinical practice guide on antithrombotic drug dosing and management of antithrombotic drug–associated bleeding complications in adults. Available from the American Society of Hematology at http://www.hematology.org/Clinician/Guidelines-Quality/Quick-Reference/.

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